Modern concepts and strategies in synthesis of biaryl compounds

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Aryl coupling method is applied to each individual coupling problem, which fulfills all regio- and stereochemical demands. Preparation and utilization of specific biaryl systems, particularly those which suffer hindered rotation, is a demanding goal in the synthesis of natural products and pharmaceuticals. However, remarkable and powerful new methods like regio- and stereoselective synthesis of important biaryl natural products such as steganone and ancistrocladine, and recycling of unwanted isomers, specific synthesis of both atropisomeres starting from the same precursor, and the ortho substituents next to the biaryl axis in the same precursor are discussed in the present paper.

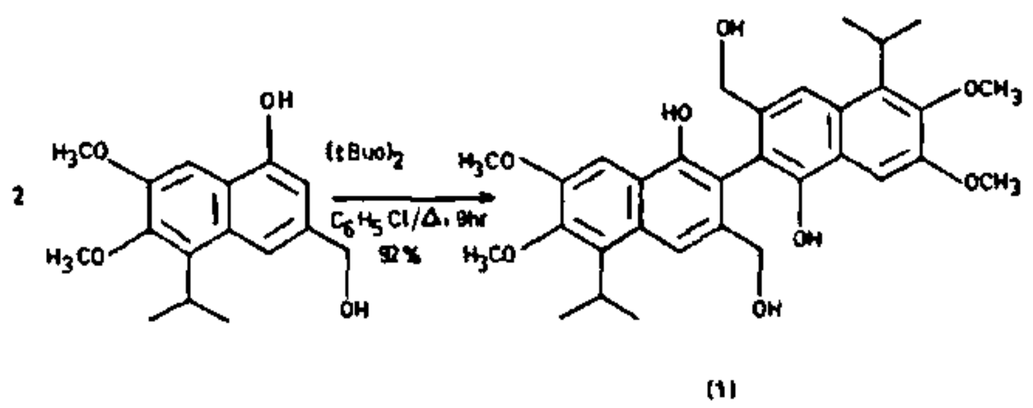
THE biaryl axis is not only a central building block but also a biosynthetic origin in many biological active natural products such as polyketides, terpenes, lignans, coumarins, flavonoids, tannins, peptides, and alkaloids[1]. The key step in such synthesis is always the coupling of the two aromatic halves of the molecule. The processes which are capable of solving the problems of 'specific cross-coupling/regioselectivity and stereoselectivity' which will be applied to the synthesis of actual sterically hindered biaryl natural products. The coupling reaction has recently become possible to separate the two formal goals of stereoselective biaryl synthesis, that is, CC bond formation and asymmetric induction whether the reaction is carried out in an inter- or intramolecular manner.

Intermolecular aryl coupling

The reductive dimerization of aryl halides is one of the oldest methods for the preparation of symmetrical biaryl compounds. The classical example is Ullmann reaction[2] for which copper bronze is used as a reducing agent and the reaction affords the highest yields in the case of electron-poor aryl iodides such as nitro groups, aldehyde-, ester-, and lactone functions. Free primary or secondary amine functions or phenolic hydroxyl groups undergo N- or O-arylation to give biaryl amines and biaryl ethers respectively.

The course of the Ullmann reaction is determined by the position of the halogen. Therefore, it is specific with regard to the site of the coupling, and the regioselectivity problem is to be shifted to the preceding halogenation step. Semmelhack *et al.*[3] have introduced a number of new modifications to avoid the often very high reaction temperatures required by Ullmann reaction. Nickel(0) complex such as $[Ni(cod)_2]$ is used in stoichiometric amounts instead of copper, and the aryl halides thus reacted afford[3] high yields in homogeneous solution at temperatures as low as 40–50°C. Nitro groups are not compatible with this or other nickel-mediated processes, because of the formation of nitrosonickel(0) complexes, whereas nitrile or even free amines are tolerated. Proton donors change the course of the reaction dramatically leading to hydrodehalogenation[4].

The oxidative phenolic coupling reactions, showing biomimetic characters[5], require the use of electron-rich aromatic compounds with free phenolic groups. These reactions are only limited preparative use, though they are applied to the construction of constitutionally symmetrical biaryls, because a number of unwanted side products such as formation of poly ethers are formed if the aromatic substrates have several sterically and electronically comparable positions[6]. Attack at benzylic positions often compete with the desired coupling process, for example, Gossypol analogue (1) has been synthesized with excellent 92% yields (Scheme 1)[7].



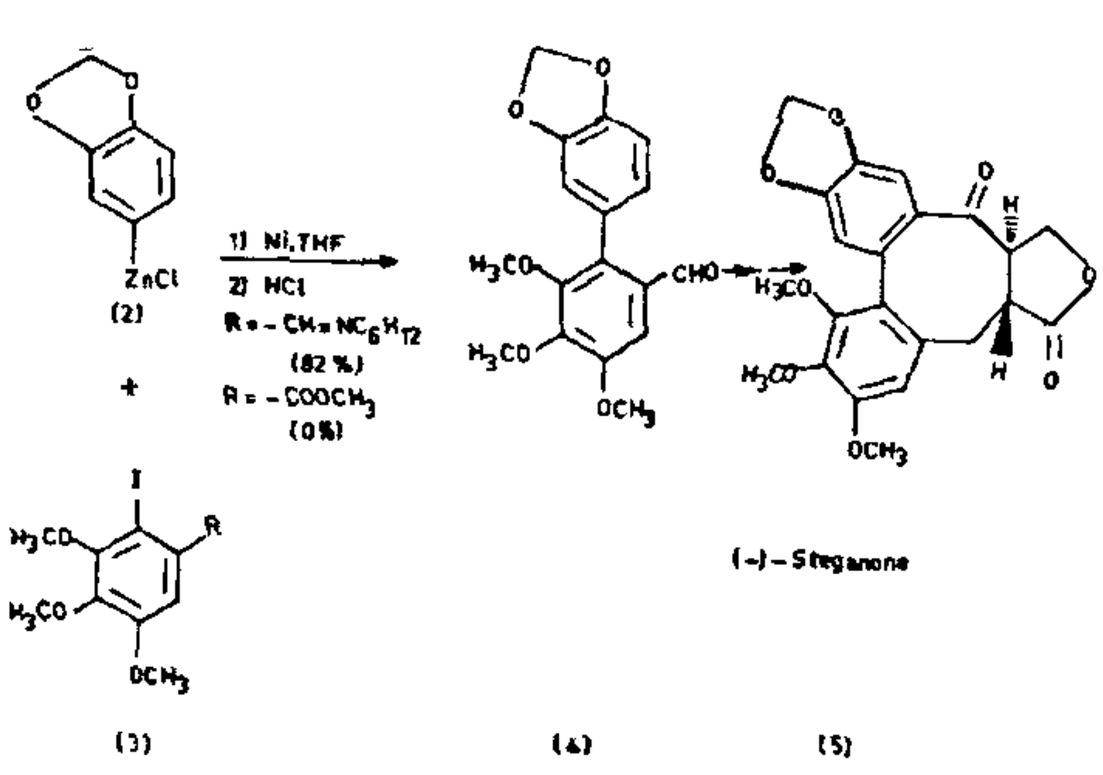
Scheme 1.

Unsymmetrical racemic biaryls by intermolecular cross-coupling

In intermolecular processes, satisfactory yields of cross-coupled products are obtained if the two aromatic compounds used are functionally or electronically very different. Both in reductive and oxidative processes, electron-rich compounds must be allowed to react with electron-

poor partners in order to shift the normally statistical product distribution towards the crossed products. It is much more effective to use the two aromatic compounds in the form of an electrophile/nucleophile pair. This can be done even within the framework of a formal Ullmann coupling in which an aryl copper compound is first prepared separately and then allowed to react with an aryl iodide[8]. Reactions of electron-rich aromatic compounds with quinol acetate have given good yields[9].

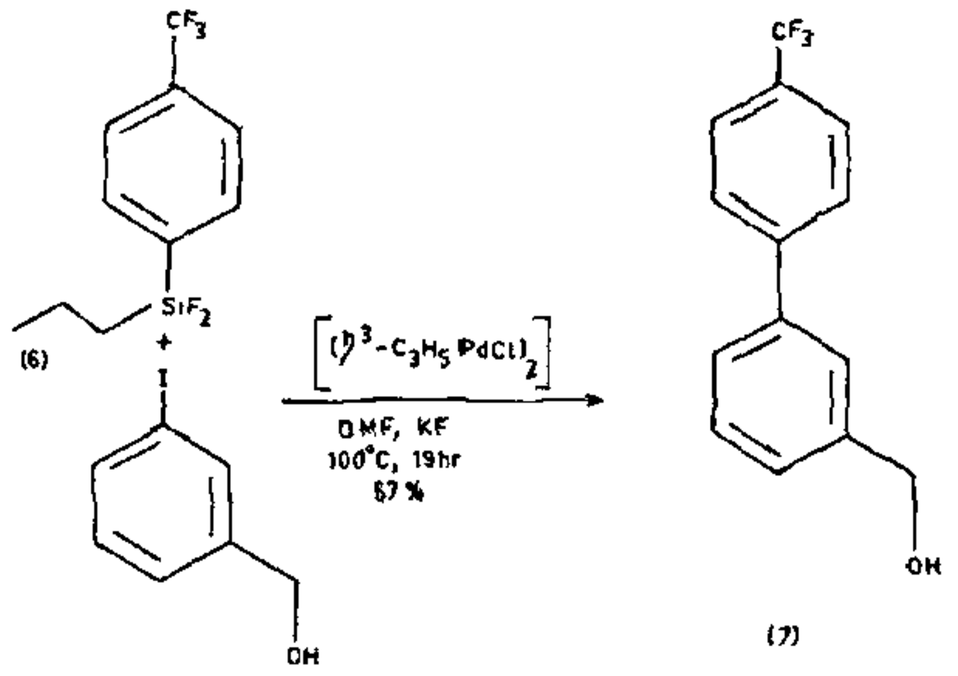
A preparatively favourable combination of electrophilic or nucleophilic aromatic molecules is provided by the pairing of aryl halides with arylmetal compounds. Since the reactions of aryl-Grignard compounds with organic halides (the Kharash reaction) can be accelerated by nickel or palladium derivatives, and this method can often be used for CC bond formation[10]. In order to avoid unwanted addition reactions to carbonyl groups, recourse is sometimes taken to use the less aggressive zinc analogues of the reactive Grignard compounds and such organozinc derivatives are readily obtained by transmetalation of the corresponding lithium compounds, as in the steganone synthesis[11]. The key step in the synthesis of steganone is the regioselective coupling between the organozinc compound (2) and the aryl halide (3), and the reaction (Scheme 2) that poses no



Scheme 2.

steric problem in this formation of the biaryl (4) which has only two substituents in the ortho position with respect to the biaryl axis.

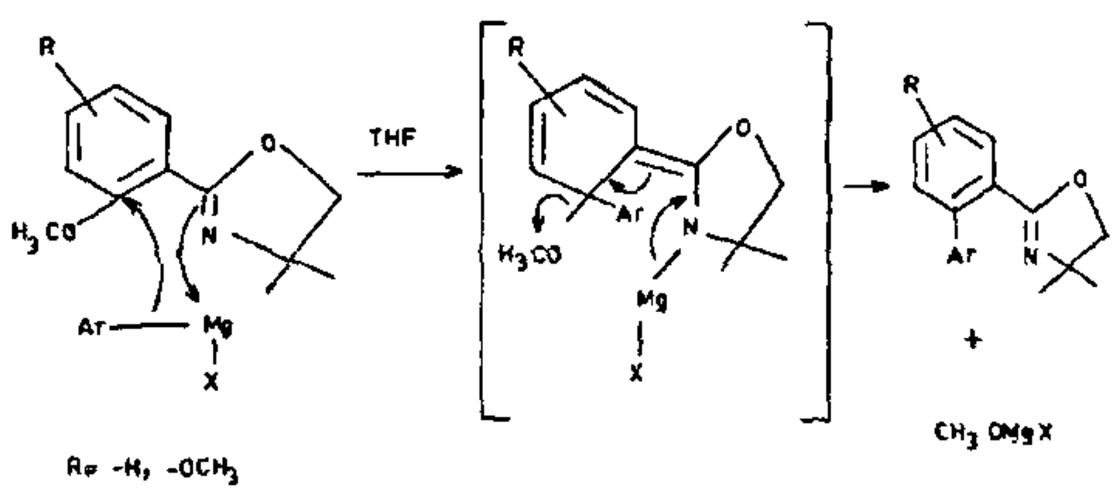
However, when sterically more demanding reactants are used, almost no coupling products are obtained, and even the presence of one ortho substituent on each of the two aromatic compounds causes the yield to fall dramatically[12]. Organocopper and organomercury derivatives are also capable of undergoing analogous palladium-catalysed cross-coupling reactions, although such reactions have as yet hardly been applied[13]. The presence of carbonyl groups do lead to the formation of by-products under the above 'Grignard coupling' conditions[14]. This disadvantage can be avoided by the use of organic derivatives of the less electropositive metals or metalloids such as boron, silicon and tin[15]. A method which has widespread use in organic synthesis is palladium-catalysed coupling of the readily available arylboric acids with aryl halides in the presence of auxillary bases such as potassium carbonate[14]. Steric hindrance of the coupling position by ortho substituents, particularly in boric acid fragment, has a very negative effect on the yields of coupling product when this method is used[16]. The palladium-catalysed synthesis of the biphenyl (7) (Scheme 3), in a yield of not less than 67% by



Scheme 3.

fluoride-induced cross-coupling of arylfluorosilanes (6) with aryl iodides shows that the reaction even tolerates the presence of free hydroxyl groups[17].

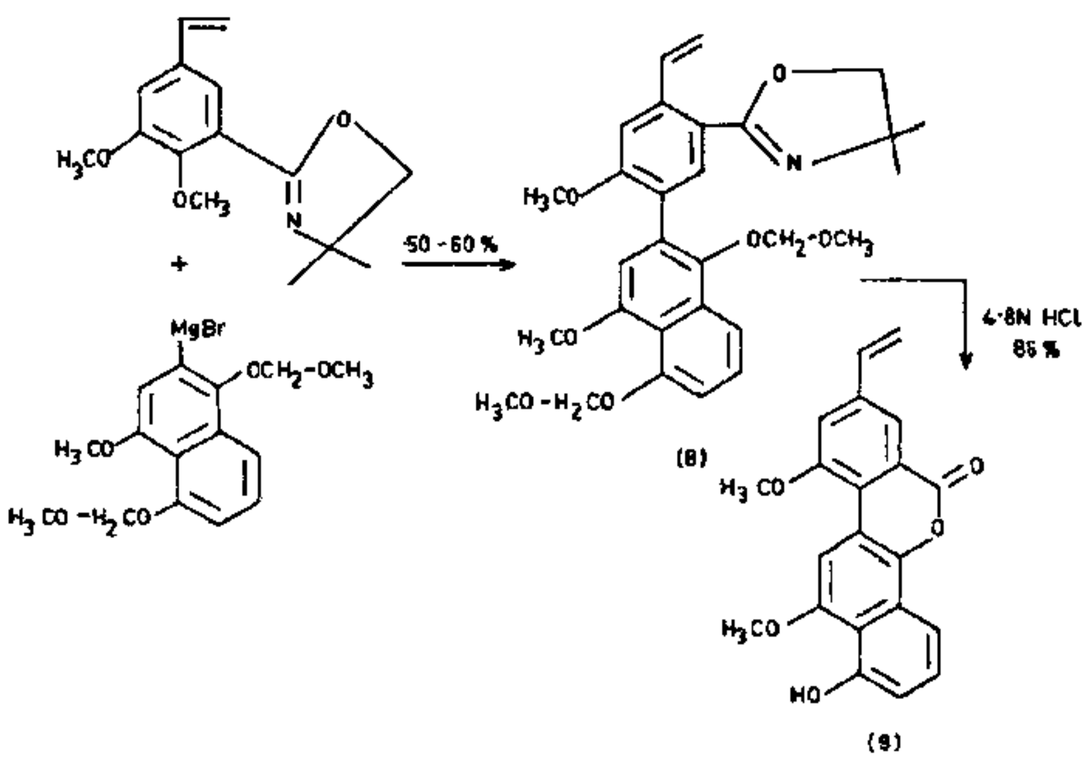
An efficient route to constitute unsymmetrical biaryls cross-coupling between two different aromatic compounds is the Meyers oxazoline method[18]. In contrast to previous cases, this is an uncatalysed reaction and requires the activating influence of an oxazoline moiety in the ortho position, which increases the electrophilicity at the reaction centre and functions, and at the same time as an additional directing complex ligand for the attacking Grignard species (Scheme 4). The aryl residue is thus



Scheme 4.

introduced in the form of a Grignard reagent by nucleophilic aromatic substitution of a methoxy group bound to an aromatic nucleus.

The auxillary group can subsequently undergo hydrolysis to give the biarylcarboxylic acid either under alkaline conditions (after quaternization of the nitrogen with methyl iodide) or under (very harsh) acid conditions, it can be converted into the corresponding alcohol or aldehyde, and this advantage is used in the synthesis of biaryl natural products[19]. For example, the biaryloxazoline (8) has been synthesized[20] and directly cyclized to the antimicrobially active lactone, defucogilvocarcine V (9) (Scheme 5)[21].

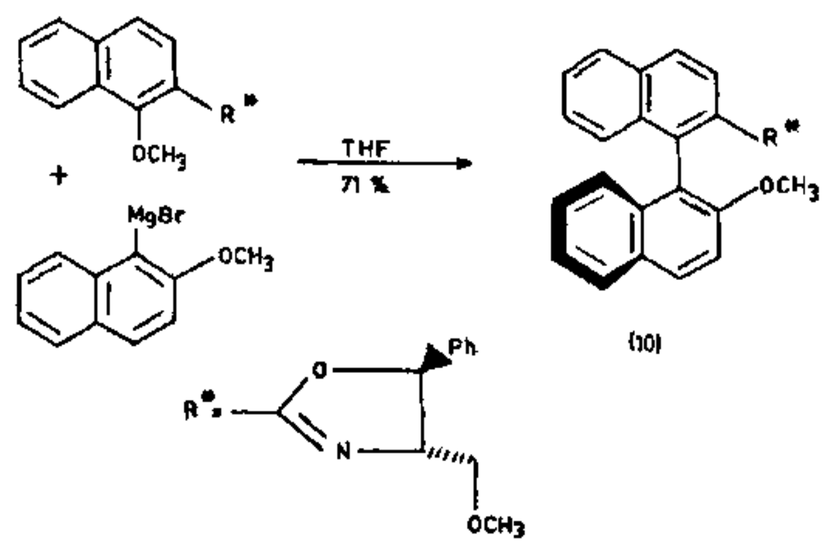


Scheme 5.

Intermolecular atropisomer–selective aryl coupling

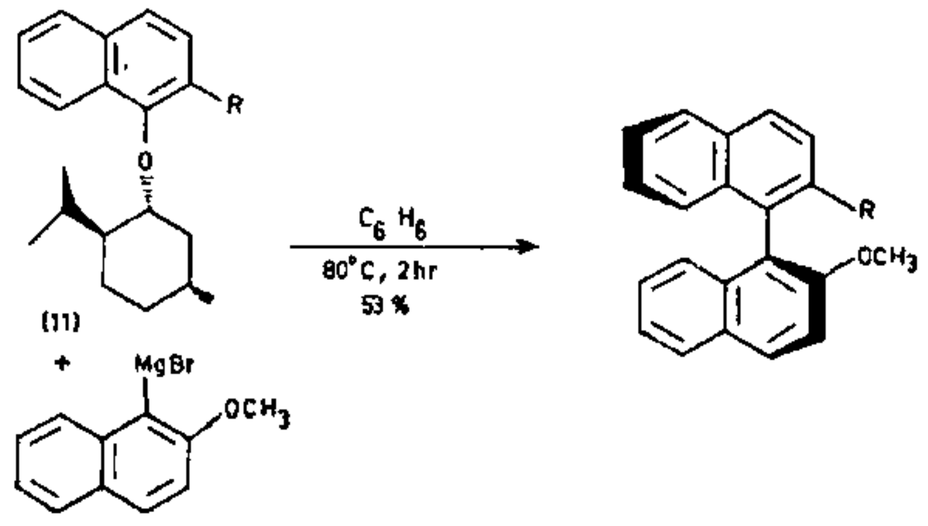
Bulky ortho substituents next to the coupling position in many of the natural or synthetic biaryls lead to hindrance of free rotation around the biaryl axis, and thus more or less stable atropisomers having three or two ortho substituents exist. The directed synthesis of such axially chiral compounds requires the unambiguous assignment of the configuration of a biaryl unit thus formed. The most important method for the direct determination of the absolute configuration at the axis is the measurement of circular dichroism (CD)[22]. X-ray crystal structure determinations will provide information on the absolute stereochemistry at the axis less frequency, but will at least afford very reliable statements regarding the axial-chiral situation relative to stereocenters likewise present in the molecule. An unambiguous assignment of the relative configuration can also be obtained chemically, by means of an atropisomer-differentiating ring closure reaction to give ansa-like macrocycles[23].

Nucleophilic aromatic substitution method can be carried out in an atropisomer-selective manner when enantiomerically pure chiral oxazolines are used. For example, binaphthalene (10) has been synthesized (Scheme 6) by nucleophilic aromatic substitution method[24].



Scheme 6.

A decisive influence on stereoselection in these nucleophilic substitution is suggested to be exerted by the metal cation, since the geometry of the primarily formed addition product is determined by the more favourable mode of complexation[24]. This is also true for the procedure due to Cram, in which the required asymmetric induction is obtained by means of a chiral nucleofuge[25]. However, while the use of chiral oxazolines affords diastereomeric mixtures, which can readily be separated by chromatography, the Cram procedure may make it necessary to separate the undesired atrop-enantiomer. The highest 'chirality transfer efficiency' has been observed in sterically strongly hindered systems in the reaction of the (–)-methoxynaphthalene (11) with the naphthyl Grignard reagent (12) (Scheme 7)[25].

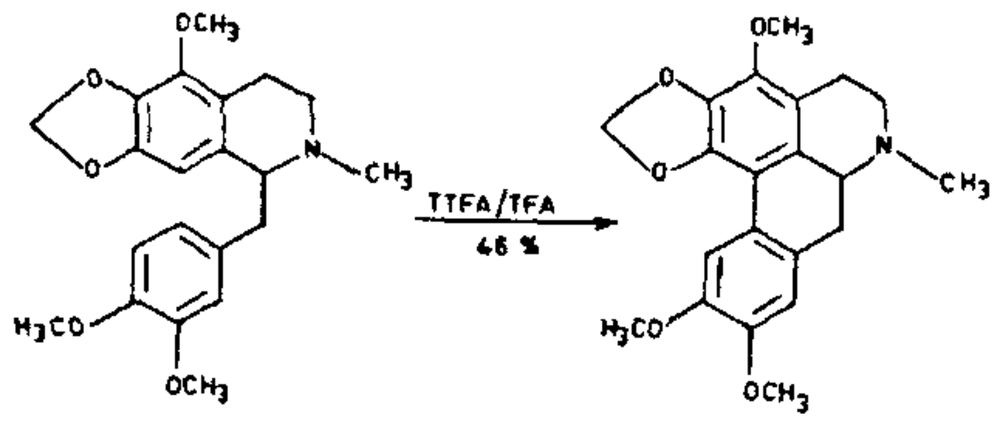


Scheme 7.

Intramolecular aryl coupling

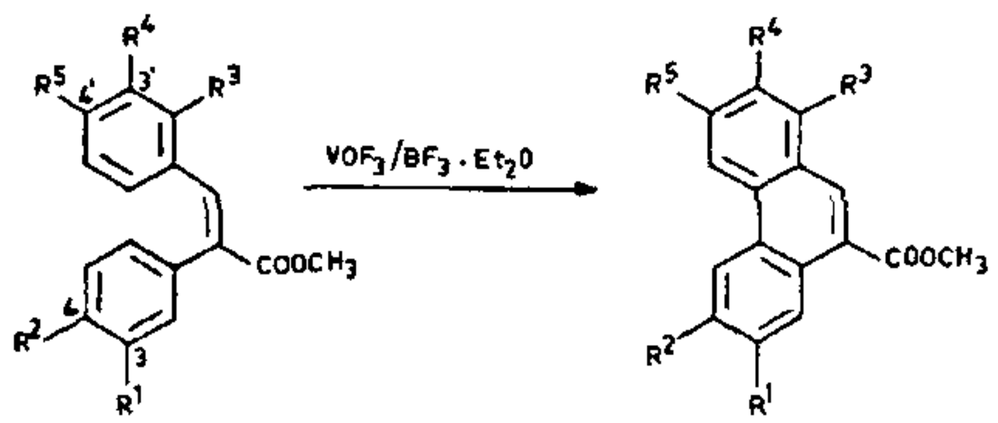
The two main problems in intermolecular aryl coupling processes are the lack of regioselectivity, and the formation of homo-coupling products when cross-coupling is required. These problems are solved in intramolecular

coupling methods. For example, the aporphine alkaloid has been prepared by the oxidative coupling of phenol ethers ('non-phenolic' coupling) using the selective reagents of thallium(III) trifluoroacetate (TTFA) and trifluoroacetic acid (TFA) with no by-products (Scheme 8)[26].



Scheme 8.

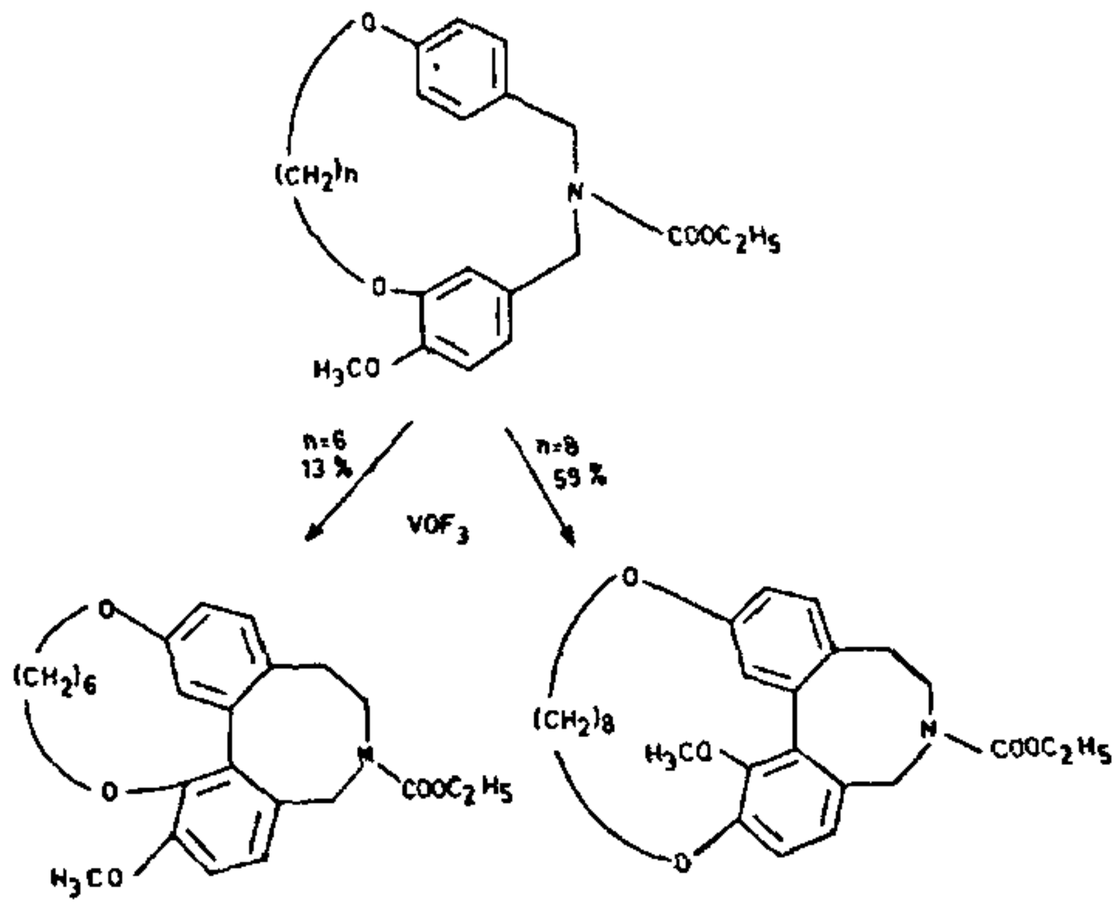
For a successful coupling, at least one of the rings of the substrate (13) to be oxidized must bear oxygen substituents in positions 3 and 4 with respect to biaryl bridge and the other ring must not be subjected to such constraints and can even be oxygen-free (Scheme 9) (Table 1)[27].



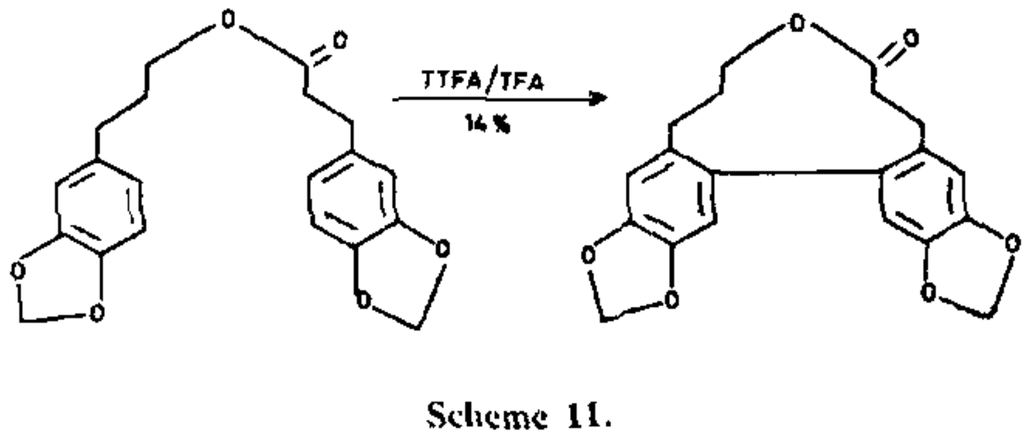
Scheme 9.

The bridge between the two aromatic rings to be coupled induces good yields in cross-coupling and reliable regioselectivities particularly when the bridge is short, because of the intramolecular nature of the reaction. The loss of the regioselectivity observed for larger rings such as eight-membered rings with two equivalent coupling positions can sometimes be compensated by using an additional (auxillary) bridge, the size of which must be varied according to the particularly synthetic problem (Scheme 10)[28].

Coupling can also be carried out successfully for analogous seven-membered ring systems (e.g. homoaporphines and colchicine analogues)[29], and even eleven-membered rings can be obtained in this manner, though with considerably lower coupling yield and regiocontrol are observed (Scheme 11)[30].



Scheme 10.



Scheme 11.

In simple, regiochemically non-problematic cases (e.g. when only one free ortho position is present next to the bridge) the intramolecular coupling reaction can also be carried out under redox-neutral conditions by palladium-catalysed or free radical or photochemical dehydrohalogenation[13]. In some cases, it has been reported to obtain unusually large ring systems in surprisingly good yields by intramolecular aryl coupling[31]. A very important disadvantage of the redox-neutral coupling reaction is that *hydrodehalogenation without coupling* is almost always observed. Since the by-products so formed can generally not be reintroduced into the reaction process by regioselective halogenation, they are no longer available for the required synthesis[13,31].

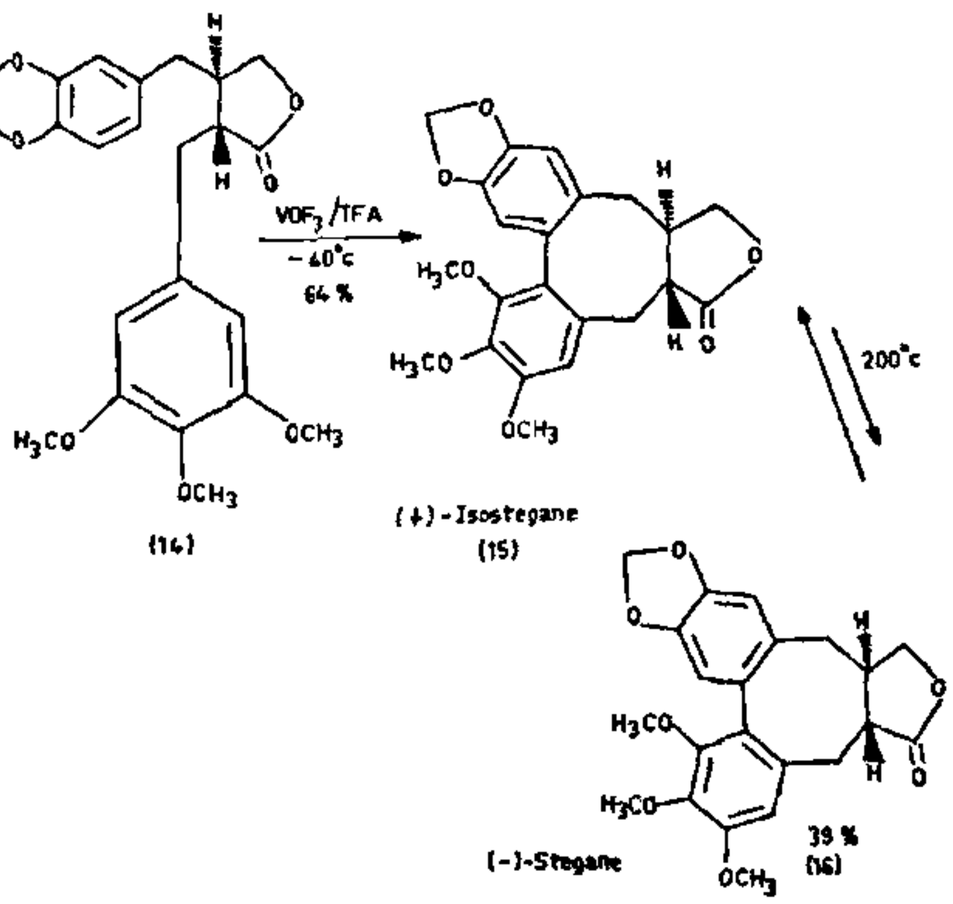
Table 1. Percentage of yield with respect to substituents in intramolecular aryl coupling

R^1	R^2	R^3	R^4	R^5	Yield
OMe	OMe	H	OMe	OMe	96%
OMe	OMe	H	H	H	81%

Intramolecular atropisomer–selective aryl coupling

In many oxidative intramolecular coupling reactions, the 'bridge' is not only a constituent part of the target molecule but it also determines the steric course of the

coupling reaction. For example, the reaction of 14 with VOF_3 gives an unwanted atropisomer 15 (of the isostegane type) which on heating gives the atropisomer mixture of 15 and 16 in the ratio of 3:2 respectively, from which the natural rotational isomer 16 of the 'stegane type' is isolated in 39% yield (Scheme 12)[32]

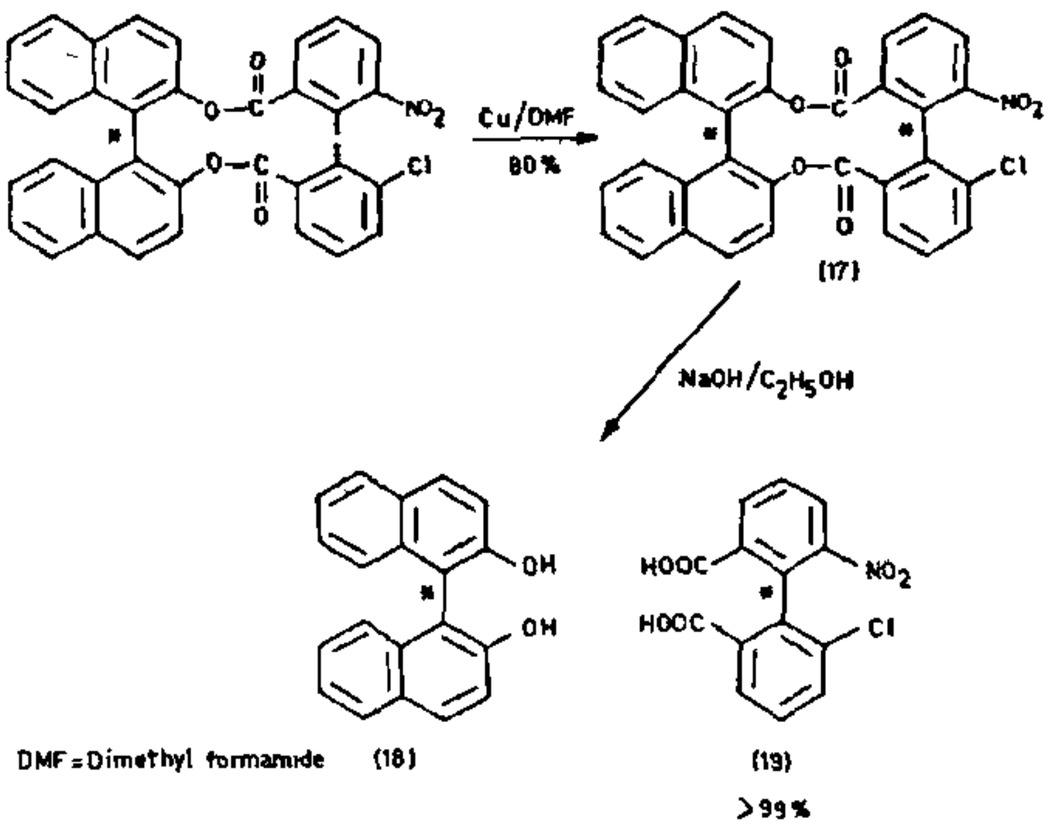


Scheme 12.

The barrier to atropisomerization as well as the kinetically controlled preferred formation of the isostegane-type isomer is determined here mainly by the configurational inflexibility of the cyclooctadiene system, so that analogous coupling lead to the isostegane type even when only two substituents ortho to the biaryl axis are present[33]. Without this additional stabilization the barrier to atropisomerization sinks dramatically, and thermodynamicly controlled rotational isomer mixtures are formed[33].

When the target molecule does not contain a 'bridge' as an integral part of its structure it is possible to take advantage of an intramolecular stereoselective reaction pathway, by pre-fixing the two aromatic moieties by means of an artificial chiral bridge. Thus, Miyano *et al.* developed a process for an atrop-diastereoselective intramolecular Ullmann reaction with the help of optically active auxiliary bridges and the best results were obtained in this case by using the rigid template formed by a further biaryl, (R)-2,2′-binaphthol (18). Here, complete asymmetric induction is observed, and the product 19 has the same enantiomeric purity as the auxiliary bridge used (Scheme 13)[34].

The disadvantage of the high price of the chiral biaryl 18, which must be used in stoichiometric amounts, is partially compensated by the possibility of its reuse. The asymmetric induction is considerably poorer when other, cheaper chiral diols are used as bridges. The



Scheme 13.

reason for the high degree of stereoselctivity achieved, when the binaphthol bridge was used, had been suggested to be a double helix-like arrangement of the twelve-membered ring 17, which did represent the energetically most favourable conformation of the coupling products[34].

The concept of aryl coupling via helically twisted bridged biaryls has been shown clearly in the regio- and stereoselective total synthesis[35]. Ancistrocladine, the most well-known naphthylisoquinoline alkaloid, has been *synthesized by this concept, and it is configurationally* stable at its rotationally hindered axis up to over 200°C. Because of steric hindrance at the axis, the bridged biaryl precursor is not planarized, but splits into helicene-like distorted atropisomers which can be converted into ancistrocladine and its naturally occurring atropisomer hamatine with a clear atropisomer excess, 4.7:1 respectively[35].

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Received 12 July 1993, revised accepted 10 March 1994