The Biginelli Dihydropyrimidine Synthesis

Abstract

The cyclocondensation of suitable CH-acidic carbonyl compounds, aldehydes, and urea-type blocks under acidic conditions provides multifunctionalized derivatives. The discovery of this three-component condensation process was made by Biginelli in 1893, therefore this reaction is called the "Biginelli reaction," "Biginelli condensation," or the "Biginelli dihydropyrimidine synthesis." While the early examples of this cyclocondensation process typically involved a beta-ketoester, aromatic aldehyde, and urea, the scope has now been extended considerably by variation of three building blocks, allowing access to a large number of multifunctionalized pyridmidine derivatives. The importance of multicomponent reactions in combinatorial chemistry has generated a renewed interest in the Biginelli reaction and the number of patents and publications on this subject is growing.

In this chapter, all three-component condensations involving suitable CH-acidic carbonyl compounds, aldehydes, and urea-type building blocks following the Biginelli concept are covered. Therefore, reactions involving 1,3-diketones or nitroacetone as building blocks leading to dihydropyrimides that follow the discussed substitution pattern are included in contrast to earlier articles. Patents are only cited if they contain information not otherwise available.

1. Introduction

The cyclocondensation of suitable CH-acidic carbonyl compounds, aldehydes, and urea-type building blocks under acidic conditions provides multifunctionalized dihydropyrimidine derivatives (Eq. 1). The discovery of this three-component condensation process was made by Biginelli in 1893; (1) therefore, a reaction of this type is nowadays referred to as the "Biginelli reaction," "Biginelli condensation," or as the "Biginelli dihydropyrimidine synthesis." While the early examples of this cyclo-condensation process typically involved a β-ketoester, aromatic aldehyde, and urea, the scope of this heterocycle synthesis has now been extended considerably by variation of all three building blocks, allowing access to a large number of multifunctionalized pyrimidine derivatives of type 1. For this particular heterocyclic scaffold the acronym DHPM has been adopted in the literature and is also used throughout this chapter. The importance of multicomponent reactions in combinatorial chemistry has generated a renewed interest in the Biginelli reaction, and the number of publications and patents describing the synthesis of novel DHPM analogs is constantly growing.

An earlier, comprehensive review of the Biginelli reaction and of the synthetic potential of DHPMs appeared in 1993. (2) In 2000, the biological properties of DHPM derivatives were reviewed, (3) and recent trends in the Biginelli method were highlighted. (4)

In this chapter, all three-component condensations involving suitable CH-acidic carbonyl compounds, aldehydes, and urea-type building blocks following the Biginelli concept are covered. Therefore, reactions involving 1,3-diketones or nitroacetone as building blocks leading to DHPMs that follow the substitution pattern outlined in Eq. 1 are included, in contrast to earlier review articles. (2) Patents are only cited if they contain information that is otherwise not accessible.

$$\tag{1}$$

E = ester, amide, acyl, nitro
Z = O, S, NR
R^1-R^3 = H, alkyl, (het)aryl

1, DHPM
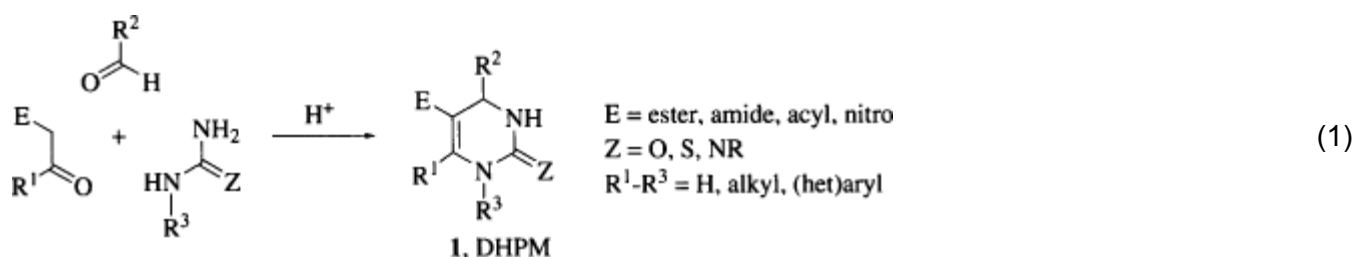
2. Mechanism

The mechanism of the Biginelli reaction has been investigated by several research groups. (5-7) Its

dependence upon acidic catalysis has been experimentally established and all three possible primary reaction pathways of the three-component Biginelli system have been thoroughly studied. (5)

In the currently accepted mechanistic pathway outlined in Scheme 1, (7) the key step in the Biginelli sequence involves the acid-catalyzed formation of an *N*-acyliminium ion intermediate of type **2** from the aldehyde and urea precursors. Interception of the iminium ion **2** by the CH-acidic carbonyl component, presumably through its enol tautomer, produces an open-chain ureide **3**, which subsequently cyclizes to hexahydropyrimidine **4**. Acid-catalyzed elimination of water from **4** ultimately leads to the final DHPM product **1**. The reaction mechanism can therefore be classified as an α -amidoalkylation, or, more specifically, as an α -ureidoalkylation. (8) Consistent with this mechanistic formulation, monosubstituted ureas and thioureas furnish exclusively the *N*-1 alkylated DHPMs. (2) *N,N′*-Disubstituted ureas do not react under the reaction conditions.
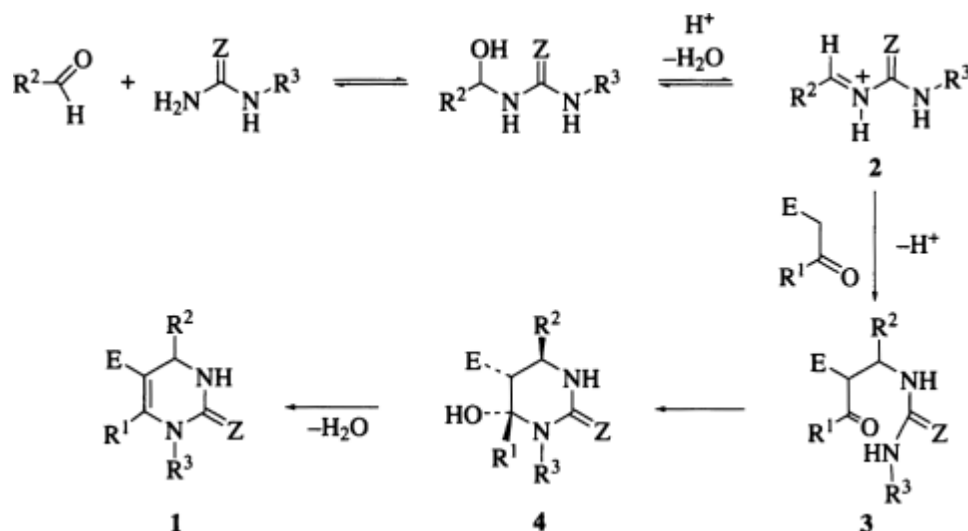
Scheme 1.

Although the highly reactive *N*-acyliminium ion species **2** cannot be isolated or directly observed, evidence for the mechanism depicted in Scheme 1 is derived from the isolation of a hexahydropyrimidine analog **4** employing electron-deficient 1,3-dicarbonyl compounds (see also Eq. 13). When R^1 = CF_3, for example, the sequence stops at the hexahydropyrimidine stage unless forcing dehydration conditions are used. (9) In general, all DHPMs obtained by conventional Biginelli condensations are obtained as racemates (see below).

The elucidation of the mechanism of the Biginelli multicomponent reaction has prompted a renewed interest in improving the efficiency of this process. Novel catalysts, in particular Lewis acids, are now used to favor the formation and interception of the key *N*-acyliminium ion intermediates. It is proposed that these Lewis acids stabilize the *N*-acyliminium ion by coordination to the urea oxygen. (10) In some reactions, chelation of the 1,3-dicarbonyl component by suitable Lewis acids, which stabilizes the enol tautomer, has also been inferred. (10) Lewis acid conditions are discussed in detail in the Experimental Conditions section.

3. Scope and Limitations

3.1. Building Blocks
3.1.1.1. Aldehydes
Of the three building blocks in the Biginelli reaction, the aldehyde component can be varied to the greatest extent. In general, the reaction works best with aromatic aldehydes. These can be substituted in the ortho, meta, or para position with either electron-withdrawing or -donating groups. Good yields are usually obtained with meta- or para-substituted aromatic aldehydes carrying electron-with-drawing substituents. For ortho-substituted benzaldehydes having bulky substituents, yields can be significantly lower. Heterocyclic aldehydes derived from furan, thiophene, and pyridine also generally furnish acceptable yields of DHPM products.

Aliphatic aldehydes provide poor yields in the Biginelli reaction (10–40%) unless special reaction conditions are employed, i.e., Lewis acid catalysts/solvent-free methods, or using the aldehydes in

protected form. For example, the 4-cyanomethyl-DHPM **5** is obtained successfully by treatment of oxazolidine-protected cyanoacetaldehyde with ethyl acetoacetate and urea (Eq. 2). (11) The C4 unsubstituted DHPM can be prepared in a similar manner employing suitable formaldehyde synthons. (11)

5 (68%)

(2)
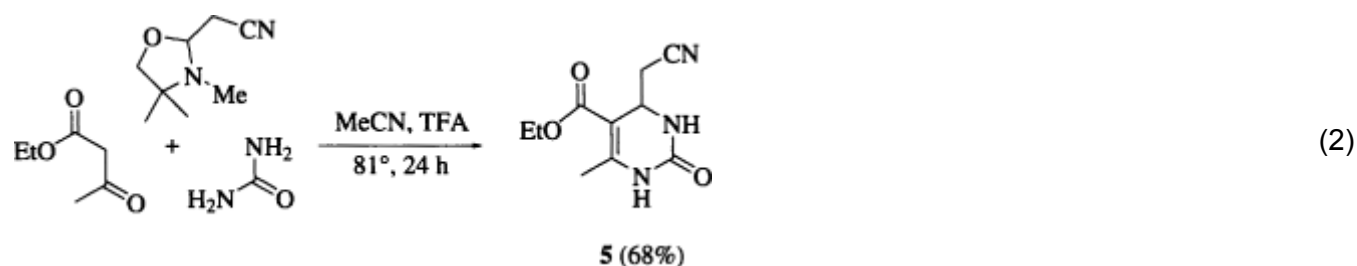
Of particular interest are reactions in which the aldehyde component is derived from a carbohydrate. (12-20) In such transformations, DHPMs having a sugar-like moiety at position 4 (C-nucleoside analogs) are obtained (Eq. 3). (20) The use of such chiral aldehydes is also of interest in the context of developing an asymmetric version of the Biginelli reaction (see below), but so far the chemical yields and diastereoselectivities that are achievable are not of practical use.

(60%) 5:1 mixture of diastereoisomers

(3)
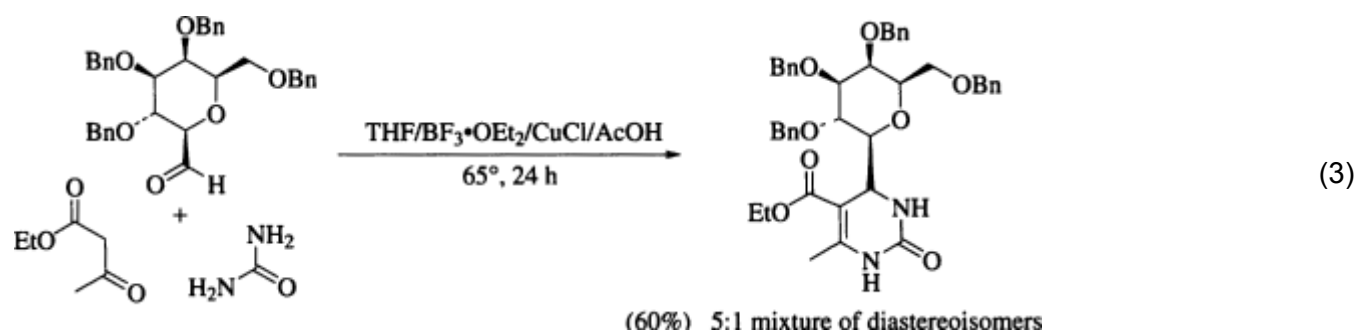
Bisaldehydes have been used as synthons in Biginelli reactions. (21, 22) For example, the use of terephthalaldehyde under microwave irradiation provides the expected bis-DHPM product in good yields (Eq. 4). (22)

(78%)

(4)
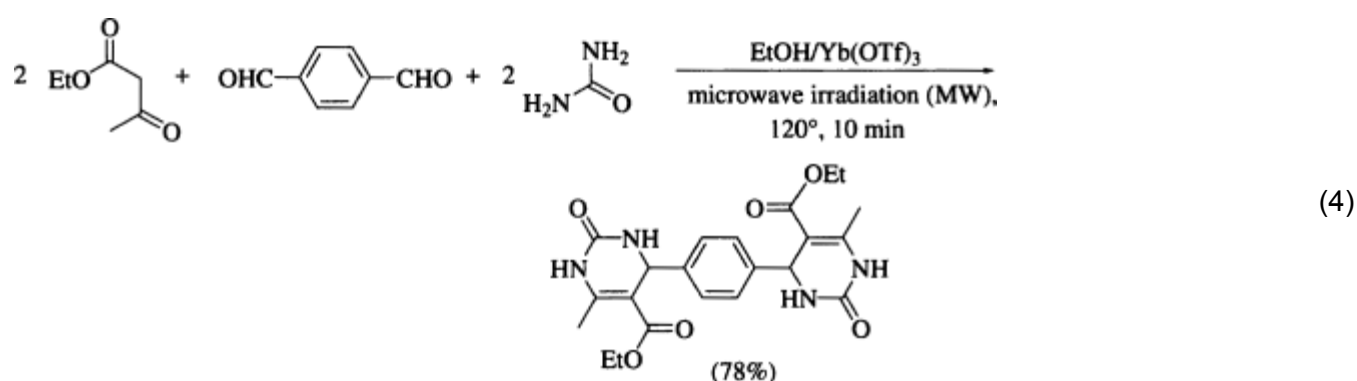
3.1.1.2. CH-Acidic Carbonyl Components

Traditionally, simple alkyl acetoacetates are employed as CH-acidic carbonyl building blocks, but other types of 3-oxoalkanoic esters or thioesters can also be used successfully. With ethyl 4-bromoacetoacetate, for example, the corresponding 6-bromomethyl-substituted DHPMs, which can serve as valuable templates for further synthetic transformations, are obtained (Eq. 5). (23)

(5)
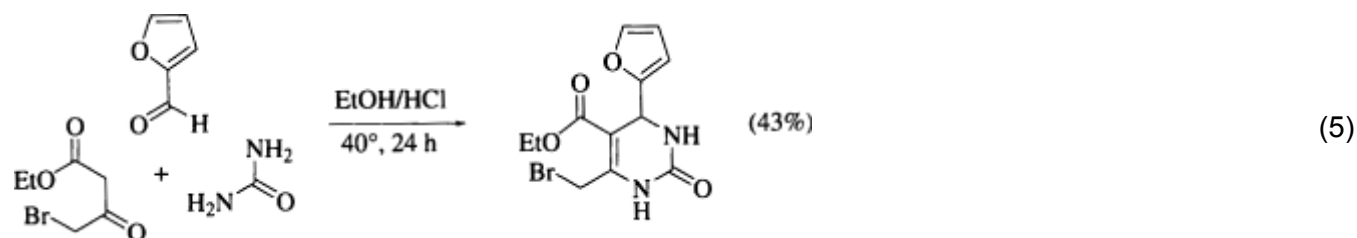
Benzoylacetic esters react analogously, but yields are usually significantly lower and the overall condensation process is more sluggish. Primary, secondary, and tertiary acetoacetamides can be used in place of esters to produce pyrimidine-5-carboxamides. In addition, β -diketones serve as viable substrates in Biginelli reactions. Condensation can also be achieved using cyclic β -diketones such as cyclohexane-1,3-dione (24, 25) and other cyclic β -dicarbonyl compounds (Eq. 6). (26)

(6)
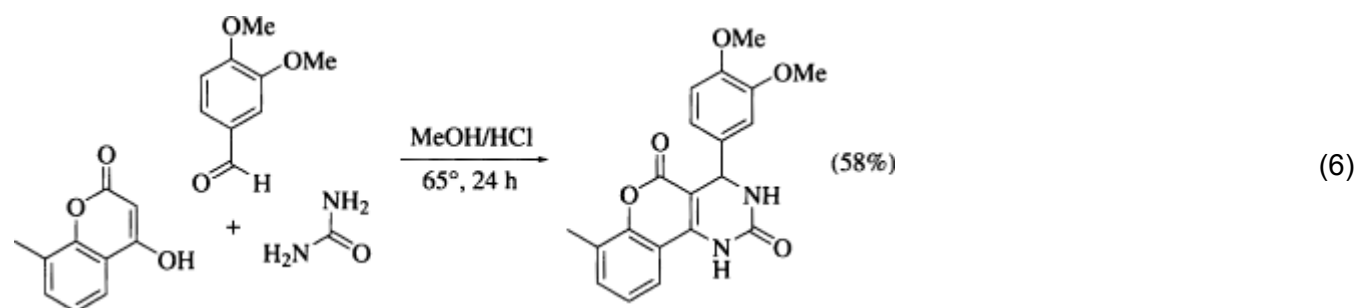
For the synthesis of a C6-unsubstituted DHPM derivative, the corresponding 3-oxopropanoic ester derivative in which the aldehyde function is masked as an acetal can be employed (Eq. 7). (22, 27) Apart from ester-derived CH-acidic carbonyl compounds, nitroacetone also serves as a good building block, leading to 5-nitro-substituted DHPM derivatives in generally high yields. (28)

(7)
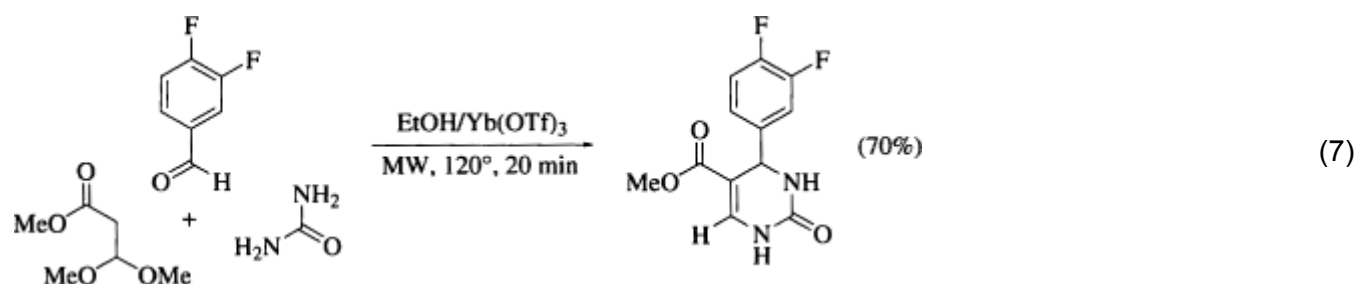
3.1.1.3. Urea Building Blocks
The urea is the most restricted component of the Biginelli reaction in terms of allowed structural diversity. Therefore, most of the published examples involve urea itself as the building block. However, simple monosubstituted alkyl ureas generally react equally well, in a regiospecific manner, to provide good yields of *N*1-substituted DHPMs (Scheme 1). The *N*3-substituted analogs cannot be obtained by classical Biginelli condensations. Also, *N,N'*-disubstituted ureas do not react under Biginelli conditions. There is little published work to demonstrate that *N*-arylureas can take part effectively in Biginelli condensations. (29, 30)

Thiourea and substituted thioureas follow the same general rules as ureas, although longer reaction times are required to achieve good conversions. Yields are typically lower compared with the corresponding urea derivatives. In a few cases, the use of unprotected guanidine has been reported in a three-component Biginelli-type condensation (Eq. 8). (31) In general, these types of cyclic guanidine derivatives need to be prepared by alternative methods (see Eq. 17).

$$(8)$$
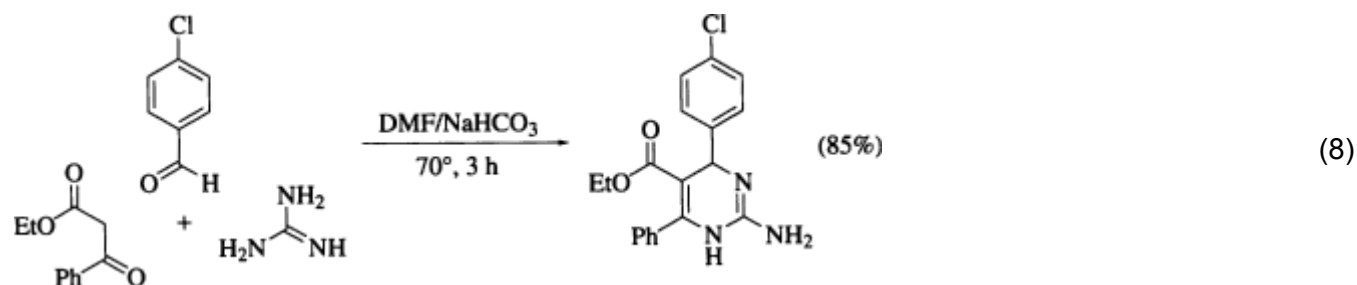
3.2. Solid-Phase, Fluorous-Phase, and Related Procedures

Multi-component reactions such as the Biginelli condensation, leading to interesting heterocyclic scaffolds, are particularly useful for the creation of diverse chemical libraries for biological screening. The combination of three low-molecular weight building blocks in a single operation leads to high combinatorial efficacy. As the experimental conditions for the traditional Biginelli reaction are rather straight-forward, small libraries of DHPMs are readily accessible using parallel synthesis or related robotic techniques. (32-34) In addition to these conventional solution-phase methods for preparing DHPM libraries, it is also possible to employ polymer-supported reagents to aid in the product purification and reaction work-up. The use of a polymer-supported Lewis acid [Yb(III)-reagent supported on Amberlyst 15] in combination with polymer-supported scavenging resins (Amberlyst 15 and Ambersep 900 OH) that remove excess urea allows for a rapid parallel Biginelli synthesis with a simplified purification strategy. (35)

An even higher degree of throughput and automation is possible with solid-phase protocols (Merrifield type synthesis). In one example, a γ -aminobutyric acid derived urea is attached to a Wang resin using standard procedures. The resulting polymer-bound urea can be condensed with excess β -ketoester and aromatic aldehydes in the presence of a catalytic amount of hydrochloric acid to afford the corresponding immobilized DHPMs. Subsequent cleavage of product from the polystyrene resin by trifluoroacetic acid provides the free DHPMs in high yields and excellent purities (Eq. 9). (36)

$$(9)$$
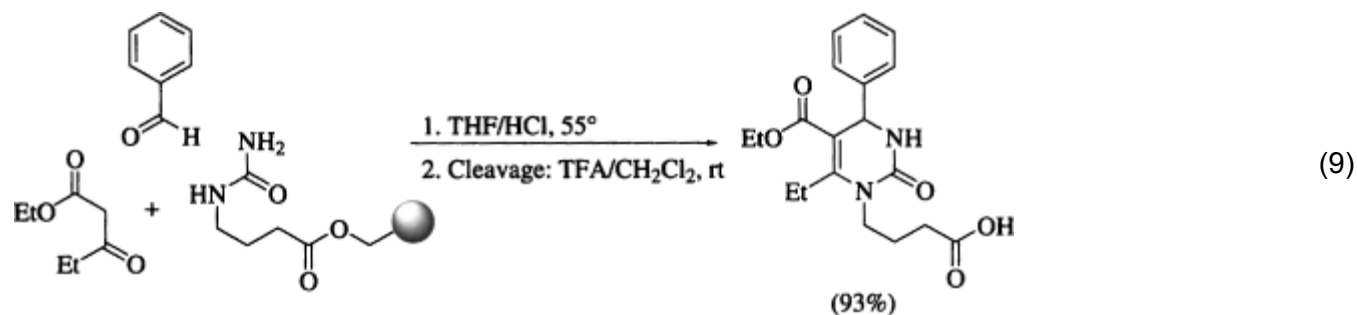
In a variation of the above procedure, the Biginelli synthesis is adapted to fluorous-phase conditions. Here a fluorous urea derivative is prepared by attaching a suitable fluorous tag to hydroxyethylurea (Eq. 10). (37, 38) The fluorous urea is then condensed with an excess of acetoacetates and aldehydes in a suitable solvent containing hydrochloric acid. After extraction of the fluorous DHPMs with a fluorous solvent (perfluorohexanes, FC-72), desilylation with tetrabutylammonium fluoride (TBAF) followed by extractive purification provides the "organic" Biginelli products in good overall yields.

In contrast to the methods described previously where the urea component is linked to the solid (or fluorous) support via the amide nitrogen, it is also possible to attach the acetoacetate building block to the solid support. Thus, Biginelli condensation of Wang-bound acetoacetates with excess aldehydes and urea/thiourea provides DHPMs on solid support. Subsequent cleavage with trifluoroacetic acid furnishes the free carboxylic acids in high overall yields (Eq. 11). (39)

$$\text{(10)}$$

$R_{fh} = C_{10}F_{21}CH_2CH_2^-$

BTF = benzotrifluoride, TBAF = tetrabutylammonium fluoride

1. THF/BTF, HCl, 50°, 3 d
2. TBAF in THF/BTF, 25°, 30 min

(70%)

$$\text{(11)}$$

1. Dioxane/HCl, 70°, 18 h
2. Cleavage: TFA/DCM, rt

(73%)
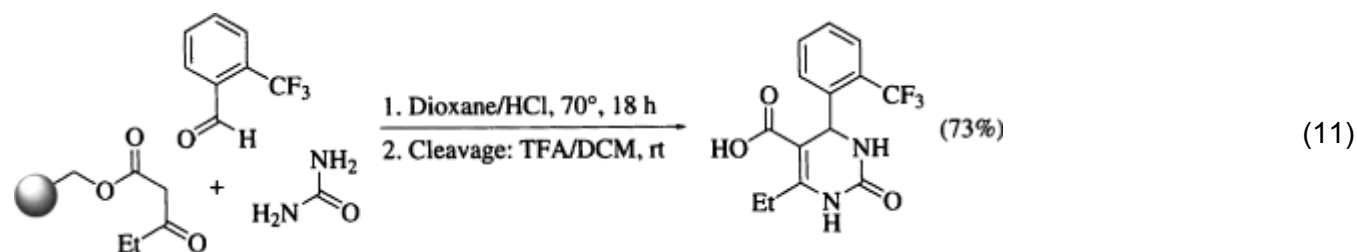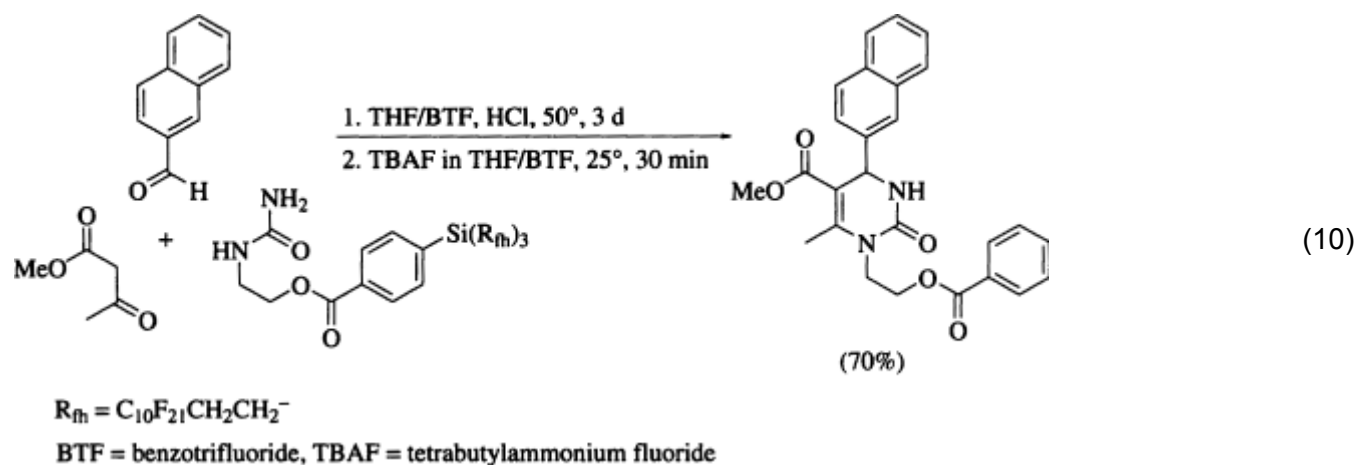
There are a number of alternative solid-phase procedures described in the literature for the generation of DHPMs that use the so-called Atwal modification instead of the classical three-component Biginelli approach (see Eq. 17). (40, 41) By employing any of the solid-phase synthesis methods described above, libraries of DHPMs can be generated in a relatively straightforward fashion.

3.3. Asymmetric Biginelli Synthesis
Since dihydropyrimidines (DHPMs) are inherently asymmetric molecules they are generally obtained as racemic mixtures in the traditional Biginelli reaction as well as in related processes (see below). The dramatic influence of the absolute configuration at the stereogenic center at C4 of the pyrimidine ring on the biological activity of some DHPMs is well documented. (27, 42-46) Therefore, access to enantiomerically pure DHPMs is of interest. In the absence of any known general asymmetric synthesis for this heterocyclic system, resolution strategies are the methods of choice to obtain enantiomerically pure DHPM analogs. These methods include fractional crystallization techniques involving diastereomeric α -methylbenzylammonium salts (47) or covalently linked derivatives, (27, 42, 43, 46) or rely on biocatalytic resolution. (48, 49) Analytically, separation of DHPM derivatives can be readily achieved by enantioselective HPLC using a variety of different chiral stationary phases. (32, 33, 50) Alternatively, chiral separation can also be performed by capillary electrophoresis (CE) with chiral modifiers and buffers. (51, 52) The absolute configuration of enantiomerically pure DHPMs is easily derived from circular dichroism (CD) spectra. (53, 54)

Efforts to develop a practical asymmetric version of the Biginelli reaction itself have so far failed. Although chiral acetoacetates, e.g., (–)-menthyl acetoacetate, show no diastereoselectivity, (47) chiral aldehydes derived from carbohydrates can induce chirality at C4 of the pyrimidine ring (see Eq. 3). This latter approach, however, is of limited use because only moderate chemical yields and selectivities are achieved. (20) Also, the method does not allow for the preparation of the important class of 4-aryl-substituted DHPMs. Therefore, a general asymmetric access to DHPMs of the Biginelli type remains a highly desirable goal. The only known asymmetric variations of the Biginelli reaction are of an intramolecular nature and have been applied to the synthesis of natural products (see Eq. 12).

3.4. Intramolecular (Tethered) Biginelli Reactions
A special variant of the Biginelli reaction are intramolecular, or so-called tethered, Biginelli condensations where the aldehyde and urea components are linked together in one building block (Eq. 12). The "tethered Biginelli strategy" has been used in the synthesis of various polycyclic guanidinium alkaloids (e.g., batzelladine alkaloids A and D) that all have the hexahydropyrrolo[1,2-c]pyrimidine fragment 7 in common. For example, condensation of the chiral hemiaminal precursor 6 with a suitable β -ketoester

leads to the desired hexahydropyrrolo[1,2-*c*]pyrimidine scaffold. (55) Importantly, depending on the reaction conditions (A or B), both the syn and anti stereoisomers of **7** can be obtained with high selectivities. When typical Knoevenagel conditions (morpholinium acetate) are used, cis stereoselection (4–7:1) is observed. In contrast, when the condensation is carried out in the presence of polyphosphate ester, trans stereoselection (4–20:1) is found. (55) As both types of stereoisomers are present in several alkaloids, this method provides an elegant way for the enantioselective total synthesis of natural products of this type. Tethered Biginelli strategies have been used to synthesize batzelladine B, (56) batzelladine D, (57) ptilomycalin A, (58, 59) 13,14,15-isocrambescidin 800, (60, 61) 13,14,15-isocrambescidin 657, (60) crambescidin 657, (59) crambescidin 800 (59), and batzelladine F. (62)

(12)
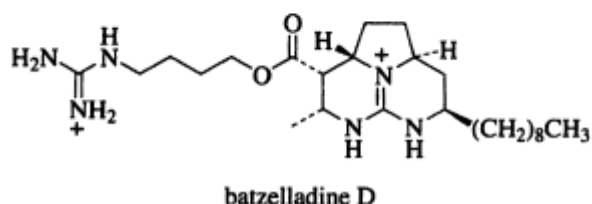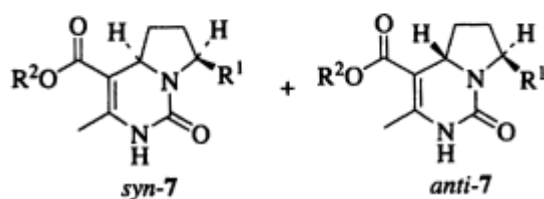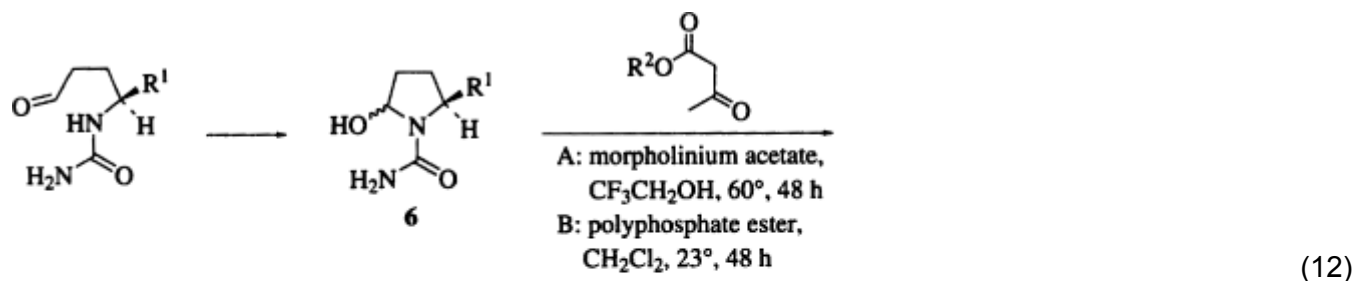
3.5. Related Biginelli-Type Reactions

For 1,3-dicarbonyl building blocks having a strong electron-withdrawing substituent such as a trifluoromethyl group, the Biginelli sequence generally stops at the hexahydropyrimidine stage (see Scheme 1). (9, 63) In fact, a variety of hexahydropyrimidines can be synthesized in this way using perfluorinated 1,3-dicarbonyl compounds or β-ketoesters as building blocks (Eq. 13). (63) The stereochemistry of hexahydropyrimidine **8** was confirmed by an X-ray analysis. (9)

(13)
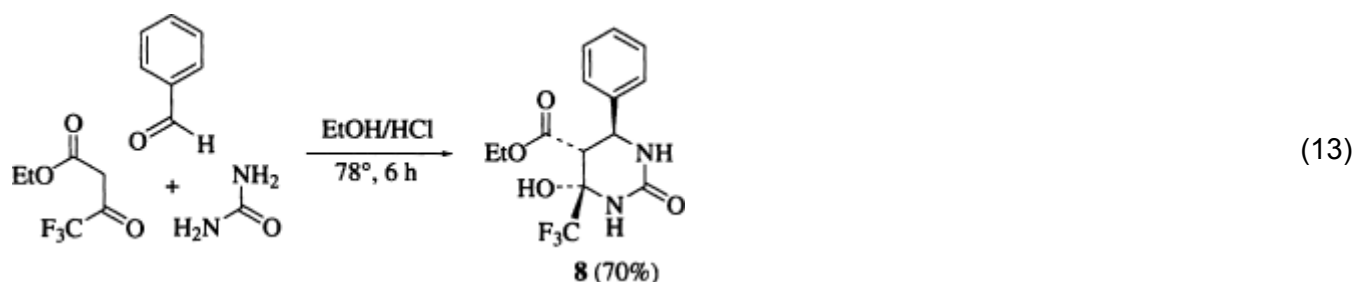
The steric proximity of a hydroxy substituent in the ortho position of the aromatic ring and the C6 carbon of the pyrimidine ring in DHPMs enables the formation of a six-membered ring via intramolecular Michael addition. For example, with aromatic aldehydes such as salicylaldehyde, the expected product of a Biginelli condensation is not a simple DHPM but rather an 8-oxa-10,12-diazatricyclo[7.3.1.0^{2,7}]tridecatriene derivative (Eq. 14). (64) Several examples of these unusual domino Biginelli condensation/Michael addition sequences are known. (65, 66)

$$(14)$$
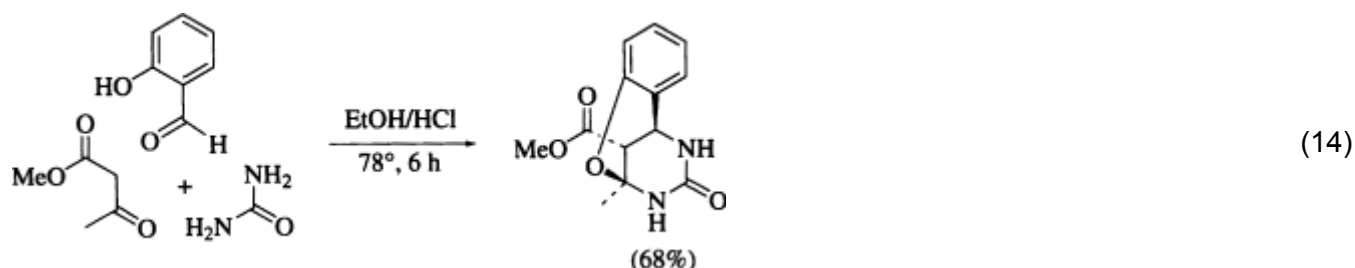
As mentioned previously (Eq. 6), cyclic β-diketones such as cyclohexane-1,3-dione and other cyclic β-dicarbonyl compounds are known to function well in the Biginelli condensation. However, for tetronic acid the reaction takes an entirely different course, following a pseudo four-component pathway to give spiro heterobicyclic products in good yields (Eq. 15). (67) The reaction proceeds by a regiospecific condensation of two molecules of aldehyde with the other reagents to afford products having the C4 and C6 substituents exclusively in cis configuration. The classical Biginelli product was not detected.

$$(15)$$
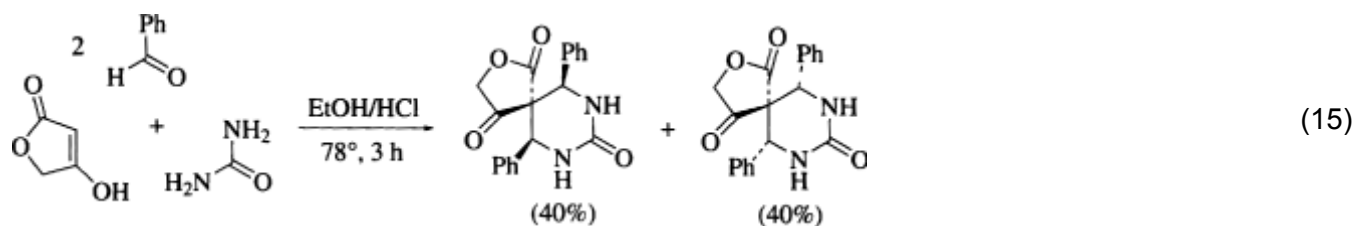
Another interesting variation of the standard Biginelli reaction involves the use of β-keto carboxylic acids as CH-acidic carbonyl compounds. Under suitable reaction conditions, oxalacetic acid is an excellent substrate in such condensations. (68) Cyclization and in situ decarboxylation cleanly yield 5-unsubstituted 3,4-dihydropyrimidin-2(1H)-ones. By using trifluoroacetic acid (TFA) as the acidic catalyst and dichloroethane (DCE) as the solvent, excellent yields of products can be obtained (Eq. 16).

$$(16)$$
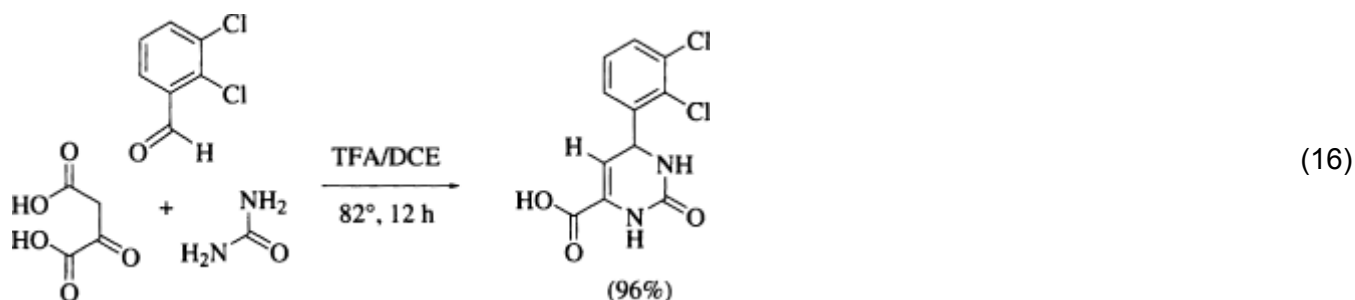
4. Comparison with Other Methods

Apart from the traditional Biginelli three-component condensation there are only a few other efficient synthetic methods available to prepare DHPM products. Since most of these syntheses lack the experimental and conceptual simplicity of the one-pot, one-step Biginelli procedure, few of those have any real significance today. One noticeable exception is the so-called "Atwal modification" of the Biginelli reaction. (69-71) An enone of type 9, derived from the CH-acidic carbonyl component and the aldehyde

component by Knoevenagel condensation, is first reacted with a suitable protected urea or thiourea derivative **10a,b** under almost neutral conditions. Deprotection of the resulting 1,4-dihydropyrimidine **11** using suitable reagents leads to the desired DHPMs (Eq. 17). Similar results are obtained when enone **9** is condensed with guanidine derivatives to give 2-amino-substituted pyrimidines. Although these methods require prior synthesis of enones **9**, their general reliability and broad applicability make them an attractive alternative to the traditional one-step Biginelli condensation. In some cases, a direct three-component condensation of the protected urea/thiourea with the CH-acidic carbonyl compound and the aldehyde component is also possible. (72, 73) In addition, 1,4-dihydropyrimidines **11** can be acylated regiospecifically at N3, thereby making those pharmacologically relevant analogs available. (71) This sequence is important because direct regiospecific acylation or alkylation of DHPMs is troublesome. (2) Most other procedures that lead to Biginelli-type products are very limited in their scope and are rarely used for synthetic purposes. (2, 74)

$$a: Z = O, R = Me$$
$$b: Z = S, R = 4\text{-methoxybenzyl}$$

(17)
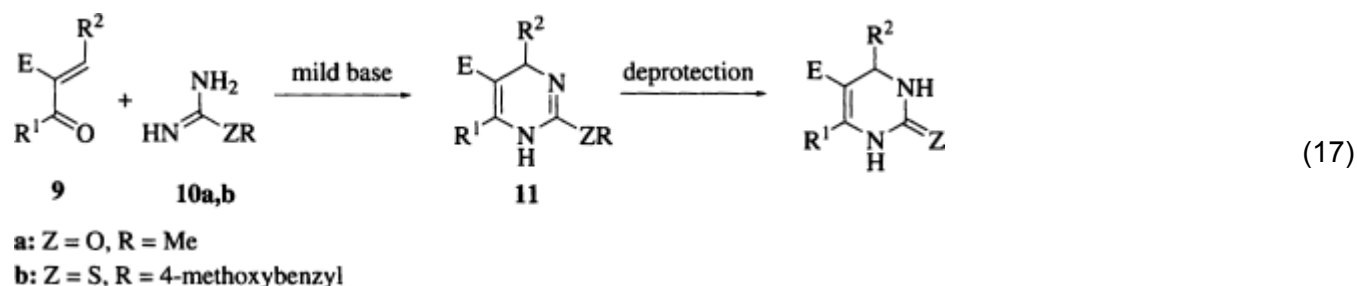
5. Experimental Conditions

There is a great variety of suitable reaction conditions for carrying out Biginelli condensations. For the condensation of ethyl acetoacetate with benzaldehyde and urea, more than 40 different experimental conditions are now known. Traditionally, Biginelli condensations are carried out in a solvent such as ethanol or methanol, but more recently aprotic solvents such as tetrahydrofuran, (10, 36, 75) dioxane, (39) or acetonitrile (76) have also been used successfully. In some reactions, it is necessary to use acetic acid as a solvent. (77-79) This is particularly important where condensation of an aromatic aldehyde and urea leads to precipitation of an insoluble bisureide derivative, i.e., $ArCH(NHCONH_2)_2$, (7) which might not react further along the desired pathway outlined in Scheme 1 when ethanol is used as a solvent. Biginelli reactions in water (80) and ionic liquids (81) are also known. A recent trend is to perform the condensation without any solvent, with the components either adsorbed on an inorganic support, (82) or in the presence of a suitable catalyst. (34, 83)

The Biginelli condensation is strongly dependent on the amount of acidic catalyst present in the reaction medium. (5) Traditionally, strong Brønsted acids such as hydrochloric or sulfuric acid have been employed, (2) but now the use of Lewis acids such as $BF_3 \cdot OEt_2$ and CuCl, (10) $LaCl_3$, (84) $FeCl_3$, (85-87) $NiCl_2$, (88) $Yb(OTf)_3$, (83) $La(OTf)_3$, (89) $InCl_3$, (90) $InBr_3$, (91) $BiCl_3$, (76) $LiClO_4$, (92) $Mn(OAc)_3$, (93) or $ZrCl_4$ (94) is preferred. It is also possible to use a solid acid catalyst, such as an acidic clay, (82) a zeolite, (95) or Amberlyst material. (79) In addition, amidosulfonic acid has been utilized as catalyst. (96)

Biginelli condensations generally proceed rather slowly at room temperature. (7) Therefore, it is necessary to activate these processes by heating. Apart from traditional heating methods, microwave heating employing some of the solvent/catalyst systems mentioned above has been used to shorten reaction times significantly. (22, 30, 34, 79, 86, 97-102) It is also feasible to carry out Biginelli reactions using ultrasound activation. (103)

With regard to the molar ratio of the building blocks, Biginelli reactions generally employ an excess of the CH-acidic carbonyl or the urea components, rather than an excess of the aldehyde. As DHPM products are usually only sparingly soluble in solvents such as methanol or ethanol at room temperature, work-up in many cases simply involves isolation of the product by filtration. It may also be possible to precipitate the product by addition of water.

6. Experimental Procedures
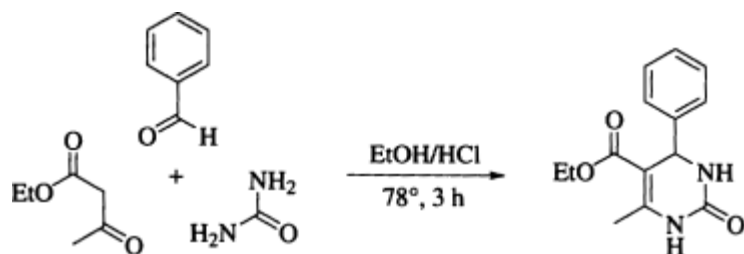
6.1.1.1. Ethyl 6-Methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate [Biginelli Condensation Utilizing Ethanol/ HCl as the Solvent/Catalyst System] (78)

A mixture of 0.5 mol (53 g) of benzaldehyde, 0.5 mol (30 g) of urea, 0.75 mol (97.5 g) of ethyl acetoacetate, 200 mL EtOH, and 40 drops of concentrated HCl was heated under reflux for 3 hours. The reaction mixture was then cooled to 0°, and the pyrimidine was collected by filtration and dried at 50°, yielding 93.6 g of crude product. The filtrate was refluxed for an additional 2 hours and finally distilled until 155 mL of EtOH were collected. On cooling the residue an additional 21.3 g of the pyrimidine was isolated, resulting in a total yield of crude product of 88.4%. For purification, the substance was divided into two equal portions, and each was dissolved in 800 mL of 95% boiling alcohol. On cooling, the pyrimidine separated as colorless crystals, mp 202–204°. The yield of purified material was 102 g (78%); IR[22] (KBr) 3240, 3110, 1725, 1700, 1645 cm^{-1}; ^{1}H NMR[22] (200 MHz, DMSO-d_6) δ 1.12 (t, J = 7.5 Hz, 3H), 2.28 (s, 3H), 4.03 (q, J = 7.5 Hz, 2H), 5.17 (d, J = 3.5 Hz, 1H), 7.22–7.41 (m, 5H), 7.78 (br s, 1H), 9.22 (br s, 1H).
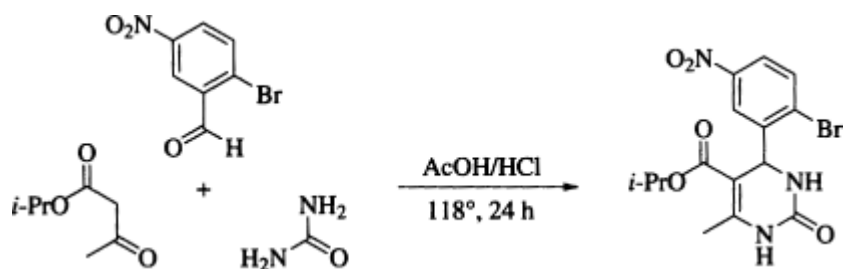
6.1.1.2. Isopropyl 4-(2-Bromo-5-nitrophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate [Biginelli Condensation Utilizing Acetic Acid/ HCl as the Solvent/Catalyst System] (77)

A mixture of 16 mmol (2.30 g) of isopropyl acetoacetate, 11 mmol (2.43 g) of 2-bromo-5-nitrobenzaldehyde, 11 mmol (0.95 g) of urea, and acetic acid (20 mL) containing 100 μL (ca. 4 drops) of concentrated HCl was heated under reflux for 24 hours; after the first 6 hours an additional quantity of concentrated HCl (100 μL) was added. After the mixture remained at room temperature overnight, the precipitate was collected by filtration and recrystallized from acetic acid to give 2.89 g (66%) of the desired pyrimidine as a colorless solid: mp 241°; IR (KBr) 3380, 3080, 2950, 1710, 1650, 1520, 1450 cm^{-1}; ^{1}H NMR (DMSO-d_6), δ 0.79, 1.12 (2 d, J = 6.4 Hz, 6H), 2.36 (s, 3H), 4.75 (m, J = 6.4 Hz, 1H), 5.70 (s, 1H), 7.80–8.10 (m, 4H), 9.45 (br s, 1H); Anal. Calcd for $C_{15}H_{16}BrN_3O_5$: C, 45.20; H, 4.00; N, 10.60. Found: C, 45.58; H, 4.00; N, 10.24.
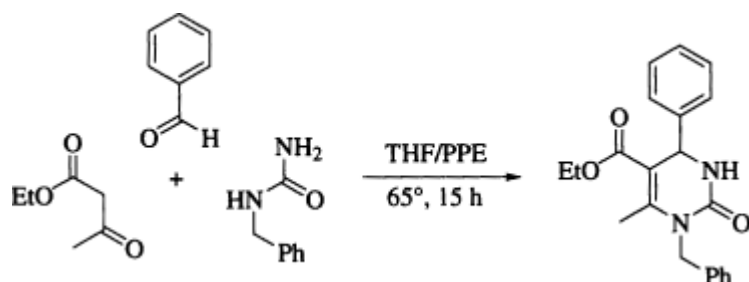
6.1.1.3. Ethyl 1-Benzyl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate [Biginelli

A mixture of 2 mmol (260 mg) of ethyl acetoacetate, 2 mmol (212 mg) of benzaldehyde, 3 mmol (450 mg) of benzylurea, and THF (4 mL) containing 300 mg of polyphosphate ester (PPE) was heated under reflux and stirring for 15 hours. After cooling, the reaction mixture was poured onto crushed ice (10 g). Stirring was continued for several hours. The solid product was collected by filtration, washed with ice water, and dried, yielding 637 mg (91%), mp 157° (EtOH); IR (KBr) 3210, 3100, 1710, 1690, 1620 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.11 (t, J = 7.5 Hz, 3H), 2.38 (s, 3H), 4.03 (q, J = 7.5 Hz, 2H), 4.88, 5.11 (2 d, J = 17.5 Hz, 2H), 5.25 (d, J = 3.0 Hz, 1H), 7.05–7.39 (m, 10H), 8.13 (d, J = 3.0 Hz, 1H); Anal. Calcd for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33; N, 7.99. Found: C, 72.30; H, 6.52; N, 7.95.
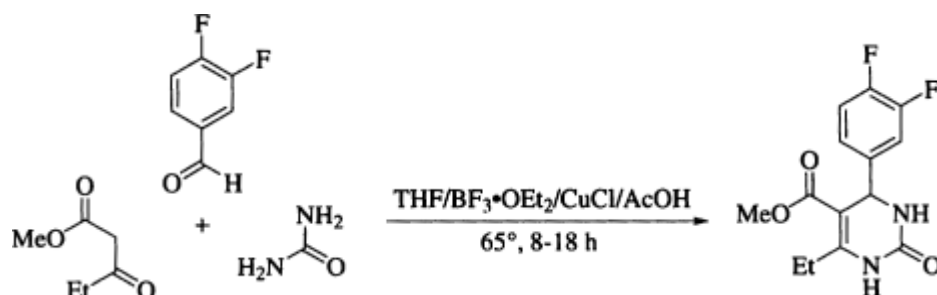
6.1.1.4. Methyl 4-(3,4-Difluorophenyl)-6-ethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate [Biginelli Condensation Utilizing Lewis Acids as the Catalyst System] *(10)*

A 50-mL three-neck round-bottom flask fitted with a thermocouple and reflux condenser was charged under N_2 with sieve-dried THF (30 mL), 15.4 mmol (2.00 g) of methyl 3-oxopentanoate, 15.4 mmol (2.19 g) of 3,4-difluorobenzaldehyde, 23.1 mmol (1.39 g) of urea, 20.0 mmol (2.84 g) of BF$_3$·OEt$_2$, 1.54 mmol (0.15 g) of CuCl, and 1.54 mmol (0.1 mL) of glacial acetic acid. The mixture was heated to reflux (65°) for 8–18 hours. The solution was cooled to room temperature and quenched with 10% Na$_2$CO$_3$ solution (30 mL). Ethyl acetate (30 mL) was added, the layers were separated, and the green aqueous solution was discarded. The organic layer was concentrated and the residue was dissolved in toluene (40 mL), cooled to room temperature, and left overnight. The resulting suspension was filtered, and the collected solid was rinsed with toluene (1 × 10 mL), and dried in vacuo at 40° to afford the desired pyrimidine as a crystalline solid in 82% yield (3.74 g), mp 182–185°; IR (KBr) 3237, 3112, 2960, 2879, 1701, 1634, 1517 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.11 (t, J = 7.4 Hz, 3H), 2.65 (m, 2H), 3.54 (s, 3H), 5.14 (d, J = 3.4 Hz, 1H), 6.61–6.69 (m, 3H), 7.06 (m, 1H), 7.20 (m, 1H), 7.40 (m, 1H), 7.80 (s, 1H), 9.31 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 12.8, 24.0, 50.8, 52.8, 97.4, 114.9, 115.2, 117.4, 117.6, 142.2, 152.0, 154.8, 165.1; Anal. Calcd for $C_{14}H_{14}F_2N_2O_3$: C, 56.76; H, 4.76; N, 9.46. Found: C, 56.85; H, 4.70; N, 9.35.
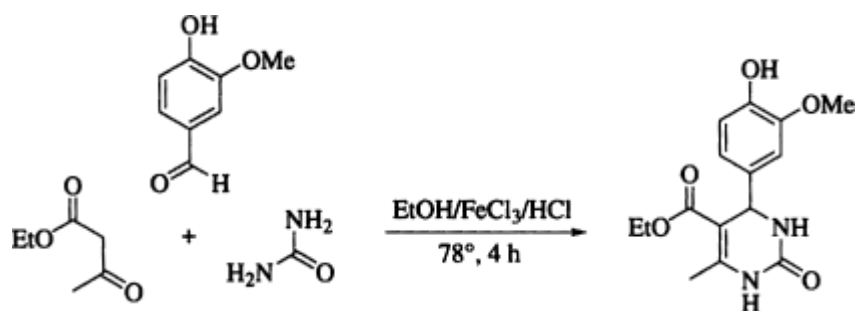
6.1.1.5. Ethyl 4-(4-Hydroxy-3-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate [Biginelli Condensation Utilizing Lewis Acids as the Catalyst System] *(85)*

A solution of 50 mmol (6.50 g) of ethyl acetoacetate, 50 mmol (7.60 g) of vanillin (4-hydroxy-3-methoxy-benzaldehyde), 75 mmol (4.55 g) of urea, 30 mmol (8.1 g) of FeCl$_3$·6H$_2$O , and 2–3 drops of concentrated HCl in EtOH (40 mL) was heated under reflux for 4 hours. The solution was cooled to room temperature and poured onto 200 g of crushed ice. Stirring was continued for several minutes. The solid product was collected by filtration, washed with ice-water and a mixture of EtOH/water (1:1), dried, and crystallized from hot EtOH, yielding 13.2 g (86%) of product.
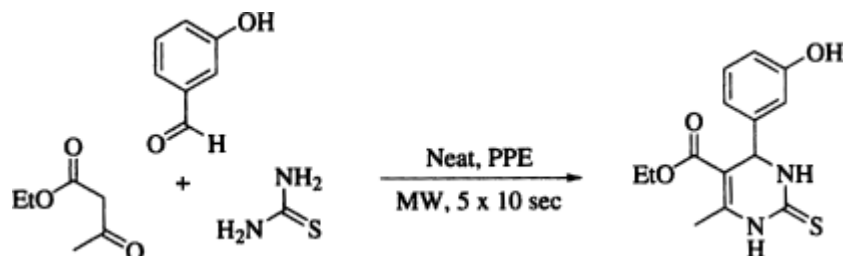
6.1.1.6. Ethyl 4-(3-Hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate [Microwave-Assisted Biginelli Condensation under Solvent-Free Conditions] (105)

A mixture of 2.3 mmol (300 mg) of ethyl acetoacetate, 2.0 mmol (244 mg) of 3-hydroxybenzaldehyde, 5 mmol (380 mg) of thiourea, and 300 mg of polyphosphate ester (PPE) was placed in a 20-mL glass beaker. The mixture was stirred for 10–20 seconds with a spatula, after which the beaker was inserted into a bed of neutral alumina (150 g) contained in a 400-mL Pyrex beaker. This set-up was irradiated in a domestic microwave oven 5 times at full power (800 W) for 10 seconds each with 1–2 minutes cooling periods between each irradiation cycle. EtOH (5 mL) was added to the hot reaction mixture, which was subsequently poured onto ice (50 g). The precipitated crude product was purified by silica gel chromatography (hexane/ EtOAc 2:1) to yield 350 mg (60%) of colorless product, mp 184–186° (CH_3CN); IR (KBr) 3300, 3180, 2900–2600, 1670, 1655, 1620, 1575 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.14 (t, J = 7.5 Hz, 3H), 2.30 (s, 3H), 4.03 (q, J = 7.5 Hz, 2H), 5.11 (d, J = 3.5 Hz, 1H), 6.61–6.69 (m, 3H), 7.06–7.17 (m, 1H), 9.45, 9.62, 10.31 (3 br s); ^{13}C NMR (DMSO-d_6) δ 14.0, 17.2, 54.0, 59.6, 100.8, 113.3, 114.6, 117.0, 129.5, 144.8, 144.9, 157.5, 165.2, 174.2; Anal. Calcd for $C_{14}H_{16}N_2O_3S$: C, 57.52; H, 5.52; N, 9.58. Found: C, 57.33; H, 5.52; N, 9.34.
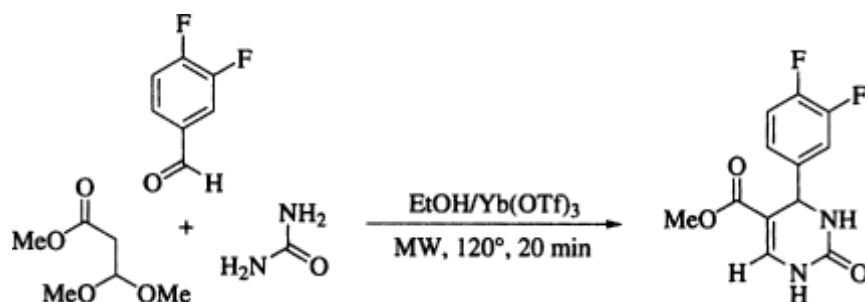
6.1.1.7. Methyl 4-(3,4-Difluorophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate [Microwave-Assisted Biginelli Condensation Utilizing Lewis Acids as the Catalyst System] (22)

To a 5-mL reaction vial were added 4 mmol (592 mg) of methyl 3,3-dimethoxypropionate, 4 mmol (568 mg) of 3,4-difluorobenzaldehyde, 4 mmol (240 mg) of urea, 0.4 mmol (250 mg) of Yb(OTf)$_3$, and 2 mL of EtOH. The vessel was heated in a EmrysSynthesizer^{TM} microwave reactor at 120° for 20 minutes, and subsequently cooled. The vessel was removed from the cavity and placed in the refrigerator for approximately 1 hour. The precipitate formed was collected by suction filtration, washed with ice-cold EtOH, and dried, yielding 377 mg (35%) of the pyrimidine, mp 229–231° (EtOH); ^{1}H NMR (360 MHz, DMSO-d_6) δ 3.56 (s, 3H), 5.15 (d, J = 3.0 Hz, 1H), 7.11 (br s, 1H), 7.22–7.45 (m, 3H), 7.75 (s, 1H), 9.28 (br s, 1H). Anal. Calcd for $C_{12}H_{10}F_2N_2O_3$: C, 53.74; H, 3.76; N, 10.44. Found: C, 53.36; H, 3.81; N, 10.62.
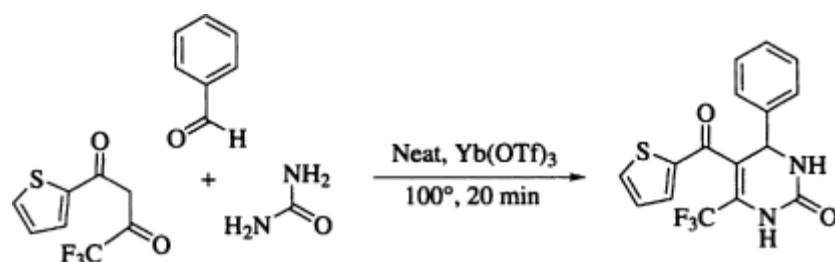
6.1.1.8. 4-Phenyl-5-(thiophene-2-carbonyl)-6-trifluoromethyl-1,2,3,4-tetrahydropyrimidin-2-one [Biginelli Condensation Utilizing Lewis Acids under Solvent-Free Conditions] (83)

Two and one-half mmol (555.5 mg) of 4,4,4-trifluoro-1-(thiophen-2-yl)-butane-1,3-dione, 2.5 mmol (265.3 mg) of benzaldehyde, 3.7 mmol (222 mg) of urea, and 0.125 mmol (5 mol%) of Yb(III)-triflate were heated at 100° for 20 minutes under slight stirring. Water was added, and the product was extracted with EtOAc. After the organic layer was dried (Na_2SO_4) and evaporated, the residue was recrystallized from EtOAc/hexane to afford 828 mg (94%) of the dihydropyrimidine, mp 99–102°; IR (KBr) 3200, 1670 cm^{-1}; ^{1}H NMR δ 5.25 (s, 1H), 6.61–6.69 (m, 3H), 7.11–7.34 (m, 5H), 7.52 (d, J = 3.8 Hz, 1H), 7.90 (s, 1H), 8.03 (d, J = 5.0 Hz, 1H), 9.79 (s, 1H).
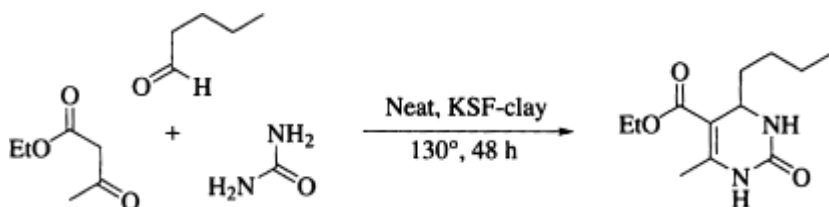
6.1.1.9. Ethyl 4-Butyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate [Biginelli Condensation Utilizing KSF-Clay as the Catalyst System] (82)

A mixture of 0.5 g montmorillonite KSF-clay, 10 mmol (1.30 g) of ethyl acetoacetate, 10 mmol (0.86 g) of pentanal, and 15 mmol (0.90 g) of urea was heated at 130° with stirring for 48 hours. Hot MeOH (100 mL) was added and the mixture was filtered to remove the catalyst. The product crystallized after several hours and was recovered by filtration, yielding 2.05 g (86%) of pyrimidine as a white solid, mp 161–162°; IR (KBr) 3244, 3117, 1727, 1707, 1653 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.85 (t, J = 6.4 Hz, 3H), 1.18 (t, J = 7.1 Hz, 3H), 1.1–1.3 (m, 4H), 1.3–1.5 (m, 2H), 2.16 (s, 3H), 4.05 (q, J = 7.1 Hz, 2H), 4.1–4.2 (m, 1H), 7.28 (s, 1H), 8.89 (s, 1H); Anal. Calcd for $C_{12}H_{20}N_2O_3$: C, 60.0; H, 8.4; N, 11.7. Found: C, 60.1; H, 8.5; N, 11.9.
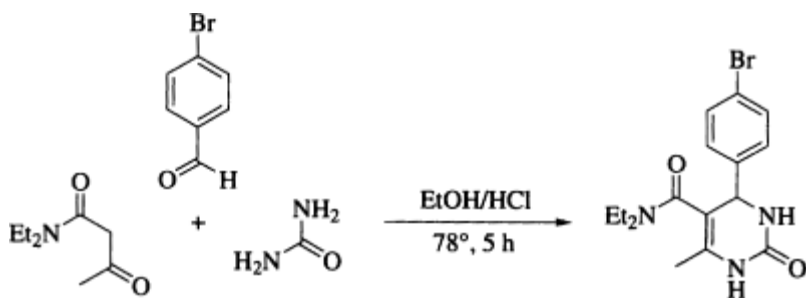
6.1.1.10. Diethyl 4-(4-Bromophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide [Biginelli Condensation Utilizing Ethanol/ HCl as the Solvent/Catalyst System] (106)

A mixture of 20 mmol (3.7 g) of 4-bromobenzaldehyde, 20 mmol (1.2 g) of urea, and 15 drops of concentrated HCl was added to a solution of 20 mmol (3.14 g) of N,N-diethylacetoacetamide in absolute EtOH (50 mL). The mixture was heated under reflux for 5 hours, and then cooled to yield 4.75 g (65%) of a colorless crystalline precipitate, mp 227–229° (butanol); ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.05 (t, J = 7.0 Hz, 6H), 1.64 (s, 3H), 2.30 (s, 3H), 3.05 (q, J = 7.0 Hz, 4H), 4.99 (d, J = 3.0 Hz, 1H), 7.15 (d, J = 8.0 Hz, 2H), 7.32 (br s, 1H), 7.51 (d, J = 8.0 Hz, 2H), 8.48 (br s, 1H); Anal. Calcd for $C_{16}H_{20}BrN_3O_2$: C, 52.47; H, 5.50; N, 11.47. Found: C, 52.1; H, 5.7; N, 11.1.
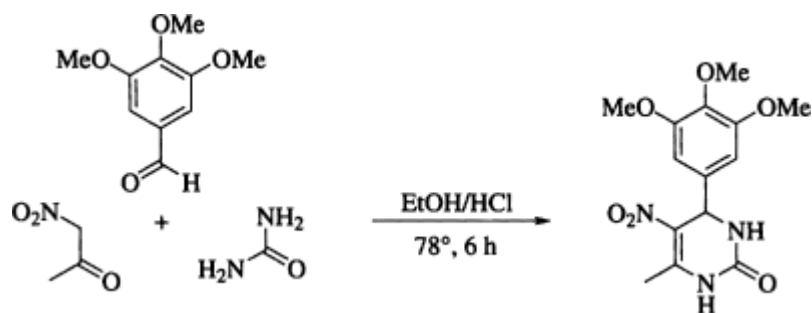
6.1.1.11. 6-Methyl-5-nitro-4-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydropyrimidin-2-one [Biginelli Condensation Utilizing Ethanol/ HCl as the Solvent/Catalyst System] (107)

A mixture of 56.5 mmol (5.82 g) of nitroacetone, 56.5 mmol (11.08 g) of 3,4,5-trimethoxybenzaldehyde, and 113 mmol (6.78 g) of urea in absolute EtOH (100 mL) containing 20 drops of concentrated HCl was heated to reflux for 6 hours. The precipitate formed was collected by filtration, dried, and recrystallized from EtOH, yielding 14.6 g (80%) of the desired pyrimidine, mp 243–245°; ^{1}H NMR δ 2.82 (s, 3H), 3.87 (s, 3H), 3.97 (s, 6H), 5.84 (d, J = 3.5 Hz, 1H), 6.87 (s, 2H), 8.36 (d, 1H), 10.15 (s, 1H).
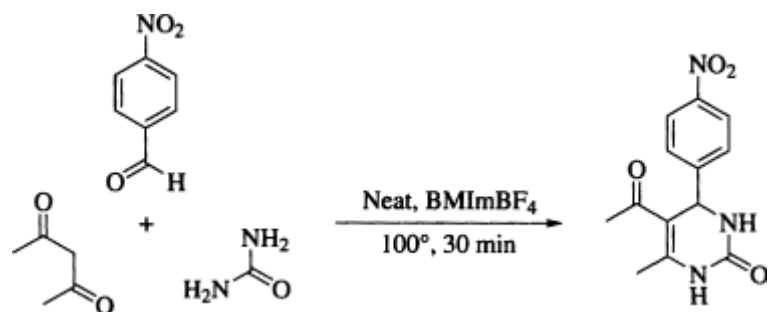
6.1.1.12. 5-Acetyl-6-methyl-4-(4-nitrophenyl)-1,2,3,4-tetrahydropyrimidin-2-one [Biginelli Condensation Utilizing Ionic Liquids as the Reaction Medium] (81)

Twenty-five mmol (3.78 g) of 4-nitrobenzaldehyde, 25.0 mmol (2.50 g) of acetylacetone, 37.5 mmol (2.25 g) of urea, and 0.1 mmol (22.6 mg) of 1-butyl-3-methylimidazoliumtetrafluoroborate (BMImBF$_4$, ionic liquid) were successively charged into a 50-mL round-bottomed flask equipped with a magnetic stirring bar. The reaction proceeded at 100° for 30 minutes, during which time a solid product gradually formed. After the reaction was complete, the resulting pale yellow solid product was crushed, washed with water, collected by filtration, and dried in vacuo to afford the crude product in 92% yield (6.33 g). A pure product was obtained by further crystallization of the crude product from EtOAc.
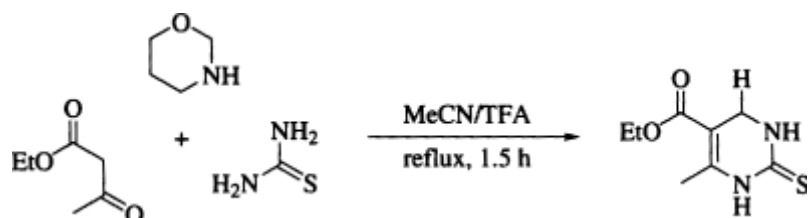
6.1.1.13. Ethyl 6-Methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate [Biginelli Condensation Employing a Masked Aldehyde Precursor] (11)

A solution of 10 mmol (0.87 g) of 1,3-oxazinane, 10 mmol (1.30 g) of ethyl acetoacetate, and 10 mmol (0.72 g) of thiourea in anhydrous CH$_3$CN (30–40 mL) containing trifluoroacetic acid (TFA) (0.5 mL) was heated at reflux until the reaction was completed (TLC). The reaction mixture was made basic with cold aqueous sodium carbonate solution and extracted with CHCl$_3$ (3 × 50 mL). The extract was washed with cold water (2 × 50 mL) and dried (Na$_2$SO$_4$). The solvent was removed and the residue was crystallized to afford 1.86 g (93%) of the desired pyrimidine, mp 236°; IR (KBr) 3180, 1715 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.25 (t, J = 7.0 Hz, 3H), 2.23 (s, 3H), 3.98 (s, 2H), 4.11 (q, J = 7.0 Hz, 2H), 6.68 (br s, 1H), 9.58 (br s,

1H); ^{13}C NMR (CDCl$_3$) δ 13.2, 16.1, 40.2, 58.6, 94.8, 144.2, 164.3, 175.2; Anal. Calcd for C$_8$H$_{12}$N$_2$O$_2$S : C, 48.00; H, 6.00; N, 14.00. Found: C, 48.32; H, 5.82; N, 13.87.
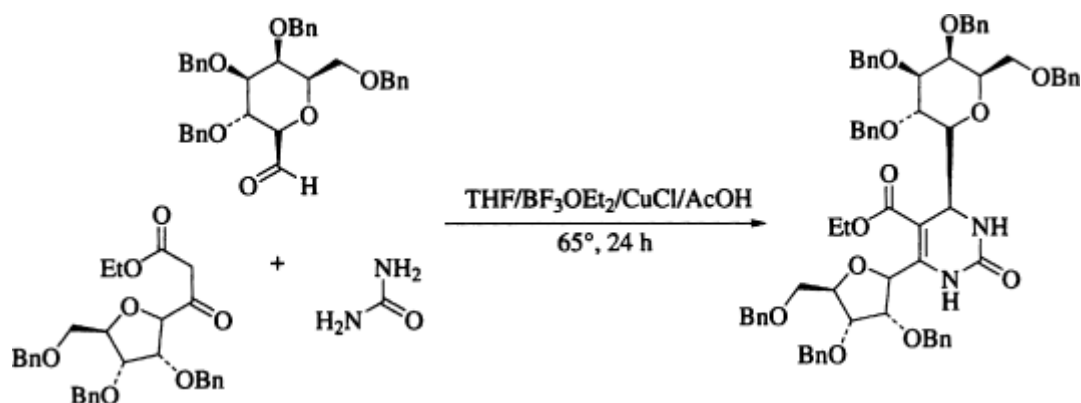
6.1.1.14. C-Galactosylpyrimidine [Biginelli Condensation Involving a Carbohydrate-Derived Aldehyde and a β -Ketoester Building Block] (20)

The cyclocondensation of 1.0 equivalent of ethyl 3-(3,4-bis-(benzyloxy)-5-benzyloxymethyltetrahydrofuranyl)-3-oxo-propionate, 1.0 equivalent of 3,4,5-tris-(benzyloxy)-6-benzyloxymethylte-trahydropyran-2-carboxaldehyde, and 1.5 equivalents of urea in THF (previously dried over molecular sieves) at 65° was promoted by CuCl (1.0 equivalent), BF$_3$·OEt$_2$ (1.3 equivalents), and acetic acid (0.2 equivalents) to give, after 24 hours, the *C*-galactosylpyrimidine as a mixture of diastereomers in 35% overall yield.
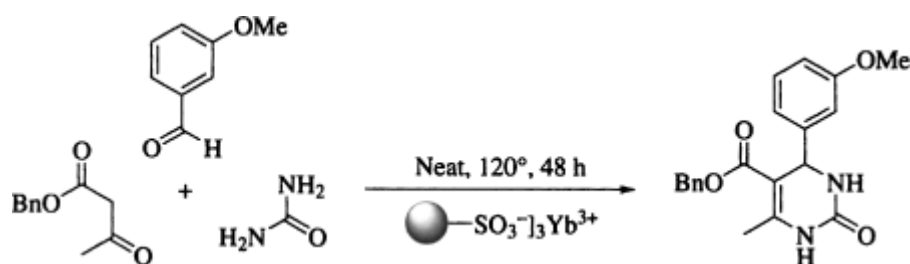
6.1.1.15. Benzyl 4-(3-Methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate [Biginelli Condensation Utilizing a Supported Lewis Acid Catalyst] (35)

A screw-capped vial, equipped with a magnetic stirring bar, was charged first with 160 mg of Yb-(III)-resin [Yb(III)-reagent supported on Amberlyst 15], then with 1.5 mmol (90 mg) of urea, 0.5 mmol (68.3 mg) of 3-methoxybenzaldehyde, and 0.5 mmol (96.1 mg) of benzyl acetoacetate and heated at 120° for 5 minutes. Then another 170 mg of Yb(III)-resin was added and the reaction mixture was heated at 120° under gentle stirring for 48 hours. After cooling to 60°, MeOH (1 mL) was added. The suspension was stirred for additional 30 minutes, after which the resin was removed by filtration and washed thoroughly with EtOAc. Amberlyst 15 (400 mg) and Ambersep 900 OH (400 mg) were added to the combined filtrates. After the suspension was shaken for 2 hours, the resins were removed by filtration and washed thoroughly with MeOH. The combined filtrates were concentrated to give the desired pyrimidine in 70% yield.
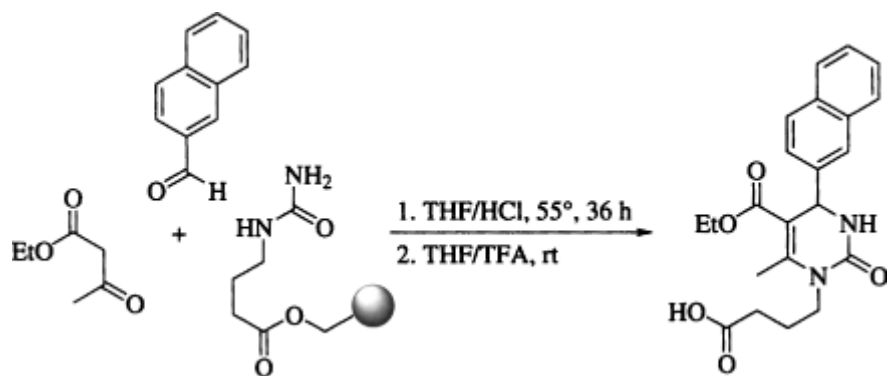
6.1.1.16. Ethyl 1-(3-Carboxypropyl)-6-methyl-4-(naphthalen-2-yl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate [Biginelli Condensation Employing a Polystyrene-Supported Urea Building Block] (36)

A suspension of 0.048 mmol (50 mg) of polymer-bound urea (modified Wang-resin) in 1.5 mL of THF in a dram vial was treated with 4 equivalents (0.192 mmol, 30 mg) of 2-naphthaldehyde, 4 equivalents (0.192 mmol, 25 mg) of ethyl acetoacetate, and 50 µL of a 4:1 THF/concentrated HCl solution. The reaction mixture was stirred at 55° for 36 hours, and the resin was collected by filtration and washed with THF (3 × 5 mL), hexanes (3 × 5 mL), MeOH (3 × 5 mL), and CH_2Cl_2 (3 × 5 mL). Subsequently, the resin was washed with 3 mL of TFA, followed by 2 × 3 mL of CH_2Cl_2. The latter filtrate was concentrated in vacuo, yielding 16.5 mg (87%) of the pyrimidine.
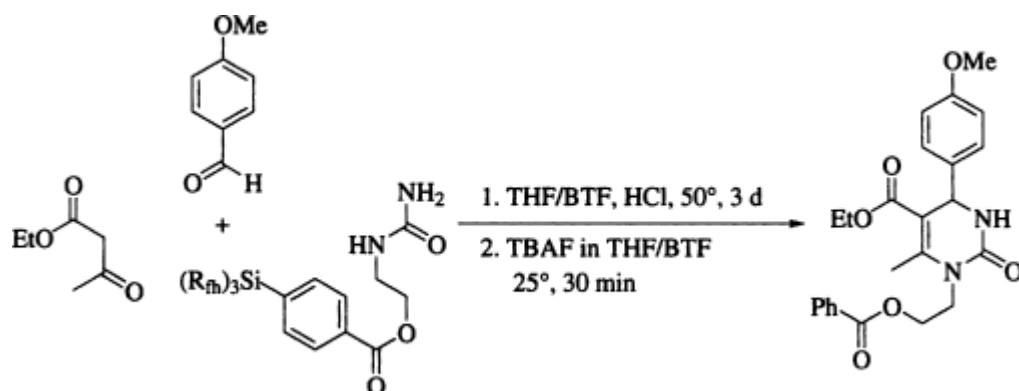
6.1.1.17. Ethyl 1-(2-Benzoyloxyethyl)-6-methyl-4-(4-methoxyphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate [Biginelli Condensation Employing a Fluorous Urea Building Block] (38)

A solution of 9.6 µmol (18 mg) of (2-((4-(tris(2-(perfluorodecyl)ethyl)silyl)benzoyl)oxy)ethyl)urea in 0.75 mL of THF/benzotrifluoride (BTF) (2:1) was treated at 25° with 96 µmol (12.5 mg) of ethyl acetoacetate, 96 µmol (13.1 mg) of 4-methoxybenzaldehyde, and 1 µL of concentrated HCl. After 3 days at 50°, the volatiles were removed in vacuo and FC-84 (fluorocarbon liquid, containing isomers of C_7F_{16}, bp 80°) and toluene (10 mL each) were added. The toluene phase was extracted with FC-84 (5 × 5 mL). The combined fluorous phases were filtered and concentrated. The resulting white solid was treated with 0.5 mL of THF/BTF (1:1) and then dropwise with a 1 M tributylammonium fluoride (TBAF) solution in THF (10 µL, 10 µmol). After the mixture was stirred for 0.5 hours at 25°, the volatiles were removed in vacuo and FC-84 and toluene (10 mL each) were added. The fluorous phase was extracted with toluene (3 × 5 mL). The combined toluene phases were extracted with saturated aqueous $NaHCO_3$ solution (3 × 10 mL) and brine (3 × 10 mL), dried (Na_2SO_4), filtered, and concentrated, yielding 2.9 mg (6.6 µmol, 69%) of the desired pyrimidine, mp 75°; IR ($CHCl_3$) 3425, 3025, 1704, 1677, 1621, 1514 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.19 (t, J = 7.1 Hz, 3H), 2.60 (s, 3H), 3.66 (s, 3H), 3.95–4.15 (m, 3H), 4.40–4.50 (m, 3H), 5.34 (br s, 2H), 6.62 (d, J = 8.7 Hz, 2H), 7.14 (d, J = 8.7 Hz, 2H), 7.41 (t, J = 7.6 Hz, 2H), 7.56 (t, J = 7.6 Hz, 1H), 7.96 (d, J = 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.3, 16.5, 40.9, 53.3, 55.1, 60.3, 63.6, 105.8, 113.9, 127.4, 128.5, 129.7, 133.2, 135.5, 147.9, 153.9, 159.0, 166.2, 166.4.

7. Tabular Survey

The tabular survey in this chapter covers all examples of the classical Biginelli three-component cyclocondensation reported in the literature from 1932 through December of 2001. Not covered are Biginelli reactions that do not lead to the expected dihydropyrimidine products, intramolecular (tethered) Biginelli reactions, and modifications that do not involve the traditional three-component condensation approach (see above). The survey begins with reactions involving urea as a building block in Table 1, continues with examples concerning the use of substituted ureas in Table 2, and thioureas in Table 3, respectively. These three parts are further organized into sub-tables according to the type of the CH-acidic carbonyl compound, i.e.: A. β -keto esters, B. β -keto amides, C. β -diketones, and D. other CH-acidic carbonyl compounds. Table 4 summarizes the examples for Biginelli reactions involving guanidine, Table 5 covers transformations on solid supports, and Table 6 presents fluorous phase Biginelli reactions.

Within each table, the entries are listed according to increasing carbon number of the respective CH-acidic carbonyl compound and, furthermore, by increasing carbon number of the aldehyde building block used. Within sub-tables, the entries are listed by increasing carbon numbers of the R-group.

Reaction conditions including solvent, temperature, and time are presented as they are available from the original references; yields are given in parentheses. A dash, "(—)," indicates that no yield is reported in the reference. All data have been reproduced as provided in the original references. Ratios of diastereomers are not reported in reactions involving chiral reactants; for none of the examples in the tables where chiral reactants were used have the absolute configurations of the products been established.

The following abbreviations have been used in the tables:

AcOH	acetic acid
$BF_3 \cdot OEt_2$	boron trifluoride etherate
$BMImBF_4$	1-butyl-3-methylimidazolium tetrafluoroborate
BMImCl	1-butyl-3-methylimidazolium chloride
$BMImPF_6$	1-butyl-3-methylimidazolium hexafluorophosphate
BTF	benzotrifluoride
BuOH	*n*-butanol
CAN	ceric ammonium nitrate
DCE	dichloroethane
DCM	dichloromethane
DMF	dimethylformamide
KSF	montmorillonite KSF-clay
K-10	montmorillonite K-10-clay
MeCN	acetonitrile
MW	microwave irradiation
PPA	polyphosphoric acid
PPE	polyphosphate ester (ethyl polyphosphate)
PS	polystyrene
p-TsOH	*p*-toluenesulfonic acid
TBAF	tetrabutylammonium fluoride
TFA	trifluoroacetic acid
THF	tetrahydrofuran
US	ultrasonification

The term "*superheating*" under microwave conditions indicates heating of the solvent above its boiling

point at atmospheric pressure and "*open vessel*" under microwave conditions denotes introducing an open glass beaker in a domestic microwave oven.

8. Acknowledgments

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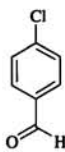
TABLE 1. REACTIONS INVOLVING UREA

A. β-Keto Esters
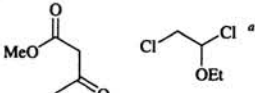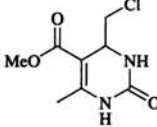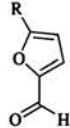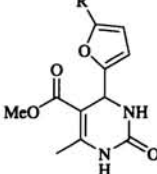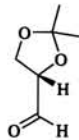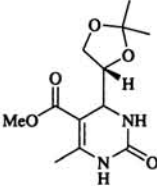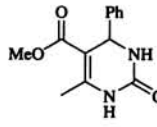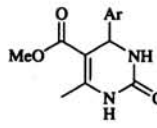
β-Keto Ester and Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.

C5

| | EtOH/HCl, 78°, 4 h | (17) | 108 |

Conditions	R	Temp	Time		Refs.
MeOH/HCl	H	65°	3 h	(65)	109
Neat, MW	H	—	5.7 min	(40)	101
MeOH/HCl	NO_2	65°	6 h	(—)	110
EtOH/Yb(OTf)$_3$, MW	NO_2	100°	10 min	(34)	22

| | EtOH, 78°, 5 h | (16) | 13 |

Conditions	Temp	Time		Refs.
THF/BF$_3$•OEt$_2$/CuCl/AcOH	65°	8–18 h	(88)	10
EtOH/H$_2$SO$_4$	78°	18 h	(42)	10
EtOH/LaCl$_3$	78°	5 h	(97)	11
EtOH/FeCl$_3$	78°	4 h	(86)	84, 85
Neat/Yb(OTf)$_3$	100°	20 min	(98)	83
THF/InCl$_3$	65°	7 h	(92)	90
Neat, MW	—	1 min	(—)	101
MeCN/BiCl$_3$	81°	5 h	(92)	76
MeOH/HCl	65°	4 h	(81)	112
MeCN/LiClO$_4$	81°	6 h	(90)	92
Neat/Yb(III)-resin	120°	48 h	(71)	35

Conditions	Ar	Temp	Time		Refs.
Neat, MW	2-ClC$_6$H$_4$	—	0.7 min	(66)	101
Neat/Yb(III)-resin	2-BrC$_6$H$_4$	120°	48 h	(68)	35
Neat/Yb(III)-resin	4-BrC$_6$H$_4$	120°	48 h	(68)	35
Neat/Yb(OTf)$_3$	2,4-Cl$_2$C$_6$H$_3$	100°	20 min	(83)	83
Neat, MW	2,4-Cl$_2$C$_6$H$_3$	—	1 min	(48)	101
Neat, MW	2,6-Cl$_2$C$_6$H$_3$	—	13 min	(51)	101
Neat, MW	3-O$_2$NC$_6$H$_4$	—	1 min	(66)	101
Neat/Yb(OTf)$_3$	4-FC$_6$H$_4$	100°	20 min	(81)	83
AcOH/EtOH, Yb(OTf)$_3$, MW	4-FC$_6$H$_4$	120°	10 min	(81)	22
Neat/Yb(III)-resin	4-FC$_6$H$_4$	120°	48 h	(70)	35
THF/BF$_3$•OEt$_2$/CuCl/AcOH	3,4-F$_2$C$_6$H$_3$	65°	8–18 h	(88)	10, 27
EtOH/H$_2$SO$_4$	3,4-F$_2$C$_6$H$_3$	78°	18 h	(62)	10

TABLE 1. REACTIONS INVOLVING UREA (*Continued*)

A. β-Keto Esters (*Continued*)

β-Keto Ester and Aldehyde	Conditions	Product(s) and Yield(s) (%)				Refs.

C₅

First entry (methyl acetoacetate + 4-chlorobenzaldehyde):

Conditions	Temp	Time		Refs.
THF/BF₃•OEt₂/CuCl/AcOH	65°	8-18 h	(95)	10
EtOH/H₂SO₄	78°	18 h	(56)	10
EtOH/LaCl₃	78°	5 h	(96)	111
EtOH/FeCl₃	78°	4 h	(96)	84, 85
THF/InCl₃	65°	9 h	(93)	90
Neat, MW	—	2.6 min	(68)	101
MeCN/BiCl₃	81°	5 h	(90)	76

Second entry (4-nitrobenzaldehyde):

Conditions	Temp	Time		Refs.
THF/BF₃•OEt₂/CuCl/AcOH	65°	8-18 h	(92)	10
EtOH/H₂SO₄	78°	18 h	(41)	10
PPE, MW	—	3 x 40 sec	(86)	34
EtOH/LaCl₃	78°	5 h	(68)	111
EtOH/FeCl₃	78°	4 h	(88)	84, 85
Neat/Yb(OTf)₃	100°	20 min	(91)	83
THF/InCl₃	65°	6 h	(91)	90
MeCN/BiCl₃	81°	6 h	(89)	76
THF/PPE	65°	15 h	(84)	104

Third entry:

Conditions	Yield	Refs.
EtOH, 78°, 5 h	(43)	15

Fourth entry:

Conditions	Yield	Refs.
EtOH, 70-80°, 55 h	(38)	19

Fifth entry (4-methoxybenzaldehyde):

Conditions	Temp	Time		Refs.
THF/BF₃•OEt₂/CuCl/AcOH	65°	8-18 h	(87)	10
EtOH/H₂SO₄	78°	18 h	(28)	10
EtOH/LaCl₃	78°	5 h	(82)	111
EtOH/FeCl₃	78°	4 h	(88)	84, 85
Neat/Yb(OTf)₃	100°	20 min	(99)	83
THF/InCl₃	65°	9 h	(91)	90
MeCN/BiCl₃	81°	5 h	(92)	76
Neat/Yb(III)-resin	120°	48 h	(71)	35

TABLE 1. REACTIONS INVOLVING UREA (*Continued*)

A. β-Keto Esters (*Continued*)

β-Keto Ester and Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.

C₅

	Ar	Temp	Time		
PPE, MW	2-MeC₆H₄	—	3 x 40 sec	(86)	34
THF/PPE	2-MeC₆H₄	65°	15 h	(88)	104
EtOH/Yb(OTf)₃, MW	2-MeC₆H₄	120°	10 min	(73)	22
MeOH/HCl	2-MeC₆H₄	65°	4 h	(68)	112
MeOH/HCl	3-MeC₆H₄	65°	4 h	(78)	112
MeCN/BiCl₃	4-MeC₆H₄	81°	5 h	(91)	76
Neat/Yb(III)-resin	4-(F₃C)C₆H₄	120°	48 h	(65)	35
Neat/Yb(III)-resin	3-MeOC₆H₄	120°	48 h	(71)	35
EtOH/Yb(OTf)₃, MW	3-MeOC₆H₃OH-4	100°	15 min	(46)	22
EtOH/HCl	2-(CHF₂O)C₆H₄	78°	3 h	(68)	113, 114
EtOH/HCl	2-(CHF₂S)C₆H₄	rt	12 h	(52)	115
THF/BF₃•OEt₂/CuCl/AcOH	2,5-Me₂C₆H₃	65°	8-18 h	(96)	10
EtOH/H₂SO₄	2,5-Me₂C₆H₃	78°	18 h	(62)	10

EtOH, 78°, 5 h

(49)

15

EtOH/HCl, 78°, 10 h

(60)

116

R = H, OMe

EtOH/HCl, 78°, 10 h

(65)

116

1. THF/BF₃•OEt₂/CuCl/AcOH, 65°, 8-18 h
2. PPA, 100°, 30 min

(4)

27
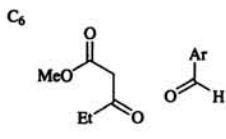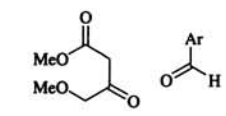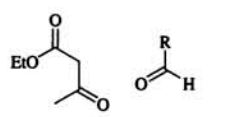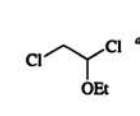
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TABLE 1. REACTIONS INVOLVING UREA (*Continued*)
A. β-Keto Esters (*Continued*)

β-Keto Ester and Aldehyde	Conditions	Product(s) and Yield(s) (%)				Refs.

C₆

	Conditions	Ar	Temp	Time		Refs.
	THF/BF₃•OEt₂/CuCl/AcOH	Ph	65°	8-18 h	(81)	10
	EtOH/H₂SO₄	Ph	78°	18 h	(42)	10
	THF/InCl₃	Ph	65°	6 h	(95)	90
	THF/BF₃•OEt₂/CuCl/AcOH	4-ClC₆H₄	65°	8-18 h	(89)	10
	EtOH/H₂SO₄	4-ClC₆H₄	78°	18 h	(66)	10
	THF/InCl₃	4-ClC₆H₄	65°	7 h	(92)	90
	THF/BF₃•OEt₂/CuCl/AcOH	4-O₂NC₆H₄	65°	8-18 h	(90)	10
	EtOH/H₂SO₄	4-O₂NC₆H₄	78°	18 h	(64)	10
	THF/InCl₃	4-O₂NC₆H₄	65°	6 h	(91)	90
	THF/BF₃•OEt₂/CuCl/AcOH	3,4-F₂C₆H₃	65°	8-18 h	(82)	10
	EtOH/H₂SO₄	3,4-F₂C₆H₃	78°	18 h	(55)	10
	PPE, MW	3,4-F₂C₆H₃	—	3 x 40 sec	(65)	34
	AcOH/EtOH, Yb(OTf)₃, MW	3,4-F₂C₆H₃	120°	10 min	(64)	22
	THF/BF₃•OEt₂/CuCl/AcOH	4-MeOC₆H₄	65°	8-18 h	(85)	10
	EtOH/H₂SO₄	4-MeOC₆H₄	78°	18 h	(25)	10
	THF/InCl₃	4-MeOC₆H₄	65°	8 h	(91)	90

β-Keto Ester and Aldehyde	Conditions	Product	Ar	Refs.
	A. AcOH/EtOH, Yb(OTf)₃, MW, 120°, 10 min		A. 3-O₂NC₆H₄ (35)	22
	B. THF/BF₃•OEt₂/CuCl/AcOH, 65°, 8-18 h		B. 3,4-F₂C₆H₃ (94)	27

	Conditions	R	Temp	Time		Refs.
	AcOH/HCl	H	118°	5 h	(—)	78, 117
	H₂O, pH 6.6	H	rt	12 h	(2.5)	80
	Piperidine	H	170°	40 min	(65)	118
	MeCN/TFA[b]	H	81°	1 h	(90)	11
	Toluene/Zeolite	H	110°	48 h	(64)	95
	EtOH/HCl	Me	78°	3 h	(26)	78
	Dioxane/HCl	Me	100°	2 h	(47)	78
	H₂O, pH 1.0	Me	rt	12 h	(20)	80
	THF/PPE	Me	65°	15 h	(53)	75, 104
	EtOH/ *p*-toluenesulfinic acid	Me	78°	5 h	(40)	119
	MeCN/TFA[b]	Me	81°	6 h	(95)	11
	MeOH/KSF-clay	Me	65°	—	(90)	120
	THF/InCl₃	Me	65°	7 h	(75)	90
	EtOH/HCl, MW	Me	120°	20 min	(67)	22
	Toluene/Zeolite	Me	110°	48 h	(42)	95

β-Keto Ester and Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
	EtOH/HCl, 78°, 4 h	(32)	108

TABLE 1. REACTIONS INVOLVING UREA (*Continued*)
A. β-Keto Esters (*Continued*)

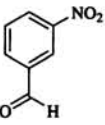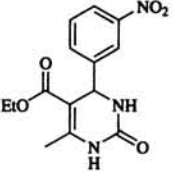| β-Keto Ester and Aldehyde	Conditions	Product(s) and Yield(s) (%)				Refs.

C₆
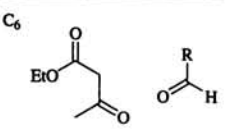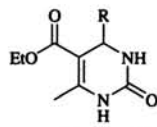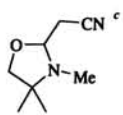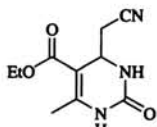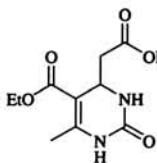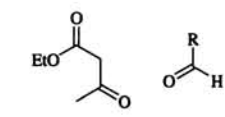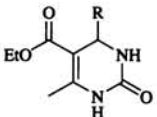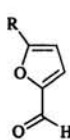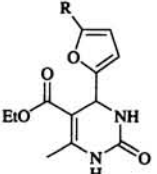
		R	Temp	Time		
	H₂O, pH 1.0	Et	rt	12 h	(15)	80
	EtOH/*p*-toluenesulfinic acid	Et	78°	5 h	(38)	119
	MeCN/TFA[b]	Et	81°	8 h	(86)	11
	H₂O, pH 2.1-6	propenyl	rt	12 h	(44)	80
	EtOH/*p*-toluenesulfinic acid	Pr	78°	5 h	(35)	119
	EtOH/LaCl₃	Pr	78°	5 h	(60)	111
	EtOH/FeCl₃	Pr	78°	4 h	(73)	84, 85
	THF/InCl₃	Pr	65°	7 h	(85)	90
	MeCN/BiCl₃	Pr	81°	6 h	(72)	76
	EtOH/HCl	Pr	78°	4 h	(15)	73

| | MeCN/TFA, 81°, 12 h | | (68) | | | 11 |

| | MeCN/TFA, 81°, 12 h | | (78) | | | 11 |

		R	Temp	Time		
	EtOH/HCl	*i*-Pr	78°	6 h	(32)	121
	EtOH/*p*-toluenesulfinic acid	*i*-Pr	78°	5 h	(27)	119
	EtOH/LaCl₃	*i*-Pr	78°	5 h	(56)	111
	EtOH/FeCl₃	*i*-Pr	78°	4 h	(53)	84, 85
	Neat/Yb(OTf)₃	*i*-Pr	100°	20 min	(83)	83
	THF/InCl₃	*i*-Pr	65°	8 h	(83)	90
	MeCN/BiCl₃	*i*-Pr	81°	8 h	(54)	76
	EtOH/HCl	*i*-Pr	78°	4 h	(10)	73
	Neat/KSF-clay	*n*-Bu	130°	48 h	(86)	82
	Neat/Yb(OTf)₃	*n*-Bu	100°	40 min	(87)	83
	EtOH/HCl	*n*-Bu	78°	3 h	(31)	122

		R	Temp	Time		
	EtOH/LaCl₃	H	78°	5 h	(67)	111
	EtOH/Yb(OTf)₃, MW	H	100°	20 min	(50)	22
	MeOH, US, (A) CAN	H	—	3 h	(87)	103
	(B) Oxone®	H	—	4.5 h	(73)	103
	MeCN/LiClO₄	H	81°	5 h	(85)	92
	EtOH/HCl	NO₂	78°	3 h	(—)	123

TABLE 1. REACTIONS INVOLVING UREA (*Continued*)
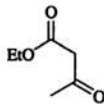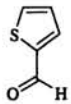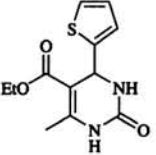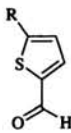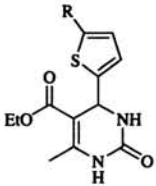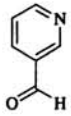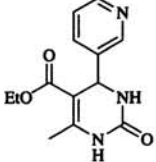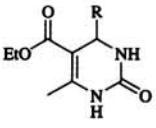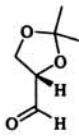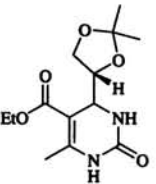
A. β-Keto Esters (*Continued*)

β-Keto Ester and Aldehyde	Conditions	Product(s) and Yield(s) (%)				Refs.

C₆

			Temp	Time		
	EtOH/HCl		78°	3–4 h	(70)	73, 122
	MeOH/HCl		65°	2 h	(—)	124
	THF/PPE		65°	15 h	(84)	75, 104
	AcOH, MW		—	2 min	(97)	79
	Toluene/Amberlyst 15		110°	6 h	(83)	79
	MeCN/BiCl₃		81°	6 h	(89)	76
	EtOH/AcOH, Yb(OTf)₃		120°	10 min	(89)	22
	MeOH, US, (A) CAN		—	3.5 h	(90)	103
	(B) Oxone®		—	3 h	(78)	103
	MeCN/LiClO₄		81°	5 h	(90)	92

			R			
	EtOH/HCl, 78°, 3 h		H	(83)		125
			NO₂	(85)		
			Br	(80)		

	EtOH/AcOH, Yb(OTf)₃	(31)				22
	MW, 120°, 10 min					

			R	Temp	Time	
	Ionic liquid (BMImBF₄)		n-C₅H₁₁	100°	30 min	(93)	81
	EtOH/AcOH, Yb(OTf)₃, MW		n-C₅H₁₁	120°	10 min	(35)	22
	MeCN/LiClO₄		n-C₅H₁₁	81°	7 h	(82)	92
	MeCN/BiCl₃		c-C₆H₁₁	81°	6 h	(92)	76
	MeOH, US, (A) CAN		c-C₆H₁₁	—	3 h	(90)	103
	(B) Oxone®		c-C₆H₁₁	—	5 h	(76)	103
	MeCN/LiClO₄		c-C₆H₁₁	81°	8 h	(87)	92
	H₂O, pH 1.0		n-C₆H₁₃	rt	12 h	(12)	80
	EtOH/p-toluenesulfinic acid		n-C₆H₁₃	reflux	5 h	(23)	119
	THF/InCl₃		n-C₆H₁₃	65°	8 h	(81)	90
	MeCN/BiCl₃		n-C₆H₁₃	81°	9 h	(50)	76
	MeOH, US, (A) CAN		n-C₆H₁₃	—	3 h	(85)	103
	(B) Oxone®		n-C₆H₁₃	—	4 h	(77)	103
	DMF/ClSiMe₃, urea added after 12 h		n-C₆H₁₃	20°	14 h	(37)	126
	DMF/ClSiMe₃, urea added after 12 h		n-C₇H₁₅	20°	14 h	(32)	126

	EtOH, 78°, 5 h	(25)				13

TABLE 1. REACTIONS INVOLVING UREA (*Continued*)
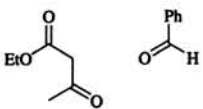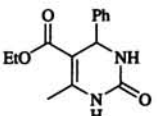
A. β-Keto Esters (*Continued*)

β-Keto Ester and Aldehyde	Conditions			Product(s) and Yield(s) (%)	Refs.

C$_6$

		Temp	Time		
	EtOH/HCl	78°	1.5-4 h	(80)	33, 73, 99, 117, 127-130
	H$_2$O, pH 2.1-7	rt	12 h	(40)	80
	MeOH/H$_2$O, HCl	rt	3 d	(80)	6
	Piperidine	170°	1.5 h	(68)	118
	EtOH/HCl, MW	—	3.5 min	(90)	97
	Neat on inorganic support, MW,				
	(A) SiO$_2$	—	12 min	(85)	98
	(B) Al$_2$O$_3$ (neutral)	—	10 min	(87)	98
	(C) Al$_2$O$_3$ (basic)	—	10 min	(90)	98
	(D) Al$_2$O$_3$ (acidic)	—	10 min	(97)	98
	THF/BF$_3$·OEt$_2$/CuCl/AcOH	65°	8-18 h	(94)	10
	EtOH/H$_2$SO$_4$	78°	18 h	(71)	10
	THF/PPE	65°	15 h	(94)	75, 104
	EtOH/p-toluenesulfinic acid	78°	5 h	(73)	119
	Neat/KSF-clay	130°	18 h	(82)	82
	PPE, MW	—	3 x 40 sec	(85)	34
	MeCN/TFA[b]	81°	4 h	(94)	11
	MeOH/KSF-clay	65°	—	(92)	120
	EtOH/LaCl$_3$	78°	5 h	(95)	111
	EtOH/FeCl$_3$	78°	4 h	(94)	84, 85
	Neat/Yb(OTf)$_3$	100°	20 min	(98)	83
	THF/InCl$_3$	65°	7 h	(95)	90
	EtOH/HCl, MW, (A) reflux	78°	3 h	(80)	100
	(B) superheating	96°	3 h	(80)	100
	(C) open vessel	—	15 x 20 sec	(78)	100
	Neat/HCl, MW, open vessel	—	15 x 20 sec	(50)	100
	AcOH, MW	—	2 min	(86)	79
	Toluene/Amberlyst 15	110°	12 h	(80)	79
	MeCN/BiCl$_3$	81°	5 h	(95)	76
	Ionic liquid, (A) BMImBF$_4$	100°	30 min	(92)	81
	(B) BMImPF$_6$	100°	30 min	(94)	81
	(C) BMImCl	100°	30 min	(56)	81
	EtOH/AcOH, Yb(OTf)$_3$, MW	120°	10 min	(92)	22
	MeOH, US, (A) CAN	—	3.5 h	(92)	103
	(B) Oxone®	—	5 h	(88)	103
	MeCN/LiClO$_4$	81°	6 h	(89)	92
	MeCN/Mn(OAc)$_3$	81°	2 h	(96)	93
	Neat/Yb(III)-resin	120°	48 h	(80)	35
	Toluene/Zeolite	110°	12 h	(80)	95
	DMF/ClSiMe$_3$,				
	(A) urea added after 12 h	20°	14 h	(80)	126
	(B) all components together	20°	2 h	(61)	126

TABLE 1. REACTIONS INVOLVING UREA (*Continued*)

A. β-Keto Esters (*Continued*)

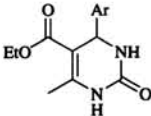| β-Keto Ester and Aldehyde	Conditions	Product(s) and Yield(s) (%)					Refs.

C6

(EtO β-keto ester + 4-hydroxybenzaldehyde)

Product structure (4-OH-phenyl dihydropyrimidinone)

Conditions	Temp	Time		Refs.
EtOH/HCl, MW	—	3.5 min	(87)	97
Neat/KSF-clay	130°	48 h	(88)	82
EtOH/LaCl₃	78°	5 h	(89)	111
EtOH/FeCl₃	78°	4 h	(84)	84, 85
THF/InCl₃	65°	8 h	(91)	90
AcOH, MW	—	2 min	(86)	79
Toluene/Amberlyst 15	110°	12 h	(76)	79
MeCN/Mn(OAc)₃	81°	4 h	(79)	93
Toluene/Zeolite	110°	18 h	(76)	95

(ArCHO)

Product structure (Ar dihydropyrimidinone)

Conditions	Ar	Temp	Time		Refs.
EtOH/HCl	2-HOC₆H₄	78°	3 h	(19)	122
H₂O, pH 2.1-6.6	2-HOC₆H₄	rt	12 h	(87)	80
EtOH/LaCl₃	2-HOC₆H₄	78°	5 h	(70)	111
THF/InCl₃	2-HOC₆H₄	65°	7 h	(91)	90
THF/InCl₃	3-HOC₆H₄	65°	9 h	(88)	90
EtOH/HCl	2-HOC₆H₃Br-5	78°	3 h	(86)	131

(2-chlorobenzaldehyde)

Product structure (2-Cl-phenyl dihydropyrimidinone)

Conditions	Temp	Time		Refs.
EtOH/HCl	78°	3 h	(51)	132
H₂O, pH 1.0	rt	12 h	(20)	80
THF/PPE	65°	15 h	(83)	75, 104
PPE, MW	—	2 x 40 sec	(95)	34
EtOH/AcOH, Yb(OTf)₃, MW	120°	10 min	(68)	22
MeCN/Mn(OAc)₃	81°	2 h	(76)	93

(4-chlorobenzaldehyde)

Product structure (4-Cl-phenyl dihydropyrimidinone)

Conditions	Temp	Time		Refs.
EtOH/HCl	78°	3 h	(37)	122, 133
THF/BF₃•OEt₂/CuCl/AcOH	65°	8-18 h	(92)	10
EtOH/H₂SO₄	78°	18 h	(56)	10
Neat/KSF-clay	130°	48 h	(76)	82
MeOH/KSF-clay	65°	—	(93)	120
EtOH/LaCl₃	78°	5 h	(92)	111
EtOH/FeCl₃	78°	4 h	(90)	84, 85
Neat/Yb(OTf)₃	100°	20 min	(97)	83
THF/InCl₃	65°	6.5 h	(92)	90
AcOH, MW	—	3 min	(84)	79
Toluene/Amberlyst 15	110°	15 h	(79)	79
MeCN/BiCl₃	81°	5 h	(90)	76
Ionic liquid, (A) BMImBF₄	100°	30 min	(96)	81
(B) BMImPF₆	100°	30 min	(98)	81
MeOH, US, (A) CAN	—	4 h	(89)	103
(B) Oxone®	—	6.5 h	(85)	103
MeCN/Mn(OAc)₃	81°	3.5 h	(78)	93
Neat/Yb(III)-resin	120°	48 h	(68)	35

(ArCHO)

Product structure (Ar dihydropyrimidinone)

Conditions	Ar	Temp	Time		Refs.
EtOH/HCl, MW	3-FC₆H₄	—	12 x 30 sec	(80)	30
EtOH/HCl	4-FC₆H₄	78°	3 h	(63)	122, 134
EtOH/HCl, MW	4-FC₆H₄	—	12 x 30 sec	(86)	30
Neat/Yb(OTf)₃	4-FC₆H₄	100°	20 min	(94)	83
Neat/Yb(III)-resin	4-FC₆H₄	120°	48 h	(68)	35
EtOH/LaCl₃	3-ClC₆H₄	78°	5 h	(87)	111
EtOH/FeCl₃	3-ClC₆H₄	78°	4 h	(82)	84, 85
Neat/Yb(OTf)₃	2-BrC₆H₄	100°	20 min	(97)	83
Neat/Yb(III)-resin	2-BrC₆H₄	120°	48 h	(68)	35
EtOH/LaCl₃	3-BrC₆H₄	78°	5 h	(97)	111
EtOH/FeCl₃	3-BrC₆H₄	78°	4 h	(83)	84, 85

TABLE 1. REACTIONS INVOLVING UREA (*Continued*)

A. β-Keto Esters (*Continued*)

β-Keto Ester and Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.

C₆

	H₂O, pH 1-3	Temp	Time		
		rt	12 h	(50)	80
	THF/PPE	65°	5-15 h	(84)	75, 104
	MeCN/TFA[b]	81°	4 h	(88)	11
	EtOH/AcOH, Yb(OTf)₃, MW	120°	10 min	(54)	22
	MeCN/Mn(OAc)₃	81°	4 h	(77)	93

		Temp	Time		
	EtOH/HCl, MW	—	4 min	(88)	97
	THF/PPE	65°	5-15 h	(87)	75, 104
	PPE, MW	—	3 x 40 sec	(93)	34
	MeCN/TFA[b]	81°	5 h	(90)	11
	AcOH, MW	—	4 min	(90)	79
	Toluene/Amberlyst 15	110°	14 h	(84)	79
	MeCN/BiCl₃	81°	6 h	(85)	76
	MeCN/Mn(OAc)₃	81°	4 h	(75)	93

Solvent/Catalyst

		Temp	Time		
	EtOH/HCl, MW	—	4 min	(70)	97
	THF/BF₃•OEt₂/CuCl/AcOH	65°	8-18 h	(91)	10
	EtOH/H₂SO₄	78°	18 h	(—)	10
	THF/PPE	65°	15 h	(77)	75, 104
	MeOH/KSF-clay	65°	—	(89)	120
	EtOH/LaCl₃	78°	4.5 h	(80)	111
	EtOH/FeCl₃	78°	4 h	(83)	84, 85
	Neat/Yb(OTf)₃	100°	20 min	(94)	83
	THF/InCl₃	65°	6 h	(93)	90
	AcOH, MW	—	4 min	(88)	79
	Toluene/Amberlyst 15	110°	15 h	(79)	79
	MeCN/BiCl₃	81°	6 h	(90)	76
	Ionic liquid, (A) BMImBF₄	100°	30 min	(90)	81
	(B) BMImPF₆	100°	30 min	(92)	81
	MeOH, US, (A) CAN	—	7 h	(85)	103
	(B) Oxone®	—	9.5 h	(73)	103
	MeCN/LiClO₄	81°	5 h	(90)	92
	Neat/Yb(III)-resin	120°	48 h	(72)	35
	Toluene/Zeolite	110°	12 h	(68)	95

TABLE 1. REACTIONS INVOLVING UREA (*Continued*)

A. β-Keto Esters (*Continued*)

β-Keto Ester and Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.

C₆

	Ar	Temp	Time		
THF/BF₃•OEt₂/CuCl/AcOH	3,4-F₂C₆H₃	65°	8-18 h	(81)	10
EtOH/H₂SO₄	3,4-F₂C₆H₃	78°	18 h	(66)	10
THF/PPE	3,4-F₂C₆H₃	65°	15 h	(84)	75, 104
PPE, MW	3,4-F₂C₆H₃	—	3 x 40 sec	(87)	34
EtOH/Yb(OTf)₃, MW	3,4-F₂C₆H₃	120°	10 min	(61)	22
EtOH/HCl	2-ClC₆H₃F-6	78°	3 h	(—)	133
EtOH/HCl	2-ClC₆H₃OH-5	78°	3 h	(30)	132
EtOH/HCl, MW	2,3-Cl₂C₆H₃	—	3.5 min	(85)	97
THF/PPE	2,3-Cl₂C₆H₃	65°	15 h	(79)	75, 104
PPE, MW	2,3-Cl₂C₆H₃	—	3 x 40 sec	(91)	34
EtOH/LaCl₃	2,4-Cl₂C₆H₃	78°	5 h	(93)	111
Neat/Yb(OTf)₃	2,4-Cl₂C₆H₃	100°	20 min	(89)	83
Toluene/Zeolite	2,4-Cl₂C₆H₃	110°	12 h	(74)	95
MeOH, US, (A) CAN	3,4-Cl₂C₆H₃	—	5 h	(90)	103
(B) Oxone®	3,4-Cl₂C₆H₃	—	7.5 h	(83)	103
MeCN/LiClO₄	3,4-Cl₂C₆H₃	81°	10 h	(85)	92
EtOH/HCl	3,4-Cl₂C₆H₃	78°	3 h	(59)	134
AcOH/HCl	2,6-Cl₂C₆H₃	118°	8 h	(65)	135
AcOH, MW	2,6-Cl₂C₆H₃	—	4 min	(82)	79
Toluene/Amberlyst 15	2,6-Cl₂C₆H₃	110°	15 h	(71)	79
EtOH/HCl	3,5-(O₂N)₂C₆H₃	78°	3 h	(—)	33

MeOH, US, (A) CAN, 6 h		(91)	103
(B) Oxone®, 6 h		(87)	

EtOH/Yb(OTf)₃, MW, 120°, 10 min		(78)	22

EtOH, 78°, 5 h		(—)	16

TABLE 1. REACTIONS INVOLVING UREA (*Continued*)

A. β-Keto Esters (*Continued*)

β-Keto Ester and Aldehyde	Conditions	Product(s) and Yield(s) (%)				Refs.

C6

		Temp	Time		
H₂O, pH 2.1-6.6		rt	12 h	(75)	80
EtOH/HCl, MW		—	3 min	(98)	97
Neat/inorganic support, MW,					
(A) SiO₂		—	12 min	(80)	98
(B) Al₂O₃ (neutral)		—	10 min	(85)	98
(C) Al₂O₃ (basic)		—	10 min	(85)	98
(D) Al₂O₃ (acidic)		—	9 min	(92)	98
THF/BF₃•OEt₂/CuCl/AcOH		65°	8-18 h	(85)	10
EtOH/H₂SO₄		78°	18 h	(37)	10
Neat/KSF-clay		130°	18 h	(78)	82
MeCN/TFA[b]		81°	4 h	(92)	11
MeOH/KSF-clay		65°	—	(82)	120
EtOH/LaCl₃		78°	5 h	(93)	111
EtOH/FeCl₃		78°	4 h	(94)	84, 85
Neat/Yb(OTf)₃		100°	20 min	(96)	83
THF/InCl₃		65°	9 h	(90)	90
AcOH, MW		—	2 min	(88)	79
Toluene/Amberlyst 15		110°	12 h	(71)	79
MeCN/BiCl₃		81°	6 h	(90)	76
Ionic liquid, (A) BMImBF₄		100°	30 min	(95)	81
(B) BMImPF₆		100°	30 min	(98)	81
Toluene/Zeolite		110°	12 h	(71)	95

	Ar	Temp	Time		
MeOH/KSF-clay	4-MeC₆H₄	65°	—	(88)	120
AcOH, MW	4-MeC₆H₄	—	2 min	(85)	79
Toluene/Amberlyst 15	4-MeC₆H₄	110°	8 h	(73)	79
MeCN/BiCl₃	4-MeC₆H₄	81°	5 h	(97)	76
THF/PPE	4-MeC₆H₄	65°	15 h	(86)	104
MeCN/LiClO₄	4-MeC₆H₄	81°	7 h	(89)	92
THF/PPE	2-(F₃C)C₆H₄	65°	15 h	(68)	75, 104
PPE, MW	2-(F₃C)C₆H₄	—	3 x 40 sec	(76)	34
EtOH/AcOH Yb(OTf)₃, MW	2-(F₃C)C₆H₄	120°	20 min	(49)	22
Neat/Yb(OTf)₃	4-(F₃C)C₆H₄	100°	20 min	(87)	83
Neat/Yb(III)-resin	4-(F₃C)C₆H₄	120°	48 h	(70)	35
THF/PPE	2-MeOC₆H₄	65°	15 h	(83)	104
THF/InCl₃	3-MeOC₆H₄	65°	9 h	(90)	90
EtOH/HCl	2-(F₂HCO)C₆H₄	78°	3 h	(—)	113, 114
EtOH/HCl	3,4-(OCH₂O)C₆H₃	78°	3 h	(49)	78
EtOH/HCl, MW	3,4-(OCH₂O)C₆H₃	—	3.5 min	(85)	97
EtOH/LaCl₃	3,4-(OCH₂O)C₆H₃	78°	5 h	(91)	111
EtOH/FeCl₃	3,4-(OCH₂O)C₆H₃	78°	4 h	(82)	84, 85
AcOH, MW	3,4-(OCH₂O)C₆H₃	—	2 min	(87)	79
Toluene/Amberlyst 15	3,4-(OCH₂O)C₆H₃	110°	10 h	(72)	79
MeCN/LiClO₄	3,4-(OCH₂O)C₆H₃	81°	7 h	(90)	92
EtOH/HCl, MW	3-MeOC₆H₃OH-4	—	4 min	(90)	97
EtOH/LaCl₃	3-MeOC₆H₃OH-4	78°	5 h	(92)	111
EtOH/FeCl₃	3-MeOC₆H₃OH-4	78°	4 h	(86)	84, 85
MeCN/Mn(OAc)₃	3-MeOC₆H₃OH-4	81°	4 h	(76)	93
EtOH/HCl	3-MeOC₆H₂OH-4-I-5	78°	3.5 h	(85)	131
EtOH/HCl	2,4-(MeO)₂C₆H₃	78°	4.5 h	(—)	33

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TABLE 1. REACTIONS INVOLVING UREA (*Continued*)

A. β-Keto Esters (*Continued*)

β-Keto Ester and Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.

C₆

	Ar	Temp	Time		
MeCN/TFA[b]	3,4,5-(MeO)₃C₆H₂	81°	2 h	(84)	11
MeCN/BiCl₃	3,4,5-(MeO)₃C₆H₂	81°	3.5 min	(95)	76
MeOH, US, (A) CAN	3,4,5-(MeO)₃C₆H₂	—	12 h	(90)	103
(B) Oxone®		—	3 h	(85)	103
EtOH/HCl	3,4,5-(MeO)₃C₆H₂	78°	8 h	(65)	134
EtOH/HCl, MW	2,4,6-(MeO)₃C₆H₂	—	14 min	(70)	97
Toluene/Zeolite	2,4,6-(MeO)₃C₆H₂	110°	12 h	(71)	95
EtOH/HCl	3,4-(EtO)₂C₆H₃	78°	12 min	(55)	132
MeCN/LiClO₄	3,4-(EtO)₂C₆H₃	81°	10 min	(90)	92

	Temp	Time		
AcOH/HCl	118°	8 h	(60)	135
EtOH/HCl, MW	—	3 min	(96)	97
THF/PPE	65°	15 h	(75)	75, 104
MeCN/TFA[b]	81°	6 h	(82)	11
EtOH/HCl, MW, (A) reflux	78°	3 h	(54)	100
(B) superheating	96°	3 h	(75)	100
(C) open vessel	—	15 x 20 sec	(78)	100
Neat/HCl, open vessel, (A) MW	—	15 x 20 sec	(53)	100
(B) thermal	120°	30 min	(50)	100
AcOH, MW	—	3 min	(85)	79
Toluene/Amberlyst 15	110°	13 h	(78)	79
EtOH/HCl, MW	120°	10 min	(52)	22
MeOH, US, (A) CAN	—	3 h	(90)	103
(B) Oxone®	—	4.5 h	(92)	103
MeCN/LiClO₄	81°	8 h	(87)	92
MeCN/Mn(OAc)₃	81°	3.5 h	(94)	93

THF/PPE, 65°, 15 h		(92)	75, 104

TABLE 1. REACTIONS INVOLVING UREA (*Continued*)

A. β-Keto Esters (*Continued*)
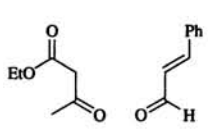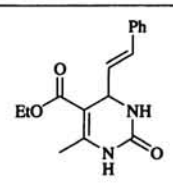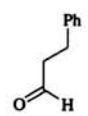
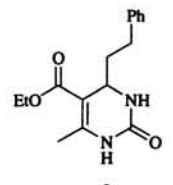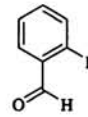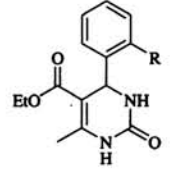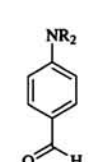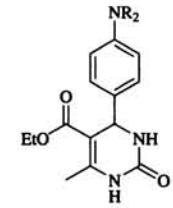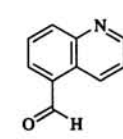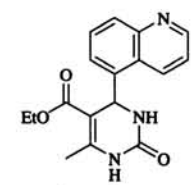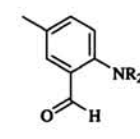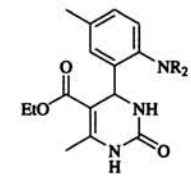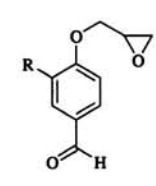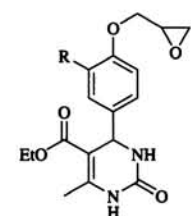| β-Keto Ester and Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.

C₆

	EtOH/HCl, 78°, 3-6 h	(—)	1, 121
	Neat/KSF-clay, 130°, 48 h	(70)	82
	Neat/Yb(OTf)₃, 100°, 20 min	(81)	83
	THF/InCl₃, 65°, 9 h	(90)	90
	MeCN/BiCl₃, 6 h	(90)	76
	MeOH, US, (A) CAN	(85)	103
	(B) Oxone®	(82)	103
	MeCN/LiClO₄, 81°, 7 h	(83)	92

MeCN/LiClO₄, 81°, 7 h (81) 92

MeOH/HCl, 65°, 15 h

R	
vinyl	(74)	136, 137
allyl	(39)	136

		R	Temp	Time		
EtOH/HCl		Me	78°	3 h	(65)	138, 139
H₂O, pH = 1		Me	rt	12 h	(10)	80
MeOH, US, (A) CAN		Me	—	4 h	(88)	103
(B) Oxone®		Me	—	6 h	(70)	103
Toluene/Zeolite		Me	110°	12 h	(63)	95
EtOH/HCl		Et	78°	3 h	(72)	132
EtOH/HCl		CH₂CH₂Cl	78°	3 h	(33)	122

EtOH/HCl, 78°, 3 h (27) 122

EtOH/HCl, 78°, 3 h

R	
Me	(34)	122
CH₂CH₂Cl	(39)	

EtOH/HCl, 78°, 15-18 h

R	
H	(38)	140
MeO	(—)	

48

49

TABLE 1. REACTIONS INVOLVING UREA (Continued)

A. β-Keto Esters (Continued)

β-Keto Ester and Aldehyde	Conditions	Product(s) and Yield(s) (%)							Refs.

C₆

EtOH/HCl, 78°, 15-18 h (—) 140

		R¹	R²	R³	Temp	Time		
EtOH/HCl		MeO	MeO	Et	78°	13-15 h	(49)	141
EtOH/HCl		MeO	EtO	Et	78°	13-15 h	(50)	141
EtOH/HCl		MeO	MeO	Pr	78°	13-15 h	(53)	141
EtOH/HCl		EtO	MeO	Et	78°	13-15 h	(49)	141
Neat/inorganic support, MW,		EtO	MeO	Et				
(A) SiO₂					—	14 min	(80)	98
(B) Al₂O₃ (neutral)					—	12 min	(82)	98
(C) Al₂O₃ (basic)					—	12 min	(85)	98
(D) Al₂O₃ (acidic)					—	10 min	(89)	98
EtOH/HCl		MeO	EtO	Pr	78°	13-15 h	(40)	141
EtOH/HCl		EtO	MeO	Pr	78°	13-15 h	(48)	141
Neat/inorganic support, MW,		EtO	MeO	Pr				
(A) SiO₂					—	14 min	(75)	98
(B) Al₂O₃ (neutral)					—	12 min	(80)	98
(C) Al₂O₃ (basic)					—	12 min	(82)	98
(D) Al₂O₃ (acidic)					—	10 min	(90)	98
EtOH/HCl		EtO	EtO	Et	78°	13-15 h	(44)	141
EtOH/HCl		EtO	EtO	Pr	78°	13-15 h	(54)	141

	Temp	Time		
EtOH/HCl	78°	3 h	(—)	33
MeCN/BiCl₃	81°	5 h	(91)	76
MeCN/LiClO₄	81°	8 h	(87)	92

	Temp	Time		
EtOH/HCl	78°	3 h	(—)	33
AcOH, MW	—	3 min	(88)	79
Toluene/Amberlyst 15	110°	11 h	(77)	79
MeOH, US,				
(A) CAN	—	4.5 h	(84)	103
(B) Oxone®	—	6 h	(78)	103

MeOH/H₂O, 2M HCl, rt, 3 d (—) 142

EtOH/HCl, 78°, 3 h (—) 33

TABLE 1. REACTIONS INVOLVING UREA (*Continued*)

A. β-Keto Esters (*Continued*)

β-Keto Ester and Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C₆			

C₆
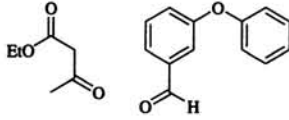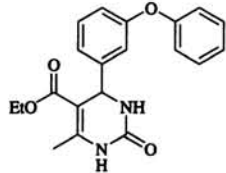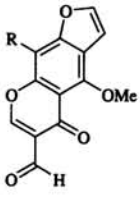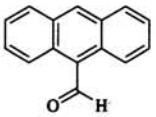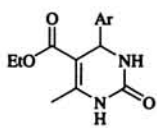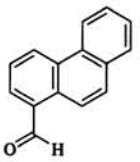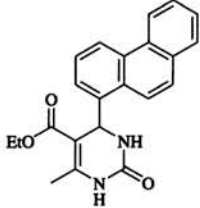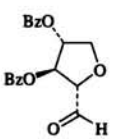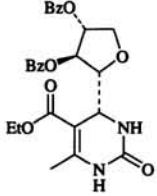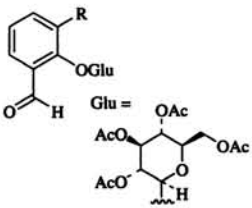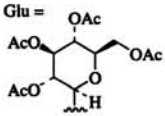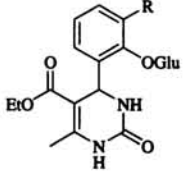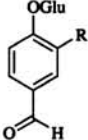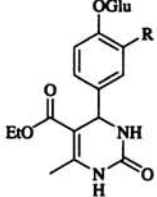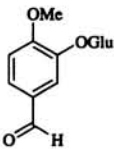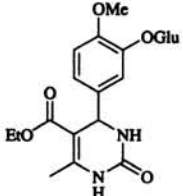
	MeCN/LiClO₄, 81°, 6 h	(90)	92
	EtOH/HCl, 78°, 10 h	R — H (65), MeO (65)	116
	MeCN/LiClO₄, 81°, 12 h	Ar = 9-anthracenyl (81)	92
	EtOH/HCl, 78°, 3 h	(28)	122
	EtOH/HCl, 78°, 5 h	(58)	12
	EtOH, 78°, 20 h	R — H (—), EtO (—)	143
	EtOH, 78°, 20 h	R — H (—), NO₂ (—), MeO (—), EtO (—)	143
	EtOH, 78°, 20 h	(—)	143

TABLE 1. REACTIONS INVOLVING UREA (*Continued*)

A. β-Keto Esters (*Continued*)

β-Keto Ester and Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.

C₆

	EtOH, 78°, 5 h	(—)	16
	THF/BF₃•OEt₂/CuCl/AcOH, 65°, 24 h	(63)	20
	EtOH, 78°, 15 h	(—)	15
	THF/BF₃•OEt₂/CuCl/AcOH, 65°, 24 h	(60)	20

EtOH/HCl, 40°, 24 h

Ar	
2-furyl	(43)
Ph	(62)
4-HOC₆H₄	(52)
4-MeOC₆H₄	(57)

23

1. EtOH/HCl, 78°, 6 h; or THF/PPE, 65°, 15 h
2. Toluene/*p*-TsOH, 110°, 6 h

(62) 9

MeOH, US,
(A) CAN
(B) Oxone®

Ar		Time	
4-MeC₆H₄	(A)	5 h	(88)
	(B)	8 h	(81)
4-MeOC₆H₄	(A)	4 h	(88)
	(B)	5 h	(80)
3,4-(OCH₂O)C₆H₃	(A)	4.5 h	(90)
	(B)	4 h	(85)

103

EtOH/HCl, 78°, 5 h

Ar	
Ph	(49)
4-O₂NC₆H₄	(60)
4-BrC₆H₄	(44)

144

54

55

TABLE 1. REACTIONS INVOLVING UREA (*Continued*)
A. β-Keto Esters (*Continued*)

β-Keto Ester and Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.

C₇

Conditions	Ar	Temp	Time		Refs.
THF/BF₃•OEt₂/CuCl/AcOH	Ph	65°	8-18 h	(83)	10
EtOH/H₂SO₄	Ph	78°	18 h	(41)	10
THF/InCl₃	Ph	65°	7 h	(89)	90
THF/BF₃•OEt₂/CuCl/AcOH	4-ClC₆H₄	65°	8-18 h	(84)	10
EtOH/H₂SO₄	4-ClC₆H₄	78°	18 h	(56)	10
THF/InCl₃	4-ClC₆H₄	65°	6 h	(92)	90
THF/BF₃•OEt₂/CuCl/AcOH	4-O₂NC₆H₄	65°	8-18 h	(90)	10
EtOH/H₂SO₄	4-O₂NC₆H₄	78°	18 h	(44)	10
THF/InCl₃	4-O₂NC₆H₄	65°	6 h	(90)	90
THF/BF₃•OEt₂/CuCl/AcOH	3,4-F₂C₆H₃	65°	8-18 h	(82)	10
EtOH/H₂SO₄	3,4-F₂C₆H₃	78°	18 h	(61)	10
THF/BF₃•OEt₂/CuCl/AcOH	4-MeOC₆H₄	65°	8-18 h	(79)	10
EtOH/H₂SO₄	4-MeOC₆H₄	78°	18 h	(40)	10
THF/InCl₃	4-MeOC₆H₄	65°	8 h	(85)	90

Conditions		Refs.
1. EtOH/HCl, 78°, 6 h 2. Toluene/*p*-TsOH, 6 h	(64)	63

Conditions	Ar	Temp	Time		Refs.
THF/PPE	Ph	65°	15 h	(84)	75, 104
EtOH/Yb(OTf)₃, MW	Ph	120°	10 min	(50)	22
Neat/Yb(III)-resin	Ph	120°	48 h	(78)	35
PPE, MW	3-O₂NC₆H₄	—	3 x 40 sec	(94)	34
THF/PPE	3-O₂NC₆H₄	65°	15-24 h	(88)	48, 104
EtOH/Yb(OTf)₃, MW	3-O₂NC₆H₄	120°	10 min	(73)	22
Neat/Yb(III)-resin	4-O₂NC₆H₄	120°	48 h	(73)	35
AcOH/HCl	2-BrC₆H₃NO₂-5	118°	24 h	(66)	77
Neat/Yb(III)-resin	2-BrC₆H₄	120°	48 h	(70)	35
Neat/Yb(III)-resin	4-ClC₆H₄	120°	48 h	(64)	35
Neat/Yb(III)-resin	4-FC₆H₄	120°	48 h	(71)	35
Neat/Yb(III)-resin	3-MeOC₆H₄	120°	48 h	(73)	35
Neat/Yb(III)-resin	4-MeOC₆H₄	120°	48 h	(75)	35
EtOH/HCl	2-(CHF₂O)C₆H₄	78°	3 h	(—)	113, 114
Neat/Yb(III)-resin	4-(F₃C)C₆H₄	120°	48 h	(68)	35

C₈

Conditions		Refs.
EtOH/Yb(OTf)₃, MW, 120°, 10 min	(41)	22

TABLE 1. REACTIONS INVOLVING UREA (*Continued*)
A. β-Keto Esters (*Continued*)

β-Keto Ester and Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.

C8
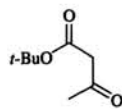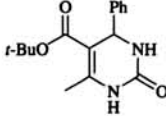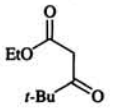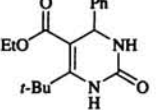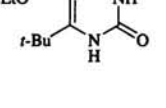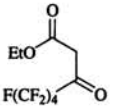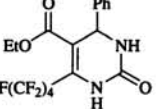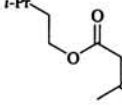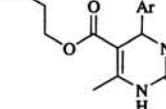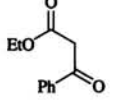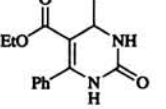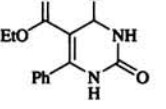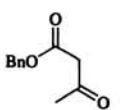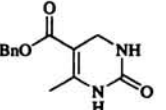
		Temp	Time		
EtOH/HCl		78°	3 h	(51)	145
PPE, MW		—	3 x 40 sec	(81)	34
THF/PPE		65°	15 h	(77)	104
EtOH/Yb(OTf)3, MW		120°	10 min	(51)	22

C9

(A) THF/BF3•OEt2/CuCl/AcOH, 65°, 8-18 h — A (85) — 10
(B) EtOH/H2SO4, 78°, 18 h — B (32) — 10

1. EtOH/HCl, 78°, 6 h
2. Toluene/*p*-TsOH, 6 h — (56) — 63

EtOH/HCl, 78°, 3 h — (—) — 113, 114

Ar = C6H4OCHF2-2

C11

EtOH/HCl, 78°, 18 h — (2) — 108

	R	Temp	Time		
AcOH/HCl	Me	118°	44 h	(21)	146
EtOH/HCl	Me	50°	48 h	(46)	145
EtOH/HCl	Ph	78°	3 h	(31)	145
THF/BF3•OEt2/CuCl/AcOH	Ph	65°	8-18 h	(70)	10
EtOH/H2SO4	Ph	78°	18 h	(10)	10
MeOH/KSF-clay	Ph	65°	—	(80)	120
THF/LaCl3	Ph	65°	9 h	(84)	90
MeCN/LiClO4	Ph	81°	10 h	(75)	92
AcOH/EtOH, Yb(OTf)3, MW	4-O2NC6H4	120°	20 min	(40)	22

AcOH/HCl, 118°, 5 h — (—) — 147

58

59

TABLE 1. REACTIONS INVOLVING UREA (*Continued*)

A. β-Keto Esters (*Continued*)

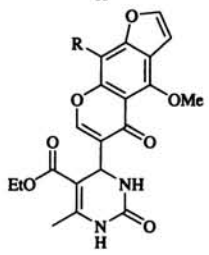| β-Keto Ester and Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.

C₁₁

	R	Temp	Time	
AcOH/HCl	H	118°	5 h	(25)
EtOH/HCl	Me	78°	5 h	(42)
EtOH/HCl	Ph	78°	3 h	(68)

Neat/Yb(III)-resin, 120°, 48 h

Ar	
Ph	(80)
4-FC₆H₄	(73)
3-MeOC₆H₄	(70)
4-MeOC₆H₄	(75)

35

C₁₆

EtOH/HCl

R	Temp	Time	
Me	50°	48 h	(40)
Ph	78°	8 h	(42)

145

C₃₁

THF/CuCl/BF₃•OEt₂/AcOH, 65°, 24 h

(92)

20

THF/CuCl/BF₃•OEt₂/AcOH, 65°, 24 h

(42)

20

THF/CuCl/BF₃•OEt₂/AcOH, 65°, 24 h

(35)

20

C₃₉

THF/CuCl/BF₃•OEt₂/AcOH, 65°, 24 h

(75)

20

a This structure is a protected aldehyde.

b The aldehyde was protected as an oxazinane.

c The aldehyde was protected as an oxazolidine.

TABLE 1. REACTIONS INVOLVING UREA (*Continued*)
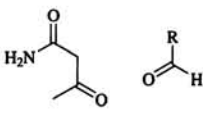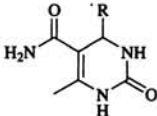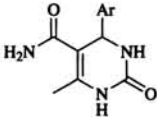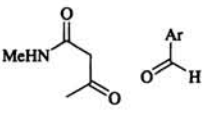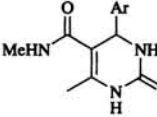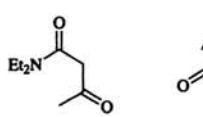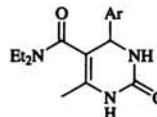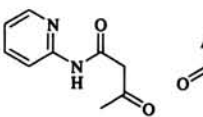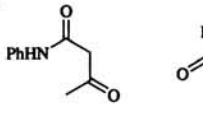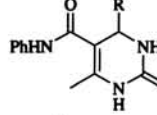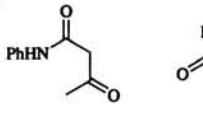
B. β-Keto Amides

β-Keto Amide and Aldehyde	Conditions	Product(s) and Yield(s) (%)		Refs.

C₄

MeOH/HCl, 65°

R	
Pr	(—)
i-Pr	(—)

148

Conditions	Ar	Yield	Refs.
EtOH/HCl, 78°, 5 h	Ph	(41)	106, 148
EtOH/HCl, 78°, 5 h	4-BrC₆H₄	(46)	106
EtOH/HCl, 78°, 5 h	3-O₂NC₆H₄	(39)	106
EtOH/HCl, 78°, 5 h	4-O₂NC₆H₄	(52)	106
EtOH/HCl, MW, 120°, 15 min	4-O₂NC₆H₄	(59)	22

C₅

EtOH/HCl, 78°, 3 h

Ar		149
Ph	(90)	
4-HOC₆H₄	(60)	
4-ClC₆H₄	(60)	
2-O₂NC₆H₄	(80)	
3-O₂NC₆H₄	(90)	
4-O₂NC₆H₄	(60)	
2,4-Cl₂C₆H₃	(90)	
3,4-Cl₂C₆H₃	(70)	
4-MeOC₆H₄	(60)	
3-MeOC₆H₃OH-2	(89)	
3,4-(OCH₂O)C₆H₃	(74)	
3,4-(MeO)₂C₆H₃	(60)	
3,4,5-(MeO)₃C₆H₂	(65)	

C₈

Conditions	Ar	Temp	Time	Yield	Refs.
AcOH	Ph	118°	10 h	(73)	106
AcOH	3-O₂NC₆H₄	118°	10 h	(81)	106
EtOH/HCl	4-O₂NC₆H₄	78°	5 h	(75)	106
EtOH/HCl	4-BrC₆H₄	78°	5 h	(65)	106
EtOH/AcOH, Yb(OTf)₃, MW	4-BrC₆H₄	120°	10 min	(66)	22

C₉

EtOH/HCl, 78°, 5 h

Ar		
Ph	(83)	
4-O₂NC₆H₄	(65)	106
4-BrC₆H₄	(51)	
4-Me₂NC₆H₄	(61)	
3,4,5-(MeO)₃C₆H₂	(66)	

I

AcOH, 118°, 10 h   **I** Ar = 3-O₂NC₆H₄ (49)   106

C₁₀

Conditions	R	Temp	Time	Yield	Refs.
MeOH/HCl	Pr	65°	—	(—)	148
MeOH/HCl	i-Pr	65°	—	(—)	148
AcOH	Ph	118°	10 h	(50)	106
MeOH/HCl	Ph	65°	—	(—)	148
EtOH/AcOH, MW	Ph	120°	20 min	(55)	22
AcOH	4-O₂NC₆H₄	118°	10 h	(64)	106
AcOH	4-BrC₆H₄	118°	10 h	(63)	106
AcOH	3-MeOC₆H₃OH-4	118°	10 h	(61)	106
EtOH/HCl, MW	3-MeOC₆H₃OH-4	100°	15 min	(28)	22
AcOH	4-Me₂NC₆H₄	118°	10 h	(89)	106

TABLE 1. REACTIONS INVOLVING UREA (*Continued*)

B. β-Keto Amides (*Continued*)

β-Keto Amide and Aldehyde	Conditions	Product(s) and Yield(s) (%)		Refs.
C₁₅	EtOH/HCl, 78°, 3-5 h	Ar		134
		Ph	(71)	
		4-FC₆H₄	(69)	
		4-ClC₆H₄	(66)	
		4-BrC₆H₄	(78)	
		4-O₂NC₆H₄	(63)	
		3,4-Cl₂C₆H₃	(70)	
		4-MeOC₆H₄	(60)	
		3,4,5-(MeO)₃C₆H₂	(62)	

TABLE 1. REACTIONS INVOLVING UREA (*Continued*)

C. β-Diketones

β-Diketone and Aldehyde	Conditions	Product(s) and Yield(s) (%)		Refs.
C₅		R		
	Piperidine, 170°, 40 min	H	(72)	118
	EtOH/HCl, 50°, 6 h	Me	(4)	150
	EtOH/HCl, 78°, 5 h	Et	(32)	151
	AcOH, 118°, 3 h		(—)	151
	THF/InCl₃, 65°, 8 h		(90)	90
	THF/InCl₃, 65°, 6 h		(93)	90
	EtOH/HCl, 78°, 3 h		(—)	13

TABLE 1. REACTIONS INVOLVING UREA (Continued)
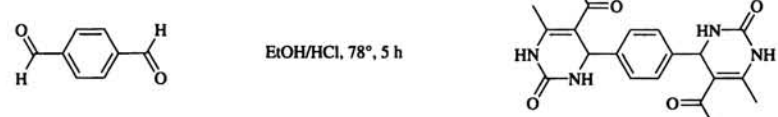
C. β-Diketones (Continued)

β-Diketone and Aldehyde	Conditions	Product(s) and Yield(s) (%)		Refs.

		Temp	Time		
EtOH/HCl		78°	3.5 h	(55)	151-153
Piperidine		170°	40 min	(64)	118
Neat/KSF-clay		130°	48 h	(74)	82
Neat/Yb(OTf)₃		100°	20 min	(94)	83
THF/InCl₃		65°	7 h	(94)	90
Ionic liquid (BMImBF₄)		100°	30 min	(99)	81
EtOH/Yb(OTf)₃		120°	10 min	(53)	22
MeCN/LiClO₄		81°	7 h	(88)	92
Neat/Yb(III)-resin		120°	48 h	(71)	35
DMF/ClSiMe₃,					
(A) urea added after 12 h		20°	14 h	(62)	126
(B) all components together		20°	2 h	(57)	126

	Ar	Temp	Time		
EtOH/HCl	2-HOC₆H₄	78°	2 h	(49)	151
EtOH/HCl	2-ClC₆H₄	78°	5 h	(32)	153
EtOH/HCl	3-ClC₆H₄	78°	5 h	(31)	153
EtOH/HCl	4-ClC₆H₄	78°	5 h	(37)	151, 153
EtOH/HCl	2-BrC₆H₄	78°	5 h	(25)	153
EtOH/HCl	3-BrC₆H₄	78°	5 h	(27)	153
Neat/Yb(III)-resin	4-FC₆H₄	120°	48 h	(70)	35
EtOH/HCl	3-O₂NC₆H₄	78°	3 h	(70)	151
Neat/Yb(OTf)₃	4-O₂NC₆H₄	100°	20 min	(90)	83
Ionic liquid (BMImBF₄)	4-O₂NC₆H₄	100°	30 min	(92)	81
EtOH/HCl	2-MeC₆H₄	78°	5 h	(34)	153
EtOH/HCl	3-MeC₆H₄	78°	5 h	(39)	153
EtOH/HCl	4-MeC₆H₄	78°	5 h	(38)	153
EtOH/HCl	2-MeOC₆H₄	78°	3 h	(40)	151, 153
EtOH/HCl	3-MeOC₆H₄	78°	5 h	(29)	153
THF/InCl₃	3-MeOC₆H₄	65°	9 h	(92)	90
Neat/Yb(III)-resin	3-MeOC₆H₄	120°	48 h	(65)	35
Neat/Yb(OTf)₃	4-MeOC₆H₄	100°	20 min	(91)	83
THF/InCl₃	4-MeOC₆H₄	65°	9 h	(91)	90
Neat/Yb(III)-resin	4-MeOC₆H₄	120°	48 h	(71)	35
EtOH/HCl	3-MeOC₆H₃OH-4	78°	3.5 h	(64)	151
EtOH/HCl	3,4-(MeO)₂C₆H₃	78°	1 h	(44)	151
EtOH/HCl	4-Me₂NC₆H₄	78°	3 h	(40)	151

	Conditions	Product		Refs.
	EtOH/HCl, 78°, 5 h		(78)	21

TABLE 1. REACTIONS INVOLVING UREA (*Continued*)

C. β-Diketones (*Continued*)
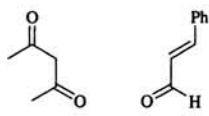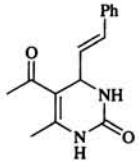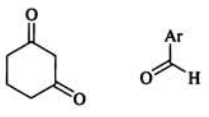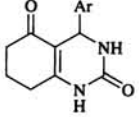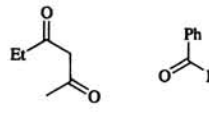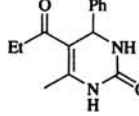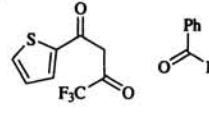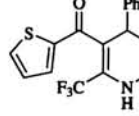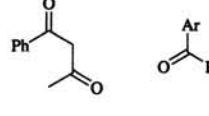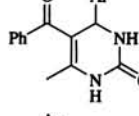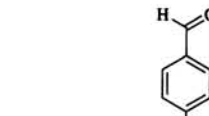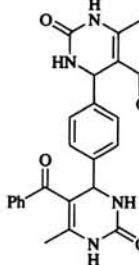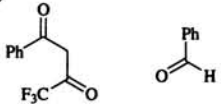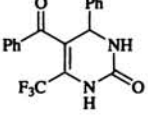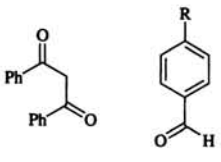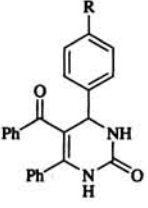
β-Diketone and Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.

C5

AcOH, 118°, 3 h   (—)   151

C6

EtOH/HCl, 78°, 20 h

Ar		
Ph	(46)	24, 25
2-FC6H4	(—)	24
2-ClC6H4	(80)	24, 154
3-ClC6H4	(62)	24, 25
4-ClC6H4	(54)	24, 25, 155
2-BrC6H4	(44)	24, 25
3-BrC6H4	(45)	24, 25
4-BrC6H4	(44)	24, 25
3-O2NC6H4	(50)	25
4-O2NC6H4	(46)	25
2,3-Cl2C6H3	(56)	24
2,4-Cl2C6H3	(50)	24
2,6-Cl2C6H3	(20)	24
3,4-Cl2C6H3	(61)	24
2-MeC6H4	(45)	24, 25, 155
3-MeC6H4	(57)	24
4-MeC6H4	(43)	24, 25
2-MeOC6H4	(30)	24, 25
3-MeOC6H4	(42)	24, 25
4-MeOC6H4	(48)	24, 25

EtOH/HCl, 78°, 3.5 h   (47)   152

C8

Neat/Yb(OTf)3, 100°, 20 min   (94)   83

C10

		Ar		
EtOH/HCl, 78°, 3.5 h		Ph	(—)	152
Neat/KSF-clay, 130°, 48 h		Ph	(74)	82
THF/InCl3, 65°, 9 h		Ph	(88)	90
THF/InCl3, 65°, 9 h		4-MeOC6H4	(90)	90

EtOH/HCl, 78°, 5 h   (71)   21

68

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TABLE 1. REACTIONS INVOLVING UREA (Continued)

C. β-Diketones (Continued)

β-Diketone and Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{10}$	Neat/Yb(OTf)$_3$, 100°, 20 min	(96)	83
C$_{15}$	BuOH/HCl, 118°, 3.5 h ^{a}	R H (60) Me (40)	152

^{a} These conditions are applied to the aldehyde and the bisureide of the starting β-diketone.

TABLE 1. REACTIONS INVOLVING UREA (Continued)

D. Other CH-Acidic Carbonyl Compounds

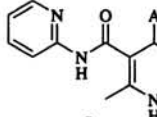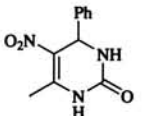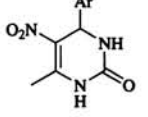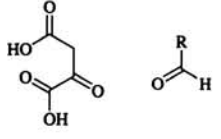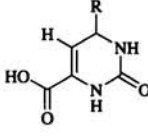| CH-Acidic Carbonyl Compound and Aldehyde	Conditions	Product(s) and Yield(s) (%)		Refs.
C$_3$	EtOH/LaCl$_3$, MW, 100°, 15 min	(83)		22
	EtOH/HCl, 78°, 6 h		Ar	
			Ph (91)	107, 156, 157
			4-HOC$_6$H$_4$ (82)	157
			2-O$_2$NC$_6$H$_4$ (26)	157
			3-O$_2$NC$_6$H$_4$ (67)	157
			2-ClC$_6$H$_4$ (79)	157
			4-ClC$_6$H$_4$ (82)	157
			4-MeOC$_6$H$_4$ (84)	107, 157
			2-(F$_3$C)C$_6$H$_4$ (65)	157
			2-(CHF$_2$O)C$_6$H$_4$ (43)	157
			2-(CHF$_2$S)C$_6$H$_4$ (61)	157
			3,4-(OCH$_2$O)C$_6$H$_3$ (45)	157
			3,4,5-(MeO)$_3$C$_6$H$_2$ (80)	107, 157
C$_4$	(A) EtOH/H$_2$SO$_4$, 78°, 12 h (B) TFA/DCE, 82°, 12 h		R (A/B) 2-Thienyl (51/72) Ph (55/88) cyclohexyl (50/75) 3-O$_2$NC$_6$H$_4$ (73/99) 2,3-Cl$_2$C$_6$H$_3$ (34/96) 3,5-(MeO)$_2$C$_6$H$_3$ (62/75)	68

TABLE 1. REACTIONS INVOLVING UREA (*Continued*)

D. Other CH-Acidic Carbonyl Compounds (*Continued*)
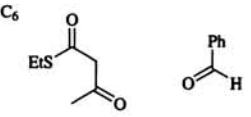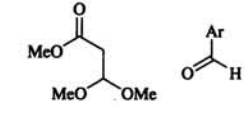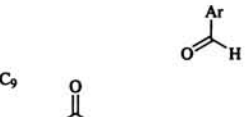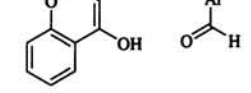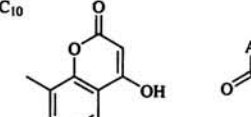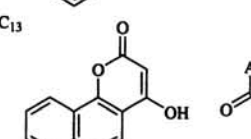
CH-Acidic Carbonyl Compound and Aldehyde	Conditions	Product(s) and Yield(s) (%)		Refs.
C₆	EtOH/HCl, 78°		(85)	158
	EtOH/Yb(OTf)₃, MW, 120°, 20 min		Ar Ph (65) 3,4-F₂C₆H₃ (70) 3,4,5-(MeO)₃C₆H₂ (35)	22
Ar = 3,4-F₂C₆H₃	THF/BF₃•OEt₂/CuCl/AcOH, 65°, 8-24 h	**I** (—)		27
C₉	MeOH/HCl, 65°, 4 h		Ar Ph (59) 4-MeC₆H₄ (64) 4-MeOC₆H₄ (51) 3,4-(MeO)₂C₆H₃ (53)	26
C₁₀	MeOH/HCl, 65°, 4 h		Ar Ph (66) 4-MeC₆H₄ (70) 4-MeOC₆H₄ (62) 3,4-(MeO)₂C₆H₃ (58)	26
C₁₃	MeOH/HCl, 65°, 4 h		Ar Ph (46) 4-MeC₆H₄ (51) 4-MeOC₆H₄ (48) 3,4-(MeO)₂C₆H₃ (50)	26

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TABLE 2. REACTIONS INVOLVING SUBSTITUTED UREAS
A. β-Keto Esters
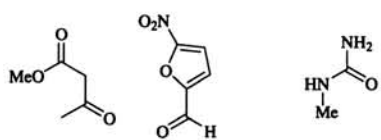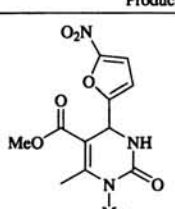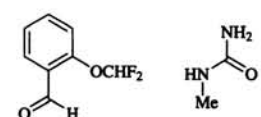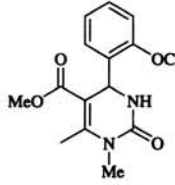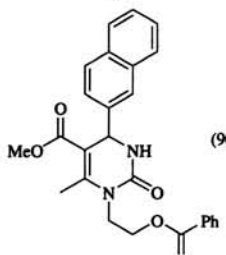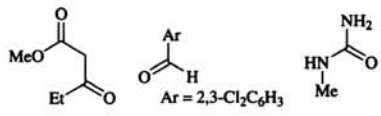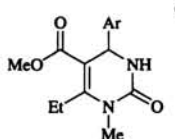
β-Keto Ester, Aldehyde, and Urea	Conditions	Product(s) and Yield(s) (%)	Refs.
C₅			
	MeOH/HCl, 65°, 3 h	(—)	159
	EtOH/HCl, 78°, 8 h	(—)	113, 114
	THF/HCl, 25°, 1-2 d	(90)	38
C₆	EtOH/Yb(OTf)₃, MW, 120°, 10 min	(26)	22

TABLE 2. REACTIONS INVOLVING SUBSTITUTED UREAS (Continued)

A. β-Keto Esters (Continued)

β-Keto Ester, Aldehyde, and Urea	Conditions	Product(s) and Yield(s) (%)	Refs.
C₆	EtOH/HCl, 78°, 2 h	(—)	160
	EtOH/HCl, 78°, 6 h	(17)	108
	EtOH/HCl, 78°, 3 h	R — Me (75); Et (70)	125
	EtOH/HCl, 78°, 3 h	(—)	33

	Conditions	Temp	Time		Refs.
	EtOH/HCl	78°	3 h	(74)	33, 127, 161, 16:
	MeOH/H₂O, HCl	rt	3 d	(—)	6
	THF/PPE	65°	15-24 h	(95)	48, 75, 104
	PPE, MW	—	3 x 40 sec	(89)	34
	DMF/ClSiMe₃,				
	(A) urea added after 12 h	20°	14 h	(73)	48
	(B) all components together	20°	2 h	(51)	126

	Conditions	Product	Ar		Refs.
	THF/PPE, 65°, 15-24 h	I	3-O₂NC₆H₄	(86)	48, 104
			2,3-Cl₂C₆H₃	(93)	48

	Conditions	Product	Ar	Refs.
	EtOH/HCl, 78°, 3 h	I (—)	2-HOC₆H₄	33
			3-O₂NC₆H₄	
			2,4-Cl₂C₆H₃	
			2,4-(O₂N)₂C₆H₃	
			3,5-(O₂N)₂C₆H₃	
			4-(NC)C₆H₄	
			3,4-(OCH₂O)C₆H₃	
			4-(F₃C)C₆H₄	
			3-MeOC₆H₄	
			4-MeOC₆H₄	
			2,4-Me₂C₆H₃	
			2,3-(MeO)₂C₆H₃	
			2,4-(MeO)₂C₆H₃	
			4-i-PrC₆H₄	
			1-naphthyl	
			2-naphthyl	

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75

β-Keto Ester, Aldehyde, and Urea	Conditions	Product(s) and Yield(s) (%)		Refs.

C₆

| | EtOH/HCl, 78°, 3 h | | Ar
5-O₂N-naphthyl
2-MeO-naphthyl
4-MeO-naphthyl
9-phenanthryl
9-anthryl
1-pyrenyl | 33 |

		R	Temp	Time		
	EtOH/HCl	Et	78°	3 h	(49)	161
	EtOH/AcOH, Yb(OTf)₃, MW	Et	120°	10 min	(18)	22
	EtOH/HCl	n-Bu	78°	3 h	(55)	161
	EtOH/HCl	n-hexyl	78°	3 h	(47)	161
	EtOH/HCl, MW	4-FC₆H₄	—	12 x 30 sec	(82)	30

Ar = 1-naphthyl

		R	Temp	Time		
	EtOH/Yb(OTf)₃, MW	allyl	120°	10 min	(41)	22
	EtOH/HCl	allyl	78°	3 h	(—)	33
	EtOH/HCl	Ph	78°	3 h	(—)	33
	EtOH/HCl	3,5-Me₂C₆H₃	78°	3 h	(—)	33

| | MeOH/HCl, 65°, 6 h | (52) | 29 |

		R	Temp	Time		
	THF/PPE	H	65°	15 h	(91)	75, 104
	EtOH/AcOH, Yb(OTf)₃, MW	H	120°	10 min	(43)	22
	THF/PPE	vinyl	65°	24 h	(47)	136

| | THF/HCl, 25°, 1-2 d | | Ar
Ph (74)
4-MeOC₆H₄ (78)
2-naphthyl (62) | 38 |

C₇

| | PPE/THF, 65°, 15-24 h | (85) | 48, 104 |
| | EtOH/AcOH, Yb(OTf)₃, MW, 120°, 10 min | (51) | 22 |

76

77

β-Keto Ester, Aldehyde, and Urea	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_7$	EtOH/AcOH, Yb(OTf)$_3$, MW, 120°, 10 min	(34)	22
	EtOH/HCl, 78°, 3 h	(—)	113, 114
	THF/HCl, 25°, 1-2 d	Ar Ph (73) 4-MeOC$_6$H$_4$ (38) 2-naphthyl (66)	41
C$_8$	EtOH/HCl, 78°, 3 h	(—)	145
C$_9$	EtOH/HCl, 78°, 3 h	(—)	113, 114
	EtOH/HCl, 78°, 3 h	(—) Ar 1-naphthyl 9-phenanthryl	33
	EtOH/HCl, 78°	(74)	158
C$_{11}$	EtOH/HCl, 50°, 48 h	R Me (—)	145
	EtOH/HCl, 50°, 20 h	Ph (—)	145, 162
	Neat/KSF-clay, 130°, 48 h	Ph (75)	82

78

79

TABLE 2. REACTIONS INVOLVING SUBSTITUTED UREAS (*Continued*)

A. β-Keto Esters (*Continued*)

β-Keto Ester, Aldehyde, and Urea	Conditions	Product(s) and Yield(s) (%)	Refs.

C11

EtOH/HCl

R	Temp	Time	
H	78°	3.5 h	(—)
Me	50°	48 h	(—)

145

Ar	Temp	Time	
Ph	78°	3 h	(64)
Ph	65°	15-24 h	(93)
2,3-Cl$_2$C$_6$H$_3$	65°	15 h	(93)
2,3-Cl$_2$C$_6$H$_3$	120°	10 min	(25)
3,4-F$_2$C$_6$H$_3$	78°	5 h	(79)
2-naphthyl	65°	20 h	(70)

Conditions	Refs.
EtOH/HCl	145
PPE/THF	48, 104
PPE/THF	75, 104
EtOH/AcOH, Yb(OTf)$_3$, MW	22
EtOH/HCl	27
MeOH/tartaric acid	47

C12

THF/HCl, 25°, 1-2 d

Ar	
Ph	(56)
4-MeOC$_6$H$_4$	(18)
2-naphthyl	(33)

38

C14

Ar = 2-naphthyl

MeOH/tartaric acid, 65°, 20 h

(53)

47

C14

Ar = 2-naphthyl

EtOH/HCl, 78°, 3 h

(—)

33

Ar = 1-naphthyl

EtOH/HCl, 78°, 3 h

(—)

33

Ar = 1-naphthyl

EtOH/HCl, 78°, 3 h

(—)

33

C16

EtOH/HCl

R	Temp	Time	
Me	50°	48 h	(45)
Ph	50°	24 h	(50)

145

a This structure is a protected aldehyde.

TABLE 2. REACTIONS INVOLVING SUBSTITUTED UREAS (*Continued*)
B. β-Keto Amides

β-Keto Amide, Aldehyde, and Urea	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_4$			
	EtOH/HCl, 78°, 5 h	Ph (85)	163
	EtOH/HCl, 78°, 3 h	1-naphthyl (—)	33
C$_6$ Ar = 1-naphthyl	EtOH/HCl, 78°, 3 h	(—)	33
C$_8$	EtOH/HCl, 78°, 3 h	Me (75) Et (52) *n*-Bu (45) *n*-hexyl (41)	161
C$_{11}$ Ar = 1-naphthyl	EtOH/HCl, 78°, 3 h	(—)	33

82

TABLE 2. REACTIONS INVOLVING SUBSTITUTED UREAS (*Continued*)
C. β-Diketones

β-Diketone, Aldehyde, and Urea	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_5$	EtOH/HCl, 50°, 6 h	(3)	150
C$_6$	EtOH/HCl, 78°, 20 h	(57)	24, 25

83

TABLE 2. REACTIONS INVOLVING SUBSTITUTED UREAS (*Continued*)

D. Other CH-Acidic Carbonyl Compounds
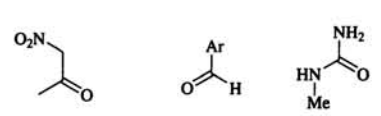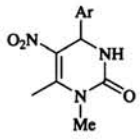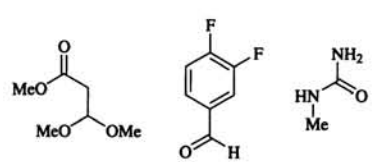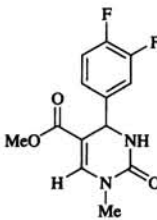
CH-Acidic Carbonyl Compound, Aldehyde, and Urea	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_3$			
	EtOH/HCl, 78°, 6 h	Ar: Ph (64); 2-O$_2$NC$_6$H$_4$ (59); 3-O$_2$NC$_6$H$_4$ (79); 2-ClC$_6$H$_4$ (75); 2-(CF$_3$)C$_6$H$_4$ (49); 3,4,5-(MeO)$_3$C$_6$H$_2$ (75)	156, 157 157 157 157 157 157
C$_6$			
	THF/BF$_3$•OEt$_2$/CuCl/AcOH, 65°, 8-24 h	(—)	27

TABLE 3. REACTIONS INVOLVING THIOUREAS

A. β-Keto Esters
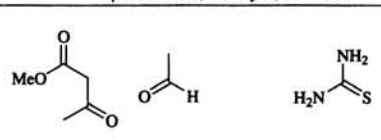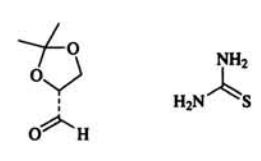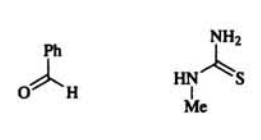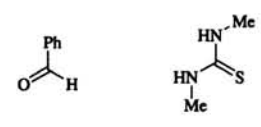
β-Keto Ester, Aldehyde, and Urea	Conditions	Product(s) and Yield(s) (%)	Refs.
C₅			
	2-Propanol/EtOH/HCl, rt	(45)	164
	EtOH, 70-80°, 55 h	(27)	19
	EtOH, 78°, 12 h	(—)	18
	AcOH/HCl, 118°, 6-8 h	(71)	165
	AcOH/HCl, 118°, 6-8 h	(60)	165

TABLE 3. REACTIONS INVOLVING THIOUREAS (*Continued*)

A. β-Keto Esters (*Continued*)

β-Keto Ester, Aldehyde, and Urea	Conditions	Product(s) and Yield(s) (%)	Refs.

	Conditions	Temp	Ar	Time		Refs.
	EtOH/HCl	78°	Ph	3-8 h	(88)	165-170
	2-Propanol/HCl	rt	Ph	24 h	(—)	164
	EtOH/HCl	78°	2-FC$_6$H$_4$	3-4 h	(—)	177
	EtOH/HCl	78°	2-ClC$_6$H$_4$	8 h	(50)	166, 168, 169
	EtOH/HCl	78°	3-ClC$_6$H$_4$	8 h	(76)	166-169
	EtOH/HCl	78°	4-ClC$_6$H$_4$	8 h	(79)	167-169
	EtOH/HCl	78°	2-BrC$_6$H$_4$	8 h	(75)	167
	EtOH/HCl	78°	4-BrC$_6$H$_4$	3-10 h	(79)	167-169, 171
	2-Propanol/HCl	rt	4-BrC$_6$H$_4$	24 h	(—)	164
	EtOH/HCl	78°	2-HOC$_6$H$_3$Br-5	12 h	(48)	168
	2-Propanol/HCl	rt	2-ClC$_6$H$_3$F-6	24 h	(—)	164
	2-Propanol/HCl	rt	3,4-Cl$_2$C$_6$H$_3$	24 h	(—)	164
	EtOH/HCl	78°	2-O$_2$NC$_6$H$_4$	8-48 h	(73)	166-168
	EtOH/HCl	78°	3-O$_2$NC$_6$H$_4$	3-12 h	(73)	166-168
	2-Propanol/HCl	rt	3-O$_2$NC$_6$H$_4$	24 h	(—)	164
	EtOH/HCl	78°	4-O$_2$NC$_6$H$_4$	9 h	(68)	168, 169
	EtOH/HCl	78°	2-MeC$_6$H$_4$	—	(—)	166
	EtOH/HCl	78°	3-MeC$_6$H$_4$	—	(—)	166
	EtOH/HCl	78°	4-MeC$_6$H$_4$	3-9 h	(73)	167-169, 171, 172
	2-Propanol/HCl	rt	4-MeC$_6$H$_4$	24 h	(—)	164
	EtOH/LaCl$_3$, MW	120°	4-MeC$_6$H$_4$	10 min	(58)	22
	EtOH/HCl	78°	2-MeOC$_6$H$_4$	1-3 h	(87)	166, 168, 169
	2-Propanol/HCl	rt	2-MeOC$_6$H$_4$	24 h	(—)	164
	EtOH/HCl	78°	3-MeOC$_6$H$_4$	—	(—)	166
	EtOH/HCl	78°	4-MeOC$_6$H$_4$	3-9 h	(75)	167-169, 171, 172
	2-Propanol/HCl	rt	4-MeOC$_6$H$_4$	24 h	(—)	164
	EtOH/HCl	78°	4-(MeCONH)C$_6$H$_4$	3 h	(77)	168, 169
	2-Propanol/EtOH/HCl	rt	4-Me$_2$NC$_6$H$_4$	24 h	(—)	164
	2-Propanol/HCl	rt	3,4,5-(MeO)$_3$C$_6$H$_2$	24 h	(—)	164

	Conditions	Product(s) and Yield(s) (%)	Refs.
	EtOH/HCl, 78°, 10 h	(95)	116

TABLE 3. REACTIONS INVOLVING THIOUREAS (*Continued*)

A. β-Keto Esters (*Continued*)

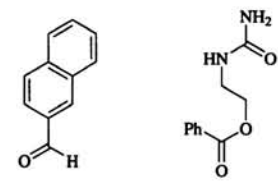| β-Keto Ester, Aldehyde, and Urea	Conditions	Product(s) and Yield(s) (%)	Refs.

C₅

EtOH/HCl, 78°, 10 h

R	
H	(70)
MeO	(70)

116

C₆

EtOH/HCl, 78°, 3 h

Ar		
2-MeC₆H₄	(32)	173
3-MeC₆H₄	(27)	173
2-MeOC₆H₄	(71)	167, 173
3-MeOC₆H₄	(38)	173

MeCN/TFA, reflux

R	Time		
H	1.5 h	(93)	11
Me	8 h	(84)	

EtOH/HCl, 78°, 3 h

R		
Me	(22)	121, 164
i-Pr	(21)	121

	Temp	Time			
PPE/EtOH, MW	—	5 x 10 sec	3-HOC₆H₄	(60)	105
EtOH/Yb(OTf)₃, MW	120°	20 min	3-HOC₆H₄	(45)	22
EtOH/HCl	78°	—	4-HOC₆H₄	(—)	139
EtOH/HCl, MW	—	12 x 30 sec	4-FC₆H₄	(81)	30
EtOH/HCl	78°	3 h	4-ClC₆H₄	(73)	99, 133, 139, 174, 175
2-Propanol/HCl	rt	24 h	4-BrC₆H₄	(—)	164
EtOH/HCl	78°	3 h	4-BrC₆H₄	(76)	175
EtOH/HCl, MW	—	4 min	2-O₂NC₆H₄	(50)	97
EtOH/HCl	78°	8 h	3-O₂NC₆H₄	(24)	170
EtOH/HCl, MW	—	8 x 30 sec	3-O₂NC₆H₄	(78)	30
PPE, MW	—	3 x 40 sec	3-O₂NC₆H₄	(71)	34
EtOH/HCl, MW	—	15 x 20 sec	3-O₂NC₆H₄	(50)	100
Neat/HCl,			3-O₂NC₆H₄		
(A) MW	—	15 x 20 sec		(53)	100
(B) thermal	120°	30 min		(50)	100
EtOH/HCl	78°	3 h	2,4-F₂C₆H₃	(75)	130
EtOH/HCl, MW	—	3.5 min	2,3-Cl₂C₆H₃	(90)	97
EtOH/HCl	78°	3 h	3,4-Cl₂C₆H₄	(71)	134, 175
2-Propanol/EtOH/HCl	rt	24 h	3,4-Cl₂C₆H₄	(—)	164
2-Propanol/HCl	rt	24 h	3-O₂NC₆H₃Cl-4	(—)	164
2-Propanol/HCl	rt	24 h	2-FC₆H₃Cl-6	(—)	164
EtOH/HCl	78°	—	2-FC₆H₃Cl-6	(—)	99, 133

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TABLE 3. REACTIONS INVOLVING THIOUREAS (*Continued*)

A. β-Keto Esters (*Continued*)

β-Keto Ester, Aldehyde, and Urea	Conditions	Product(s) and Yield(s) (%)				Refs.

C₆

			Temp	Time		
	EtOH/HCl		78°	2-8 h	(76)	33, 99, 127, 139, 160, 170, 174, 176
	MeOH/H₂O, HCl		rt	3 d	(70)	177
	MeOH/H₂O, 2M HCl		rt	24 h	(80)	178
	EtOH/HCl, MW		—	3 min	(90)	97
	2-Propanol/HCl		rt	18 h	(60)	164
	Neat/inorganic support, MW,					
	(A) SiO₂		—	12 min	(62)	98
	(B) Al₂O₃ (neutral)		—	10 min	(85)	98
	(C) Al₂O₃ (basic)		—	10 min	(85)	98
	(D) Al₂O₃ (acidic)		—	9 min	(92)	98
	PPE, MW		—	3 x 40 sec	(82)	34
	MeCN/TFA[b]		reflux	4 h	(95)	11
	EtOH/LaCl₃		78°	5 h	(96)	111
	THF/InCl₃		65°	9 h	(91)	90
	EtOH/HCl, MW,					
	(A) reflux		78°	3 h	(33)	100
	(B) superheating		96°	3 h	(35)	100
	(C) open vessel		—	15 x 20 sec	(58)	100
	Neat/HCl, open vessel,					
	(A) MW		—	15 x 20 sec	(62)	100
	(B) thermal		120°	30 min	(67)	100
	EtOH/AcOH, LaCl₃, MW		120°	20 min	(56)	22
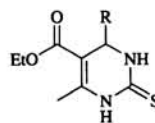
		R	Temp	Time		
	EtOH/HCl	2-furyl	78°	8 h	(53)	179
	MeOH/HCl	3-MeC₆H₄	rt	3 d	(70)	177
	EtOH/HCl, MW	3-MeC₆H₄	—	3.5 min	(88)	97
	2-Propanol/EtOH/HCl	4-MeC₆H₄	rt	24 h	(—)	164
	EtOH/HCl	4-MeC₆H₄	78°	3 h	(—)	176
	AcOH	2-MeOC₆H₄	118°	—	(—)	180
	THF/InCl₃	3-MeOC₆H₄	65°	9 h	(90)	90
	MeOH/HCl (1:1)	4-MeOC₆H₄	rt	3 d	(70)	177
	EtOH/HCl	4-MeOC₆H₄	78°	3 h	(75)	174
	EtOH/HCl, MW	4-MeOC₆H₄	—	3 min	(99)	97
	2-Propanol/HCl	4-MeOC₆H₄	rt	24 h	(—)	164
	Neat/inorganic support, MW,					
	(A) SiO₂	4-MeOC₆H₄	—	12 min	(85)	98
	(B) Al₂O₃ (neutral)	4-MeOC₆H₄	—	13 min	(86)	98
	(C) Al₂O₃ (basic)	4-MeOC₆H₄	—	10 min	(90)	98
	(D) Al₂O₃ (acidic)	4-MeOC₆H₄	—	10 min	(98)	98
	MeCN/TFA[b]	4-MeOC₆H₄	reflux	4 h	(87)	11
	EtOH/LaCl₃	4-MeOC₆H₄	78°	5 h	(85)	111
	EtOH/HCl	2,5-(MeO)₂C₆H₃	78°	3 h	(70)	181
	EtOH/HCl	4-Me₂NC₆H₄	78°	3 h	(65)	132, 139, 174,
	2-Propanol/HCl	4-Me₂NC₆H₄	rt	24 h	(—)	175
	EtOH/HCl	4-Et₂NC₆H₄	78°	3 h	(54)	164
	EtOH/HCl	β-styryl	78°	6 h	(78)	132
						121

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TABLE 3. REACTIONS INVOLVING THIOUREAS (*Continued*)

A. β-Keto Esters (*Continued*)
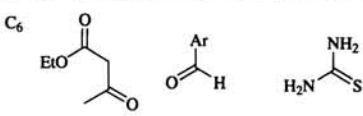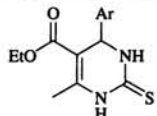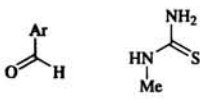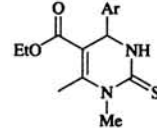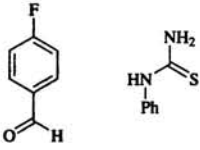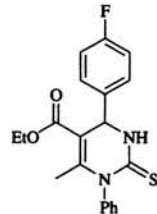
β-Keto Ester, Aldehyde, and Urea	Conditions	Product(s) and Yield(s) (%)				Refs.

		Ar	Temp	Time		
	EtOH/HCl	3-MeO-4-HOC₆H₂Br-5	78°	3 h	(85)	131
	EtOH/HCl	3,4-(MeO)₂C₆H₃	78°	3 h	(48)	132
	MeOH/H₂O, HCl	3,4-(MeO)₂C₆H₃	rt	3 d	(—)	177
	EtOH/HCl, MW	3,4-(MeO)₂C₆H₃	—	3 min	(90)	97
	EtOH/HCl	3,4-(EtO)₂C₆H₃	78°	—	(/69)	132, 175
	2-Propanol/HCl	3,4,5-(MeO)₃C₆H₂	rt	24 h	(—)	164
	EtOH/HCl	3,4,5-(MeO)₃C₆H₂	78°	3 h	(77)	134
	EtOH/HCl	2-EtO-4-MeOC₆H₂Et-5	78°	13-15 h	(54)	141
	Neat/inorganic support, MW,	2-EtO-4-MeOC₆H₂Et-5				
	(A) SiO₂		—	13 min	(73)	98
	(B) Al₂O₃ (neutral)		—	12 min	(79)	98
	(C) Al₂O₃ (basic)		—	12 min	(80)	98
	(D) Al₂O₃ (acidic)		—	11 min	(87)	98
	EtOH/HCl	2-EtO-4-MeOC₆H₂Pr-5	78°	13-15 h	(48)	141
	Neat/inorganic support, MW,	2-EtO-4-MeOC₆H₂Pr-5				
	(A) SiO₂		—	14 min	(75)	98
	(B) Al₂O₃ (neutral)		—	12 min	(80)	98
	(C) Al₂O₃ (basic)		—	12 min	(82)	98
	(D) Al₂O₃ (acidic)		—	10 min	(90)	98
	EtOH/HCl	2,4-(MeO)₂C₆H₂Et-5	78°	13-15 h	(48)	141
	EtOH/HCl	2,4-(MeO)₂C₆H₂Pr-5	78°	13-15 h	(47)	141
	EtOH/HCl	2,4-(EtO)₂C₆H₂Et-5	78°	13-15 h	(44)	141
	EtOH/HCl	2,4-(EtO)₂C₆H₂Pr-5	78°	13-15 h	(50)	141
	EtOH/HCl	2-MeO-4-EtOC₆H₂Et-5	78°	13-15 h	(52)	141
	EtOH/HCl	2-MeO-4-EtOC₆H₂Pr-5	78°	13-15 h	(44)	141

		Ar	Temp	Time		
	EtOH/HCl	Ph	78°	3 h	(83)	33, 127, 182
	PPE, MW	Ph	—	3 x 40 sec	(78)	34
	K-10-clay, MW	Ph	—	20 min	(38)	183
	EtOH/LaCl₃, MW	Ph	120°	10 min	(41)	22
	MeOH/H₂O, 2M HCl	Ph	rt	24 h	(70)	178
	K-10-clay, MW	4-BrC₆H₄	—	20 min	(38)	183
	K-10-clay, MW	3,4-Cl₂C₆H₃	—	20 min	(64)	183
	MeOH/H₂O, 2M HCl	4-MeOC₆H₄	rt	24 h	(72)	178
	MeOH/H₂O, 2M HCl	3,4-(OCH₂O)C₆H₃	rt	24 h	(75)	178
	MeOH/H₂O, 2M HCl	3,4-(MeO)₂C₆H₃	rt	24 h	(70)	178

	EtOH/HCl, MW, 12 x 30 sec		(88)		30

TABLE 3. REACTIONS INVOLVING THIOUREAS (*Continued*)

A. β-Keto Esters (*Continued*)

β-Keto Ester, Aldehyde, and Urea	Conditions	Product(s) and Yield(s) (%)	Refs.
C₆			
	EtOH/HCl, MW	Ar — Time 3-O₂NC₆H₄ — 14 x 30 sec — (70) 4-MeOC₆H₄ — 12 x 30 sec — (75)	30
Ar¹ = 4-FC₆H₄			
	EtOH/HCl, MW	Ar — Time Ph — 22 x 30 sec — (86) 4-FC₆H₄ — 20 x 30 sec — (65)	30
Ar¹ = 2-CF₃C₆H₄			
	MeOH/H₂O, HCl, rt, 3 d	(—)	142
	EtOH/HCl, 78°, 3 h	R H — (80) MeO — (—)	33, 130 33
R = H, OMe	EtOH/HCl, 78°, 3 h	(—)	33
	EtOH/HCl, 78°, 10 h	(60)	116
	EtOH/HCl, 78°, 10 h	(70)	116

94

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TABLE 3. REACTIONS INVOLVING THIOUREAS (*Continued*)

A. β-Keto Esters (*Continued*)
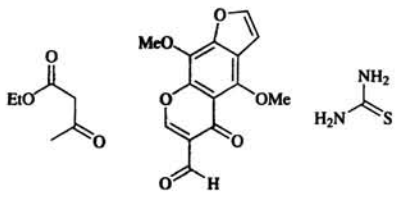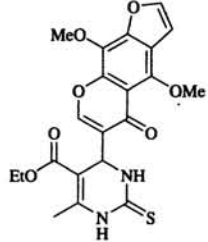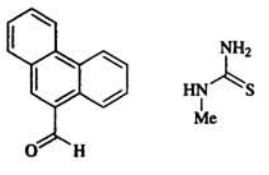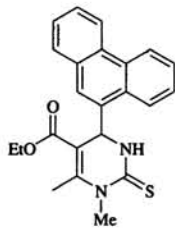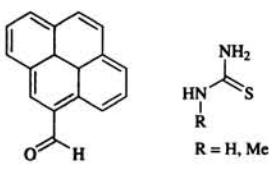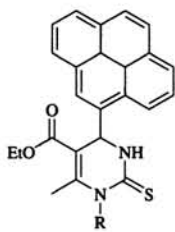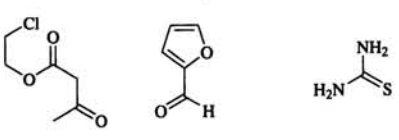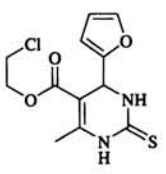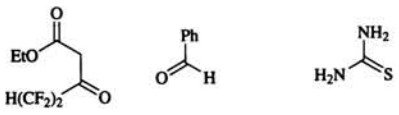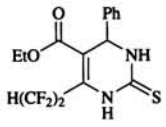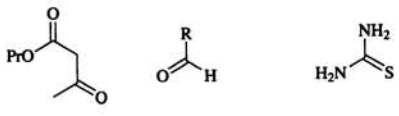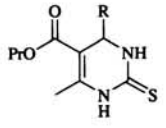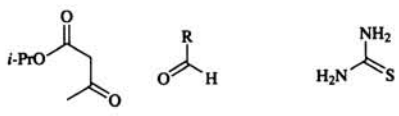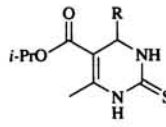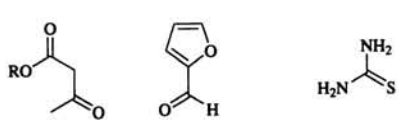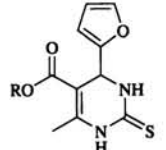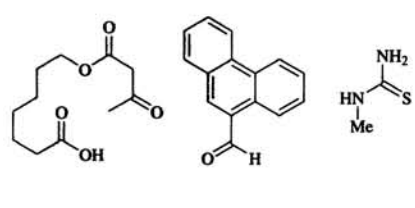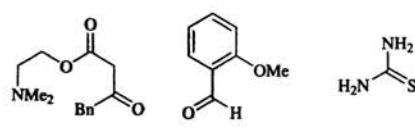
β-Keto Ester, Aldehyde, and Urea	Conditions	Product(s) and Yield(s) (%)	Refs.
C₆			
	EtOH/HCl, 78°, 10 h	(70)	116
	EtOH/HCl, 78°, 3 h	(—)	33
	EtOH/HCl, 78°, 3 h	(—)	33
R = H, Me			
	EtOH/HCl, 78°, 8 h	(58)	179
C₇			
	1. EtOH/HCl, 78°, 6 h 2. Toluene/*p*-TsOH, 110°, 6 h	(40)	63

For the PrO ester / R-aldehyde / thiourea (EtOH/HCl, 78°, 8 h):

R		Refs.
2-furyl	(90)	179
Ph	(38)	170
3-O₂NC₆H₄	(30)	170

For the *i*-PrO ester / R-aldehyde / thiourea (EtOH/HCl, 78°, 8 h):

R		Refs.
2-furyl	(47)	179
Ph	(37)	170
3-O₂NC₆H₄	(24)	170

C₈ — RO ester / furfural / thiourea (EtOH/HCl, 78°, 8 h):

R		Refs.
n-Bu	(41)	179
i-Bu	(65)	
s-Bu	(44)	
t-Bu	(39)	

TABLE 3. REACTIONS INVOLVING THIOUREAS (*Continued*)
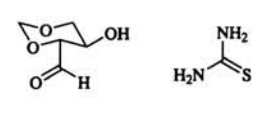
A. β-Keto Esters (*Continued*)

β-Keto Ester, Aldehyde, and Urea	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_8$	AcOH, 118°	Ar: 2-FC$_6$H$_4$, 2-ClC$_6$H$_4$, 2-MeC$_6$H$_4$, 2-MeOC$_6$H$_4$, 3-MeOC$_6$H$_4$, 4-MeOC$_6$H$_4$, 2-EtOC$_6$H$_4$, 2-*i*-PrOC$_6$H$_4$ (—)	180
C$_9$	EtOH/HCl, 78°, 8 h	(54)	179
	1. EtOH/HCl, 78°, 6 h 2. Toluene/*p*-TsOH, 110°, 6 h	(48)	63
(Ar = 2-MeOC$_6$H$_4$)	AcOH, 118°	(—)	180
(Ar = 2-MeOC$_6$H$_4$)	AcOH, 118°	(—)	180
C$_{10}$	AcOH, 118°	(—)	180
	2-Propanol/EtOH/HCl, rt	R: Me, Et, 4-MeOC$_6$H$_4$, 4-O$_2$NC$_6$H$_4$, 2-ClC$_6$H$_3$F-6 (—)	164
C$_{11}$	2-Propanol/EtOH/HCl, rt	R = Me (30)	164
	2-Propanol/EtOH/HCl, rt	R = Et (—)	164
	EtOH/HCl, 78°, 3 h	R = Ph (70)	174
	2-Propanol/EtOH/HCl, rt	R = 4-MeOC$_6$H$_4$ (—)	164
	2-Propanol/EtOH/HCl, rt	R = 4-O$_2$NC$_6$H$_4$ (—)	164
	2-Propanol/EtOH/HCl, rt	R = 2-ClC$_6$H$_3$F-6 (—)	164
	EtOH/HCl, 78°, 8 h	(46)	179

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TABLE 3. REACTIONS INVOLVING THIOUREAS (*Continued*)

A. β-Keto Esters (*Continued*)

β-Keto Ester, Aldehyde, and Urea	Conditions	Product(s) and Yield(s) (%)		Refs.
C₁₁	EtOH/HCl, 78°, 3 h		(—)	33
C₁₄	AcOH, 118°		(—)	180

ᵃ This structure is an aldehyde protected as an oxazinane.

ᵇ The aldehyde was protected as an oxazinane.

TABLE 3. REACTIONS INVOLVING THIOUREAS (*Continued*)
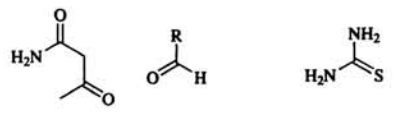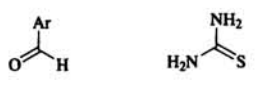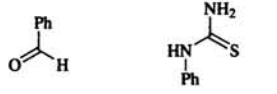
B. β-Keto Amides

β-Keto Amide, Aldehyde, and Urea	Conditions	Product(s) and Yield(s) (%)			Refs.
C₄	MeOH/HCl, 65°		(—)	R Pr *i*-Pr 2-furyl	148 148 184
	A. MeOH/HCl, 65° B. EtOH/HCl, 78°		(—)	Ar A. Ph B. 2-ClC₆H₄ B. 4-HOC₆H₄ B. 4-O₂NC₆H₄ B. 4-MeOC₆H₄	148 184 184 184 184
	EtOH/HCl, MW, 120°, 15 min		(21)		22
	EtOH/HCl, 78°		(—)		184

TABLE 3. REACTIONS INVOLVING THIOUREAS (*Continued*)

B. β-Keto Amides (*Continued*)

β-Keto Amide, Aldehyde, and Urea	Conditions	Product(s) and Yield(s) (%)	Refs.

C₅

	EtOH/HCl, 78°, 3 h	**Ar**	
		Ph (85)	
		4-HOC₆H₄ (89)	149
		4-ClC₆H₄ (68)	
		2-O₂NC₆H₄ (90)	
		3-O₂NC₆H₄ (91)	
		4-O₂NC₆H₄ (65)	
		2,4-Cl₂C₆H₃ (80)	
		3,4-Cl₂C₆H₃ (64)	
		4-MeOC₆H₄ (62)	
		3-MeOC₆H₃OH-2 (80)	
		3,4-(OCH₂O)C₆H₃ (68)	
		3,4-(MeO)₂C₆H₃ (62)	
		3,4,5-(MeO)₃C₆H₂ (79)	

	EtOH/AcOH, Yb(OTf)₃, MW, 120°, 10 min	**I** (66) Ar = 2-O₂NC₆H₄	22

C₈

Ar = 2-MeOC₆H₄

	AcOH, 118°	(—)	180

C₁₀

R = Me, Et

R = Pr, *i*-Pr

	2-Propanol/EtOH/HCl, rt	(—)	164
	MeOH/HCl, 65°	(—)	148

		R	
	MeOH/HCl, 65°	Ph (—)	148
	EtOH/HCl, 78°, 3 h	Ph (71)	185
	2-Propanol/HCl, rt	Ph (—)	164
	EtOH/HCl, 78°, 3 h	2-ClC₆H₄ (84)	185
	EtOH/LaCl₃, MW, 120°, 10 min	2-ClC₆H₄ (89)	22
	EtOH/HCl, 78°, 3 h	4-ClC₆H₄ (70)	185
	2-Propanol/HCl, rt	4-BrC₆H₄ (—)	164
	2-Propanol/HCl, rt	3-O₂NC₆H₄ (—)	164
	EtOH/HCl, 78°, 3 h	4-O₂NC₆H₄ (72)	185
	2-Propanol/HCl, rt	3-O₂NC₆H₃Cl-4 (—)	164
	2-Propanol/HCl, rt	3,4-Cl₂C₆H₃ (—)	164
	2-Propanol/HCl, rt	2-FC₆H₃Cl-6 (—)	164
	2-Propanol/HCl, rt	4-MeC₆H₄ (—)	164
	EtOH/HCl, 78°, 3 h	2-MeOC₆H₄ (82)	185
	EtOH/HCl, 78°, 3 h	4-MeOC₆H₄ (65)	185
	EtOH/HCl, 78°, 3 h	4-Me₂NC₆H₄ (65)	185
	2-Propanol/HCl, rt	3,4,5-(MeO)₃C₆H₂ (—)	164

	EtOH, 78°, 6 h		186

Ar	
Ph	(63)
4-O₂NC₆H₄	(60)
4-ClC₆H₄	(57)
3,4,5-(MeO)₃C₆H₂	(54)

TABLE 3. REACTIONS INVOLVING THIOUREAS (*Continued*)

B. β-Keto Amides (*Continued*)
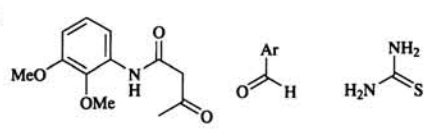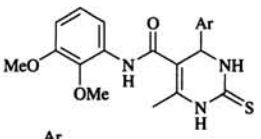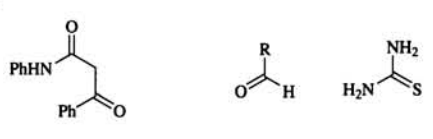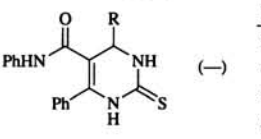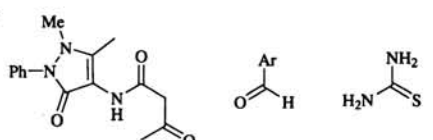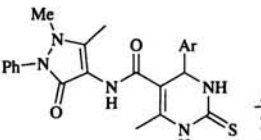
β-Keto Amide, Aldehyde, and Urea	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{12}$	EtOH, 78°, 6 h	 **Ar** Ph (62) 2-O$_2$NC$_6$H$_4$ (52) 4-ClC$_6$H$_4$ (48) 4-MeOC$_6$H$_4$ (61) 3,4-(MeO)$_2$C$_6$H$_3$ (39) 3,4,5-(MeO)$_3$C$_6$H$_2$ (56)	186
C$_{15}$	2-Propanol/HCl, rt	(—) **R** Me 4-O$_2$NC$_6$H$_4$ 2-ClC$_6$H$_3$F-6 4-MeOC$_6$H$_3$	164
C$_{15}$	EtOH/HCl, 78°, 3-5 h	 **Ar** Ph (66) 4-FC$_6$H$_4$ (54) 4-ClC$_6$H$_4$ (73) 4-BrC$_6$H$_4$ (75) 4-O$_2$NC$_6$H$_4$ (58) 3,4-Cl$_2$C$_6$H$_3$ (79) 4-MeOC$_6$H$_4$ (55) 3,4,5-(MeO)$_3$C$_6$H$_2$ (69)	134

TABLE 3. REACTIONS INVOLVING THIOUREAS (*Continued*)
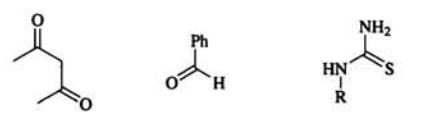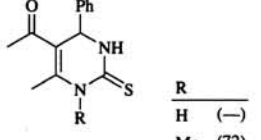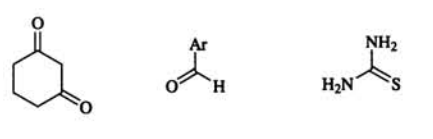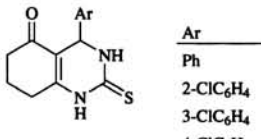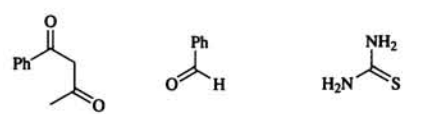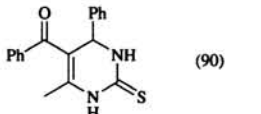
C. β-Diketones

β-Diketone, Aldehyde, and Urea	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_5$	EtOH/HCl, 78° MeOH/H$_2$O, 2 M HCl, rt, 24 h	 **R** H (—) Me (72)	99 178
C$_6$	EtOH/HCl, 78°	 **Ar** Ph 20 h (35) 2-ClC$_6$H$_4$ 20 h (42) 3-ClC$_6$H$_4$ 20 h (49) 4-ClC$_6$H$_4$ 20 h (51) 2-BrC$_6$H$_4$ 20 h (46) 3-BrC$_6$H$_4$ 20 h (25) 4-BrC$_6$H$_4$ 20 h (56) 4-FC$_6$H$_4$ 3-4 h (84) 2-MeC$_6$H$_4$ 20 h (53) 3-MeC$_6$H$_4$ 20 h (41) 4-MeC$_6$H$_4$ 20 h (41) 2-MeOC$_6$H$_4$ 20 h (49) 3-MeOC$_6$H$_4$ 20 h (37) 4-MeOC$_6$H$_4$ 20 h (45)	187 187 187 187 187 187 187 188, 189 187 187 187 187 187 187
C$_{10}$	THF/InCl$_3$, 65°, 8 h	(90)	90

TABLE 3. REACTIONS INVOLVING THIOUREAS (*Continued*)

C. β-Diketones (*Continued*)

β-Diketone, Aldehyde, and Urea	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{10}$	EtOH/HCl, 78°, 5 h	(88)	21

TABLE 3. REACTIONS INVOLVING THIOUREAS (*Continued*)

D. Other CH-Acidic Carbonyl Compounds

CH-Acidic Carbonyl Compound, Aldehyde, and Urea	Conditions	Product(s) and Yield(s) (%)		Refs.
C$_9$	MeOH/HCl, 65°, 4 h	Ar		26
		Ph	(54)	
		4-MeC$_6$H$_4$	(59)	
		4-MeOC$_6$H$_4$	(50)	
		3,4-(MeO)$_2$C$_6$H$_3$	(47)	
C$_{10}$	MeOH/HCl, 65°, 4 h	Ar		26
		Ph	(61)	
		4-MeC$_6$H$_4$	(59)	
		4-MeOC$_6$H$_4$	(55)	
		3,4-(MeO)$_2$C$_6$H$_3$	(49)	
C$_{13}$	MeOH/HCl, 65°, 4 h	Ar		26
		Ph	(45)	
		4-MeC$_6$H$_4$	(50)	
		4-MeOC$_6$H$_4$	(47)	
		3,4-(MeO)$_2$C$_6$H$_3$	(46)	

TABLE 4. REACTIONS INVOLVING GUANIDINE
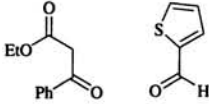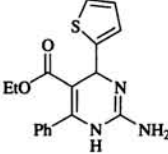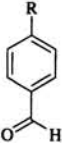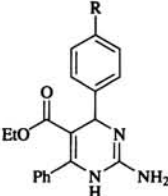
β-Keto Ester and Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.

C$_{11}$

| | DMF/NaHCO$_3$, 70°, 3 h | (85) | 31 |

| | DMF/NaHCO$_3$, 70°, 3 h | R | 31 |

R
H   (75)
Cl   (85)
Me   (85)
MeO (75)

TABLE 5. REACTIONS ON SOLID PHASE
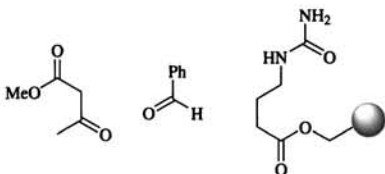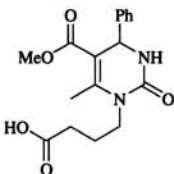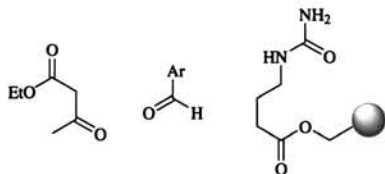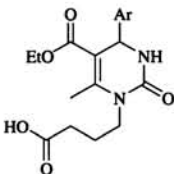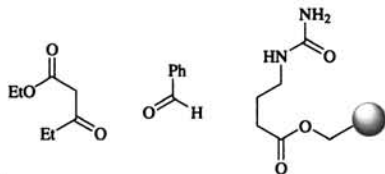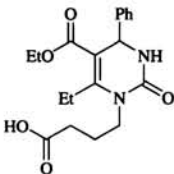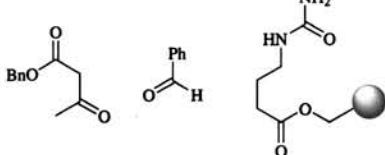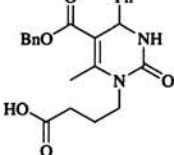
β-Keto Ester, Aldehyde, and Urea	Conditions	Product(s) and Yield(s) (%)	Refs.

C$_5$

Urea on PS-Wang resin
1. THF/HCl, 55°
2. Cleavage: TFA/DCM, rt

 (93)

36

C$_6$

Urea on PS-Wang resin
1. THF/HCl, 55°
2. Cleavage: TFA/DCM, rt

Ar	
Ph	(80)
3-O$_2$NC$_6$H$_4$	(98)
2-ClC$_6$H$_4$	(87)
4-HOC$_6$H$_4$	(87)
4-MeOC$_6$H$_4$	(93)
2-naphthyl	(87)

36

C$_7$

Urea on PS-Wang resin
1. THF/HCl, 55°
2. Cleavage: TFA/DCM, rt

 (93)

36

C$_{11}$

Urea on PS-Wang resin
1. THF/HCl, 55°
2. Cleavage: TFA/DCM, rt

 (93)

36

TABLE 5. REACTIONS ON SOLID PHASE (*Continued*)

β-Keto Ester, Aldehyde, and Urea	Conditions	Product(s) and Yield(s) (%)	Refs.
C₁₁	Ester on PS-Wang resin 1. Dioxane/HCl, 70°, 18 h 2. Cleavage: TFA/DCM, rt		39
		$\underline{\text{Y}}$ O (81) S (44)	
	Ester on PS-Wang resin 1. Dioxane/HCl, 70°, 18 h 2. Cleavage: TFA/DCM, rt	$\underline{\text{Ar}}$ 3-O₂NC₆H₄ (86) 4-O₂NC₆H₄ (80) 2-ClC₆H₄ (77) 2,3-Cl₂C₆H₃ (86) 3,4-F₂C₆H₃ (73) 4-MeC₆H₄ (83) 2-(CF₃)C₆H₄ (70)	39
C₁₂	Ester on PS-Wang resin 1. Dioxane/HCl, 70°, 18 h 2. Cleavage: TFA/DCM, rt	$\underline{\text{Ar}}$ 3-O₂NC₆H₄ (88) 3,4-F₂C₆H₃ (73)	39
C₁₃	Urea on PS-Wang resin 1. THF/HCl, 55° 2. Cleavage: TFA/DCM, rt	(67)	36

TABLE 6. REACTIONS IN FLUOROUS PHASE

β-Keto Ester, Aldehyde, and Urea	Conditions	Product(s) and Yield(s) (%)	Refs.
C₅	1.THF/BTF, HCl, 50°, 3 d 2. TBAF in THF/BTF, 25°, 30 min	(70)	38
C₆	1. THF/BTF, HCl, 50°, 3 d 2. TBAF in THF/BTF, 25°, 30 min	Ar Ph (71) 4-MeOC₆H₄ (69) 2-naphthyl (55)	38
C₇	1. THF/BTF, HCl, 50°, 3 d 2. TBAF in THF/BTF, 25°, 30 min	Ar Ph (47) 2-naphthyl (60)	38 37, 38

Microbial Arene Oxidations

Abstract

The metabolism of organic molecules by living organisms is of fundamental interest to biologists, microbiologists, and biochemists. The primary avenue of metabolism in most living organisms is via oxidative pathways. The aromatic hydrocarbons (arenes) are subject to such oxidative degradation; their mammalian and microbial systems have been extensively studied. It is the capacity of certain microorganisms to convert by oxidation arenes into arene *cis*-dihydrodiols that provide the foundation of this chapter. Arenes are subject to a variety of oxidations, but the expression "microbial arene oxidation" is used for the specific oxidation discussed here.

The assignment of dihydrodiol configuration and the use of mutant strains of microorganisms laid the groundwork for the development of arene oxidation as a process useful to organic synthesis. Other advances discussed in this chapter led to the development of microbial arene oxidations that are suitable for organic synthesis. Attractive features include: the process is one of a very few that disrupts the aromatic system of arenes; the array of functional groups generated in the dihydrodiol products is useful; the process is highly enantioselective, affording pure enantiomerically pure products in most cases.

For this chapter, the literature has been reviewed through 2001.

1. Introduction

The metabolism of organic molecules by living organisms is of fundamental interest to biologists, microbiologists, and biochemists. The primary avenue of metabolism in most living organisms is via oxidative pathways. The aromatic hydrocarbons (arenes) are subject to such oxidative degradation; their metabolism by both mammalian and microbial systems has been extensively studied. It is the capacity of certain microorganisms to oxidatively convert arenes into arene cis-dihydrodiols that provides the foundation of this chapter. Arenes are subject to a variety of metabolic oxidations but when the expression "microbial arene oxidation" is used within the field of organic chemistry, it generally refers to the oxidation exemplified by Eq. 1. The focus of this chapter is the oxidative transformation and the valuable molecules that are generated by the process.

$$\text{(1)}$$

Throughout this chapter the shortened term, "dihydrodiol," is used for the array of functional groups shown in the structure of *cis*-3,5-cyclohexadiene-1,2-diol (**1**). Also, note that the words "oxidation" and "oxygenation" are used interchangeably as are "microbial" and "microbiological." Please refer to the Glossary for definitions of unfamiliar terminology.

When considering microbial arene oxidations, it is important to be aware of the distinction between bacteria and fungi. The cis-dihydrodiols are produced only by bacteria. As early as 1953, an optically active dihydrodiol was isolated from fermentation of naphthalene with a bacterium. (1) However, the stereochemical relationship of the hydroxy groups was not determined; rather, the stereochemical relationship of these groups was assigned as trans by analogy to the trans-dihydrodiol produced by mammalian metabolism of naphthalene. Arene oxidations performed by fungi also produce trans-dihydrodiols. In the following years several other dihydrodiols obtained from the fermentations of arenes with bacteria were likewise interpreted to have the trans-diol configuration. A seminal study by Gibson and coworkers in 1968 placed the chemistry and stereochemistry of microbial arene oxidations on solid footing. These investigators demonstrated a fundamental difference in the first step of arene metabolism in mammalian and bacterial systems. Using the bacterium *Pseudomonas putida* F1, they showed conclusively that *cis*-3,5-cyclohexadien-1,2-diol is produced from benzene by this microorganism, as shown in Eq. 1. (2) The early history of arene oxidations and of these discoveries are included in an excellent review by Gibson. (3)

The next crucial step in the development of the microbial arene oxidation was a mutagenesis experiment with *P. putida* F1. Treatment of the microorganism with *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG) gave a number of mutant strains of the organism. One of these mutant strains, designated *P. putida* 39/D, was devoid of the enzyme cis-dihydrodiol dehydrogenase normally present in the natural strain. This enzyme carries out the dehydrogenation of the dihydrodiol, efficiently converting it into a catechol. The absence of this enzyme allows the accumulation of the dihydrodiol during the fermentation, a factor essential to isolation of useful quantities of these compounds. (3, 4)

The assignment of dihydrodiol configuration and the use of mutant strains of microorganisms laid the groundwork for the development of microbial arene oxidations as a process useful to organic synthesis. Other important developments that have contributed toward achievement of that goal include: (a) determination of enantiomeric purities and absolute configurations of the dihydrodiols, (b) discovery of other organisms that can produce dihydrodiols, (c) cloning of the genes for the dioxygenase enzyme complex and their expression in *Escherichia coli*, and (d) a demand for the dihydrodiols as a consequence of their potential value in organic synthesis.

These advances have led to the development of microbial arene oxidations that are suitable for organic synthesis. The attractive features of these oxidations are three-fold. First, the process is one of a very few that disrupts the aromatic system of arenes. Second, the array of functional groups generated in the dihydrodiol products is useful. Third, the process is highly enantioselective, affording enantiomerically pure products in most cases.

For this chapter, the literature has been reviewed through 2001. As noted above, the early literature was reviewed in 1971. (3) Progress from 1971 to 1984, (5) and the generation of dihydrodiols from halogenated aryls, (6) from polychlorinated biphenyls, (7) and from phthalates (8) are all included in a book devoted to microbial degradation of organic molecules (see ref. 5). The microbial degradation of polycyclic aromatic hydrocarbons, including formation of dihydrodiols, has been reviewed (9) as have the reactions catalyzed by naphthalene dioxygenases. (10) The oxygenations of polycyclic aromatic hydrocarbons are the subject of a recent review article. (11) Enzymic structure-function relationships of the dioxygenases have been reviewed (12) and the role of Rieske centers in dioxygenases is included as part of a larger review. (13) Several articles combine summaries of dihydrodiol preparation with applications to organic syntheses (14-16) including a detailed review of the stereochemistry of the process. A fascinating personal account of his involvement in the development of the field has been written by Gibson. (17) Finally, references to numerous reviews devoted primarily to synthetic applications based on the use of dihydrodiols are enumerated later in this Chapter.

2. Mechanism and Stereochemistry

The "reagents" used in microbial arene oxidations are oxygen and an enzyme complex. The oxygenation reaction takes place within the cells of the living microorganisms where the enzyme complex is found. A key component of the enzyme complex is a dioxygenase that catalyzes the addition of oxygen to an arene, generating the dihydrodiol. The dioxygenase requires the support of electron transport and oxygen transport systems, with which it is coupled, in order to achieve the oxygenation. Not surprisingly, there are small differences in the dioxygenases found in different microorganisms with the consequence that there are several versions of the reagent. Distinctions between the different enzymes are made on the basis of the substrate that the microorganism was originally found to oxidize. More than a dozen classes of dioxygenases are known but the four most widely used for arene oxygenations will be emphasized in this chapter. They are: (a) toluene dioxygenase (TDO), (b) naphthalene dioxygenase (NDO), (c) biphenyl dioxygenase (BPDO), and (d) benzoic acid (or benzoate) dioxygenase (BZDO). Fortunately, the specificity of each of these dioxygenases is not nearly as stringent as the names imply. Each of the four classes of enzymes catalyzes the dioxygenation of a broad range of substrates. There also is considerable overlap between the four classes so that some arenes are oxygenated by more than one of the enzyme classes. More than one microorganism may carry the dioxygenase of any given class. These may be different natural microorganisms, mutant strains of the natural microorganisms, or recombinant strains expressing the dioxygenase of the natural microorganisms. Further discussion of these microorganisms and how they are related may be found in the "Scope and Limitations" section.

The unequivocal demonstration of a cis-diol configuration in the dihydrodiols clearly differentiates the mechanism of arene oxidations by bacteria from the mechanism in mammalian and fungal systems. Whereas mammalian and fungal oxidations occur via an arene oxide intermediate, the cis-configuration

of the diols suggests addition of both atoms of the oxygen molecule in bacterial oxidations. Several studies confirm this mode of oxygenation with experiments in which the fermentations were done using mixtures of $^{16}O_2$ and $^{18}O_2$. Analysis of the dihydrodiols produced under these conditions clearly shows that both atoms of the oxygen molecule are incorporated into the same dihydrodiol. Although these results are consistent with the intermediacy of an arene-dioxetane, such an intermediate has yet to be isolated or detected.

The dramatic progress in recent years in the X-ray crystallographic study of protein structure has greatly enhanced understanding of the mechanisms of enzyme-catalyzed reactions. This technique has been successfully applied to bacterial dioxygenases. The first X-ray crystallographic studies of an aryl dioxygenase are of a naphthalene dioxygenase (18, 19) (NDO) from *Pseudomonas* sp. 9816-4 expressed in a recombinant strain of *E. coli*. (20) Three different versions of the structure have been reported; they include: (a) enzyme with no substrate, (18) (b) enzyme with indole bonded via dioxygen to iron in the catalytic site, (21) and (c) the enzyme after crystals were soaked with indole. (21) Indole is known to be a substrate of NDO and is oxidized to indoxyl, which, in turn, undergoes further air oxidation to indigo. (22)

The crystallographic studies indicate that the catalytic site of the enzyme is a flattened and elongated cavity having the approximate dimensions of 6 Å by 8 Å by 10 Å. Computational docking studies with the enzyme structure suggest that the cavity can nicely accommodate substrates such as naphthalene and biphenyl. The cavity is mostly lined by hydrophobic amino acids with the exception of a polar area at the bottom located near a mononuclear iron center. (21)

Further development and refinement of X-ray structural data combined with computational analysis are very likely to lead to models useful for the prediction of regio- and stereochemical outcomes of microbial arene oxidations. In the meantime, enough empirical data is available from the structure assignments already in the literature to generate a predictive model for the stereochemical course of many dioxygenation reactions. (23) The scheme shown in Figure 1 is useful for predicting the regio- and stereochemical outcome for the dioxygenation of most benzenes as well as for many bicyclic and polycyclic arenes.
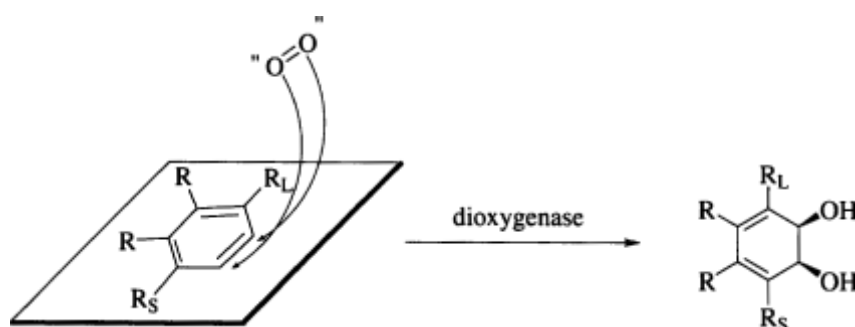
Figure 1. An empirical model for predicting the sense of enantioselectivity in the dioxygenation of arenes by TDOs, NDOs, and BPDOs. R_L is a large (in terms of space occupied) substituent group; R_S is a small substituent group.

To use the model shown in Figure 1, mono-substituted benzenes are oriented so that the substituent is in the position of R_L. The model then predicts that dioxygenation will produce a dihydrodiol having the constitution and absolute configuration shown. All monosubstituted dihydrodiols for which complete stereochemical data is available are consistent with the model. Nearly all dioxygenations of monosubstituted benzenes give dihydrodiols with >95% ee. One exception is fluorobenzene for which the derived dihydrodiol has an ee of ~60%, (24-25) reflecting the approximately equal volume of space occupied by the hydrogen and fluorine atoms. These observations are consistent with the steric effect, as opposed to an electronic effect, of the substituent(s) being dominant in direction of the oxygenation process.

Di- and polysubstituted benzenes are likewise oriented in the model with the largest substituent in the position of R_L. (23) Where there is ambiguity about which group to rank as the largest, some guidance may be found from the results summarized in Table 1. These results provide the following preferences in order of decreasing van der Waals radii of the substituent, CF_3 > I > Br > CH_3 ≥ Cl > F > H. This ranking is derived from a very limited sample set, however, and should be used with caution in making predictions.

Naphthalene is oriented in the model so that the second ring occupies the positions of R_L and the adjacent R. This orientation predicts oxygenation at C-1 and C-2 rather than at C-2 and C-3 of the naphthalene ring, consistent with observed results. Substituted naphthalenes likewise are oriented so that the ring to which the substituent is attached occupies the positions of R_L and the adjacent R. Now, however, the model is not sufficiently detailed to allow a choice to be made between the two different orientations that are possible for the substituent-bearing ring. As illustrated in Figure 2, a 2-substituted naphthalene can be aligned in the model in the two orientations shown. Each orientation predicts a different regioselectivity of the oxygenation process. In practice, two or three dihydrodiols are obtained from the oxygenation (Eq. 2). (26)
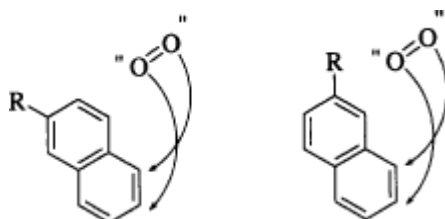
Figure 2. Two orientations of a 2-substituted naphthalene in the model of Figure 1.

(2)
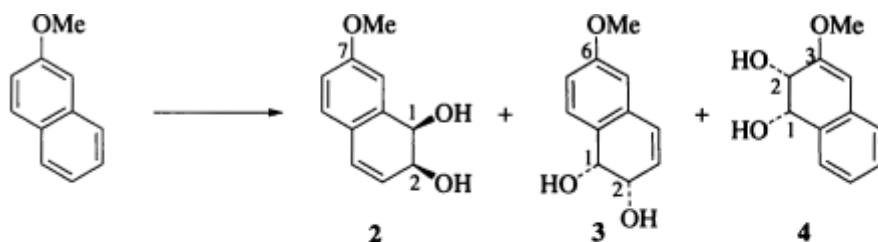
Microorganism	Dioxygenase Type	(Yield of crude diols), 2:3:4
Pseudomonas putida 39D	TDO	(29%), 12:73:15
Escherichia coli JM109(pDTG601)	TDO	(64%), 17:69:14
Pseudomonas putida NCIB 9816	NDO	(6%), 93:7:0
Escherichia coli JM109(pDTG141)	NDO	(57%), 93:7:0
Escherichia coli C534(ProR/Sac)	NDO	(61%), 92:8:0
Beijerinckia sp. B8/36	BPDO	(36%), 74:26:0

Although the names given the classes of dioxygenases, e.g., toluene dioxygenase (TDO), suggest highly selective reagents, the dioxygenases are quite broad in their substrate specificity. Naphthalenes, for example, may be oxygenated with TDOs or BPDOs as well as with NDOs. This permits some latitude in choosing a microorganism to use for a dioxygenation process. It is important, then, to consider if regio- and stereoselectivity of dioxygenation is sensitive to (a) the class of dioxygenase, and (b) to different microorganisms within the same class of dioxygenase (see Eq. 2). Oxygenation of 2-methoxynaphthalene can generate the three constitutionally different dihydrodiols, (1*R-cis*)-7-methoxy-, (1*R-cis*)-6-methoxy-, and (1*S-cis*)-3-methoxy-1,2-dihydronaphthalene-1,2-diol (**2**, **3**, and **4**) shown in the equation. The results from oxygenation of 2-methoxynaphthalene with six different microorganisms are summarized. Note that the six include two TDO organisms (one mutant strain and one recombinant strain, see TDO section below), three NDO organisms (one mutant and two recombinant strains, see NDO section below), and one BPDO organism (a mutant strain, see BPDO section below). In these results, the regioselectivity of dioxygenation varies considerably between microorganisms having different classes of dioxygenase but only slightly between microorganisms of the same dioxygenase class. The absolute configurations of all three dihydrodiols are those that would be predicted by the model shown in Figure 1.

In another example, the oxygenation of 4-iodotoluene with two TDO-producing organisms, one the mutant strain *P. putida* UV4 (derived from the natural strain *P. putida* NCIMB 11767) and the other the recombinant strain *Escherichia coli* JM109(pDTG601) (derived from *P. putida* F1), is compared (Eq. 3). (23, 27) Both organisms convert the substrate into (1*S-cis*)-3-iodo-6-methyl-3,5-cyclohexadiene-1,2-diol (**5**) but the product from the mutant strain has 80% ee whereas that from the recombinant strain has

>98% ee. This difference in ee may reflect slight differences between the two TDOs, since each is derived from a different natural strain of *P. putida*. It should be added that the transformations from a wild-type organism to a mutant or to a recombinant strain are not expected to alter the amino acid sequence of the dioxygenase and its catalytic selectivity.

(3)
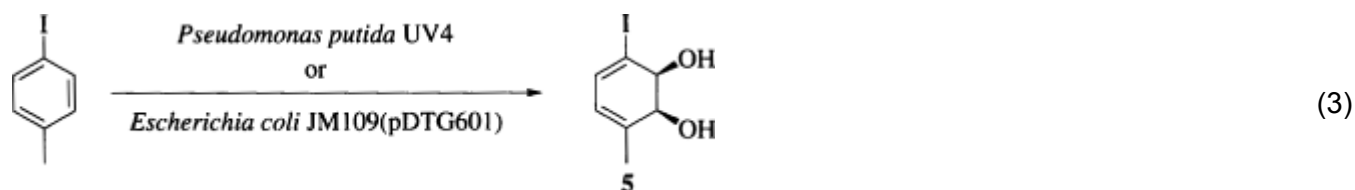
The use of the model to predict the stereoselectivity of oxygenation of polycyclic aromatic hydrocarbons must also be done with care. Orientation of anthracene in the model so that the fused rings take the positions of R_L and the adjacent R correctly predicts the structure of the oxygenation product (Eq. 4). (28, 29) Orientation of phenanthrene presents the same dilemma that was faced with the 2-substituted naphthalenes. Two orientations of phenanthrene are possible and dihydrodiols from both are obtained from the oxygenation process (Eq. 5). (28, 30, 31) Similar considerations hold when the model is used for predicting oxygenation of polycyclic hydrocarbons having more than three rings.

(4)

(5)
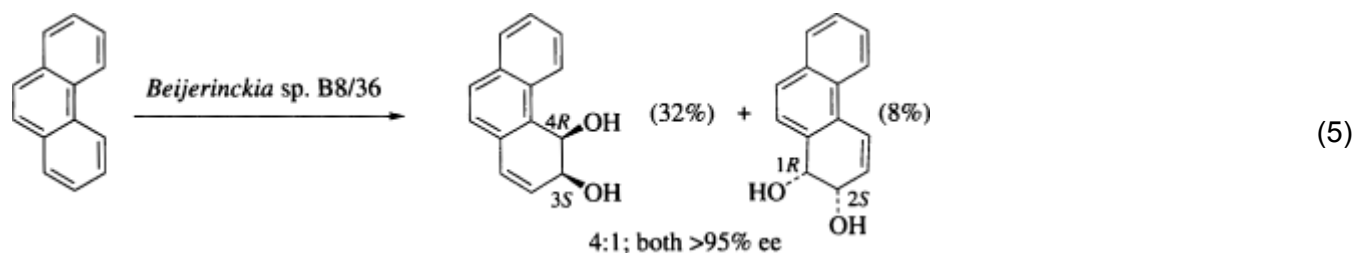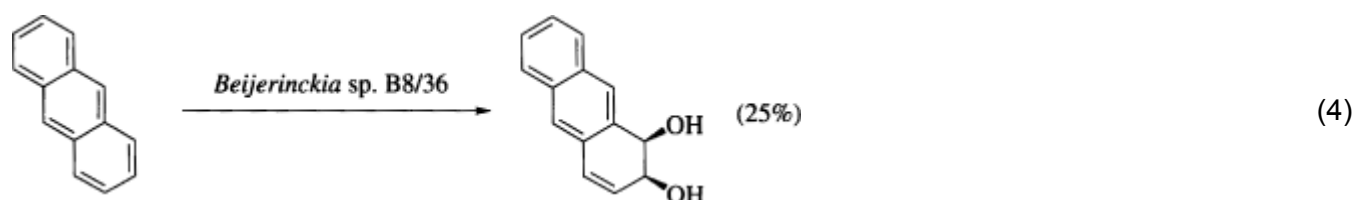
The model may also be applied, with care, in the oxygenations of heteroaromatic compounds. Oxygenation of phenazine with *S. yanoikuyae* B8/36 produces a dihydrodiol having constitution and absolute configuration consistent with the model of Figure 1 (Eq. 6). (32) Also produced in the fermentation is another, more polar product that was determined to be the product of bis-dihydroxylation of phenazine. In a separate experiment, the mono-dihydrodiol was shown to be a substrate for the second dioxygenation process. (32)

(6)
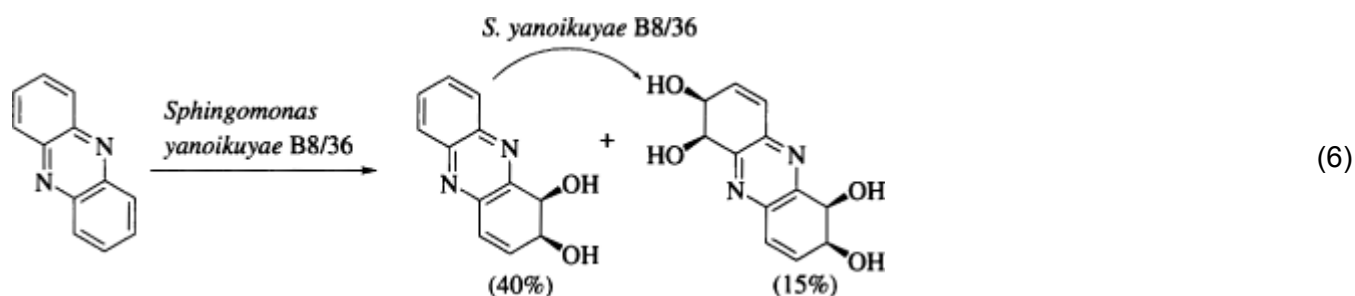
A different regiochemistry is found for BZDO (Eq. 7). (33-36) The enantioselectivity of BZDO oxidations has not been sufficiently studied to develop an empirical model for predicting stereochemistry. In fact, the absolute configuration of only one product of BZDO oxidations,

(1*S*-*cis*)-1,6-dihydroxy-2,4-cyclohexadiene-1-carboxylic acid (**6**), has been determined (Eq. 7). (33)

(7)
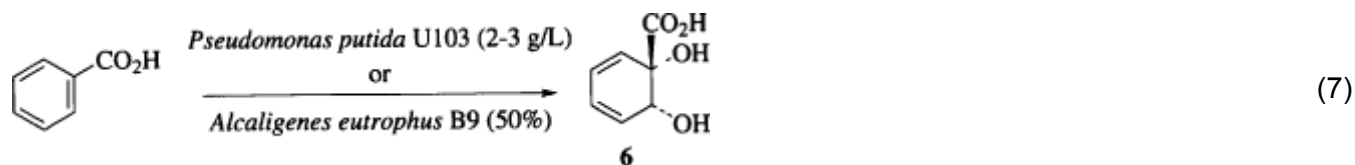
Several general methods have been developed for assignment of absolute configuration to new chiral dihydrodiols. These include preparation of chiral boronate derivatives coupled with NMR analysis, (37) preparation of 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) adducts followed by derivatization as the Mosher esters and NMR analysis, (25) and circular dichroism correlations (29) of the dihydrodiols and their derivatives and of cyclic η^4-diene complexes of tricarbonyliron. (38)

Further aspects of the regio- and stereochemistry of dioxygenations catalyzed by the different dioxygenases are included in the next section.

3. Scope and Limitations

When used in the context of organic chemistry, the expression "microbial arene oxidations" describes the oxidative conversion of arenes into cis-dihydrodiols by microorganisms. This transformation is attractive to chemists because, in one reaction, the aromatic system of the arene is disrupted in a controlled manner and a useful array of functional groups is generated. In addition, the oxygenation process usually is highly enantioselective as described in the preceding section.

The range of arenes that can be converted into dienediols by this method is broad. Benzene, numerous substituted benzenes, and a variety of naphthalenes all are good substrates for the reaction. (A "good substrate" is one that is converted in good yield into a dienediol.) Polycyclic aromatic hydrocarbons also are subject to dioxygenation by microorganisms although, at the present stage of process development, the yields of dienediols are not synthetically useful. Heteroaromatic compounds also have been widely studied as substrates for dioxygenation and many are converted into dienediols. The list of heteroaromatic compounds that have been converted into dienediols includes: thiophenes, benzo- and dibenzothiophenes, benzo- and dibenzofurans, indole (the final product is indigo), quinolines, isoquinolines, quinoxalines, quinazolines, acridines, phenazines, chromenes, and thiachromenes as well as several other polycyclic heteroaromatic compounds.

Oxygenations of substituted arenes by dioxygenases are not limited to the π -electron system. Depending on the groups attached or fused to the arene nucleus, other oxidation products may be formed. In some reactions, these become the major products of the oxygenation process. Indenes and indanes are prominent among such substrates. With indenes, oxidations of both the cyclopentene double bond and of the benzylic position are observed, and with indanes, benzylic oxidations predominate. Another oxidative "side-reaction" is the oxidation of thioethers, usually to sulfoxides. These oxidations are described further in a later section of this chapter.

Another limitation of microbial arene oxidations as a route to enantiomerically pure diols is that, in most cases, only one enantiomer can be accessed by this method. In a few cases (see "Applications to Synthesis"), the dihydrodiol can be manipulated chemically to produce the opposite enantiomer. In these cases, however, the additional chemical steps detract somewhat from the convenience of the one-step microbial generation of a dihydrodiol. A promising approach to production of both enantiomers of a dihydrodiol is in the very early stages of development. The combination of genetic engineering with site-directed mutagenesis of the dioxygenase can alter dramatically the stereochemical outcome of the oxygenation process. This approach is described further in the section on "Site-Directed Mutagenesis of Dioxygenases."

Many microorganisms catalyze the dioxygenation of arene molecules, requiring a choice to be made when planning to perform such an experiment. Most of the work leading to practical preparations of dihydrodiols has been done with microorganisms of the four classes already outlined, i.e., TDO, NDO, BPDO, and BZDO. Benzene dioxygenase (BDO) is sometimes considered a fifth class of dioxygenase but in this review it is included as part of the TDO class. These four classes of dioxygenases and the

microorganisms that produce them are discussed below.

Within each of the four classes of dioxygenases, two or three microbial strains have been studied extensively for biotransformation of the arene substrates. A listing of the most frequently used microorganisms, and their mutant and recombinant strains, for each of the four classes of enzymes is given in Table A. Coordination of this information with the examples given in the Tables at the end of the chapter may be helpful in making the choice of an organism to use for a desired dioxygenation process.

Table A. Microorganisms Frequently Used in Oxygenation of Arenes

	Microorganism (type); Dioxygenase inducer(s)[a]	Source	Reference
TDO	*P. putida* F1 (wild type)	ATCC 700007; DSM 6899	2
	P. putida 39/D (mutant of *P. putida* F1); toluene	ATCC 700008; DSM 6414	39, 40
	E. coli JM109(pDTG601) (clone of *P. putida* F1 dioxygenase); IPTG[b]		41
TDO	*P. putida* NCIMB 11767 (wild type); toluene		42, 43
	P. putida UV4 (mutant of *P. putida* NCIMB 11767); no inducer required	Proprietary	42
	E. coli JM109(pKST11) (clone of *P. putida* NCIMB 11767 dioxygenase); IPTG[b]		44
NDO	*Pseudomonas* sp. NCIB 9816-4		45, 10
	Pseudomonas sp. NCIB 9816-11 (mutant of *P.* NCIB 9816-4); salicylate		46, 10
	E. coli JM109(DE3)(pDTG141) (clone of *P.* NCIB 9816-4 dioxygenase); IPTG[b]		45, 10
NDO	*P. fluorescens* N3 (wild type)		47, 48
	P. fluorescens N3 TCC1 (mutant of *P. fluorescens* N3); salicylate, grown on succinate	NCIMB 40605	47, 48
BPDO	*Beijerinckia* sp. B1 ≡ *S.yanoikuyae* B1 (wild type)	ATCC 51230; DSM 6900	49, 11
	Beijerincka sp. B8/36 ≡ *S.yanoikuyae* B8/36 (mutant of *S. yanoikuyae* B1 wild type); biphenyl, *m*-xylene		49, 11
BPDO	*Pseudomonas* sp. LB400 ≡ *Burkholderia* sp. LB400		50, 51
	E. coli BL21(DE3)/pLys (clone of *B.* sp. LB400)		52
	E. coli FM4560(pGEM410) (clone of *B.* sp. LB400); grown on succinate		50
BZDO	*P. putida* JT103 (wild type)		53
	P. putida U103 (mutant); benzoate		53, 33

BZDO	*A. eutrophus* 335; wild type	ATCC 17697; DSM 531	35
	A. eutrophus 335 strain B9 (mutant of *A. eutrophus* 335); benzoate		34

[a]A discussion of inducers may be found in the section "Experimental Conditions".

[b]IPTG = isopropyl- β -D-thiogalactopyranoside

The mutant and recombinant versions of two *P. putida* strains, F1 and NCIMB 11767, are widely used for TDO oxygenations. In this case, a choice of which organism to use can be made on the basis of the availability of the strains. The mutant *P. putida* 39/D, from *P. putida* F1, can be obtained from a commercial repository such as the American Type Culture Collection (ATCC). However, the mutant *P. putida* UV4, from NCIMB 11767, is a proprietary strain that at the present time is not freely available for general use. The other natural and mutant microorganism strains given in the table are generally available from central repositories or from the research groups working with the strains. The recombinant strains of the microorganisms listed in Table A may, in most cases, be requested from the research group in which the strain was constructed. [See also the later subsection titled "Microorganisms (Cultures)."]

Some knowledge of the nomenclature of microbiology is essential to chemists when reading the literature of microbial arene oxidations for the first time. Subtle differences in names of microorganisms, particularly in designations of strains, may at first be confusing. It is also important to be able to follow the trail of names created as the microorganism containing a specific dioxygenase is modified from the natural (wild-type) microorganism to a mutant organism and to a recombinant organism. Typically, a natural—or wild-type—microorganism capable of metabolizing an arene molecule is first discovered. This is followed by development of a mutant strain of the organism that is capable of accumulating the dihydrodiol product. Until the past decade, the use of such mutant strains has been the primary means for generating large quantities of dihydrodiols. More recently, the development of recombinant strains of microorganisms into which the dioxygenase is cloned has found increasing application and holds much promise for further improvements in the production of dihydrodiols in practical quantities. Occasionally, the taxonomic classification of a microorganism is changed with the consequence that the name is changed (see both the NDO and BPDO sections below for examples). Detailed examples of microbial nomenclature are included below for the four major classes of dioxygenases.

Because scientists from a variety of disciplines have reported microbial arene oxidations, a wide range of reporting styles is found in the experimental details. The data range from detailed descriptions (including complete stereochemical assignment) of processes that yield multi-gram quantities (per liter of culture) of product to processes for which the dihydrodiol has not been isolated or characterized. Results of the latter type are placed in Table 10 to provide the reader with references that point to the potential for preparation of these dihydrodiols by microbial arene oxidation.

3.1. Toluene Dioxygenase (TDO)
Most dioxygenations of substituted benzenes are done with microorganisms expressing TDO. Among such microorganisms, two have been used for the majority of these oxidations. The first of the two is *P. putida* F1, (2, 54) the microorganism that played a key role in the discovery and development of arene oxidations (see Introduction). The designation "F1" is a descriptor given to the natural strain of this microorganism. A typical dioxygenation catalyzed by *P. putida* F1 is the conversion of toluene into (1*S*-*cis*)-3-methyl-3,5-cyclohexadiene-1,2-diol (**7**, Eq. 8). However, this natural strain contains the enzyme, *cis*-1,2-dihydrodiol dehydrogenase, which converts the dihydrodiol into a catechol, reducing the amount of dihydrodiol that can be isolated. When *P. putida* F1 was exposed to chemical mutation with MNNG, a mutant strain lacking the *cis*-1,2-dihydrodiol dehydrogenase was obtained. (39) Using the mutant strain, dihydrodiol **7** can be produced at the rate of almost 1 g/L of fermentation broth and with greater than 98% ee. (39) The mutant strain is named *P. putida* 39/D (sometimes, F39/D). (39) The genes of *P. putida* F1 responsible for dioxygenase activity have been cloned into *E. coli*. The resulting recombinant organism is named *E. coli* JM109(pDTG601). (41) In this name, JM109 refers to a strain of *E. coli* that frequently is used for cloning and (pDTG601) refers to the genetic sequence (plasmid) cloned from *P. putida* F1 into *E. coli* JM109. The *E. coli* JM109(pDTG601) also is free of *cis*-1,2-dihydrodiol dehydrogenase, permitting the dihydrodiol to accumulate.

$$(8)$$
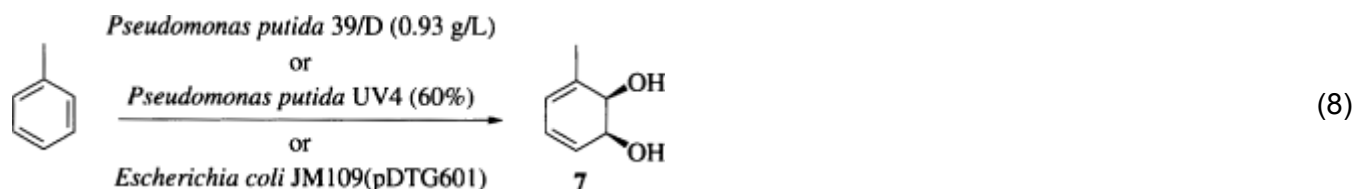
The second strain of *P. putida* that has been widely used for TDO activity is NCIMB 11767. (42) Mutation of this microorganism again produces a strain capable of accumulating dihydrodiol. This mutant strain is named *P. putida* UV4 and produces (1*S-cis*)-3-methyl-3,5-cyclohexadiene-1,2-diol in 60% yield and >98% ee. (55) A thorough description of the development of the mutant from the wild-type organism is available. (56) However, the mutant strain is proprietary and available only by request from the owners. (57) The dioxygenase genes from *P. putida* NCIMB 11767 have been cloned into *E. coli* and the resultant organism is *E. coli* JM109(pKST 11). (58) Immobilization of either *P. putida* UV4 or *E. coli* JM109(pKST 11) cells in barium alginate beads has been shown to improve the yield of dihydrodiols as measured on a mol/g of dry cell weight basis. (59) This immobilization technology has not as yet been used in preparation of dienediols for synthetic applications. Work to improve the fermentation processes for this microorganism continues. (60) *P. putida* UV4 has also been used for oxygenation of naphthalenes and various heteroaromatic compounds. Regioselectivity is lower with heteroaromatic compounds than with arenes but the level of enantioselectivity remains high. The isolated yields of the heterocyclic dienediols are low.

The sense of enantioselectivity of TDO oxidations is very consistent and allows formulation of the model shown in Figure 1. This figure summarizes existing data and can be used as an empirical model to predict the stereochemical outcome of new oxidations performed with either the mutants or the clones of these two TDO microorganisms.

Some benzoic acids and esters are substrates for TDO-containing organisms and are oxygenated to give dihydro-2,3-dihydroxy-1-carboxylic acids having regiochemistry and enantioselectivity (Eq. 9) (61) consistent with the model shown in Figure 1. A second class of microorganisms, containing the dioxygenase, BZDO, also may be used for dioxygenation of benzoic acids and esters. The regiochemistry of these dioxygenations differs from the TDO oxidations (Eq. 7). As a class, the BZDO oxygenations are discussed further in a separate section below.

$$(9)$$

As noted above, oxidation products other than dihydrodiols may be produced by TDO-containing organisms. These are discussed below in the section that addresses the issue of by-products formed in microbial arene oxidations.

3.2. Naphthalene Dioxygenase (NDO)

The groundwork for NDO and the oxygenation of naphthalene was laid with the discovery (62) of a strain of *P. putida* capable of growing on naphthalene. The wild-type strain was then transformed by mutation into *P. putida* 119, a strain that was able to accumulate the dienediol. (63) A large-scale fermentation with *P. putida* 119 produced a sufficient amount of the product for complete characterization as (1*R-cis*)-1,2-dihydro-1,2-naphthalenediol (**8**, Eq. 10). (63) The mutant strain, *P. putida* 119, subsequently was found to revert during fermentation to the wild strain and so has not been widely used in subsequent dioxygenation studies [These unpublished results of Gibson, D. T. and Klecka, G.M. are referenced (#52) in this chapter's reference 15.]

(10)
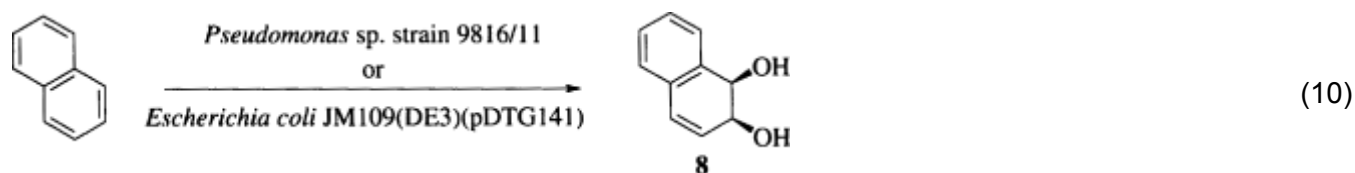
Another *Pseudomonas* strain that catalyzes the dioxygenation of naphthalene is *Pseudomonas* sp. NCIB 9816 (also known as NCIB 9816-4; or simply as 9816-4). (63) A mutant of this organism, *Pseudomonas* sp. 9816-11 (also: 9816 strain 11; 9816-11; or 9816/11) (46) that lacks the cis-dihydrodiol dehydrogenase enzyme, has been used in much subsequent work. The structural genes for the NDO in NCIB 9816-4 have been cloned and expressed in *E. coli* giving the strains JM109(DE3)(pDTG121) (64) and JM109(DE3)(pDTG141), (65) which can be used for performing dioxygenations. An excellent review summarizing oxygenations catalyzed by the NDO common to *Pseudomonas* sp. strain NCIB 9816-4, mutant strain NCIB-11, and the recombinant *E. coli* strain JM109(DE3)(pDTG141) has been published. (10)

Both *Pseudomonas* sp. NCIB 9816-11 and *E. coli* JM109(DE3)(pDTG141) oxygenate a variety of substrates other than naphthalenes. Indene and indanes are oxygenated by these organisms at benzylic positions (Eq. 11). (45) Several tricyclic (Eq. 12) (66) and heterocyclic arenes (Eq. 13) (67) are substrates for these organisms.

(11)

(12)

(13)
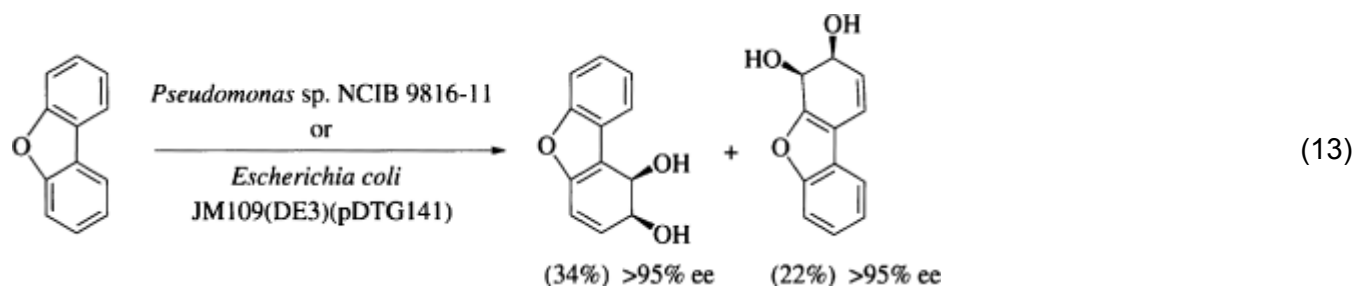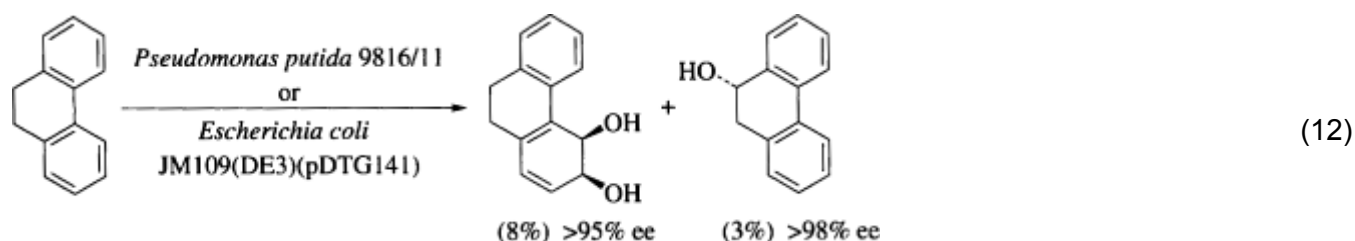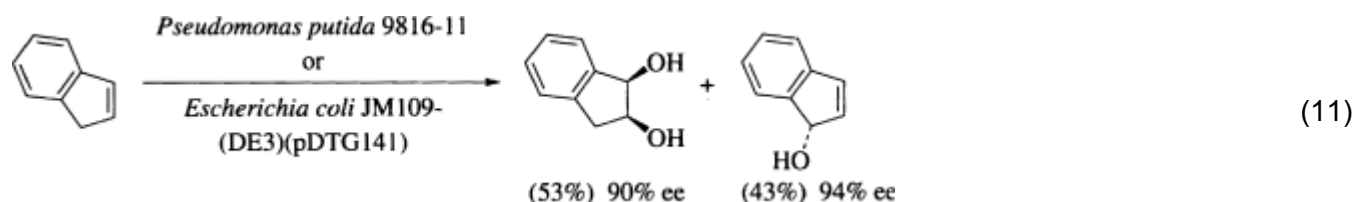
Another microorganism that has been used in the oxygenation of an extensive series of substituted naphthalenes (for example, Eq. 14) (47) is *P. fluorescens* N3 TTC1, a mutant of the wild-type *P. fluorescens* N3. (47) The dioxygenase of this organism has not been biochemically characterized as an NDO but the structural pattern of dihydrodiols produced is similar to that of *Pseudomonas* sp. NCIB 9816-11.

$$(14)$$
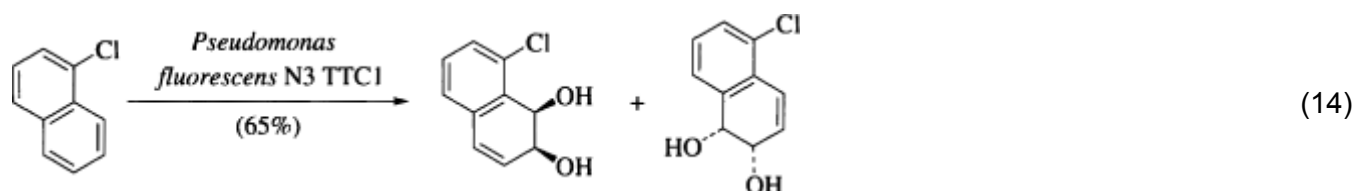
The model shown in Figure 1 can be used with care to predict the sense of regioselectivity and enantioselectivity of oxygenations catalyzed by the NDO enzymes. A later section provides descriptions of by-products of microbial arene oxidations by NDO microorganisms (see "Other Oxidations by Arene Dioxygenases").

3.3. Biphenyl Dioxygenase (BPDO)

A search for microorganisms that could be used in removal of polychlorinated biphenyls from the environment led to discovery of an organism with BPDO activity. (49) The microorganism was initially identified as a *Beijerinckia* species and was designated as species B1. (11) Mutation of the wild type gave *Beijerinckia* B8/36 in which the dihydrodiol dehydrogenase activity is blocked, allowing accumulation of the dihydrodiol. (49) In 1996 *Beijerinckia* B1 was reclassified as *Sphingomonas yanoikuyae* B1 (68) and, accordingly, *Beijerincka* B8/36 became *Sphingomonas yanoikuyae* B8/36. In this chapter, name usage corresponds to the nomenclature used in the literature references. Cloning of the genes for the BPDO activity of *S. yanoikuyae* B1 into another microorganism has so far been unsuccessful. (11) A thorough account of the history of this microorganism in the production of dihydrodiols has been published. (11)

The fermentation of biphenyl with *Beijerincka* B8/36 gives a product characterized as (1*S-cis*)-3-phenyl-3,5-cyclohexadiene-1,2-diol (**9**, Eq. 15). (49) Although the biphenyls are a structural subclass of benzenes, the oxygenation products obtained from them are listed separately in Table 3. The structurally related dibenzocyclobutane (Eq. 16) (69, 70) and fluorenes (e.g., Eq. 17) (67) are included with the biphenyls. It should be noted that biphenyl also is subject to oxygenation by NDO- and TDO-producing organisms.

$$(15)$$

$$(16)$$

$$(17)$$
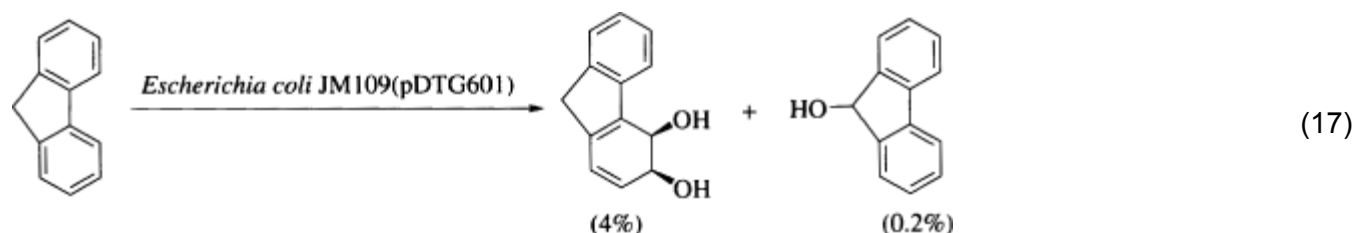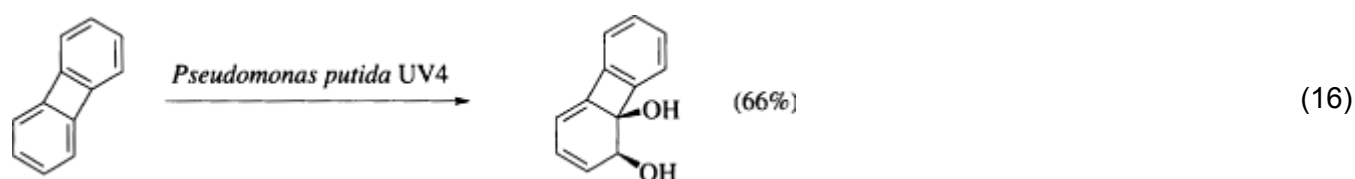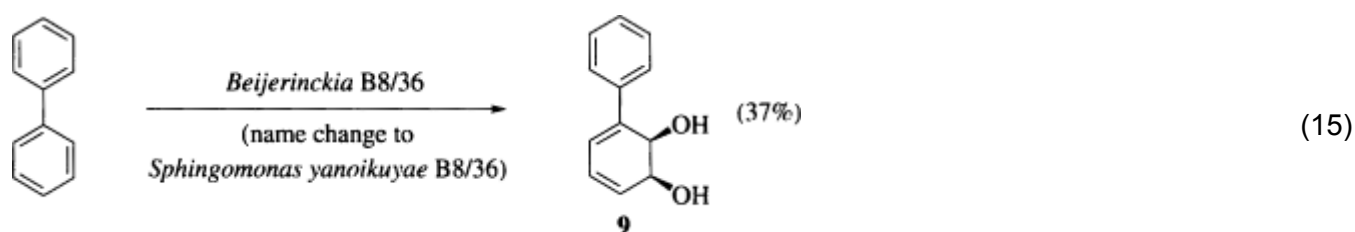
The BPDO enzyme is relatively non-specific with regard to substrate structure and has found considerable application in the dioxygenation of a variety of arenes, including a number of polycyclic aromatics (e.g., Eqs. 4 and 5) and many heteroaromatic compounds (Eq. 6). (11) Several chlorinated

biphenyls are reported to be oxygenated by *Beijerinckia* B8/36 to dihydrodiols but the results remain unpublished. (11)

Another organism capable of oxygenating biphenyl and related compounds is *Pseudomonas* sp. strain LB400. (51) This microorganism was isolated from polychlorinated biphenyl (PCB) contaminated soil. (71) *Pseudomonas* sp. LB400 has recently been reclassified as *Burkholderia* sp. strain LB400. (72) The BPDO enzyme complex from cells of *Pseudomonas* sp. LB400 has been isolated, purified and used for small scale oxygenation of chlorinated biphenyls (Eq. 18). (73) The small scale of these oxidations allowed for identification of the constitution of several dihydrodiols but not for a complete analysis of absolute configuration and enantiomeric excess.

(18)
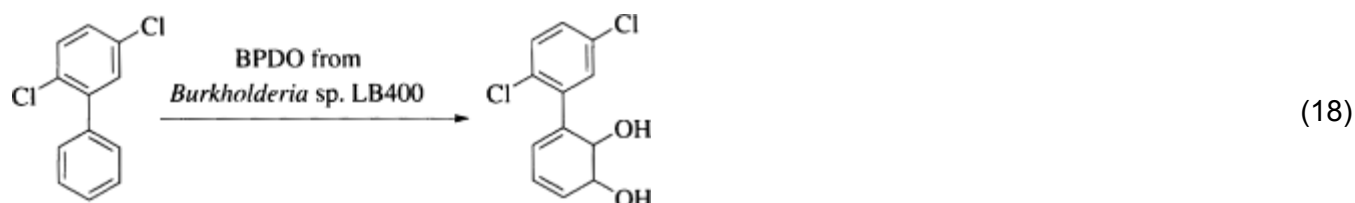
In another approach, the genes for the BPDO activity of *Burkholderia* sp. LB400 were cloned and expressed into *E. coli* giving strain BL21(DE3)/pLys. (52) Oxidations with the recombinant strain were done on a small scale and only limited characterization of dihydrodiols was therefore possible. Two dihydrodiols from this study are included in Table 3 and the remainder are included in Table 10. Yet another recombinant strain containing genes for BPDO is *E. coli* FM4560(pGEM410). This recombinant strain contains enzymes for the complete metabolic degradation of PCBs and is not useful for isolation of dihydrodiols. (50)

3.4. Benzoate Dioxygenase (BZDO)

The regiochemical differences in the dioxygenation of benzoic acids and esters by TDO and BZDO has already been noted. Oxygenations with TDOs give dihydro-2,3-dihydroxy-1-carboxylic acids (Eq. 9) whereas oxygenations with BZDOs occur at carbons 1 and 2 of the benzoic acid ring, giving dihydro-1,2-dihydroxy-1-carboxylic acids (also called ipso-cis-dihydrodiols).

Benzoic acid is converted into (1*S*-*cis*)-1,2-dihydroxy-3,5-cyclohexadiene-1-carboxylic acid (**6**, Eq. 7) by fermentation with either *Alcaligenes eutrophus* mutant strain B9 (35, 34) or with *P. putida* strain U103. (33) This dihydrodiol carboxylic acid is the only compound of this class for which the absolute configuration has been reported. Detailed descriptions have been published for carrying out the fermentation of benzoic acid with *P. putida* U103 (20–30 g dihydrodiol in 12 L) (33) or with *A. eutrophus* B9 (38 g of dihydrodiol from 6 L and 270 g from 80 L fermentations). (34)

The relative rates of dioxygenation of a series of seventeen benzoic acids by three microorganisms, *A. eutrophus* B9, *Pseudomonas* sp. B13, and *P. putida* mt-2, have been compared but no products were isolated (the results are not included in the Tables). (74) In a second report from the same laboratory, (36) the oxygenation of nine of these carboxylic acids with *A. eutrophus* B9 is described. The cis-relationships of the nine dihydrodiols are confirmed with spectral and chemical data. Circular dichroism (CD) spectral data suggest that all nine have the same absolute configuration as that of dihydrodiol **6** (Eq. 7). (36)

The mutant organism, *P. putida* PpJT103, has been used to oxidize several difluorobenzoic acids to 1,2-dihydroxy-1-carboxylic acids for which all stereochemistry except absolute configuration has been assigned. (75, 53)

Dioxygenation of naphthalene-2-carboxylic acid by *P. testosteroni* A3 produces the cis-1,2-diol in 74% yield (Eq. 19). (76)

(19)
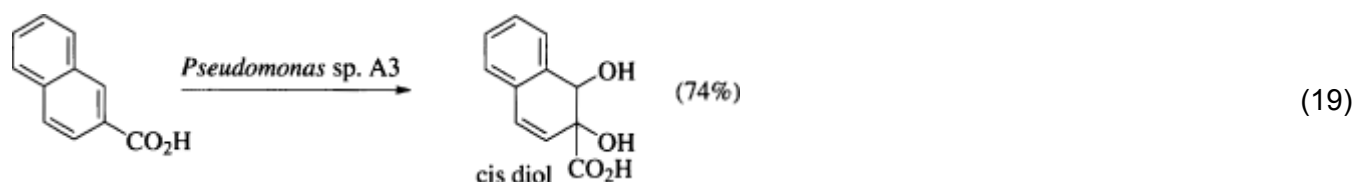
3.5. Other Dioxygenases

The cloning of the genes for the chlorobenzene dioxygenase (CDO) activity of *Pseudomonas* sp. strain P51 and their expression in *E. coli* DH5$_\alpha$ (pTCB144) has been described and the capacity of the recombinant strain for dioxygenation activity has been explored. (77) Of fifty-six compounds screened with this strain, thirty-five were substrates and were converted into one or more dihydrodiol products. Many of these dihydrodiols were not thoroughly characterized but enough analytical data was presented to allow the conclusion that both regioselectivity and enantioselectivity in these oxygenations parallels that of organisms that produce TDO. In some cases the ee's of the dihydrodiols exceed those of the analogous compound produced by a TDO. An example is the dihydrodiol obtained from 4-chlorotoluene. From fermentation with the TDO producing organism, *P. putida* UV4, the dihydrodiol has 15% ee but from *E. coli* DH5$_\alpha$ (pTCB144), the dihydrodiol has 77% ee. This recombinant strain offers promise for the dihydroxylation of a broad spectrum of arene molecules.

The marine bacterium *Nocardioides* sp. strain KP7 contains an arene dioxygenase that has been described as a phenanthrene dioxygenase. (78) The gene cluster (phdABCD) from this bacterium that codes for the dioxygenase has been introduced into *Streptomyces lividans*. The recombinant organism, *S. lividans* pIJ6021-phdABCD, converts 1-methoxynaphthalene into a mixture of 8-methoxy-1,2-dihydro-1,2-naphthalenediol and 8-methoxynapthol in a ratio of about 2:1. The organism also converts phenanthrene into *cis*-3,4-dihydroxy-3,4-dihydrophenanthrene in a nearly quantitative transformation. (78) The general usefulness of this organism for dioxygenation processes remains to be determined.

3.6. Other Oxidations by Arene Dioxygenases

A consequence of the broad substrate selectivity of the dioxygenases is that they also catalyze other types of oxidations, including: monooxygenations (usually at benzylic carbon), dihydroxylation of olefins, sulfoxidations, dehydrogenations, and *N*- and *O*-dealkylations. In some cases, these oxidations represent the major or even the exclusive transformation of a substrate. With enantiomeric substrates, the oxidations often proceed with high enantiospecificity. However, since oxidations of these types often can be achieved efficiently with chemical oxidants, the use of fermentations for these processes is of less impact. In order to place the oxidative scope of dioxygenases into larger perspective, the oxidations of olefins, of benzylic carbon, and of sulfur are included in Tables 7–9, respectively, and are discussed below.

A variety of olefinic bonds are oxygenated by dioxygenases. With styrene and substituted styrenes, oxygenation of the arene nucleus usually predominates over olefin oxygenation, a selectivity that cannot be achieved with chemical oxidants. Oxygenation of styrene with the TDO microorganisms, *P. putida* 39D and *P. putida* UV4, gives the dihydrodiol as the main product (Eq. 20). (79, 80-25) However, when the styrene olefin is confined in a second ring, such as in dihydronaphthalene or indene, oxygenation of the styrene double bond is favored over that of the arene system. Also of note in the oxygenation of indene is a reversal of enantioselectivity depending on whether a TDO or an NDO organism is used for the fermentation. Dioxygenation of indene with *P. putida* 9816-11 (45) or *E. coli* JM109(DE3)(pDTG141), (45) both NDO microorganisms, occurs at the olefinic bond giving the (1*R*,2*S*)-diol and is accompanied by benzylic hydroxylation of the indene methylene group (Eq. 21). Oxygenation of indene with *P. putida* UV4 (82) or *E. coli* D160-1, (83) TDO microorganisms, also occurs on the alkene but now gives the (1*S*,2*R*)-diol together with products of benzylic oxidation. The *E. coli* D160-1 was engineered to contain (1*R*,2*S*)-*cis*-dihydrodiol dehydrogenase in addition to TDO so that, in effect, it is able to carry out a kinetic resolution of the mixture generated by dioxygenation. The dihydroxylation of indene has received special attention because of the potential of the (1*S*,2*R*)-diol as a precursor to an anti-viral agent. (83)

(20)

(21)
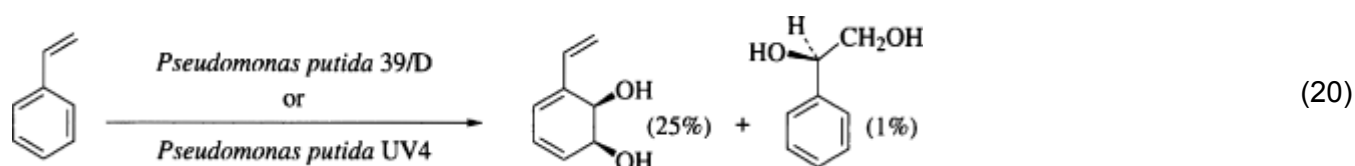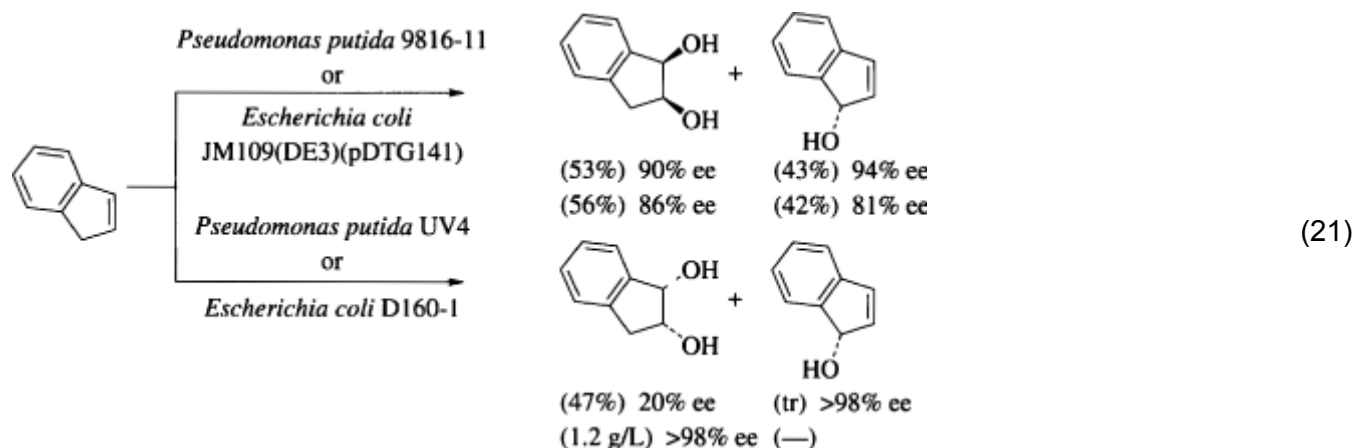
Exploration of the oxygenation of the olefinic bond has been extended to both acyclic and cyclic mono-, di-, and polyenes. 2-Methyl-1,3-butadiene is one of a series of four acyclic olefins whose oxygenation with dioxygenases has been studied. (84) Oxygenation of this substrate with *P. putida* ML 2 produced two glycols in a ratio of 4:1 (Eq. 22). Each of the two products is the result of dioxygenation of one or the other of the two olefinic bonds in the substrate. Yields were not reported in the preliminary communication but absolute configurations and enantiomeric excesses were determined.

(22)
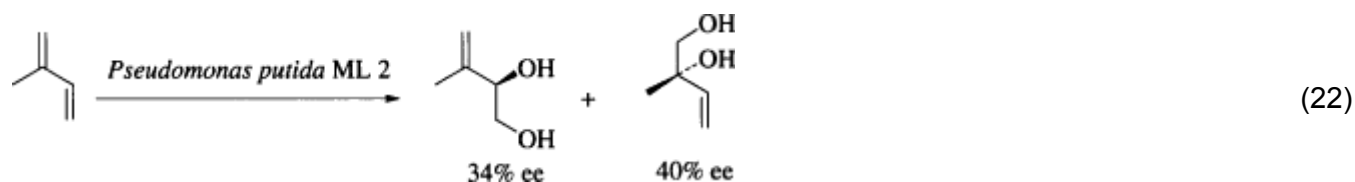
A variety of cyclic mono-, di-, and trienes ranging from 1-methylcyclohexa-2,3-diene to norbornadiene to azulene has been subjected to oxygenation by various dioxygenase-containing microorganisms, usually with good yields of cis-diols produced. For example, oxygenation of dimethylfulvene with either *P. putida* RE213 (85) or *P. putida* UV4 (86) gives the cis-(1*R*,2*S*)-diol (Eq. 23) with greater than 98% ee.

(23)
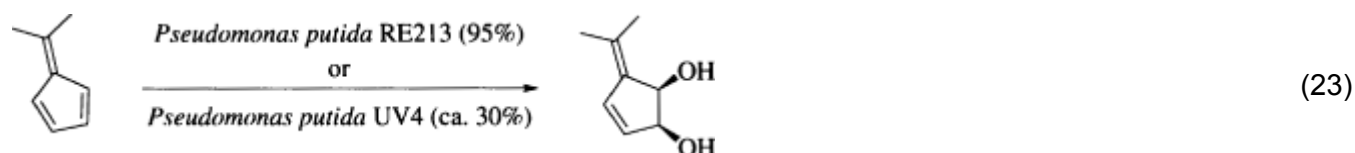
Monooxygenation at benzylic carbon is widely observed (see Table 8). Even in the dioxygenation of toluene by *P. putida* UV4, which gives the dihydrodiol in good yield, careful examination of the total product mixture reveals the presence of a small amount of triol wherein the methyl group is oxidized to a benzyl alcohol. (55) Such side reactions, usually minor, are observed in the dioxygenations of a variety of alkyl substituted benzenes with this microorganism. (55) Benzylic oxygenations also are observed in cyclic substrates such as indanes (Eq. 24) (87), indenes, dihydronaphthalenes, and a series of dimethylnaphthalenes where they often represent the major pathway of oxidation.

(24)
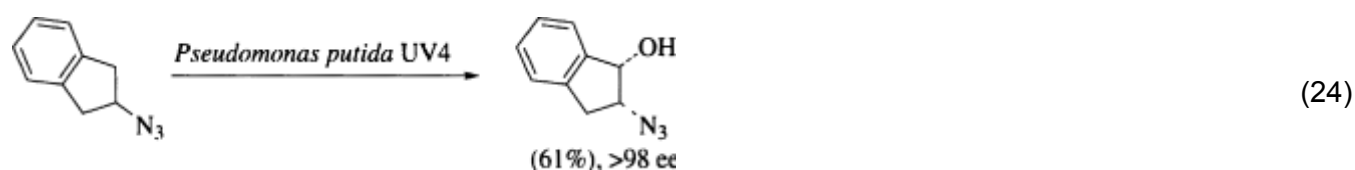
The oxidation of aryl sulfides by dioxygenases generally occurs at sulfur in preference to the arene ring (see Table 9). Sulfides are oxidized to sulfoxides and, when the sulfide is unsymmetrical, often with a

high degree of enantioselectivity. Methyl phenyl sulfide, for example, is oxidized to methyl phenyl sulfoxide and, depending on the choice of organism, either enantiomer of the sulfoxide may be formed (Eq. 25). (44, 88, 58) Thiophenes and benzthiophenes are subject to both dioxygenation and sulfoxidation leading to mixtures of four to six products. (89)

(25)
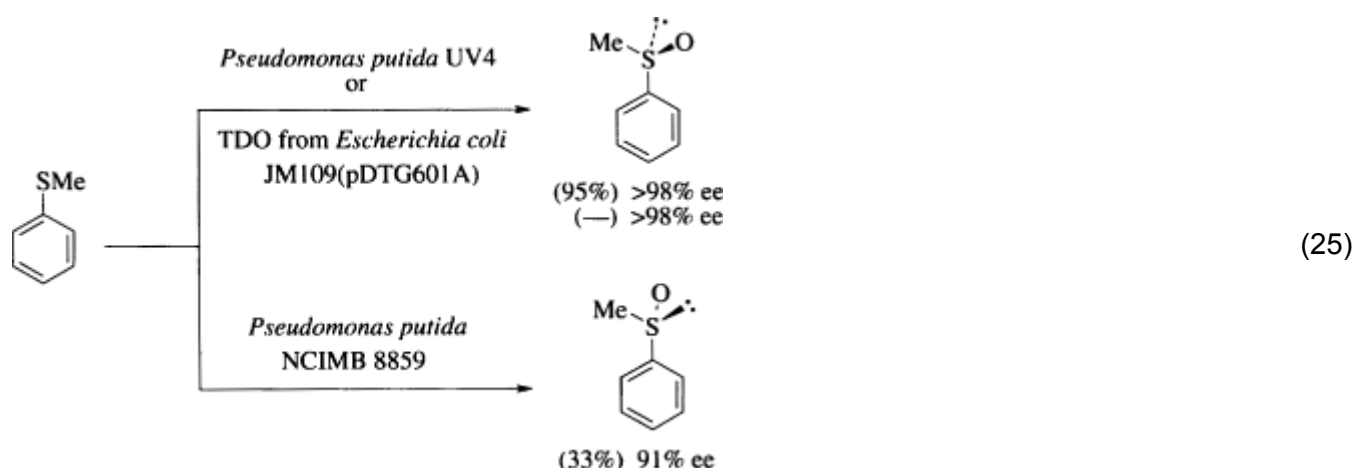
3.7. Site-Directed Mutagenesis of Dioxygenases

As noted earlier, a limitation of microbial arene oxidation is that, in most cases, only one enantiomer can be generated by this method. Site-directed mutagenesis of the microbial oxygenases offers promise as a method for obtaining either enantiomer of a dihydrodiol and changing the regiochemical outcome of the process. Biphenyl has been used as a substrate to study the effect that site-directed mutagenesis can have on the dioxygenation process. The result of oxygenation of biphenyl with *Beijerinckia* sp. B8/36 (name changed to *Sphingomonas yanoikuyae* B8/36), a BPDO producing organism, is shown in Eq. 15. Biphenyl may also be oxygenated with *E. coli* JM109(DE3)(pDTG141), an NDO producing organism, in which case the dihydrodiols, (2R,3S-cis)-dihydrodiol (>98% ee) and (3R,4S-cis)-dihydrodiol (>98% ee) (**10** and **11**, Eq. 26), are generated in a ratio of 87:13. (90, 31) When valine is substituted in place of phenylalanine-352 (code for this substitution: F352V) in the active site of this NDO, both the regiochemistry and the enantioselectivity of the oxygenation process are altered. Now the 2,3- and 3,4-dihydrodiols are obtained in a 4:96 ratio and the sense of enantioselectivity is changed such that the (3S, 4R-cis)-dihydrodiol **12** is obtained with 75% ee. (31) Fourteen other NDO variants were generated by substitution of from one to five amino acids near the active site of the native enzyme and were screened for dioxygenation of biphenyl. (91) The results shown (Eq. 26, top two lines) are the most divergent with regard to alteration of regio- and enantioselectivity.

(26)
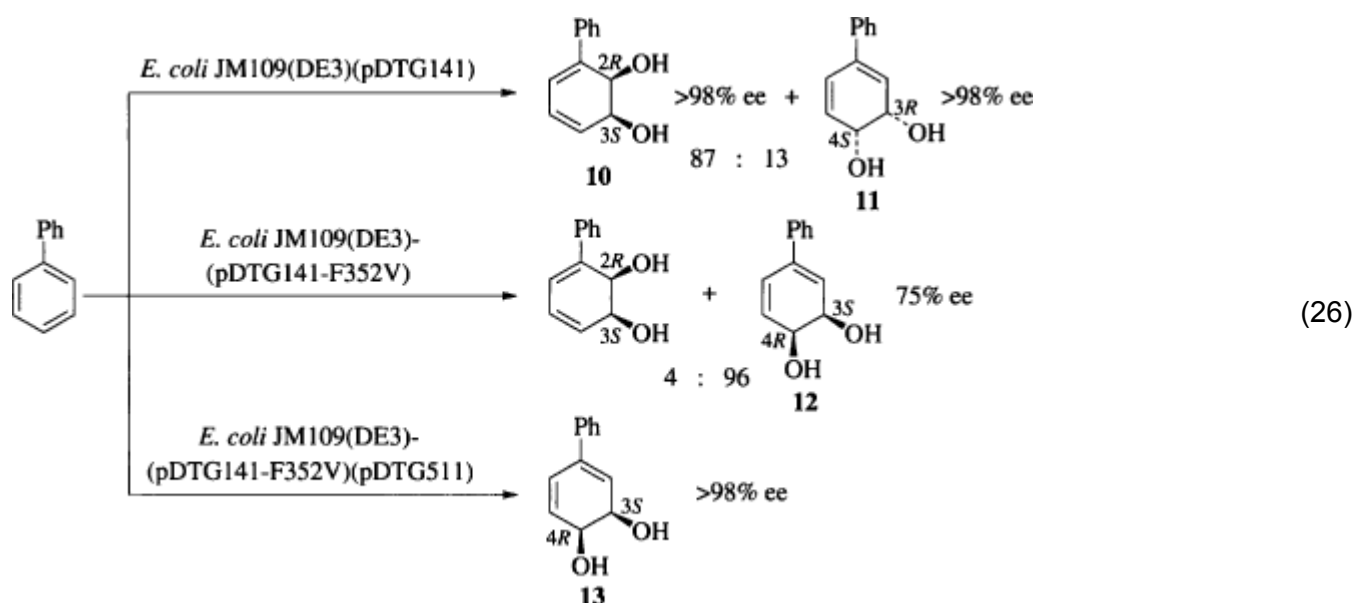
In a further step, genes encoding both the NDO F352V enzyme variant and a toluene dihydrodiol

dehydrogenase were expressed in an *E. coli* strain, JM109(DE3)(pDTG141-F352V)(pDTG511). Addition of the dihydrodiol dehydrogenase permits a kinetic resolution of the enantiomerically impure dihydrodiol oxygenation product to proceed. Fermentation of biphenyl with this *E. coli* strain gives enantiomerically pure (3S,4R-cis)-dihydrodiol **13** (Eq. 26). (31)

The oxygenation of phenanthrene with the same set of variant organisms used for biphenyl has been examined. The "baseline" dioxygenation of phenanthrene with *Beijerinckia* sp. B8/36 has been discussed previously (Eq. 5). Oxygenation of phenanthrene with *E. coli* JM109(DE3)(pDTG141-F352V) (31) gives (3S-cis)-3,4-dihydro-3,4-phenanthrenediol (**14**, > 95% ee) and (1S-cis)-1,2-dihydro-1,2-phenanthrenediol (**15**, 91% ee) (see Eq. 27) in a ratio of 17:83. Here again, a dramatic shift of regio- and enantioselectivity of oxygenation is seen with the organism altered by site-directed mutagenesis. Oxygenation of phenanthrene with all of the fourteen variants used for biphenyl gave various ratios of 1,2- and 3,4-dihydrodiols and in several cases the 9,10-dihydrodiol also was produced (Eq. 27). (91) Finally, as with biphenyl, oxygenation of phenanthrene with *E. coli* JM109(DE3)(pDTG141-F352V)(pDTG511) gave enantiomerically pure (1R-cis)-1,2-dihydro-1,2-phenanthrenediol (shown in Eq. 5). (31)

(27)
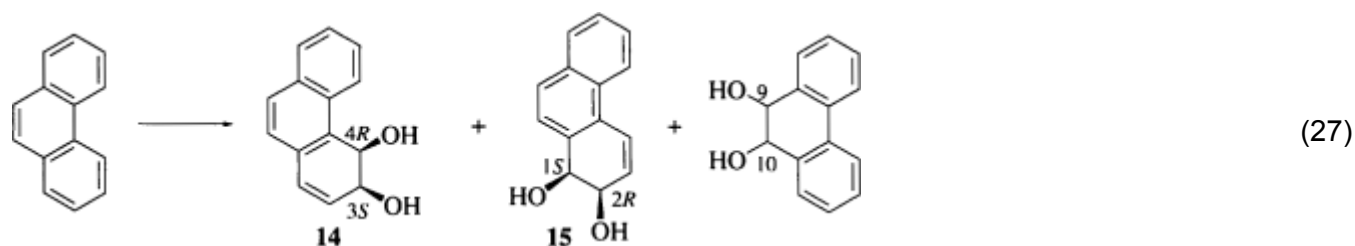
Another approach to modification of the oxygenation enzymes is directed evolution employing either DNA shuffling (92) or mutation of single genes (93) to generate libraries of modified organisms. These libraries are then screened for enhanced oxygenation of arenes. In one case, this has led to a strain that oxidizes 4-picoline to 3-hydroxy-4-picoline. (93) Although the product is not a dihydrodiol, the oxidation is assumed to proceed through the highly reactive dihydrodiol and illustrates that this approach may have potential for generating new arene dioxygenases.

3.8. Scope of Method
Because microbial arene oxidations developed from studies of metabolism, much of the initial work has examined the oxygenation of relatively simple molecules. Most substrates were simple benzenes, naphthalenes, and biphenyls having relatively few functional groups or additional complex ring structures. As the field has evolved, the method has been extended to increasingly larger aromatic hydrocarbons and their heterocyclic congeners. Such work now encompasses four- and five-ring polycyclic aromatic and heteroaromatic hydrocarbons. The conversion of the smaller arenes into dihydrodiol synthons is, of course, what has brought the method to the attention of chemists. What remains largely unexplored is application of the method to more elaborate substrates such as is exemplified in the dioxygenation of 7-oxodehydroabietic acid (**16**) by *P. abietaniphila* BKME-9 (Eq. 28). (94) Also unexplored is use of the method for introduction of a cis-diol at an intermediate or final step of a synthetic sequence. Applications to synthesis have all been based on the use of a dihydrodiol at the outset of the synthesis.

(28)
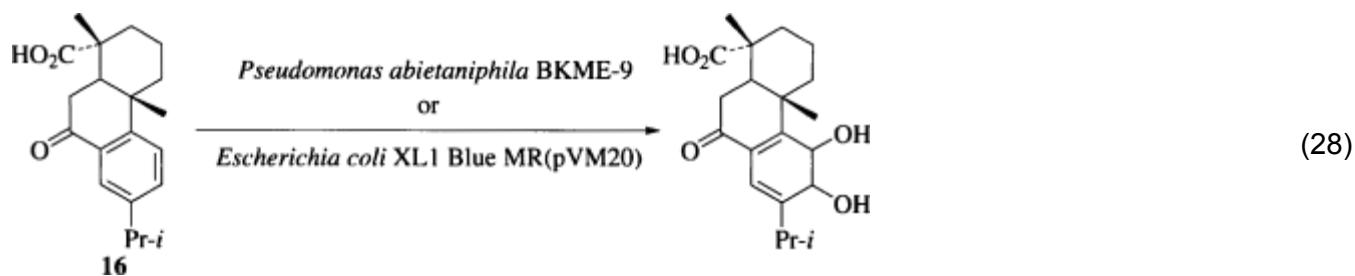
In addition, questions about the suitability of unusual arenes as substrates for different oxygenases are unanswered. For example, the capability of dioxygenases to oxygenate such unusual molecules as [2.2]-paracyclophane, bullvalene, semibullvalene, triphenylene, and biphenyls of restricted rotation should be explored. The question of whether a fullerene might be a substrate for a dioxygenase also

remains to be examined.

Several attempts have been made to utilize microbial arene oxidations in industrial scale syntheses, including the use of *cis*-3,5-cyclohexadiene-1,2-diol in polymer production (42) and of (1*R-cis*)-1,2-dihydronaphthalene-1,2-diol in the production of indinavir. (95) The fermentation step in the latter synthesis was shown to be practical but development into a full-scale industrial process failed because of the lack of proprietary control of the process. Still, there is no inherent reason that industrial arene dioxygenations cannot be implemented. Other microbial biotransformations, including monooxygenations, are performed routinely as industrial processes. Arene dioxygenation awaits another synthetic target derived from a dihydrodiol needed on a production scale to demonstrate usefulness as an industrial process.

4. Applications to Synthesis

Representative examples of the use of dihydrodiols in synthesis are presented in this section, which is divided into two parts. In the first part, some synthetic modifications of microbially produced dihydrodiols that generate other synthetic intermediates are presented. Chemical modifications of the dihydrodiols have also been reviewed elsewhere. (15, 96, 97) In the second part, representative examples in which dihydrodiols have been elaborated into more complex molecules are summarized. The work related to the second part has been extensively reviewed, (98-100) both from the point of view of natural product classes (101, 102) and of the contributions of individual research groups. (103, 104) The approach used here is to show one or more examples of syntheses derived from each of a variety of different dihydrodiols. Further, rather than showing the entire multi-step synthesis, only the starting dihydrodiol and the final natural product are shown.

4.1. Other Synthetic Intermediates by Modification of Microbially Produced Dihydrodiols
The simple, one-step modification of dihydrodiols by replacement of a reactive group provides a route to new dihydrodiols. Most modifications of this kind have been done using (1*S-cis*)-3-iodo-3,5-cyclohexadiene-1,2-diol (**17**). For example, the palladium-catalyzed reaction of this iodide with phenyl tributyltin sulfide gives (1*S-cis*)-3-phenylthio-3,5-cyclohexadiene-1,2-diol (**18**, Eq. 29). (105, 25, 27) A similar palladium-catalyzed Sonogashira coupling with trimethylsilylacetylene gives (1*S-cis*)-3-(trimethylsilyl)ethynyl-3,5-cyclohexadiene-1,2-diol. (105, 106)


$$(29)$$
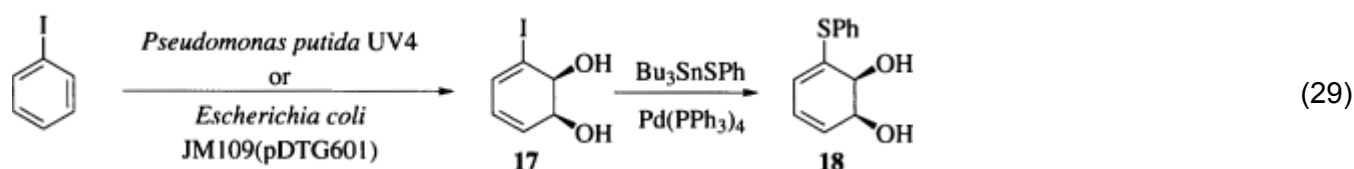
Another one-step approach to new dihydrodiols is the catalytic removal of iodine from a dihydrodiol obtained by oxygenation of a disubstituted benzene substrate. In the case of 4-fluoroiodobenzene, the microbially produced (1*S-cis*)-6-fluoro-3-iodo-3,5-cyclohexadiene-1,2-diol (**19**) has an 88% ee. (27, 23, 107) Catalytic removal of the iodine gives (1*R-cis*)-3-fluoro-3,5-cyclohexadiene-1,2-diol (**20**), still with an 88% ee (Eq. 30). (27) Fluorodihydrodiol **20** produced by this procedure is enantiomeric to that obtained from the direct oxygenation of fluorobenzene. (24-25)


$$(30)$$
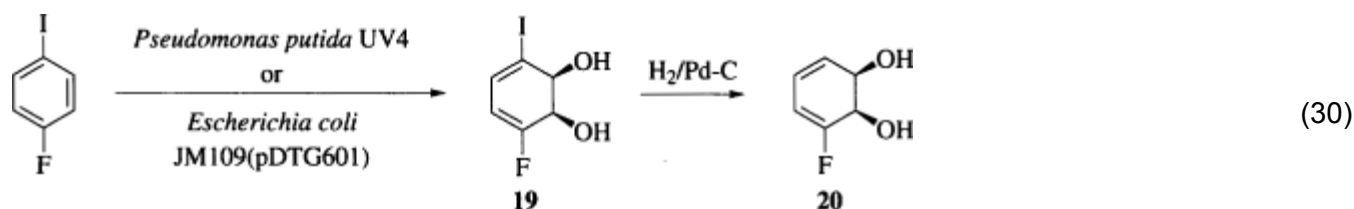
Another example employing removal of iodine illustrates routes to both enantiomers of a new dihydrodiol. Oxygenations of 2-fluoroiodobenzene and 3-fluoroiodobenzene give (1*S-cis*)-4-fluoro-3-iodo-3,5-cyclohexadiene-1,2-diol (**21**) and (1*S-cis*)-5-fluoro-3-iodo-3,5-cyclohexadiene-1,2-diol (**23**), respectively, in yields of 75% and with ee

>98%. Catalytic removal of iodine from each of these dihydrodiols produces the enantiomers, (1*S-cis*)-4-fluoro-3,5-cyclohexadiene-1,2-diol (**22**) and (1*R-cis*)-3-fluoro-3,5-cyclohexadiene-1,2-diol (**24**), respectively (Eqs. 31 and 32). (27)

(31)

(32)
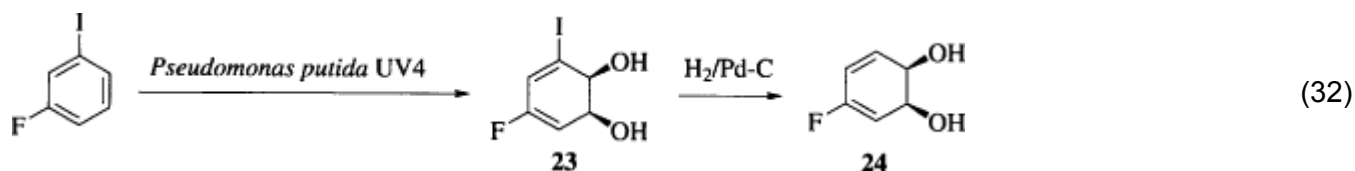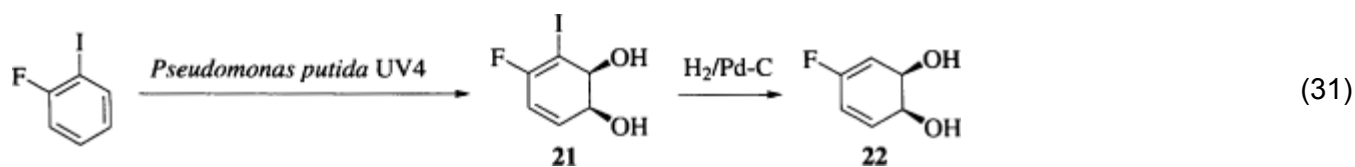
In another approach to the generation of both enantiomers of a dihydrodiol, an enzymatic kinetic resolution step is used. (1*S-cis*)-6-Bromo-3-iodo-3,5-cyclohexadiene-1,2-diol (**25**) is obtained with an ee of 22% from oxygenation of 4-bromoiodobenzene with *P. putida* UV4 (Eq. 33). (23) Hydrogenolysis of this dihydrodiol to remove the iodine gives the (1*R-cis*)-3-bromo-3,5-cyclohexadiene-1,2-diol (**26**, 22% ee) which, when placed in fermentation with the dienediol dehydrogenase-bearing organism, *P. putida* NCIMB 8859, is "upgraded" to (1*R-cis*)-3-bromo-dienediol (**27**) with ≥98% ee. (108) The enantiomeric (1*S-cis*)-3-bromo-3,5-cyclohexadiene-1,2-diol is produced in the oxygenation of bromobenzene. (106, 25) The pathway from 4-bromoiodobenzene to the (1*R*)-enantiomer is of relatively low overall yield.

(33)
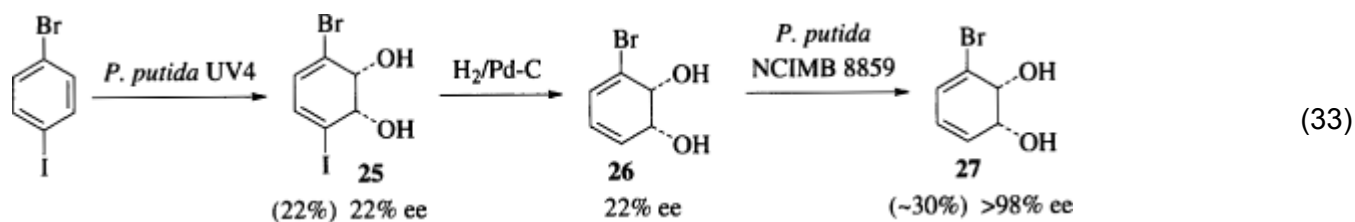
4.2. Use of Dihydrodiols in Synthesis

The use of dihydrodiols in synthesis developed very slowly. In 1983, the preparation of polyphenylene in three steps from *cis*-3,5-cyclohexadiene-1,2-diol (**1**, Eq. 34) was described. (109)

(34)

The use of this dihydrodiol as a monomer for the production of polymers became feasible with the economic production of dihydrodiols by industrial scale fermentations. (42, 56) Work to improve the process and the quality of the polymer produced has been reported. (110, 111)

The application of dihydrodiols to the synthesis of natural products was pioneered in 1987 when dihydrodiol **1** was used in a six-step synthesis of (±)-pinitol (Eq. 35). (112)

(35)

Following the synthesis of (±)-pinitol, reports describing the synthesis of both unnatural and natural products from dihydrodiol precursors rapidly increased in number. Shown below are examples that illustrate the use of a variety of dihydrodiols in synthesis. Where not immediately obvious, the disposition of the atoms of the dihydrodiol in the final product is indicated by numbering of carbon atoms.

Among the many natural products syntheses based on **1** (see Figure 3) are an eight-step synthesis of 3,4-dihydroxy- α -tropolone (**28**), (113) an eleven-step synthesis of (±)-*myo*-inositol 1,4,5-triphosphate (**29**), (114) and two-step syntheses of conduritols A (**30**) and D (**31**). (115) Dihydrodiol **1** also has been used as a precursor for several "unnatural" products. The compound, *anti-o,o'*-dibenzene (**32**) is derived from the dihydrodiol in three steps, the first of which is a photochemical dimerization. (116) Benzobarrelene (**33**) is prepared from **1** in a four-step sequence that includes addition of benzyne to the diene. (117).
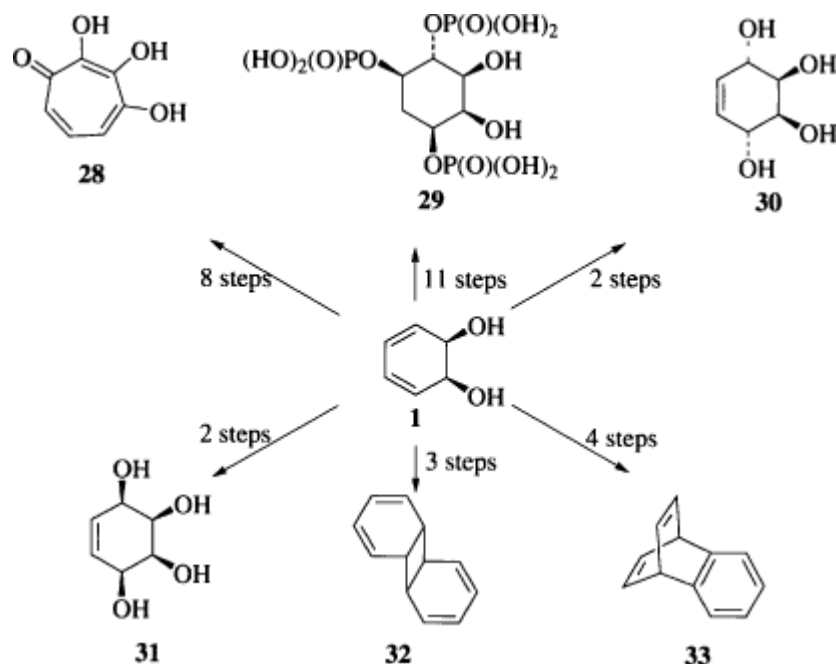
Figure 3. *cis*-3,5-Cyclohexadiene-1,2-diol (**1**) serves as the starting point for synthesis of natural and "unnatural" products.

In the acid-catalyzed dehydration of 3-substituted dihydrodiols, the predominant product in most cases is the *o*-phenol (Eq. 36). (118) An exception is found when the 3-substituent is a ketal. Acid-catalyzed dehydration of these dihydrodiols results in formation of the *m*-phenol as well as hydrolysis of the ketal (Eq. 37). The 3-acetyl or 3-formylphenols are useful precursors in the synthesis of 3-ethynylphenol. (81)

(36)

(37)

(1*S-cis*)-3-Methyl-3,5-cyclohexadiene-1,2-diol serves as the starting point for a four-step synthesis of pseudo- α -L-fucopyranose (Eq. 38). (119) Diels-Alder cycloadditions and anionic oxy-Cope

rearrangements are used as key steps in syntheses of several cis-decalins (120) and bicyclo[5.3.1]undecanes from the 3-methyldihydrodiol. (120a) The cis-decalins have potential use as intermediates leading to the synthesis of natural products such as mevinolin and artemisinic acid while the bicyclo[5.3.1]undecanes are envisioned as taxol^TM precursors.

pseudo-α-L-fucopyranose

(38)

(1S-cis)-3-Chloro-3,5-cyclohexadiene-1,2-diol is the dihydrodiol that has most frequently been used as a synthetic precursor. The compound serves as a starting point for a nine-step synthesis of L-ascorbic acid (Eq. 39). In this synthesis, the C(1) hydroxyl group of the dihydrodiol directs epoxidation of the electron rich C(5)-C(6) double bond affording the syn isomer. Subsequent manipulation of the molecule results in rehybridization of the two original carbinol atoms. (121) Among other syntheses, the 3-chlorodihydrodiol serves as the starting material for a seventeen-step synthesis of the amaryllidaceae alkaloid (+)-trianthine. (122)

L-ascorbic acid

(39)

As a synthetic intermediate, (1S-cis)-3-bromo-3,5-cyclohexadiene-1,2-diol closely parallels (1S-cis)-3-chloro-3,5-cyclohexadiene-1,2-diol. Several compounds from the amaryllidaceae family have been constructed from the bromodihydrodiol including (+)-pancratistatin, prepared in a thirteen-step synthesis (Eq. 40), (123) and the related (+)-7-deoxypancratistatin, obtained in nine steps. (124) In a seven-step synthesis of cyclopropane intermediate 34, a compound proposed for use in preparation of pyrethrins, the atoms of the starting bromodihydrodiol are barely recognizable in the final product (Eq. 40). (125)

(+)-pancratistatin

34

(40)
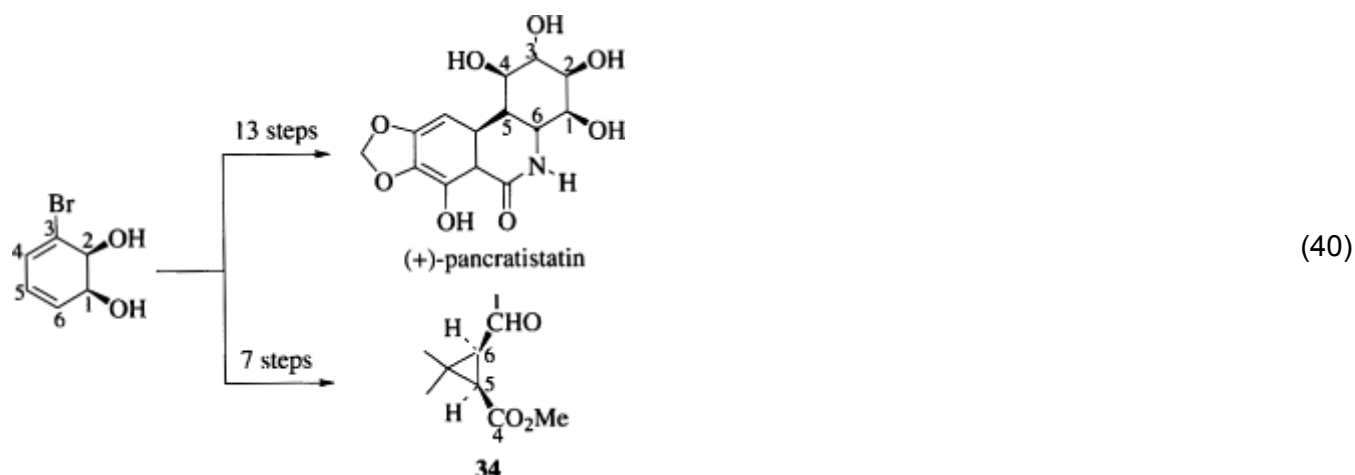
Several dihydrodiols have been used in new and different approaches to morphine. The most advanced of these uses (1S-cis)-3-(2-bromoethyl)-4-bromo-3,5-cyclohexadiene-1,2-diol as a key intermediate. Thirteen synthetic steps are used to convert the dihydrodiol into ent-C14-epi-morphinan (Eq. 41). (126, 127) (1S-cis)-3-(2-Azidoethyl)-3,5-cyclohexadiene-1,2-diol, (128)

(1*S*-*cis*)-3-(2-bromoethyl)-3,5-cyclohexadiene-1,2-diol, (129) and
(1*S*-*cis*)-3-(2,3-dimethoxyphenyl)-3,5-cyclohexadiene-1,2-diol (130) all have been used to synthesize intermediates on potential pathways to morphine.

ent-C14-*epi*-morphinan

(41)
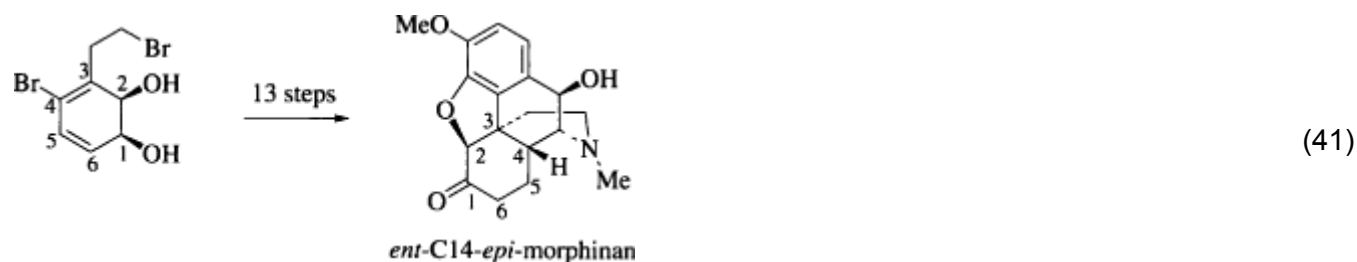
(1*S*-*cis*)-3,5-Dibromo-3,5-cyclohexadiene-1,2-diol serves as a chiral starting material in an eleven-step route to the Amaryllidaceae alkaloid (+)-narciclasine (Eq. 42). (131)

(+)-narciclasine

(42)
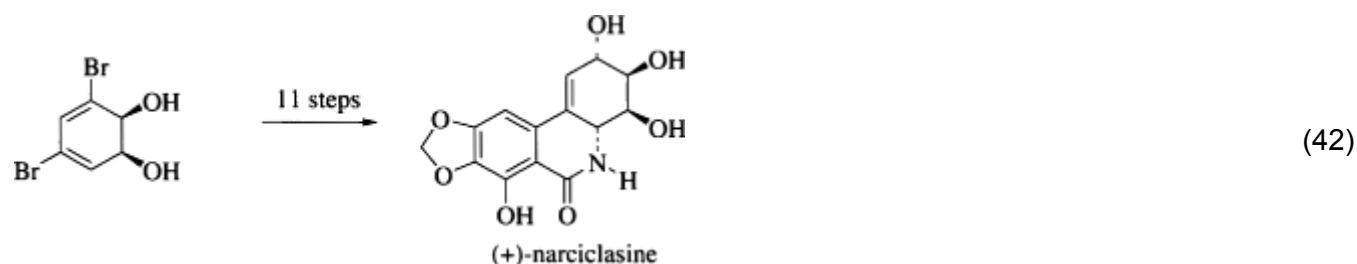
(1*S*-*cis*)-3-Vinyl-3,5-cyclohexadiene-1,2-diol is converted in eleven steps to the tricyclic natural product (−)-zeylena (Eq. 43). (132)

(−)-zeylena

(43)
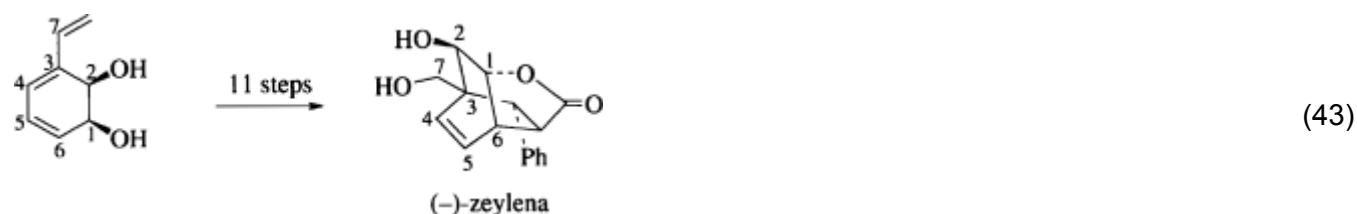
(1*R*-*cis*)-1,2-Dihydronaphthalene-1,2-diol is converted, in five steps, to polyhydroxylated tetrahydronaphthalene ethers (Eq. 44). Both of the tetrahydronaphthalene units of the ether product are derived from the dienediol. (133)

(44)
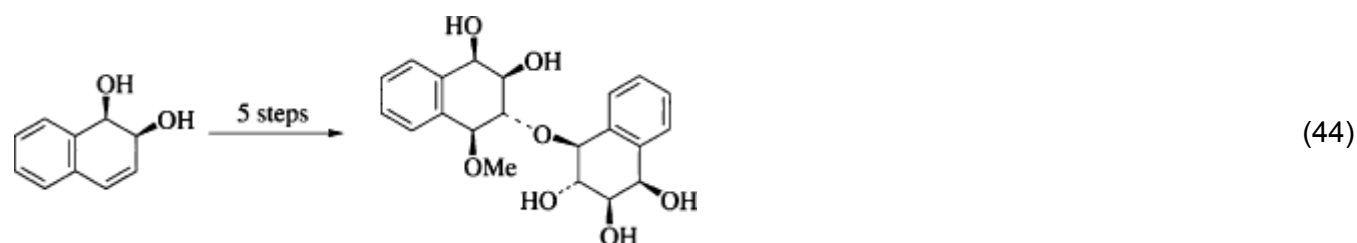
The diol moiety of the dihydrodiols is frequently protected during synthetic manipulations as an acetonide. By carrying out the ketalization reaction with a resinlinked acetonide, the dihydrodiol grouping has been used in solid-phase synthesis for the preparation (134) of small combinatorial sortiments. (135) Both (1*S*-*cis*)-3-chloro-and (1*S*-*cis*)-3-bromo-3,5-cyclohexadiene-1,2-diol are readily incorporated into the resin (134) and are used in coupling reactions (Eq. 45). (134, 136)

(45)
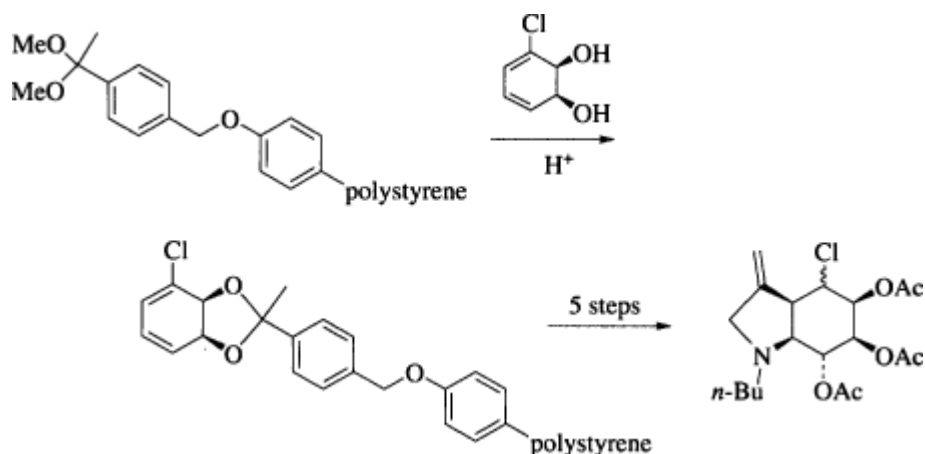
5. Comparison with Other Methods

A synthesis of *cis*-3,5-cyclohexadiene-1,2-diol from benzene described in 1959 (137) is lengthy and not easily applicable to substituted dihydrodiols. A second synthesis (of the acetonide) from 1,4-cyclohexadiene described in 1982 (138) likewise is not of general use. A photochemically induced reaction of benzene with osmium tetroxide described in 1995 is postulated to proceed through an osmate ester of *cis*-3,5-cyclohexadiene-1,2-diol but the isolated products of the reaction were a hexaacetoxycyclohexane and three isomers of chloropentaacetoxycyclohexane. (139)

6. Experimental Conditions

6.1. Comments about Yields

The yield of a reaction is of paramount importance to the synthetic chemist. Because the determination of yield is a requirement of a good experimental procedure, it usually is reported in chemistry journals. Chemical yield often is of less concern to microbiologists and therefore is not always to be found in the experimental details reported in microbiology journals. In the Tables of this chapter, yields based on starting material are provided wherever possible. Indeed, when the reported data permit, yields have been calculated and are included in the Tables.

A frequent practice in reports of microbial arene oxidations is to report g/L of product isolated from the fermentation of a given substrate. It may be that in such experiments, substrate was supplied to the fermentation in excess until product concentration was observed to reach a maximum. Volatile substrates may be partially lost from the fermentation medium by evaporation or via the air stream if the experiment is not properly designed. The yield data reported in the Tables for such experiments are given simply as g/L. On occasion, an impressive weight of product may be reported for these experiments but this value may still represent a low chemical yield.

The expression "relative yield" also is found in some literature reports and usually expresses the yield of a given product as a percentage of the total weight (or total area under GC peaks) of product(s) isolated or measured in the experiment. Clearly, such values are not true chemical yields but do serve to give a measure of the relative amount of a product formed in a fermentation.

6.2. Stability and Isolation of Dihydrodiols

The key to isolation and storage of dihydrodiols is to realize that the compounds are sensitive to acid-catalyzed dehydration. The corollary of this observation is that dihydrodiols are stable at or above pH ~9. The following approach to the isolation and storage of dihydrodiols is recommended. (140) (The method is varied slightly depending on the molecular weight of the dihydrodiol being produced.) With lower molecular weight compounds, once the oxygenation process has reached a maximum level of dihydrodiol, the fermentation mixture is centrifuged in order to separate the mixture into a solid pellet and a supernatant solution. The supernatant is separated, adjusted to pH ~9, and concentrated approximately ten-fold by evaporation of water under partially reduced pressure. At this point, the remaining aqueous solution is relatively concentrated with inorganic salts, and the dihydrodiol is stable and can be stored in this condition. When the dihydrodiol is needed, it can be extracted easily into an organic solvent and then isolated by the usual methods. For the higher molecular weight dihydrodiols (starting with the dihydrodiols from naphthalenes and biphenyls), the *addition* of water to the fermentation

mixture before performing the centrifugation and separation step is recommended to provide the aqueous volume necessary for solubilization of the product.

The stability and ease of isolation of dihydrodiols are often discussed anecdotally in the literature. For example, attempts to isolate *cis*-3,5-dimethyl-3,5-cyclohexadiene-1,2-diol from the oxygenation of *m*-xylene were unsuccessful, a result that has been attributed to the instability of the compound. (141) On the other hand, *cis*-3,6-dimethyl-3,5-cyclohexadiene-1,2-diol, the oxidation product from *p*-xylene, was isolated and characterized. The latter dihydrodiol was observed to be unstable and was converted into 2,5-dimethylphenol within six hours at room temperature. (141) The dihydrodiols derived from oxygenation of methoxy- and ethoxybenzene are characterized as unstable and subject to rapid aromatization, although derivatives from which structure and absolute configuration are determined have been prepared. (142, 25, 38) The half-life of (3*S*-*cis*)-3-chloro-3,5-cyclohexadiene-1,2-diol in a CDCl$_3$ solution was measured by NMR spectroscopy. At room temperature, the half-life was found to be four days but the diol could be stored at –20° to –80° for several months without decomposition. (40) The room temperature NMR experiment may be questioned since deuterochloroform is not a good solvent for storage of dihydrodiols because it has a propensity to generate traces of DCl.

In detailed studies leading to the production of *cis*-3,5-cyclohexadiene-1,2-diol from benzene on a ton scale, the dihydrodiol is stored following purification as a solution in ethyl acetate containing a small amount of triethylamine. (56)

Dihydrodiols are subject to acid-catalyzed elimination of water, resulting in aromatization and formation of a phenol. A study of the acid-catalyzed aromatization of a series of 3-substituted dihydrodiols has been reported. (118) The results are consistent with dehydration via a benzonium ion like intermediate. Rate constants for the process are highest for electron-releasing substituents such as alkoxy and alkyl groups and lowest for electron-withdrawing groups such a trifluoromethyl, sulfinyl, and sulfonyl. A difference in rate of 10^7 is observed between the most- and least-stabilized dihydrodiols in this study.

A practical consequence of the above results is that care should be taken to avoid acidic conditions in the isolation and handling of dihydrodiols. The precautions needed are often evident in descriptions of experimental conditions wherein pH is adjusted to >7, solvents are given alkaline washes, and chromatography is conducted with neutral adsorbents.

The sensitivity of the dihydrodiols to acid gives pause when considering oxygenation of substrates of the benzoic acid class. In several cases, the dihydrodiol-carboxylic acid products, while stated to be "unstable," have nevertheless been isolated and characterized. In the isolation of (1*S*-*cis*)-1,6-dihydroxy-2,4-cyclohexadiene-1-carboxylic acid from the fermentation broth, the pH of the mixture is kept at 4 during the extraction process. The product is isolated in good yield and is stable up to a year when stored at –20°. The sodium salt of the acid also was prepared and characterized. (33) In general, dihydrodiol-carboxylic acids may be isolated and stored as salts. The closely related (1*S*-*cis*)-1,6-dihydroxy-4-methyl-2,4-cyclohexadiene-1-carboxylic acid is described as unstable and is characterized as the sodium salt. (143) The free acid is generated as needed by acidification and rapid extraction of an aqueous solution of the salt. Alternately, the carboxylic acids can be converted into methyl esters, stabilizing the compounds.

6.3. Microorganisms (Cultures)
Culture (microorganism) procurement and handling are aspects of performing microbial arene oxidations that are likely to be unfamiliar to most organic chemists. Herewith are a few comments concerning the procurement of the specific microorganism desired for a given dioxygenation reaction. There are various sources for traditional, wild-type (natural) microorganisms. There are many central repositories throughout the world to which microbiologists submit pure cultures of new microorganisms or microbial strains as they are discovered and characterized. Several examples of such repositories are the American Type Culture Collection (10801 University Boulevard, Manassas, VA 20110; http://www.atcc.org); Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH (DSM; Mascheroder Weg 1b, D-38124 Braunschweig, Germany; http://www.dsmz.de); National Collections of Industrial, Food and Marine Bacteria (NCIMB; 23 St. Machar Drive, Aberdeen, AB24 3RY, Scotland, UK; http://www.ncimb.co.uk). These repositories maintain the pure cultures and provide "samples" or "seed cultures" of most microorganisms for a reasonable fee. If a microorganism strain is not available through such a central collection, it then is necessary to obtain the culture from the research group that has reported working with the microorganism.

As is evident from the previous sections of this chapter, the microorganisms most desirable for arene oxidations either are mutants of the wild-type strain or, increasingly, are microorganisms (usually *E. coli*) that contain plasmids encoded with the genes expressing the enzymes necessary for the dioxygenation reaction. These mutant and genetically engineered microbial strains often are not available from the aforementioned depositories. Consequently, it is necessary to request and obtain these strains from the laboratories in which they were originated or may now be in use. Publication of results in the journals of the American Society for Microbiology (ASM) implies that microorganisms described in the work will be supplied to other research groups upon request (the *Journal of Bacteriology* and *Applied and Environmental Microbiology* are the two ASM journals in which most arene oxidation work is published). Such requests require documentation of the capability to work with the microorganism. Occasionally, certain mutants or clones may be proprietary and, therefore, difficult to obtain for general use in carrying out arene oxidations.

Once obtained, transfer of the microbial culture is necessary in order to perform the fermentation that will produce the desired dihydrodiol. Basic microbiology techniques are required for such transfers. While not difficult, these techniques and standard microbiological equipment may not be familiar to the chemist. A description of some of these techniques is given in a following section (see "Experimental Procedures"). In addition, the assistance of a colleague familiar with basic microbiological manipulations can be most helpful and should be sought.

6.4. Inducers

The dioxygenases of mutant and recombinant strains of microorganisms often require that an inducer compound be added at an early phase of the fermentation to stimulate production of the enzyme. The inducer may be a natural substrate of the dioxygenase or another compound known to have the desired effect. For example, the TDO of *P. putida* 39/D is induced by toluene while the NDO of *Pseudomonas* sp. NCIB 9816-11 is induced by salicylate or succinate ions. Inducers used with some of the more frequently used microorganisms are included in Table A. The ability of a new substrate to induce the dioxygenase of a microorganism may be evaluated by using the indigo test. (40)

7. Experimental Procedures

7.1. Handling the Microorganisms

The storage, transfer, and growth of microbial cells requires use of several fundamental techniques of microbiology. These techniques are not particularly difficult to perform but they require specialized equipment and adherence to strict standards. It is important at the outset of a fermentation that one be confident that the microbial cells are of high quality. An attempt has been made to include enough information to permit the chemist to proceed on his/her own. However, at this stage, consultation with a scientist familiar with basic microbiological manipulations can be helpful.

Stock cultures of microorganisms may be stored by several different methods. A traditional method is on an agar slant (or slope) in a screw-capped vial or test tube. The agar slant is inoculated with cells of the pure culture, the inoculum is allowed to establish growth on the surface of the agar, and then the closed tube is stored at low temperature. In another method of storage, cells of the pure culture are grown in a medium, such as Luria-Bertani broth, after which aliquots of the medium and culture are transferred to cryovials. Sterile glycerol containing the same nutrients as the broth is added to the vials, which are then closed and stored at low temperatures. In a third method of storage, the medium in which the culture has been allowed to grow is lyophilized in a vial or tube. The residual dry pellet is closed in the container and stored at low temperature.

The seed culture of the microorganism will most likely arrive or be made available growing on an agar slant, i.e., a test tube in which nutrient agar has been allowed to solidify to give a slanted surface. Seed cultures also may be obtained as glycerol solutions or lyophilized powders.

The transfer of cells of a microorganism requires a strong laboratory burner (as a Meeker burner), an inoculating loop (either a wire loop or a supply of disposable loops), and either a laminar flow hood or a work area that is relatively free of drafts. The wire loop is sterilized before and after each use by heating to redness in the burner flame. Mouths of test tubes and flasks used in any transfer process are flamed before and after use to kill contaminating, adventitious microorganisms and to keep air currents moving out the container. In preparation for fermentation, the microorganism is transferred from its storage medium to the surface of an agar medium in a Petri dish. Using a sterile loop for each step, a loopful of the cells, either scraped from the surface of a slant or dipped from a glycerol storage solution is streaked

along one side of an imaginary square on the surface of the agar plate. Then, the next loop is passed through one end of the first streak and the loop is used to make a second streak along the adjoining side of the square. A third loop is likewise passed through the end of the second streak and this loop is used to make a third streak. The process is repeated one more time. The goal of this procedure is to dilute out microorganism cells such that a single colony can be isolated for use in further manipulations. The dish is covered and the cells are allowed to grow until heavy growth is observed (~24–48 hours). The fewest colonies of the microorganism should be observed to grow where the fourth streak was made and these colonies should be useful for inoculating flasks of nutrient media either for small-scale transformations of arene molecules, for further inoculation of larger fermentors, or for inoculation of an agar slant for storage of seed cells in case the working culture becomes contaminated. (40)

In the case where a large-scale fermentation is being performed, the inoculated flask is plugged with cotton and placed on a rotary shaker at 30° for ~24 hours. The contents of the flask are added to the sterile contents of the larger fermentor, flaming the mouth of the flask before the transfer.

A detailed description of the storage and handling of *P. putida* UV4 is given in the literature. (144) A detailed discussion, designed for chemists, of the experimental aspects of fermentations provides a good orientation to the subject. (145) The experimental description for the laboratory scale production of (1*S-cis*)-3-chloro-3,5-cyclohexadiene-1,2-diol is given in an *Organic Syntheses* procedure. (40)

7.2. Preparation of Media

Several forms of media will be necessary for handling of the culture. A medium is an appropriate mixture of nutrients in which the microorganism can grow and multiply. A liquid medium is needed for the fermentation and biotransformation of substrate while a solid medium is used for maintenance and storage of the culture.

Media may differ in the details of the ingredients and, consequently, different media are often used in different experimental descriptions. In reality, the media used for the microorganisms that carry out arene oxidations are quite similar to one another. The greatest difference among experimental descriptions will be in the carbon source used to support growth of the microorganism. Most of the microorganisms used for arene oxidations will grow on any of the standard media.

Listed below are components and recipes for the procedures that are found in the following section. Listed first are the stock solutions used in the preparation of the media. Listed second are the basic recipes for the media used in the procedures; variations are found in the individual procedures.

Stanier's stock solution A. (146) A 1 M aqueous buffer (pH 6.8) solution of $Na_2HPO_4 \cdot 7H_2O$ (268.1 g/L) and KH_2PO_4 (136 g/L).

Stanier's stock solution B. (146) An aqueous solution of $(NH_4)_2SO_4$ (1.0 g/L).

Stanier's stock solution C. (146) (based on Hutner's vitamin-free mineral base (147)) For 1 L, nitrilotriacetic acid (NTA; 10 g), $MgSO_4 \cdot 7H_2O$ (14.45 g), $CaCl_2 \cdot 2H_2O$ (3.335 g), $(NH_4)_6Mo_7O_{24} \cdot 4H_2O$ (9.3 mg), $FeSO_4 \cdot 7H_2O$ (99.0 mg), and Metals "44" solution (see below) (50 mL). The following procedure for mixing the components of Solution C is recommended. (40) First, the NTA is dissolved with stirring in 150 mL of distilled water. Next, a solution of the $MgSO_4 \cdot 7H_2O$ in 150 mL of distilled water is added to the NTA solution with stirring at a rate to avoid clouding of the mixture. Then a solution of the $CaCl_2 \cdot 2H_2O$ in 150 mL of distilled water is likewise added slowly so as to avoid any cloudiness of the solution (cloudiness will result in formation of insoluble precipitates). Next a solution containing both the $(NH_4)_6Mo_7O_{24} \cdot 4H_2O$ and the $FeSO_4 \cdot 7H_2O$ in 150 mL of distilled water is added with stirring. At this point, the combined solution should have a pale yellow color. The Metals 44 solution is added and the total volume is brought to 1.0 L with distilled water. The pH of the total solution should be carefully adjusted to 6.8 with 10 M aqueous NaOH solution—preferably in 0.2-mL aliquots—otherwise insoluble precipitates will form.

Metals "44" solution. (147) The Metals 44 solution is prepared as follows (for 100 mL): Ethylenediaminetetraacetic acid (EDTA; 250 mg), $ZnSO_4 \cdot 7H_2O$ (1.095 g), $FeSO_4 \cdot 7H_2O$ (500 mg), $MnSO_4 \cdot H_2O$ (154 mg), $CuSO_4 \cdot 5H_2O$ (39.2 mg), $Co(NO_3)_2 \cdot 6H_2O$ (24.8 mg), and $Na_2B_4O_7 \cdot 10H_2O$ (17.7 mg) are dissolved one at a time in 100 mL of distilled water followed by ~1–2 drops of 1 M H_2SO_4 (to retard precipitation). The resulting solution should be aquamarine blue in color.

<u>Vishniac and Santer's trace metal solution</u>. (148) For 1.0 L in H_2O , EDTA (50.0 g), $ZnSO_4 \cdot 7H_2O$ (22.0 g), $CaCl_2$ (5.54 g), $MnCl_2 \cdot 4H_2O$ (5.06 g), $FeSO_4 \cdot 7H_2O$ (4.99 g), $(NH_4)_6Mo_7O_{24} \cdot 4H_2O$ (1.10 g), $CuSO_4 \cdot 5H_2O$ (1.57 g), $CoCl_2 \cdot 6H_2O$ (1.61 g).

<u>Ribbons' trace metal solution</u>. (149, 33) For 1 L of H_2O , $ZnSO_4 \cdot 7H_2O$ (0.2 g), $CaCl_2 \cdot 2H_2O$ (4.38 g), $MnSO_4 \cdot 7H_2O$ (0.4 g), $FeSO_4 \cdot 7H_2O$ (8.0 g), $CuSO_4 \cdot 5H_2O$ (0.4 g), $CoCl_2 \cdot 6H_2O$ (0.04 g), H_3BO_4 (0.004 g), citric acid (100 g).

7.2.1.1. Mineral Salt Broth (MSB) Medium (146)
This medium is made up of, for 1 L, 40 mL of Stanier's stock solution A, 20 mL of Stanier's stock solution B, and 1.0 g of $(NH_4)_2SO_4$ brought to the final volume of 1 L with distilled water. When this medium is autoclaved, a precipitate will form. This precipitate will re-dissolve upon cooling.

7.2.2.1. Mineral Salt Broth (MSB) Agar Plates (40)
In a 1-L flask equipped with a magnetic stir bar are placed Stanier's stock solution A (20 mL), Stanier's stock solution B (10 mL), a solution containing $(NH_4)_2SO_4$ (200 mg/L; 7.5 mL), and L-arginine (2.5 g) and the total volume of the solution is brought to 250 mL by the addition of distilled water. In a second 1-L flask, Bacto-Agar (10 g) and 250 mL of distilled water are mixed. Both solutions are sterilized in an autoclave. A precipitate in the MSB flask at this point will dissolve upon cooling and stirring of the solution. When both solutions are at about 50°, they are combined, quickly mixed, and poured into 100 mm diameter Petri dishes (approximately 20 mL of solution per dish). The solution gels and solidifies upon cooling.

7.2.2.2. Mineral Salts Mixture (MSM) Medium (33)
To prepare this medium (1 L), glucose (10 g), $MgSO_4 \cdot 7H_2O$ (0.25 g), KH_2PO_4 (3 g), $(NH_4)_2SO_4$ (1 g), and polypropyleneglycol (1 g; as an antifoam agent) are dissolved in distilled water and the volume is brought to 1 L. The solution is sterilized (121°, 25 minutes) and then Ribbons' trace metal solution (10 mL) is added.

7.2.2.3. Minimal Salts Medium (150)
This medium (1.0 L) is made up of KH_2PO_4 (2 g), NH_4Cl (3 g), $MgSO_4 \cdot 7H_2O$ (0.4 g), and Vishniac and Santer's (148) trace element solution (2 mL).

7.2.2.4. M9 Medium (151)
For 1.0 L, the following are added to 750 mL of sterile deionized H_2O (cooled to 50° or lower): "5xM9" salts (200 mL); 20% appropriate carbon source (e.g., 20% glucose) (20 mL); and sterile deionized H_2O to 1 L. If necessary, the M9 medium is supplemented with stock solutions of the appropriate amino acids. The "5xM9" salts solution is made by dissolving the following salts in deionized water to a final volume of 1 L: $Na_2HPO_4 \cdot 7H_2O$ (64 g), KH_2PO_4 (15 g), NaCl (2.5 g), and NH_4Cl (5.0 g). The salt solution may be divided into 200-mL aliquots and sterilized by autoclaving for 15 minutes at 15 lb/sq. in. on a liquid cycle.

7.2.2.5. Luria-Bertani (LB) Broth
This medium (1.0 L) is made up of tryptone (10 g; Difco 0123), yeast extract (5.0 g; Difco 0127), and NaCl (10.0 g) dissolved by stirring in 1 L of distilled or deionized water. The solution may be placed as needed in appropriate containers and sterilized for 20 minutes at 121°.

7.2.2.6. Luria-Bertani (LB) Agar
This medium (1.0 L) is prepared as for Luria-Bertani broth, above, except that agar (15 g/L) is included in the aqueous solution before sterilization.

8. Fermentations

The following experimental procedures describe the production of dihydrodiols with a variety of microorganisms. Among the references from which these procedures are taken, references 40, 34 (see the Supporting Information), and 149 are especially thorough in description of experimental techniques.
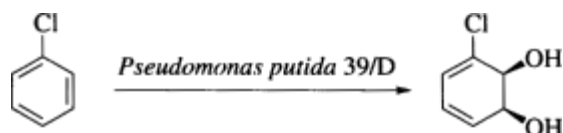
8.1.1.1. (1S-cis)-3-Chloro-3,5-cyclohexadiene-1,2-diol (40)

A flask of inoculum (50 mL in a 250-mL flask) of *Pseudomonas putida* 39/D was prepared in advance of the fermentation. Mineral salt broth (MSB) medium (0.5 L) and L-arginine hydrochloride (10 g) were placed in a 2.8-L Fernbach flask fitted with an air inlet tube and a vapor bulb extended through the closure of the flask mouth. The flask, fittings, and contents were sterilized in an autoclave. After cooling, the previously prepared flask of inoculum was transferred to the Fernbach flask using aseptic technique. The vapor bulb was charged with chlorobenzene (10 mL), and the flask was shaken on a rotary shaker at 150 rpm and 30° for 48 hours. The vapor bulb with excess chlorobenzene was removed, and the pH of the aqueous contents of the flask was measured and adjusted to pH ~9 if necessary. The aqueous mixture was divided equally into centrifuge tubes and the solids were separated by centrifugation for 30 minutes at ~8,000 rpm. The aqueous supernatant was decanted, combined, saturated with NaCl, and extracted with EtOAc (4 × 100 mL). The combined organic extracts were dried (Na_2SO_4 or $MgSO_4$), filtered, and concentrated under reduced pressure, giving 190 mg of a tan colored solid. Centrifugation was used to aid breaking of any emulsions observed with the organic extracts. Recrystallization of the solid from CH_2Cl_2-hexane gave an off-white solid, 0.160 g, mp 82–84°; $[\alpha]_D^{25}$ +54° (c 0.59, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.12 (m, 1H), 5.87 (m, 2H), 4.48 (m, 1H), 4.19 (t, J = 7.3 Hz, 1H), 2.74 (d, J = 7.3 Hz, 1H), 2.63 (d, J = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 134.9 (C), 128.0 (CH), 123.4 (CH), 122.7 (CH), 71.4 (CH), 69.1 (CH).
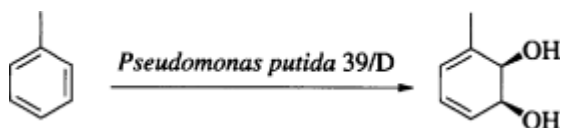
8.1.1.2. (1S-cis)-3-Methyl-3,5-cyclohexadiene-1,2-diol (39, 149)

A highly detailed description of the procedure that follows may be found in reference 149. Four 2-L flasks, each containing glucose medium (146) (500 mL), were inoculated with *P. putida* 39/D. Toluene was supplied to each fermentation flask by placing 2 mL in a glass tube suspended above the medium by a neoprene stopper. The open end of the tube above the stopper was plugged with cotton. A hole in the glass tube below the stopper allowed toluene to diffuse into the flask. The flasks were shaken on a reciprocal shaker at 30° for 30 hours. The contents of the flasks were placed in centrifuge bottles and centrifuged at ~15,000g for 30 minutes. The clear supernatant liquid was decanted and evaporated to dryness under reduced pressure while warming to no higher than 40°. The residue was extracted with MeOH. Removal of the MeOH left 2.42 g of yellow oil that was taken up in $CHCl_3$ and subjected to silica gel chromatography (column, 3 × 50 cm). The column was eluted first with $CHCl_3$ and then with 0.5% (v/v) CH_3OH in $CHCl_3$ (800 mL) to give the dihydrodiol. The dihydrodiol was crystallized two times from petroleum ether (30–60°), giving 1.94 g (83%) of (1*S*-*cis*)-3-methyl-3,5-cyclohexadiene-1,2-diol, mp 59°; (39) [α]$_D$ + 25° (c 0.4, CH_3OH); (39) ^{1}H NMR ($CDCl_3$) (149) δ 5.91–5.86 (m, 1H), 5.77–5.69 (m, 2H), 4.27 (m, 1H), 2.85–2.78 (m, 2H, exchangeable with D_2O), 1.90 (s, 3H).
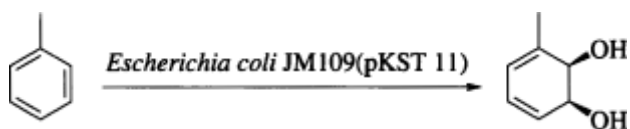
8.1.1.3. (1S-cis)-3-Methyl-3,5-cyclohexadiene-1,2-diol via a Fermentation with Immobilized E. coli JM109(pKST 11) (59)

1. Preparation of the inoculum. *E. coli* JM109(pKST 11) was maintained on Luria-Bertani agar plates containing 0.2% of a 50 mg/mL solution of ampicillin in water. A 250-mL flask containing Luria-Bertani broth (50 mL) and 0.2% of a 50 mg/mL solution of ampicillin in water was inoculated with *E. coli* JM109(pKST11) from the culture plates. The flask was shaken on a rotary shaker at 30° for 12 hours. Culture medium from the flask (20 mL) was used to inoculate a 2-L flask containing Luria-Bertani broth (500 mL) and 0.2% of a 50 mg/mL solution of ampicillin in water. After four hours

of growth on an orbital shaker at 30°, a solution of 0.1 M isopropyl- β -D-thiogalactopyranoside in water (5 mL) was added to the flask for induction of the dioxygenase. The bacteria were harvested (see next step) after 1.5 hours of further incubation at 30° on the orbital shaker and were used for immobilization and biotransformation of the substrate.

2. Immobilization of the cells. Cells from the inoculum culture (40 mL) were collected by centrifugation at 2,500 g for 6 minutes. The supernatant was removed and the bacterial pellet mixed with an autoclaved solution of 3% (w/v) sodium alginate (from *Laminaria hyperborea* supplied by Fluka Chemicals) in water (60 mL). The mixture was added dropwise to a chilled solution of 0.05 M $BaCl_2$ (500 mL). The resulting gel beads (diameter, 2–3 mm; cell load, 6–13 × 10^9 cells per gram bead) were hardened for 15 minutes at 4°. The biocatalyst mixture was filtered through a No. 1 Whatman filter and washed with distilled water (500 mL).

3. Biotransformation. Fifteen grams of beads were packed in a 250-mL glass jacketed column (3 cm × 30 cm) maintained at 30°. The reaction medium was composed of 0.1 M Tris-HCl buffer pH 7.0, 0.5% (w/v) glucose, and 10% (v / v) minimal salts medium (150) and was pumped from the bottom to the top of the column with a peristaltic pump at a flow rate of 20 mL/ minute. The beads were fluidized by an oxygen flow of 100 mL/minute. The medium was recirculated through a reservoir where the pH and temperature were controlled at 7.0 and 30°, respectively. The total volume of medium in circulation was 1.5 L. Toluene (30 mL) was mixed with 300 mL of tetradecane and added directly to the reaction medium. The production of diol was measured by HPLC. Isolation of the dihydrodiol from the reaction medium was not described.

8.1.1.4. (1S-cis)-1,6-Dihydroxy-2,4-cyclohexadiene-1-carboxylic acid

1. From benzoic acid with *Pseudomonas putida* U103. (33) In advance of the largescale fermentation, inoculum was prepared, first by inoculating mineral salts medium (33) (50 mL) in a shaker flask (250-mL) with *Pseudomonas putida* U103 and shaking the flask at 30° for 24 hours on a rotary shaker. The contents of this flask were then used to inoculate two flasks (500 mL) each containing mineral salts medium (200 mL). These flasks were shaken at 30° for 24 hours before being used to inoculate the large fermentation tank.
A 14-L New Brunswick Microferm (Model MF-114) fermentor was charged with glucose (10 g/L), $MgSO_4$ (0.25 g/L), KH_2PO_4 (3.0 g/L), $(NH_4)_2SO_4$ (1 g/L), and polypropylene glycol antifoam agent (1.0 g/L, 11.4 L), and was sterilized at 121° for 25 minutes before Ribbons' trace metal solution (114 mL) was added. After cooling, the pH of the medium was adjusted to 7.0 ± 0.1 with 10 M aqueous NH_4OH solution. The pH was controlled automatically throughout the fermentation with the use of 10 M aqueous NH_4OH solution and 4 M aqueous H_3PO_4 solution. The inocula from the two flasks prepared in advance were transferred to the fermentor and the culture was left to grow for 24 hours at 30°, pH 7, and a controlled oxygen content of 40%. With a glucose feed of 13 mmol/hour, sodium benzoate (5 mmol) was added to induce the oxygenase. Once oxidation was initiated, sodium benzoate was fed to the fermentation at a rate of 5 mmol/hour until unoxidized benzoic acid began to accumulate in the medium.
The contents of the fermentor were centrifuged in order to separate solids. The supernatant was concentrated to between 1/20th and 1/50th of the original volume by evaporation under reduced pressure at a temperature of 40° or less. The pH of the concentrated solution was adjusted to 4.0 by the addition of dilute aqueous HCl solution. The solution was repeatedly extracted with EtOAc until UV analysis of the solution indicated complete extraction of the product. Sodium sulfate was added to aid extraction of the product and the pH of the solution was maintained at ~4. The combined EtOAc extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure leaving a yellow solid. Much of the yellow color was removed by carefully washing the solid with CH_2Cl_2, after which (1*S-cis*)-1,6-dihydroxy-2,4-cyclohexadiene-1-carboxylic acid (20–30 g) was obtained as an off-white solid; [α]$_D$ – 106° (*c* 0.5, EtOH); λ $_{max}$ (EtOH) 261 (ε 3,400); ^{1}H NMR ($CDCl_3$ + DMSO-d$_6$) δ 4.1 (br s, 1H), 5.2 (br d, 2H), 5.2 (d m, 1H), 5.4 (br m, 1H).

2. From benzoic acid with *Alcaligenes eutrophus* B9. ([34](#)) The authors of this procedure have described two sets of conditions for medium-scale fermentations of benzoic acid with *A. eutrophus* B9. The larger scale of the two procedures is described here. The yield of product from the smaller scale procedure was higher (38 g, 74%) than from the larger scale (270 g, 39%).

A sterile pipette tip was streaked across the surface of a frozen glycerol stock solution of *A. eutrophus* B9 to produce small shards (ca. 10 mg). The frozen shards were added to a sterile, baffled 2-L Erlenmeyer flask containing mineral salt broth medium (500 mL; note: the mineral salt broth medium used in this experiment contains the same components as described in "Preparation of Media" with the exception that the concentration of Metals "44" was doubled) and aqueous sodium succinate solution (1.67 mL of a 1.5 M stock solution, 5 mM final concentration). The flask was shaken at 250 rpm for 24 hours at 30° on a rotary shaker. The white, heterogeneous mixture was added to a large-scale fermentor ([34](#)) containing mineral salt broth medium (80 L) and aqueous sodium succinate solution (267 mL of a 1.5 M stock solution, 5 mM final concentration). The solution was warmed to an internal temperature of 30° by circulating warm water through a 30′ coil of Tygon tubing (1/2" diameter). Air filtered through cotton was sparged through the medium. After 24 hours, aqueous sodium benzoate (240 mL of a 1.0 M solution) and aqueous sodium succinate (1.33 mL of a 1.5 M solution) were added to the white heterogeneous mixture. The resulting mixture was aerated vigorously for 6 hours at an internal temperature of 30°. After induction, sufficient aqueous sodium benzoate (160 to 400 mL of a 1.0 M solution, depending on the rate of consumption) was added hourly to maintain a concentration of 10–20 mM (determined by absorbance at 225 nm). Aqueous sodium succinate (135 mL of a 1.5 M solution) was added when the rate of oxidation decreased as determined by UV absorbance. The fermentation mixture was maintained at pH 6.8 (monitored every hour) by periodic additions of aqueous NaH_2PO_4 (2.0 M solution). These additions were continued for a period of 22 hours, then the fermentation mixture was aerated overnight at an internal temperature of 30° to maximize conversion. The fermentation mixture was centrifuged, in portions, at 2,000 rpm (bench top centrifuge) to remove the majority of solid material. The supernatant was concentrated to a volume of 20 L using a large-scale rotary evaporator (bath temperature <45°). The concentrate was centrifuged, in portions, at 6,000 rpm (Sorvall GS-3 rotor, model SLA-3000) to remove remaining solids. The supernatant was concentrated to 6 L using a large-scale rotary evaporator (<45°) and the concentrate was divided into three 2-L portions. The light gray solutions were cooled to 0° and acidified to pH 3.0 using concentrated HCl. The acidified solutions were each extracted repeatedly with EtOAc (~60 L) until less than 50 mg of material was isolated per 1 L of EtOAc extract. The organic extracts were dried (Na_2SO_4) and concentrated (large-scale rotary evaporator, < 45°), yielding a light brown residue. Trituration of the residue with CH_2Cl_2 (2 L) followed by drying in vacuo of the solids gave pure (1*S-cis*)-1,6-dihydroxy-2,4-cyclohexadiene-1-carboxylic acid as a white powder, mp 95–96° dec (210 g, 30%). The CH_2Cl_2 wash was concentrated, leaving a brown residue. The residue was dissolved in a minimal amount of EtOAc and the resulting solution was cooled to –20° to precipitate a light yellow solid, which was collected by filtration. The solid was triturated with CH_2Cl_2 (2 × 250 mL) followed by drying of the solid in vacuo to give additional product (60 g, 9%) as an off-white powder.
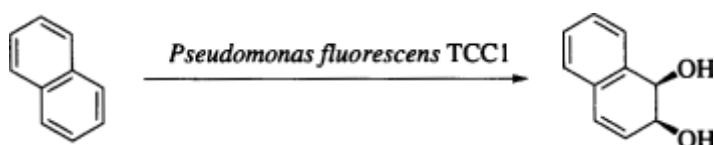
8.1.1.5. (1R-cis)-1,2-Dihydro-1,2-naphthalenediol ([47](#))

Flasks containing M9 medium (600 mL total, also containing 20 mM sodium succinate, and 10 mg of salicylic acid as an inducer) were inoculated with cells of *Pseudomonas fluorescens* TCC1 (NCIMB 40605). The flasks were incubated at 30° for 24 hours after which the cells were separated from the liquid medium by centrifugation and the clear supernatant was decanted. The cells were washed with distilled water, collected again by centrifugation and transferred to a water-jacketed stirred reactor containing M9 medium (1 L), sodium succinate (5 mM), naphthalene (6.4 g, 0.050 mol; finely ground), and polyethyleneglycol 8000 [0.1% (w/v); as an antifoaming agent]. The fermentation was maintained at 30°, stirred at 1,600 rpm, and aerated with a flow of 9 L/minute of air through a sparger controlled by an in-line flow meter. The fermentation was continued for 24 hours after which the solids were separated by centrifugation. The supernatant was extracted with EtOAc (4 × 150 mL), the extracts were dried (

Na$_2$SO$_4$), filtered, and concentrated, giving crude product. The crude material was crystallized from hexane, giving (1R-cis)-1,2-dihydronaphthalene-1,2-diol (6.51 g, 80%); [α]$_D$ + 220° (MeOH); (47) mp 115–116°; (63) [α]$_D$ + 220° (c 0.05–0.1, MeOH); (63) ^{1}H NMR (63) (CDCl$_3$) δ 4.36 (dd, J = 3.8, 5.1 Hz, 1H), 4.67 (d, J = 5.1 Hz, 1H), 6.03 (dd, 1H, J = 3.8, 9.9 Hz, 1H), 6.53 (d, J = 9.9 Hz, 1H), 7.0–7.6 (m, 4H).
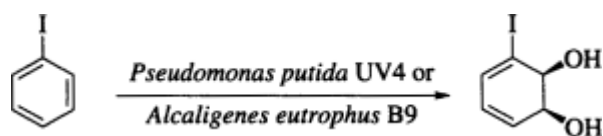
8.1.1.6. (1S-cis)-3-Iodo-3,5-cyclohexadiene-1,2-diol (25, 105)

A minimal salts medium (150) (500 mL) containing gluconate (12% w/v) in a 2-L flask was inoculated with *Pseudomonas putida* UV4 and shaken at 30° for 24 hours. (152) The cells were separated from the liquid medium by centrifugation. The clear supernatant was discarded and the cells were resuspended in minimal salts medium (500 mL) containing pyruvate (12% w / v) in a 2-L flask. Iodobenzene (2 g, 9.8 mmol) was added to the flask and the fermentation carried out for 50 hours at 30° using an orbital shaker (400 rev / min). After the contents of the flask were centrifuged, the clear supernatant was separated and saturated with solid NaCl, and then extracted with CH$_2$Cl$_2$ (5 × 100 mL). The extract was dried (Na$_2$SO$_4$), filtered, and concentrated. The residue was purified by chromatography, giving (1S-cis)-3-iodo-3,5-cyclohexadiene-1,2-diol (1.88 g, 80%); mp 64–81° (dec.); [α]$_D$ + 41° (c 0.5, MeOH); ^{1}H NMR (CDCl$_3$, TMS) δ 6.69 (d, J = 5.5 Hz, 1H), 6.03 (dd, J = 4.2, 9.4 Hz, 1H), 5.72 (m, 1H), 4.43 (m, 1H), 4.28 (d, J = 6.1 Hz, 1H).
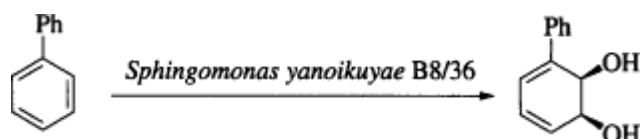
8.1.1.7. (1S-cis)-3-Phenyl-3,5-cyclohexadiene-1,2-diol (49, 153)

In preparation for a 10-L fermentation, five 500-mL flasks of glucose medium (100 mL) containing 0.2% sodium succinate and 0.1% (w/v) biphenyl were inoculated with *Beijerinckia* B8/36 (now classified as *Sphingomonas yanoikuyae* B8/36), then incubated at 27° on a rotary shaker at 150 rpm for 12 hours. This inoculum was transferred to a New Brunswick Model M14 Microferm fermentor containing glucose medium (10 L), sodium succinate (0.2%), and biphenyl (0.1% w/v). The fermentation was carried out for five hours after which the contents of the fermentor were centrifuged and the supernatant decanted. The supernatant was extracted with EtOAc (total, 3 L), and the extract was dried (Na$_2$SO$_4$), filtered, and concentrated, giving 4.6 g (37%) of white solid. Crystallization from hexane gave (1S-cis)-3-phenyl-3,5-cyclohexadiene-1,2-diol; mp 93°; λ $_{max}$ (MeOH) 303 (ε , 13,600) and 223 nm (ε , 9,200); ^{1}H NMR (CDCl$_3$) δ 7.4 (m, 5H), 6.35 (m, 1H), 5.9 (m, 2H), 4.5 (dd, 2H).
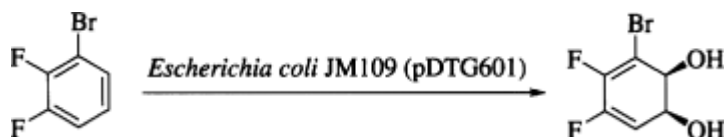
8.1.1.8. (1S-cis)-3-Bromo-4,5-difluoro-3,5-cyclohexadiene-1,2-diol (154)

E. coli JM109(pDTG601) was grown overnight at 35° in a 2.8-L Fernbach flask containing 500 mL of MSB medium supplemented with glucose (0.2%), thiamine (1 mM), isopropyl- β -D-thiogalactoside (10 mg/L), and ampicillin (100 mg/L). (26, 154) This culture was transferred to a 12-L fermentor containing 8 L of the same medium and the cells were grown to an optical density of 70 at 660 nm. The substrate, 1-bromo-2,3-difluorobenzene (unspecified amount), was added dropwise to the culture and the progress of the biotransformation was followed by observing oxygen consumption and CO$_2$ production by the culture. Diol formation was monitored by measuring absorbance at 270 nm typical of the cyclohexadiene moiety. After all metabolic activity ceased (or no further diol formation was observed), the

fermentation was stopped and the pH of the contents of the fermentor was adjusted to pH 8.4 with aqueous NaOH solution. The contents of the fermentor were centrifuged and the clear supernatant was decanted, saturated with solid NaCl, and extracted with EtOAc (previously washed with saturated aqueous NaHCO$_3$ solution). The extracts were dried (Na$_2$SO$_4$), filtered, and concentrated. The crude product residue was purified by flash chromatography over deactivated (10% H$_2$O) silica gel using hexane-EtOAc, 7:3, for elution. (1*S-cis*)-3-Bromo-4,5-difluoro-3,5-cyclohexadiene-1,2-diol was obtained in the quantity of 0.7 g/L of fermentation volume; mp 104.5–105.5°; [α]$_D$ + 34.6° (*c* 0.49, MeOH); ^{1}H NMR (CDCl$_3$) δ 5.12 (m, 1H), 4.60 (br s, 1H), 4.47 (br s, 1H); ^{13}C NMR (C$_3$D$_6$O , TMS) δ 148.5 (C, dd, *J* = 259.0, 26.3 Hz), 148.4 (C, dd, *J* = 258.6, 28.2 Hz), 109.2 (CH, dd, *J* = 9.9, 1.5 Hz), 106.8 (C, dd, *J* = 13.3, 3.4 Hz), 73.0 (CH, d, *J* = 2.3 Hz), 67.7 (CH, d, *J* = 8.4 Hz); ^{19}F NMR (CDCl$_3$) δ – 124.2 (br s), – 132.8 (br s).

9. Tabular Survey

Entries are arranged according to increasing carbon and hydrogen count of the substrate. Yields are given by the numbers in parentheses. A "(—)" indicates that no yield was provided in the original reference. Other expressions of yield may be encountered in microbiology literature and these are given as described, e.g., g/L, moles/g dry cell weight. The enantiomeric excess (ee) is given by the number following the yield parentheses. A "—" indicates that no measure of ee was provided in the original reference.

The structures of arene substrate and predominant dihydrodiol product are drawn in a consistent manner throughout the Tables. This is intended to provide the reader with a recognizable pattern related to the stereoselectivities observed in arene dioxygenations. Where the absolute configuration of a dihydrodiol has been reported, the information is reflected in the drawing of the compound. When absolute configurations are unknown, bonds are drawn with a thin line.

The entries of , "Dihydrodiols That Have Not Been Isolated," are included to give the reader a full scope of arenes that have been subjected to microbial arene oxidation. The compounds in this table have been used as substrates for fermentations, but for which product structures are assigned primarily by analogy to related examples. Biological and/or analytical data have been obtained that are consistent with the indicated dihydroxylation reactions, but the products have not been isolated or further characterized. The reader contemplating use of a microbial arene oxidation reaction should take encouragement if precedent is found in this table.

The following abbreviations are used in the tables:

AIBN	2,2′-*azobis*(isobutyronitrile)
THF	tetrahydrofuran
Ts	tosyl, toluenesulfonyl

Table 1. Microbiological Oxygenations of Benzenes

Table 2. Microbiological Oxygenations of Benzoic and Naphthoic Acids and Esters

Table 3. Microbiological Oxygenations of Biphenyls

Table 4. Microbiological Oxygenations of Naphthalenes

Table 5. Microbiological Oxygenations of Polycyclic Aromatics

Table 6. Microbiological Oxygenations of Heterocycles

Table 7. Microbiological Oxygenations of Olefins

Table 8. Microbiological Benzylic Oxygenations

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Glossary

Aerobic.
    A procedure (growth, biotransformation, fermentation, etc.) carried out in the presence of air or oxygen

Agar.
    (1) A polysaccharide from seaweed, commonly used as a base (gelling agent) for solid media. (2) A solid medium (jargon). The gelling temperature is between 25–35° and the gel remains solid to about 90°

Aseptic Techniques.
    Procedures that minimize accidental entry of undesired organisms into a culture or fermentation

Autoclave.
    An instrument in which equipment and media are sterilized at elevated temperature and high pressure

Bacteria.
    A Kingdom of cellular organisms. Bacteria are single-celled and lack a nucleus

Culture.
    A population of microorganisms that is growing and/or alive, confined in an environment in which viability is retained

Fungus.
    A member of the Fungi Kingdom, which consists of unicellular or multicellular eukaryotic organisms that lack chlorophyll. They are frequently involved in the decay of dead organic matter

Fermentation.
    The transformation of one molecule type (substrate) to another (product) by microorganisms

Incubation.
    The time during which a culture is kept under a given set of conditions for a defined time

Inoculate.
    To deliberately introduce microorganisms (usually of a single species) into a culture medium

Inoculum.
    The microorganism(s) used to inoculate

Medium (Culture Medium).
    (1) An appropriate mixture of nutrients capable of supporting the growth and multiplication of a microorganism. (2) A liquid culture medium (jargon)

Nutrient.
    A material that the microorganism uses as food or growth stimulant

Slant (or Slope).
    Agar placed in a tube and allowed to solidify at a slant

Species.
    A taxonomically distinct kind of microorganism. Individual cells within a species may differ in

biochemical properties

Spores.

Reproductive bodies, of one or more cells, at rest (non-growing) until introduced into a nutrient medium; the "seeds" of microorganisms

Sterilize.

To kill all undesired microorganisms

Strain.

A pure culture descended from a single individual of a species and thus presumably more biochemically homogeneous than the aggregate of individuals of a species. A strain often arises from a single individual cell

Substrate.

The material or compound to be acted on by an organism or an enzyme to produce a product chemically related to the substrate. For arene oxygenations, the substrates are preferably not nutrients
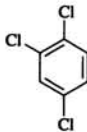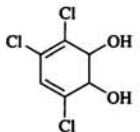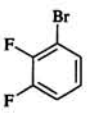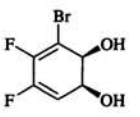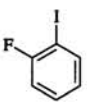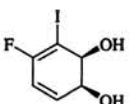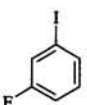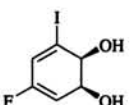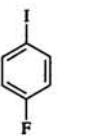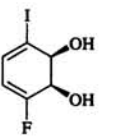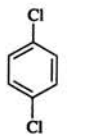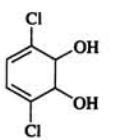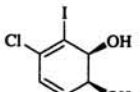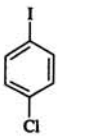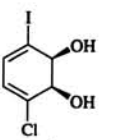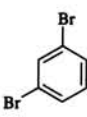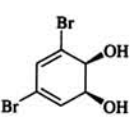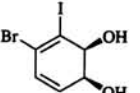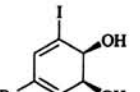
Transfer.

The introduction of a small amount of an organism into a virgin nutrient environment in order to increase the supply of the organism

Yeast.

Single celled fungi that reproduce asexually by budding or fission and sexually by haploid spores

TABLE 1. MICROBIOLOGICAL OXYGENATIONS OF BENZENES

Substrate		Microorganism, Conditions	Product(s)	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %	Refs.
C₆					
[structure: 1,2,4-trichlorobenzene]	C₆H₃Cl₃	Pseudomonas sp. PS12	[structure: cis-diol]	(—), —	155
[structure: 1-bromo-2,3-difluorobenzene]	C₆H₃BrF₂	Pseudomonas putida 39/D	[structure: cis-diol]	(50 mg/L), >98	154
		Escherichia coli JM109(pDTG601)	"	(0.7 g/L), >98	154
[structure: 1-fluoro-2-iodobenzene]	C₆H₄FI	Pseudomonas putida UV4	[structure: cis-diol]	(—), >98	27
[structure: 1-fluoro-3-iodobenzene]	C₆H₄FI	Pseudomonas putida UV4	[structure: cis-diol]	(—), >98	27
[structure: 1-fluoro-4-iodobenzene]	C₆H₄FI	Pseudomonas putida UV4	[structure: cis-diol]	(60), 88	27, 23
		Escherichia coli JM109(pDTG601)	"	(—), 88	107
[structure: 1,4-dichlorobenzene]	C₆H₄Cl₂	Xanthobacter flavus 14p1	[structure: cis-diol]	(—)	156
		Pseudomonas putida F1	"	(—)	157
		Pseudomonas sp.	"	(—)	158
[structure: 1-chloro-2-iodobenzene]	C₆H₄ClI	Pseudomonas putida UV4	[structure: cis-diol]	(—), >98	27
		Escherichia coli JM109(pDTG601)	"	(—), >98	27
[structure: 1-chloro-4-iodobenzene]	C₆H₄ClI	Pseudomonas putida UV4	[structure: cis-diol]	(25), 15	23
		Escherichia coli DH5α(pTCB144)	"	(—), 67	77
[structure: 1,3-dibromobenzene]	C₆H₄Br₂	Escherichia coli JM109 (pDTG601)	[structure: cis-diol]	(4 g/L), >99	131
[structure: 1-bromo-2-iodobenzene]	C₆H₄BrI	Pseudomonas putida UV4	[structure: cis-diol]	(—), >98	27
[structure: 1-bromo-3-iodobenzene]	C₆H₄BrI	Pseudomonas putida UV4	[structure: cis-diol]	(—), >98	27

TABLE 1. MICROBIOLOGICAL OXYGENATIONS OF BENZENES (*Continued*)
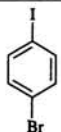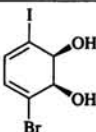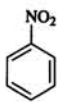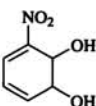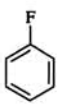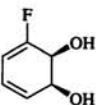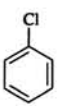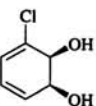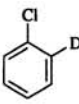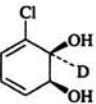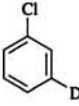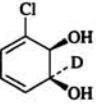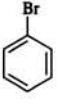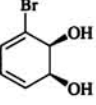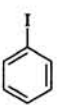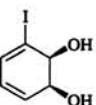
Substrate		Microorganism, Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %	Refs.
	C₆H₄BrI	*Pseudomonas putida* UV4	(22), 22	23
		Escherichia coli JM109(pDTG601)	" (—), 20	107
	C₆H₅NO₂	*Pseudomonas putida* 39/D	*cis* (—), —	159
		Pseudomonas putida TB 103	" (—), —	160
	C₆H₅F	*Pseudomonas putida* UV4	(—), *ca.* 60	24, 23, 25
		Pseudomonas putida UV4 immobilized in barium alginate beads	" (0.7 mol/g dry cell weight)	59
		Pseudomonas mutant	" (9.5 g/L)	161
		Escherichia coli DH5α(pTCB144)	" (—), —	77
	C₆H₅Cl	*Pseudomonas putida* 39/D	(1g/L), —	80, 40
		Pseudomonas putida UV4	" (80), >98	24, 25
		Pseudomonas putida UV4 immobilized in barium alginate beads	" (3.0 mol/g dry cell weight)	59
		A bacterium, strain WR1306	" (—), —	162
		Pseudomonas mutant A	" (9.5 g/L)	163
	C₆H₄DCl	*Pseudomonas putida* UV4	(—), —	164
	C₆H₄DCl	*Pseudomonas putida* UV4	(—), —	164
	C₆H₅Br	*Pseudomonas putida* UV4	(77), >98	105, 25
		Pseudomonas putida 39/D	" (—), —	81
		Escherichia coli DH5α(pTCB144)	" (—), —	77
	C₆H₅I	*Pseudomonas putida* UV4	(85), >98	105, 25
		Escherichia coli JM109(pDTG601)	" (—), >98	27
		Escherichia coli DH5α(pTCB144)	" (—), —	77

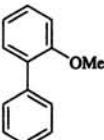TABLE 1. MICROBIOLOGICAL OXYGENATIONS OF BENZENES (*Continued*)
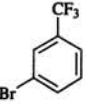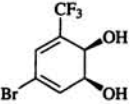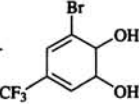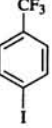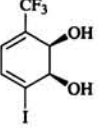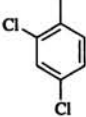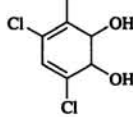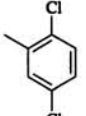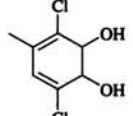
Substrate		Microorganism, Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %	Refs.
	C_6H_6	*Pseudomonas putida* F1	(1 g/L)	2, 4
		Pseudomonas putida 11767 mutant	" (40–50 g/L)	42, 56
		Pseudomonas mutant D	" (40 g/L)	163
		Pseudomonas putida UV4 immobilized in barium alginate beads	" 4.1 mol/g dry cell weight)	59
		Moraxella sp. cell-free extracts	" (—)	165
		Escherichia coli DH5α(pTCB144)	" (—)	77
		Pseudomonas putida F1/$^{18}O_2$	(0.6 g/L)	4
C_7	$C_7H_4BrF_3$	*Pseudomonas putida* 39/D	(48 mg/L), — + (2 mg/L)	154
		Escherichia coli JM109(pDTG601)	" (0.7 g/L), >98 + " (20 mg/L)	154
	$C_7H_4F_3I$	*Pseudomonas putida* UV4	(50), >98	23
	C_7H_5N	*Pseudomonas putida* UV4	(3.9 g/L), >98	61, 25
	$C_7H_5F_3$	*Pseudomonas putida* UV4	(*ca.* 65), >98	24, 25
		Pseudomonas mutant	" (1.25 g/L)	166
		Pseudomonas mutant D	" (>6 g/L)	167
	$C_7H_4DF_3$	*Pseudomonas putida* UV4	(—), —	164
	$C_7H_4DF_3$	*Pseudomonas putida* UV4	(—), —	164
	$C_7H_6Cl_2$	*Escherichia coli* DH5α(STE7)	(—), —	168
	$C_7H_6Cl_2$	*Escherichia coli* DH5α(STE7)	(—), —	168

TABLE 1. MICROBIOLOGICAL OXYGENATIONS OF BENZENES (*Continued*)
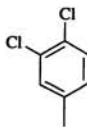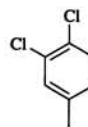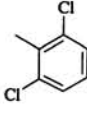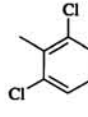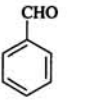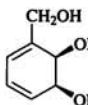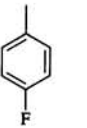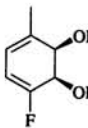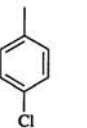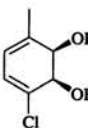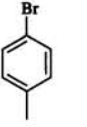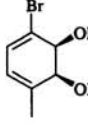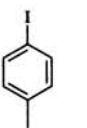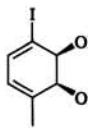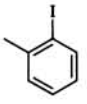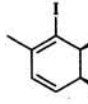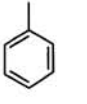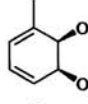
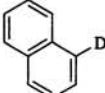| Substrate		Microorganism, Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %	Refs.
	$C_7H_6Cl_2$	*Escherichia coli* DH5$_\alpha$(STE7)	(—), —	168
	$C_7H_6Cl_2$	*Escherichia coli* DH5$_\alpha$(STE7)	(—), —	168
	C_7H_6O	*Pseudomonas putida* UV4	(8), >98	55
	C_7H_7F	*Pseudomonas putida* UV4	(21), 83	23
		Pseudomonas putida 39/D	" (—), —	153
		Escherichia coli DH5$_\alpha$(pTCB144)	" (—), 49	77
	C_7H_7Cl	*Pseudomonas putida* UV4	(20), 15	23
		Pseudomonas putida F1	" (1.5 mg/L), —	54
		Pseudomonas putida 39/D	" (—), —	153
		Pseudomonas putida JS6	" (—), —	169
		Escherichia coli DH5$_\alpha$(pTCB144)	" (—), 77	77
	C_7H_7Br	*Pseudomonas putida* UV4	(13), 37	23
		Escherichia coli DH5$_\alpha$(pTCB144)	" (—), 77	77
	C_7H_7I	*Pseudomonas putida* UV4	(24), 80-88	23, 27
		Escherichia coli JM109(pDTG601)	" (—), >98	27
		Escherichia coli DH5$_\alpha$(pTCB144)	" (—), 98	77
	C_7H_7I	*Pseudomonas putida* UV4	(—), >98	27
	C_7H_8	*Pseudomonas putida* 39/D	(0.93 g/L), —	39, 170, 171, 80
		Escherichia coli JM109(pDTG601)	" (—), —	41

TABLE 1. MICROBIOLOGICAL OXYGENATIONS OF BENZENES (*Continued*)

	Substrate	Microorganism, Conditions		Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %	Refs.
	C_7H_8	*Escherichia coli* DH5$_\alpha$(pDTG927)	"	(—), —	172
		Pseudomonas putida UV4	"	(*ca.* 60), >98 + (4), >98	24, 25, 55
		Pseudomonas putida UV4 immobilized in beads	"	(6.1 mol/g dry cell weight)	59
		Escherichia coli JM109(pKST11) immobilized in beads	"	(1.2 mol/g dry cell weight)	59
		Pseudomonas putida NG1	"	(18-24 g/L), >98	173
		Escherichia coli TG2(pTAC365)	"	(0.4 g/L), —	174, 175
		Pseudomonas mutant A	"	(16 g/L), —	163
		Rhodococcus rhodochrous strain OFS	"	(—), —	176
		Escherichia coli DH5$_\alpha$(pTCB144)	"	(—), —	77
	C_7H_7D	*Pseudomonas putida* UV4		(—), —	164
	C_7H_7D	*Pseudomonas putida* UV4		(—), —	164
	C_7H_8O	*Pseudomonas putida* 39/D		(16), —	142
		Pseudomonas putida UV4	"	(0.23 g/L), —	38
		Pseudomonas putida UV4	"	(*ca.* 10), —	25
	C_7H_7DO	*Pseudomonas putida* UV4		(—), —	164
	C_7H_7DO	*Pseudomonas putida* UV4		(—), —	164
	C_7H_8S	*Pseudomonas putida* UV4		(*ca.* 1), —	25
C_8	C_8H_6	*Pseudomonas putida* UV4		(*ca.* 10), >98	25
		Pseudomonas putida 39/D	"	(50 mg/L), —	80, 81
	C_8H_7N	*Pseudomonas putida* UV4		(20), >98 + (15), >98	55

TABLE 1. MICROBIOLOGICAL OXYGENATIONS OF BENZENES (*Continued*)

Substrate		Microorganism, Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %	Refs.
	C_8H_7NO	*Pseudomonas putida* UV4	(18), >98	55
	$C_8H_7F_3$	*Pseudomonas putida* UV4	(28), >98	23
	C_8H_7Cl	*Pseudomonas putida* 39/D	(1.4), >98 + (2.6), 73 + (tr)	79, 177
	C_8H_7Cl	*Pseudomonas putida* 39/D	(1), 54 + (2), >98 + (tr)	79
	C_8H_7Cl	*Pseudomonas putida* 39/D	(17), 15 + (4), 79	79
	C_8H_7Br	*Pseudomonas putida* 39/D	(1), 91 + (5), —	178
	C_8H_7Br	*Pseudomonas putida* 39/D	(1 g/L), — + (1 g/L), —	179
	C_8H_8	*Pseudomonas putida* 39/D	(25), >98 + (1), —	79, 80, 81
		Pseudomonas putida UV4	" (*ca.* 30), >98	25
		Rhodococcus rhodochrous NCIMB 13259	" (—), —	180
		Pseudomonas putida MST	(1), —	181
	C_8H_8	*Pseudomonas putida* UV4	(18), >98 + (13), >98 + (9), >98 + *cis* (9) + (1), 72 + (33), *ca.* 20 + (2)	69, 70

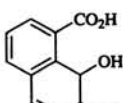TABLE 1. MICROBIOLOGICAL OXYGENATIONS OF BENZENES (*Continued*)
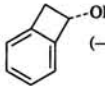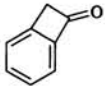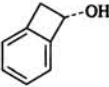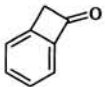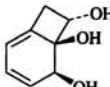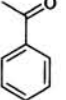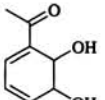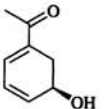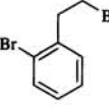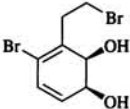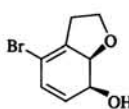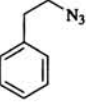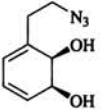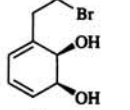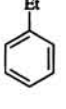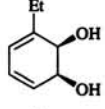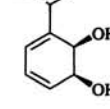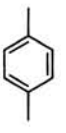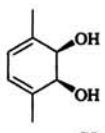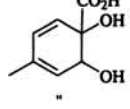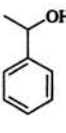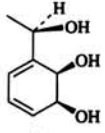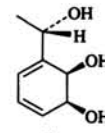
Substrate		Microorganism, Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %	Refs.
	C_8H_8	*Pseudomonas fluorescens* 127-68 XVII	(—), 0 + (—)	182
	C_8H_8O	*Pseudomonas putida* UV4	(60) + (16), >98	69
	C_8H_8O	*Pseudomonas putida* 39/D	(5), —	183, 81
		Pseudomonas putida UV4	" (—), —	38
		Pseudomonas putida ICI strain 11767	(4), —	184
	$C_8H_8Br_2$	*Pseudomonas putida* 39/D or *Escherichia coli* JM109(pDTG601)	(*ca.* 0.3 g/L), >95 + (*ca.* 0.15 g/L)	185
	$C_8H_9N_3$	*Escherichia coli* JM109(pDTG601)	(*ca.* 42), >98	186
	C_8H_9Br	*Pseudomonas putida* 39/D	(5), 96	187
	C_8H_{10}	*Pseudomonas putida* 39/D	(20), — + (<1), —	183, 153
		Pseudomonas putida UV4	" (*ca.* 60), >98	25, 55
		Escherichia coli DH5α(pTCB144)	" (—), —	77
	C_8H_{10}	*Pseudomonas putida* 39/D	(65 mg/L)	141
		Pseudomonas putida BGXM1	(—), —	143
		Pseudomonas putida Biotype A strain (ATCC 39119)	" (<1), —	188
(*R,S*)	$C_8H_{10}O$	*Pseudomonas putida* 39/D	I + II (1 g/L), —; I:II = 4:6	189, 190
			I II	
		Pseudomonas putida 39/D	I (11), —	183
		Escherichia coli JM109(pDTG601)	I+II (5 g/L), —; I:II = 1:1 "	189, 190
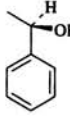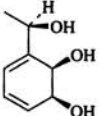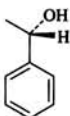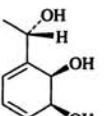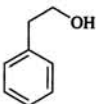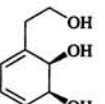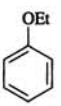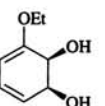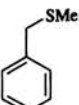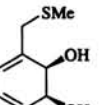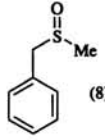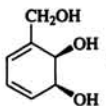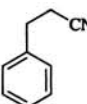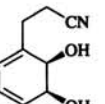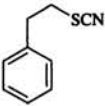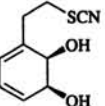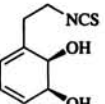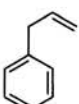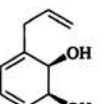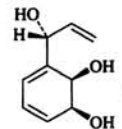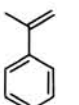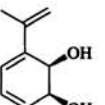
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TABLE 1. MICROBIOLOGICAL OXYGENATIONS OF BENZENES (*Continued*)

Substrate		Microorganism, Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %	Refs.
	$C_8H_{10}O$	*Pseudomonas putida* 39/D	(15), —	183
		Pseudomonas putida 39/D "	(1 g/L), —	189, 190
		Pseudomonas putida UV4 "	(20), >98	55
		Escherichia coli JM109(pDTG601) "	(1 g/L), —	189, 190
	$C_8H_{10}O$	*Pseudomonas putida* 39/D	(7), —	183
		Pseudomonas putida 39/D "	(7), —	189
		Pseudomonas putida UV4 "	(8), >98	55
		Escherichia coli JM109(pDTG601) "	(1 g/L), —	189
	$C_8H_{10}O$	*Escherichia coli* JM109(pDTG601)	(4), 94	186
	$C_8H_{10}O$	*Pseudomonas putida* UV4	(1.15 g/L), >98	191, 25
		Pseudomonas putida 39/D "	(—), —	142
	$C_8H_{10}S$	*Pseudomonas putida* UV4	(50), >98 + (8), — + (2), —	55
C₉	C_9H_9N	*Escherichia coli* JM109(pDTG601)	(23), 96	186
	C_9H_9NS	*Escherichia coli* JM109(pDTG601)	(28), 94	186
	C_9H_9NS	*Escherichia coli* JM109(pDTG601)	(4), —	186
	C_9H_{10}	*Pseudomonas putida* UV4	(18), >98 + (15), >98	55
	C_9H_{10}	Bacterial strain S107B1	(0.158 g/L), —	192

TABLE 1. MICROBIOLOGICAL OXYGENATIONS OF BENZENES (*Continued*)
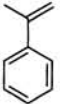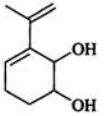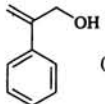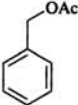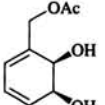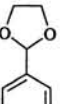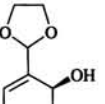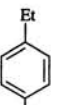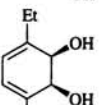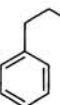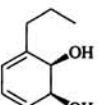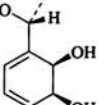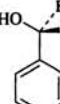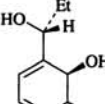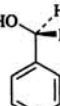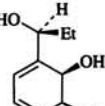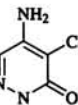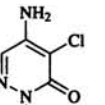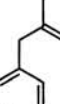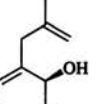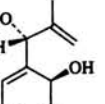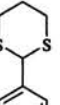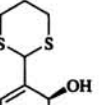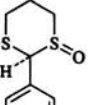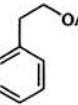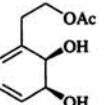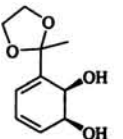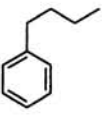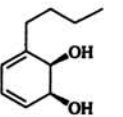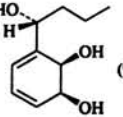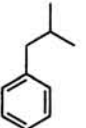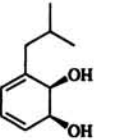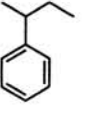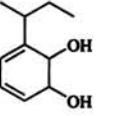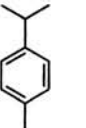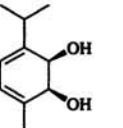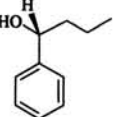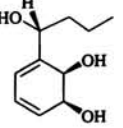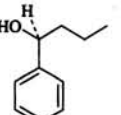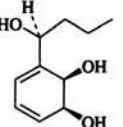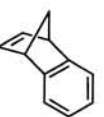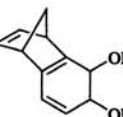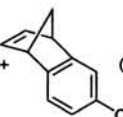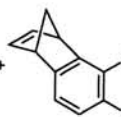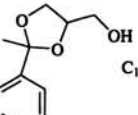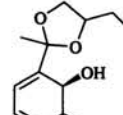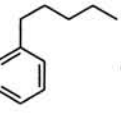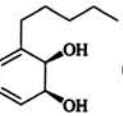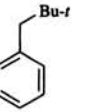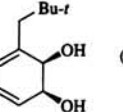
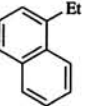| Substrate		Microorganism, Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %	Refs.
	C_9H_{10}	*Pseudomonas putida* MST	(3), — + (tr)	181
	$C_9H_{10}O_2$	*Pseudomonas putida* UV4	(*ca.* 20), >98	25, 24
		Pseudomonas mutant D	" (9.3 g/L), —	193
	$C_9H_{10}O_2$	*Pseudomonas putida* 39/D	(—), —	81
	C_9H_{12}	*Pseudomonas putida* UV4	(16), >98	55
	C_9H_{12}	*Pseudomonas putida* UV4	(15), >98 + (26), >98	55
	$C_9H_{12}O$	*Pseudomonas putida* UV4	(8), >98	55
	$C_9H_{12}O$	*Pseudomonas putida* UV4	(53), >98	55
C_{10}	$C_{10}H_8ClN_3O$	Bacterium, strain E	(—), —	194
	$C_{10}H_{12}$	*Pseudomonas putida* UV4	(9), >98 + (18), >98	55
	$C_{10}H_{12}S_2$	*Pseudomonas putida* UV4	(18), >98 + (7), >98	58
	$C_{10}H_{12}O_2$	*Escherichia coli* JM109(pDTG601)	(11), >98	186

TABLE 1. MICROBIOLOGICAL OXYGENATIONS OF BENZENES (*Continued*)

Substrate		Microorganism, Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %	Refs.
	$C_{10}H_{12}O_2$	*Pseudomonas putida* 39/D	(—), —	81
	$C_{10}H_{14}$	*Pseudomonas putida* UV4	(33), >98 + (9), >98	55
	$C_{10}H_{14}$	*Pseudomonas putida* UV4	(27), >98	55
		Pseudomonas desmolytica S449B1 or *Pseudomonas convexa* S107B1	-	195
	$C_{10}H_{14}$	*Pseudomonas* strain	(—), —	196
	$C_{10}H_{14}$	*Pseudomonas putida*, UV4	(15), >98	55
	$C_{10}H_{14}O$	*Pseudomonas putida*, UV4	(31), >98	55
	$C_{10}H_{14}O$	*Pseudomonas putida* UV4	(23), >98	55
C₁₁	$C_{11}H_{10}$	*Pseudomonas* sp. BM2 (87E2)	(1), — + (4) + (2)	197
	$C_{11}H_{14}O_3$	*Pseudomonas putida* 39/D	(—), —	81
	$C_{11}H_{16}$	*Pseudomonas putida* UV4	(17), >98	55
Bu-*t*	$C_{11}H_{16}$	*Pseudomonas putida* UV4	Bu-*t* (22), >98	55

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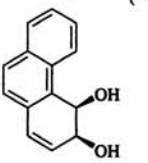TABLE 1. MICROBIOLOGICAL OXYGENATIONS OF BENZENES (*Continued*)
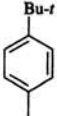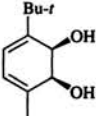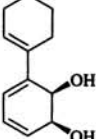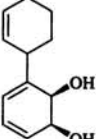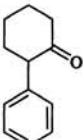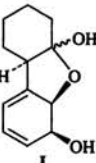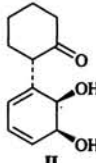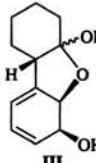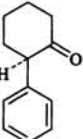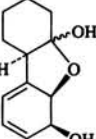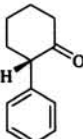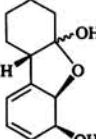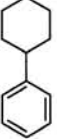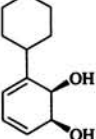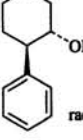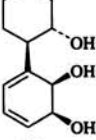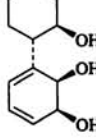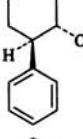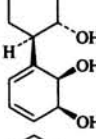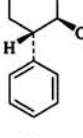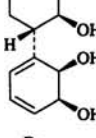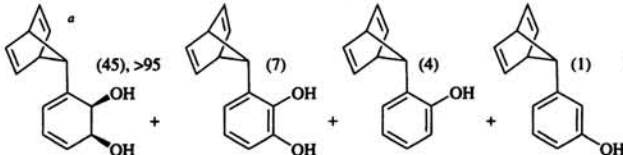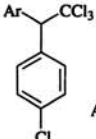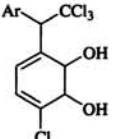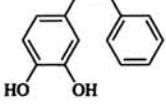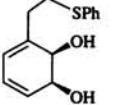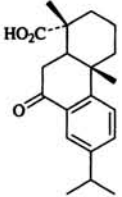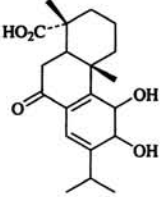
Substrate	Microorganism, Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %	Refs.
$C_{11}H_{16}$	*Pseudomonas putida* UV4	(5), >98	55
$C_{12}H_{14}$	*Escherichia coli* JM109(pDTG601)	(3 g/L), —	189, 190
$C_{12}H_{14}$	*Escherichia coli* JM109(pDTG601)	(0.8 g/L), —	190
$C_{12}H_{14}O$	*Escherichia coli* JM109(pDTG601)	I+II+III (1.0 g/L), —; I:II:III = 2:1:1	189, 190
$C_{12}H_{14}O$	*Escherichia coli* JM109(pDTG601)	(—), —	190
$C_{12}H_{14}O$	*Escherichia coli* JM109(pDTG601)	(—), —	190
$C_{12}H_{16}$	*Escherichia coli* JM109(pDTG601)	(1.8 g/L), —	189, 190
$C_{12}H_{16}O$ racemic	*Escherichia coli* JM109(pDTG601)	1 : 1 (1.2 g/L), —	189, 190
$C_{12}H_{16}O$	*Escherichia coli* JM109(pDTG601)	(1.0 g/L), —	190
$C_{12}H_{16}O$	*Escherichia coli* JM109(pDTG601)	(1.0 g/L), —	190
$C_{13}H_{12}$	*Escherichia coli* JM109(pDTG601)	(1.1 g/L), —	190

C_{12}

C_{13}

180

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TABLE 1. MICROBIOLOGICAL OXYGENATIONS OF BENZENES (*Continued*)

Substrate	Microorganism, Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %	Refs.
$C_{13}H_{12}$	*Pseudomonas* sp. BM2	(45), >95 + (7) + (4) + (1)	197
C_{14} Ar = 4-ClC$_6$H$_4$ $C_{14}H_9Cl_5$	*Alcaligenes eutrophus* A5	("near stoichiometric"), —	198
$C_{14}H_{12}$	*Pseudomonas fluorescens* N3 TTC1	(—), —	48
$C_{14}H_{14}S$	*Escherichia coli* JM109(pDTG601)	(16), 98	186
C_{20} $C_{20}H_{26}O_3$	*Pseudomonas abietaniphila* BKME-9; *Escherichia coli* XL1 Blue MR(pVM20)	(—),—	94

[a] The assignment of absolute configuration for this product is tentative.

TABLE 2. MICROBIOLOGICAL OXYGENATIONS OF BENZOIC AND NAPTHOIC ACIDS AND ESTERS
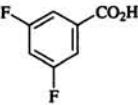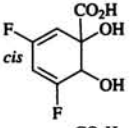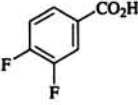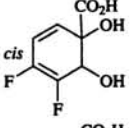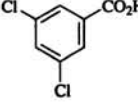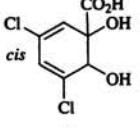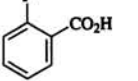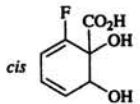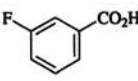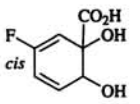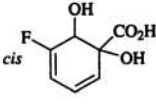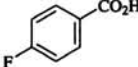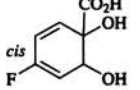
Substrate		Microorganism, Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %				Refs.
C7							
	$C_7H_4F_2O_2$	*Pseudomonas putida* JT103	*cis*	(—), —			75, 53
	$C_7H_4F_2O_2$	*Pseudomonas putida* JT103	*cis*	(—), —			53
	$C_7H_4Cl_2O_2$	*Alcaligenes eutrophus* B 9	*cis*	(—), —			36, 199
	$C_7H_5FO_2$	*Alcaligenes eutrophus* B 9	*cis*	(—), —			36, 74, 200
	$C_7H_5FO_2$	*Alcaligenes eutrophus* B 9	*cis*	(—), —			35
		Alcaligenes eutrophus B 9	"	(—), —	+	*cis* (—), —	36, 74
	$C_7H_5FO_2$	*Alcaligenes eutrophus* B 9	*cis*	(—), —			35, 36, 74

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TABLE 2. MICROBIOLOGICAL OXYGENATIONS OF BENZOIC AND NAPTHOIC ACIDS AND ESTERS *(Continued)*
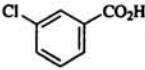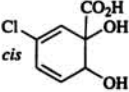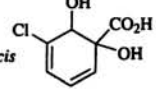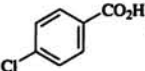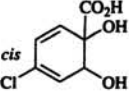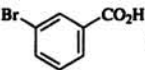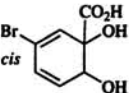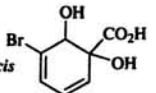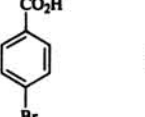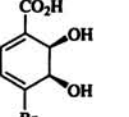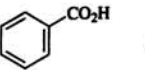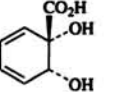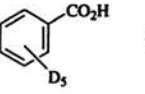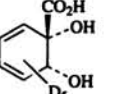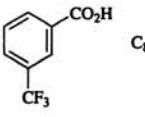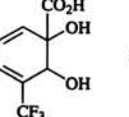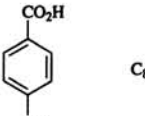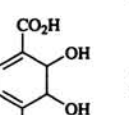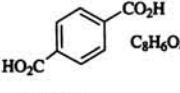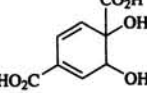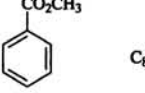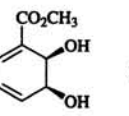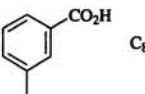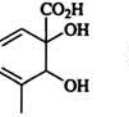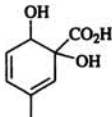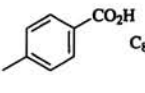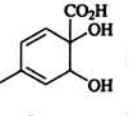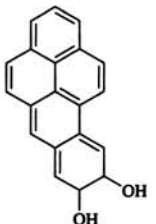
Substrate	Microorganism, Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %	Refs.
$C_7H_5ClO_2$	*Alcaligenes eutrophus* B 9	*cis* (—), —	35
	Alcaligenes eutrophus B 9	" (—), — + *cis* (—), —	201, 36, 74
$C_7H_5ClO_2$	*Alcaligenes eutrophus* B 9	*cis* (—), —	36, 74
$C_7H_5BrO_2$	*Alcaligenes eutrophus* B 9	*cis* (—), — + *cis* (—), —	36
$C_7H_5BrO_2$	*Pseudomonas putida* JT 107	(5 g/L), >98	202
$C_7H_6O_2$	*Pseudomonas putida* U103	(2-3 g/L), —	33
	Escherichia coli (pPL416, pKT570)	" (—), —	203
	Alcaligenes eutrophus B 9	" (*ca.* 50), —	35, 36
$C_7HD_5O_2$	*Pseudomonas putida* JT103	(—), —	204

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Substrate	Microorganism, Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %	Refs.
$C_8H_5F_3O_2$	*Pseudomonas putida* mt-2 (ATCC 33015)	(—), —	205
	Alcaligenes eutrophus B9	" (—), —	205
$C_8H_5F_3O_2$	*Pseudomonas putida* PL-pT-11/43	(80), —	206
	Pseudomonas putida JT107	" (—), —	207, 202
$C_8H_6O_4$	*Comamonas testosteroni* T-2	(—), —	208
$C_8H_8O_2$	*Pseudomonas putida* UV4	(42), —	61
$C_8H_8O_2$	*Alcaligenes eutrophus* B9	(—), — + (—), —	36, 35
$C_8H_8O_2$	*Alcaligenes eutrophus* B9	(—), —	36
	Pseudomonas putida BGXM1	" (48), —	143

TABLE 2. MICROBIOLOGICAL OXYGENATIONS OF BENZOIC AND NAPTHOIC ACIDS AND ESTERS *(Continued)*
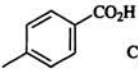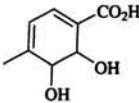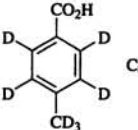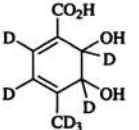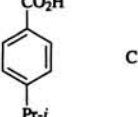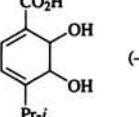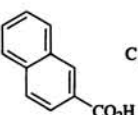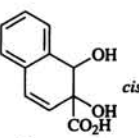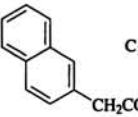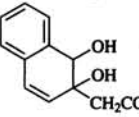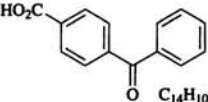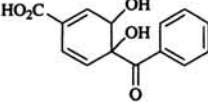
Substrate	Microorganism, Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %	Refs.
$C_8H_8O_2$	*Pseudomonas* JT 107	(10.2 g/L), —	202
$C_8HD_7O_2$	*Pseudomonas* JT 107	(—), —	204
C_{10} $C_{10}H_{12}O_2$	*Pseudomonas putida* PL-pT-11/43	(—), —	209
C_{11} $C_{11}H_8O_2$	*Pseudomonas* sp. A3	(74), — *cis*	210, 76
C_{12} $C_{12}H_{10}O_2$	*Pseudomonas* sp. C22	(—), —	210
C_{14}	*Pseudomonas fluorescens* N3 TTC1	(80), —	
$C_{14}H_{10}O_3$	*Pseudomonas* sp. POB 310	(—), —	211

TABLE 3. MICROBIOLOGICAL OXYGENATIONS OF BIPHENYLS

Substrate	Microorganism, Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %	Refs.
C₁₂			
$C_{12}H_6Cl_4$	Biphenyl 2,3-dioxygenase from *Pseudomonas* sp. LB400	(—), — + (tr), —	73
	Escherichia coli FM4110(pGEM410)	" (—), —	50
$C_{12}H_7Cl_3$	Biphenyl 2,3-dioxygenase from *Pseudomonas* sp. LB400	(—), — + (—), —	73
	Burkholderia sp. LB400	" (—), —	52
$C_{12}H_7Cl_3$	*Pseudomonas pseudoalcaligenes* KF707	I + II (—), —; I:II = 97:3	212
	Pseudomonas cepacia LB400	I+II (—), —; I:II = 5:95	212
$C_{12}H_8$	*Pseudomonas putida* UV4	(66), >98	69, 70

TABLE 3. MICROBIOLOGICAL OXYGENATIONS OF BIPHENYLS (*Continued*)
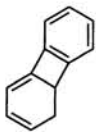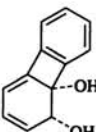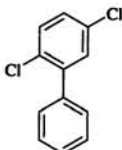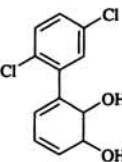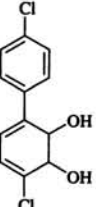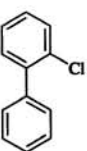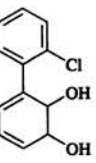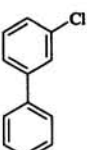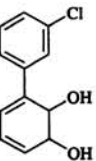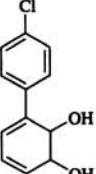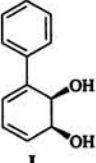
Substrate		Microorganism, Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %	Refs.
	$C_{12}H_8$	*Pseudomonas* sp. strain C250 cells, grown on carbazole	(—), >98	37
		Pseudomonas fluorescens N3	(—), —	48
	$C_{12}H_8Cl_2$	Biphenyl 2,3-dioxygenase from *Pseudomonas* sp. LB400	(—), —	73
	$C_{12}H_8Cl_2$	*Burkholderia* sp. LB400 BPDO encoded in *Escherichia coli* BL21(DE3)/pLys	(—), —	52
		Pseudomonas pseudoalcaligenes KF707	" (—), —	212
	$C_{12}H_9Cl$	Biphenyl 2,3-dioxygenase from *Pseudomonas* sp. LB400	(—), —	73
		Escherichia coli DH5$_\alpha$(pTCB144)	" (—), —	77
	$C_{12}H_9Cl$	Biphenyl 2,3-dioxygenase from *Pseudomonas* sp. LB400	(—), —	73
	$C_{12}H_9Cl$	*Escherichia coli* DH5$_\alpha$(pTCB144)	(—), —	77
	$C_{12}H_{10}$	*Beijerinckia* sp. B8/36 (name changed to *Sphingomonas yanoikuyae* B8/36)	(37), — **I**	49, 153
		Escherichia coli JM109(pDTG601)	**I** (3 g/L), —	213
		Escherichia coli JM109(pUCARA)	**I** (—), —	214
		Pseudomonas putida	**I** (—), —	215

TABLE 3. MICROBIOLOGICAL OXYGENATIONS OF BIPHENYLS *(Continued)*
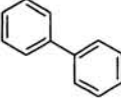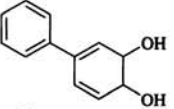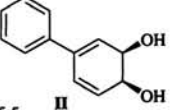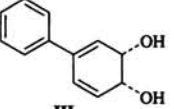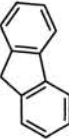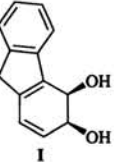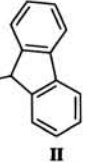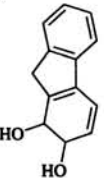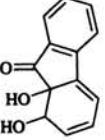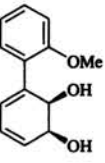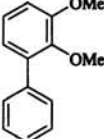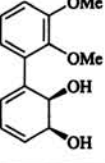
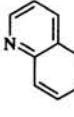| Substrate	Microorganism, Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %	Refs.
$C_{12}H_{10}$	Biphenyl 2,3-dioxygenase from *Pseudomonas* sp. LB400	**I** (—), —	51
	Pseudomonas fluorescens N3 TCC1	**I** (—), — + (—), —	48
	Escherichia coli JM109(DE3)(pDTG141)	**I** (—), >95 + (—), >98 **I:II** = 87:13	31
	Escherichia coli JM109(DE3)(pDTG141-A206I)	**I + II** (—); **I:II** = 95:5	91
	Escherichia coli JM109(DE3)(pDTG141-F352V)	**I** (—), >95 + (—), 75 **I:III** = 4:96	31
	Escherichia coli JM109(DE3)(pDTG141-F352V) (pDTG511)	**III** (—), >98	31
	Pseudomonas pseudoalcaligenes KF748	**I** (—), —	216
	Escherichia coli DH5$_\alpha$(pTCB144)	**I** (—), —	77
C_{13} $C_{13}H_{10}$	*Pseudomonas* sp. 9816/11	**I** (4), >95 + **II** (0.2)	67
	Escherichia coli JM109(DE3)(pDTG141)	**I** (57), >95 + **II** (6)	67
	Pseudomonas fluorescens N3 TCC1	**I** (—), — + (—), —	48
	Brevibacterium DPO 1361	(—), —	217
	Pseudomonas sp. F274	" (7), —	218, 219
$C_{13}H_{12}O$	*Escherichia coli* JM109(pDTG601)	(2.5 g/L), —	213
C_{14} $C_{14}H_{14}O_2$	*Escherichia coli* JM109(pDTG601)	(0.8 g/L), —	213

TABLE 4. MICROBIOLOGICAL OXYGENATIONS OF NAPHTHALENES

Substrate		Microorganism, Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %	Refs.
C₁₀				
(1-fluoronaphthalene)	$C_{10}H_7F$	*Pseudomonas fluorescens* N3 TTC1	(2), >95 + (2), >95	47
(1-chloronaphthalene)	$C_{10}H_7Cl$	Soil bacterium	(—), —	220
		Pseudomonas fluorescens N3 TTC1	(65), >95 + (14), >95	47
(2-chloronaphthalene)	$C_{10}H_7Cl$	*Pseudomonas fluorescens* N3 TTC1	(30), >95	47
(1-bromonaphthalene)	$C_{10}H_7Br$	*Pseudomonas putida* NCIB 9816-11	**I** (28), >98 + **II** (14), >98 + (tr), —	221
		Pseudomonas fluorescens N3 TTC1	**I** (25), >95 + **II** (19), >95	47
(2-bromonaphthalene)	$C_{10}H_7Br$	*Pseudomonas putida* NCIB 9816-11	(34), >98 + (tr), —	221
		Pseudomonas fluorescens N3 TTC1	" (32), >95	47
(1-nitronaphthalene)	$C_{10}H_7NO_2$	*Escherichia coli* DH5α(pDTG927)	(—), —	172
(2-nitronaphthalene)	$C_{10}H_7NO_2$	*Pseudomonas fluorescens* N3 TTC1	(34), >98	47
(naphthalene)	$C_{10}H_8$	*Pseudomonas putida* 119	(47), >98	62, 63
		Pseudomonas putida UV, immobilized in barium alginate beads	" (1.8 mol/g dry cell weight), >95	59
		Pseudomonas fluorescens N3 TTC1	" (80), >95	47
		Pseudomonas sp. NCIB 9816	(—), —	222
		Multicomponent Enzyme System from *Pseudomonas* sp. NCIB 9816	" (97, based on NADH), —	223
		Escherichia coli DH5α(pDTG800)	" (0.75 nmol/mg protein), 70	224
		Escherichia coli DH5α(pDTG832)	" (0.07 nmol/mg protein), 98	224
		Escherichia coli DH5α(pDTG833)	" (0.69 nmol/mg protein), 96	224

TABLE 4. MICROBIOLOGICAL OXYGENATIONS OF NAPHTHALENES (*Continued*)
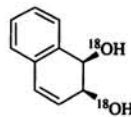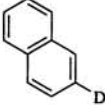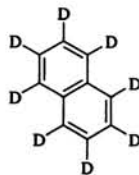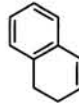
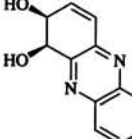| Substrate	Microorganism, Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %	Refs.
C$_{10}$H$_8$	*Escherichia coli* DH5$_\alpha$(pDTG834)	" (0.07 nmol/mg protein), 70	224
	Escherichia coli DH5$_\alpha$(pDTG141)	" (2.14 nmol/mg protein), >99	224
	Escherichia coli JM109(DE3)(pJS48)	" (0.83 nmol/mg protein), 96	224
	Escherichia coli DH5$_\alpha$(pDTG927)	" (—), 57	172
	Escherichia coli JM109(pUCARA)	" (~10), —	214
	Agmenellum quadruplicatum PR-6	" (—), —	225
	Escherichia coli JM109(pUCARA)	" (—), —	226
	Escherichia coli DH5$_\alpha$(pTCB144)	" (—), —	77
	Escherichia coli JM109(DE3)(pDTG141-A206I)	" (—), >98	91
	Escherichia coli JM109(DE3)(pDTG141-A206I-F352I)	" (—), 40	91
	Pseudomonas putida 119/^{18}O$_2$	(—), —	63
C$_{10}$H$_7$D	*Pseudomonas putida* UV4	(—), —	227, 164
C$_{10}$H$_7$D	*Pseudomonas putida* UV4	(—), —	227, 164
C$_{10}$D$_8$	*Pseudomonas putida* 119/^{18}O$_2$	(—), —	63
C$_{10}$H$_{10}$	*Pseudomonas putida* UV4	(10), >98 + (28), >98 + (8), >98 + (tr), — + (tr), —	228, 82, 229
	Sphingomonas yanoikuyae B1	(—) I:II:III = 5:0:1 **I** **II** **III**	230
	Sphingomonas yanoikuyae B8/36	I+II+III (—); I:II:III = 9:10:1	230
	Pseudomonas putida F39/D	I+II + (—) I:II:IV:V = 0:1.2:1.0:2.5 **IV** **V**	231
	Pseudomonas putida NCIB 9816/11	I+II+IV+V (—); I:II:IV:V = 1.9:1.0:0:0	231
	Escherichia coli JM109(pDTG601A)	I+II+IV+V (—); I:II:IV:V = 0:1.2:1.0:2.0	231
	Escherichia coli JM109(pDTG141)	I+II+IV+V (—); I:II:IV:V = 1.5:1.0:0:0	231

TABLE 4. MICROBIOLOGICAL OXYGENATIONS OF NAPHTHALENES (*Continued*)
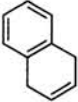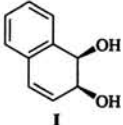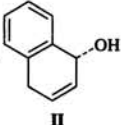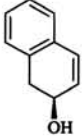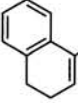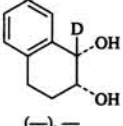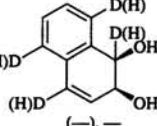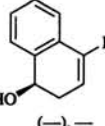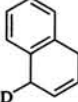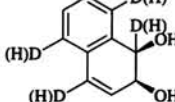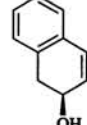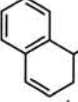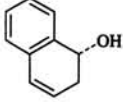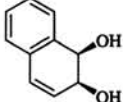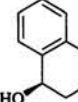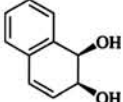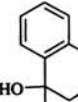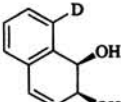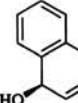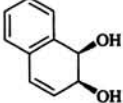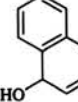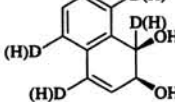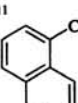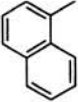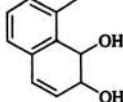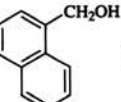
Substrate		Microorganism, Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %	Refs.
	$C_{10}H_{10}$	*Pseudomonas putida* UV4, 23 h fermentation	**I** (ca. 90), >98 + **II** (0) + **III** (0)	228, 229
		Pseudomonas putida UV4, 0.5 h fermentation	**I** (—), >98 + **II** (—), >98 + **III** (—), 3	228, 229
	$C_{10}H_9D$	*Pseudomonas putida* UV4	(—), — + (—), — + (—), —	228
	$C_{10}H_8D_2$	*Pseudomonas putida* UV4	(—), — + (—), —	228
racemic	$C_{10}H_{10}O$	*Pseudomonas putida* UV4	(8), >98 + (7), >98	229
	$C_{10}H_{10}O$	*Pseudomonas putida* UV4	(—), —	228
	$C_{10}H_9DO$	*Pseudomonas putida* UV4	(—), —	228
	$C_{10}H_{10}O$	*Pseudomonas putida* UV4	(—), —	228
	$C_{10}H_9DO$	*Pseudomonas putida* UV4	(—), —	228
C_{11}	$C_{11}H_8O_2$	*Pseudomonas maltophilia* CSV89	(—), —	232
	$C_{11}H_{10}$	*Pseudomonas fluorescens* N3 TTC1	(13), —	47
		Pseudomonas putida CSV86	" (—), — + (—), —	233

TABLE 4. MICROBIOLOGICAL OXYGENATIONS OF NAPHTHALENES (*Continued*)
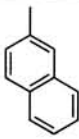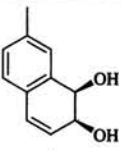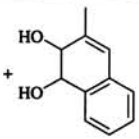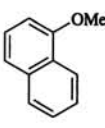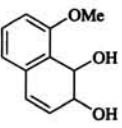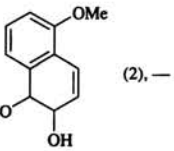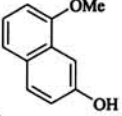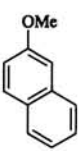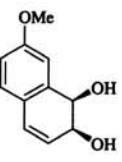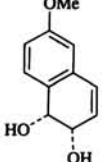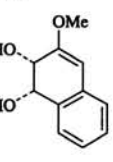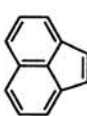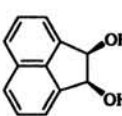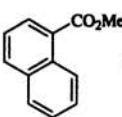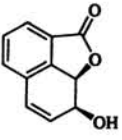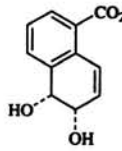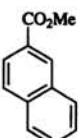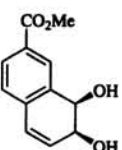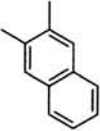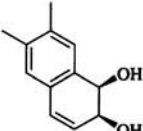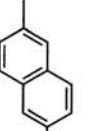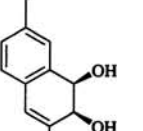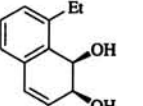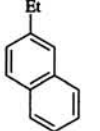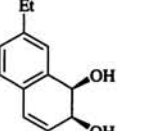
Substrate	Microorganism, Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %	Refs.
$C_{11}H_{10}$	*Pseudomonas putida* 39D	(20 mg/L), — + (—), —	234
	Pseudomonas putida NCIB 9816	" (350 mg/L), —	234
	Pseudomonas fluorescens N3 TTC1	" (20), —	47
$C_{11}H_{10}O$	*Pseudomonas fluorescens* N3 TTC1	(25), — + (2), —	47
	Streptomyces lividans pIJ6021-phdABCD	" (—), — +	78
$C_{11}H_{10}O$	*Pseudomonas putida* 39D	 **I** **II** **III** **I+II+III** (29)[a]; **I:II:III** = 12:73:15	26
	Escherichia coli JM109(pDTG601)	**I+II+III** (64)[a]; **I:II:III** = 17:69:14	26
	Pseudomonas putida NCIB 9816	**I+II+III** (6) [a]; **I:II:III** = 93:7:0	26
	Escherichia coli JM109(pDTG141)	**I+II+III** (57) [a]; **I:II:III** = 93:7:0	26
	Escherichia coli C534(ProR/Sac)	**I+II+III** (57) [a]; **I:II:III** = 92:8:0	26
	Beijerinckia sp. B8/36	**I+II+III** (36) [a]; **I:II:III** = 74:26:0	26
	Pseudomonas fluorescens N3 TTC1	**I** (64), —	47
C_{12} $C_{12}H_8$	*Beijerinckia* sp. B8/36	(3)	235
	Pseudomonas aeruginosa PAO1(pRE695)	" (—)	236
	Pseudomonas fluorescens N3 TTC1	" (—)	48
$C_{12}H_{10}O_2$	*Pseudomonas fluorescens* N3 TTC1	(23), >95 + (3), >95	47
$C_{12}H_{10}O_2$	*Pseudomonas fluorescens* N3 TTC1	(21), >95	47

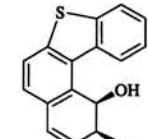TABLE 4. MICROBIOLOGICAL OXYGENATIONS OF NAPHTHALENES (*Continued*)

Substrate		Microorganism, Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %	Refs.
	$C_{12}H_{12}$	*Pseudomonas fluorescens* N3 TTC1	(21), >95	47
	$C_{12}H_{12}$	*Pseudomonas fluorescens* N3 TTC1	(3), >95	47
	$C_{12}H_{12}$	*Pseudomonas fluorescens* N3 TTC1	(22), >95	47
	$C_{12}H_{12}$	*Pseudomonas fluorescens* N3 TTC1	(70), >95	47

[a] The yield is given as percent of crude diols.

[b] This product was isolated as the methyl ester dimethyl ketal.

TABLE 5. MICROBIOLOGICAL OXYGENATIONS OF POLYCYCLIC AROMATICS
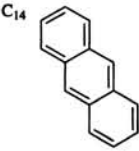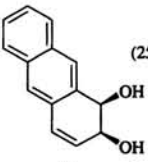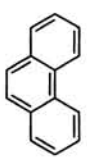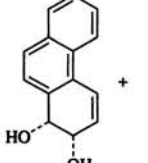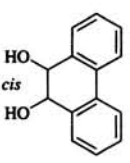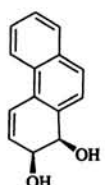
Substrate	Microorganism, Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %	Refs.
C₁₄			

	Beijerinckia sp. B8/36 or Escherichia coli JM109-(DE3)(pDTG141-F352V)	(25), >95	28, 29, 31
	Pseudomonas putida 119	" (—), —	28, 29
	Escherichia coli JM109(pUCARA)	" (—), —	214
	Pseudomonas fluorescens N3 TTC1	" (—), —	48
	Mycobacterium sp. strain PYR-1	" (—), —	237

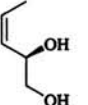| | Beijerinckia sp. B8/36 | I (32), >95   +   II (8), >95   +   III (0) | 28, 30, 31 |
	Pseudomonas putida 119	I (12), >95 + II (—), —	28, 30
	Escherichia coli JM109(pUCARA)	I (—), — + II (—), —	214
	Pseudomonas fluorescens N3 TTC1	I (—), — + II (—), —	48
	Mycobacterium sp. strain PYR-1	I (—), — + III (—), —	237
	Escherichia coli JM109(DE3)(pDTG141-F352V)	I (—), >95 + (—), 91 1 : 5	31

Substrate	Microorganism, Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %	Refs.
C₁₄H₁₂	*Pseudomonas putida* 9816/11	(7), >95 + (tr)	66
	Escherichia coli JM109(DE3)(pDTG141)	" (0.05 g/L), >95	66
C₁₄H₁₂	*Pseudomonas putida* 9816/11	(8), >95 + (3), >98	66
	Escherichia coli JM109(DE3)(pDTG141)	" (5), >95 + " (2), >98	66
C₁₆H₁₀	*Mycobacterium* sp.	*cis* (tr)	238
	Mycobacterium sp. strain PYR-1 dioxygenase genes expressed in *E. coli*	" (—)	239
	Mycobacterium sp. Strain RJGII-135	" (—)	240
	Mycobacterium sp. strain KR2	" (—)	241
	Mycobacterium flavescens (ATCC 700033)	" (—)	242
	Pseudomonas stutzeri strain P16	" (—)	243
	Bacillus cereus strain P21	" (—)	243
C₁₆H₁₀	*Escherichia coli* JM109(pUCARA)	*cis* (—), —	214
	Mycobacterium sp. strain KR20	" (—), —	244
C₁₈H₁₂	*Sphingomonas yanoikuyae* B8/36	(1), >98 + (tr), —	245, 246
C₁₈H₁₂	*Beijerinckia* sp. B8/36	**I** (10), >95 **II** (1), >95 **III** (1), >95 **I:II:III** = 73:15:12	247, 248
	Mycobacterium sp. Strain RJGII-135	**I** (—)	240
C₁₈H₁₂	*Sphingomonas yanoikuyae* B8/36	(12), >98	249
	Pseudomonas putida 9816/11	" (*ca.*1), >98	249
	Pseudomonas putida 9816/11; Triton X100	" (7), >98	249

C₁₆

C₁₈

202

203

TABLE 5. MICROBIOLOGICAL OXYGENATIONS OF POLYCYCLIC AROMATICS (*Continued*)

Substrate	Microorganism, Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %	Refs.
C_20 $C_{20}H_{12}$	*Beijerinckia* sp. B8/36	(—),— *cis* + (—),— [a]	247
$C_{20}H_{12}$	*Selenastrum capricornutum*	(—),— + (—),—	250
	Mycobacterium sp. Strain RJGII-135	" (—)	240

[a] The structure of this product is tentative.

TABLE 6. MICROBIOLOGICAL OXYGENATIONS OF HETEROCYCLES
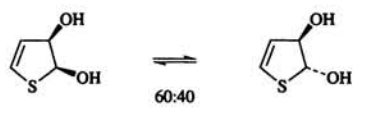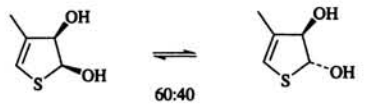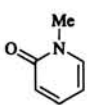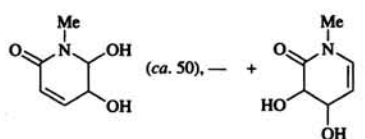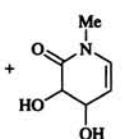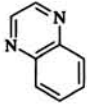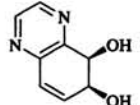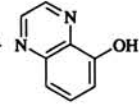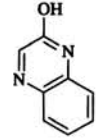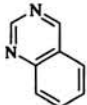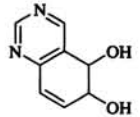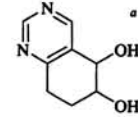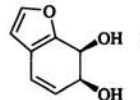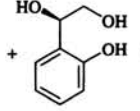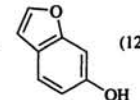
Substrate		Microorganism, Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %	Refs.
C₄				
	C₄H₄S	*Pseudomonas putida* UV4	(ca. 1), 43	251
C₅				
	C₅H₆S	*Pseudomonas putida* UV4	(11), 48	251
C₆				
	C₆H₇NO	*Escherichia coli* JM109(DE3)(pDTG141)	(ca. 50), — + (3), —	252
C₈				
	C₈H₆N₂	*Pseudomonas putida* UV4	(2), >98 + (2) + (<1)	253, 144
	C₈H₆N₂	*Pseudomonas putida* UV4	(4), — + ᵃ	253, 144
	C₈H₆O	*Pseudomonas putida* UV4	(34), >98 + (32) + (12)	254, 255, 256, 251

TABLE 6. MICROBIOLOGICAL OXYGENATIONS OF HETEROCYCLES (*Continued*)
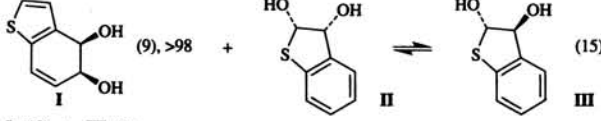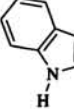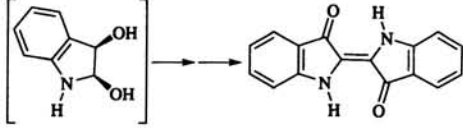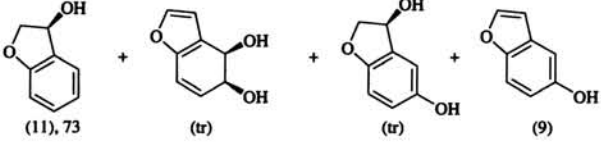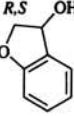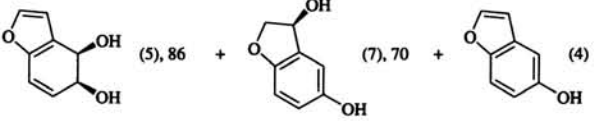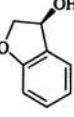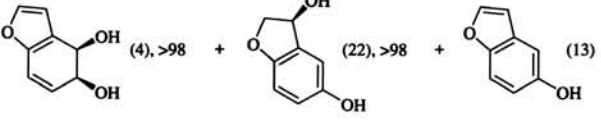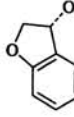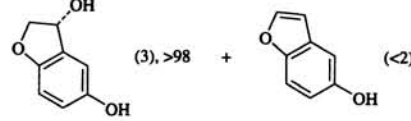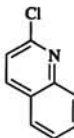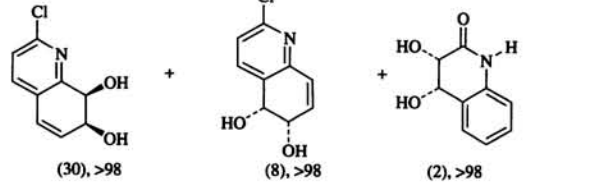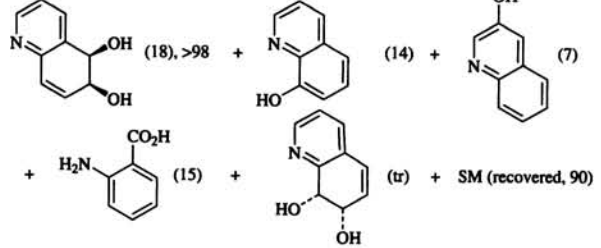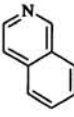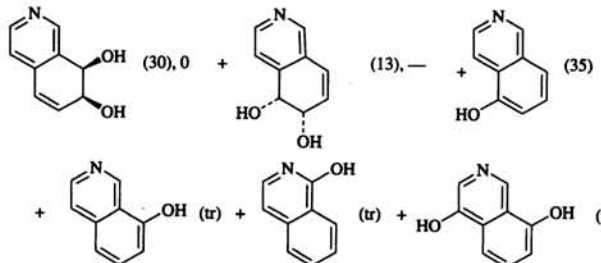
Substrate		Microorganism, Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %	Refs.

C8H6S — *Pseudomonas putida* UV4 — I (9), >98 + II ⇌ III (15) — 255, 251

Pseudomonas putida RE213 — I (12) + III (4) — 257

Pseudomonas putida UV4, immobilized in barium alginate beads — I+III; I:III = 1:3 — 59

C8H7N — *Pseudomonas putida* PpG7, or *Escherichia coli* HB101, or *Pseudomonas putida* 39/D, or *Beijerinckia* sp. B8/36, or *Pseudomonas Putida* UV4 — 258, 255

C8H8O — *Pseudomonas putida* UV4 — (11), 73 (tr) (tr) (9) — 254, 256

C8H8O2 (R,S OH) — *Pseudomonas putida* UV4 — (5), 86 + (7), 70 + (4) — 254

C8H8O2 — *Pseudomonas putida* UV4 — (4), >98 + (22), >98 + (13) — 254

C8H8O2 — *Pseudomonas putida* UV4 — (3), >98 + (<2) — 254

C9

C9H6ClN — *Pseudomonas putida* UV4 — (30), >98 + (8), >98 + (2), >98 — 259

C9H7N — *Pseudomonas putida* UV4 — (18), >98 + (14) + (7) + H2N-CO2H (15) + (tr) + SM (recovered, 90) — 144, 253

C9H7N — *Pseudomonas putida* UV4 — (30), 0 + (13), — + (35) + (tr) + (tr) + (tr) — 144, 253

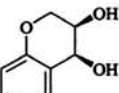TABLE 6. MICROBIOLOGICAL OXYGENATIONS OF HETEROCYCLES (*Continued*)
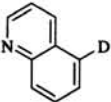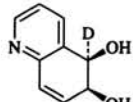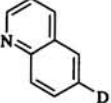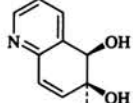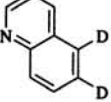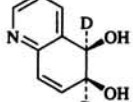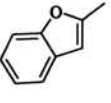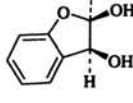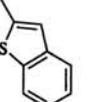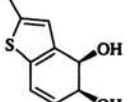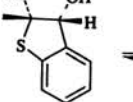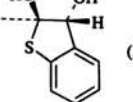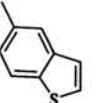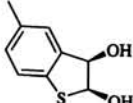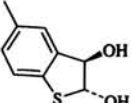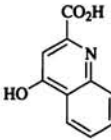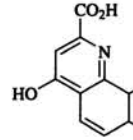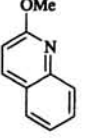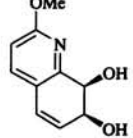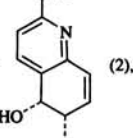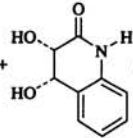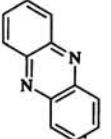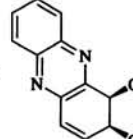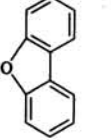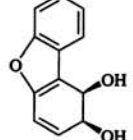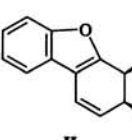
Substrate	Microorganism, Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %	Refs.
C_9H_6DN	*Pseudomonas putida* UV4	(—), —	227, 164
C_9H_6DN	*Pseudomonas putida* UV4	(—), —	227, 164
$C_9H_5D_2N$	*Pseudomonas putida* UV4	(—), —	227, 164
C_9H_8O	*Pseudomonas putida* UV4	(8), 80	251
C_9H_8S	*Pseudomonas putida* UV4	(25), — + 9:1 (3), 9	251
C_9H_8S	*Pseudomonas putida* UV4	78:28 (79), >98	251
C_{10} $C_{10}H_7NO_3$	*Pseudomonas fluorescens*	(—), —	260
$C_{10}H_9NO_3$	*Pseudomonas putida* UV4	(7), >98 + (2), >98 + (13), >98	259
C_{12} $C_{12}H_8N_2$	*Sphingomonas yanoikuyae* B8/36	(40), >98 + (15), >98	32
$C_{12}H_8O$	*Pseudomonas* sp. NCIB 9816-11	**I** (27), >95 + **II** (12), >95	67
	Escherichia coli JM109(DE3)(pDTG141)	**I** (34), >95 + **II** (22), >95	67
	Beijerinckia sp. B8/36	**I** (—), — + **II** (—), —	261
	Pseudomonas fluorescens TTC1	**I** (1.6 g/L, total), >95 + **II** (—), >95; **I**:**II** = 3:2	262

TABLE 6. MICROBIOLOGICAL OXYGENATIONS OF HETEROCYCLES (*Continued*)
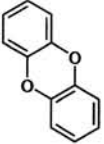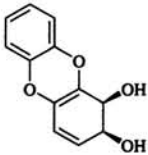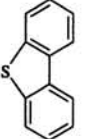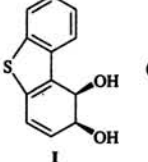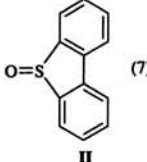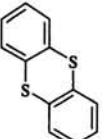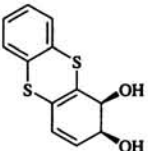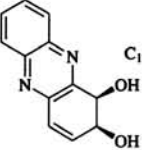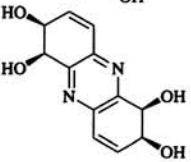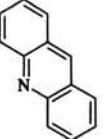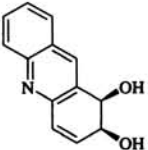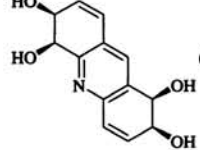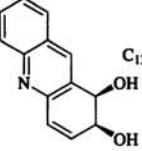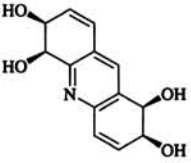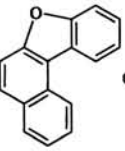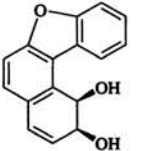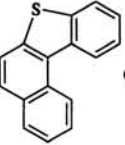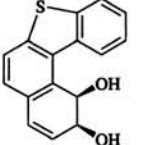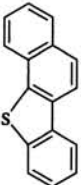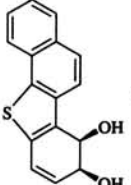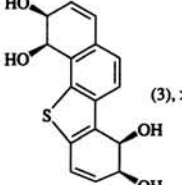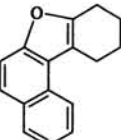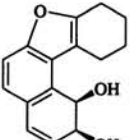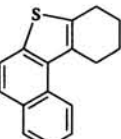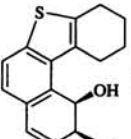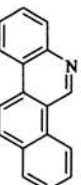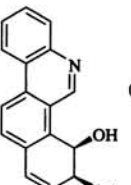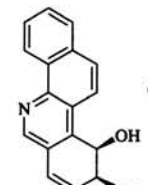
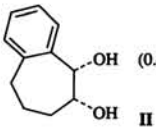| Substrate	Microorganism, Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %	Refs.
$C_{12}H_8O_2$	*Pseudomonas* sp. NCIB 9816-11	(4), —	46
	Beijerinckia sp. B8/36	" (1), —	263
$C_{12}H_8S$	*Beijerinckia* sp. B8/36	I (20), — + II (7)	264
	Pseudomonas sp. NCIB 9816-11	I (15), >95 + II (3)	67
	Escherichia coli JM109(DE3)(pDTG141)	I (49), >95 + II (5)	67
	Pseudomonas fluorescens TTC1	I (0.45 g/L, total), >95 + II (—), >95; I:II = 15:1	262
$C_{12}H_8S_2$	*Pseudomonas fluorescens* TTC1	(0.22 g/L), —	262
$C_{12}H_{10}N_2O_2$	*Sphingomonas yanoikuyae* B8/36	(—), >98	32
C₁₃			
$C_{13}H_9N$	*Sphingomonas yanoikuyae* B8/36	(50), >98 + (12), >98	32
	Pseudomonas fluorescens TTC1	" (0.22 g/L), —	262
$C_{13}H_{11}NO_2$	*Sphingomonas yanoikuyae* B8/36	(—), >98	32
C₁₆			
$C_{16}H_{10}O$	*Sphingomonas yanoikuyae* B8/36	(14), >98	249
	Pseudomonas putida 9816/11	" (11), >98	249
$C_{16}H_{10}S$	*Sphingomonas yanoikuyae* B8/36	(2), >98	249

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TABLE 6. MICROBIOLOGICAL OXYGENATIONS OF HETEROCYCLES (*Continued*)

Substrate		Microorganism, Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %		Refs.
	C₁₆H₁₀S	*Sphingomonas yanoikuyae* B8/36	(7), >98 +	(3), >98	246
	C₁₆H₁₄O	*Pseudomonas putida* 9816/11	(8), >98		249
	C₁₆H₁₄S	*Sphingomonas yanoikuyae* B8/36	(3), >98 +	(1.5), >98	249
	C₁₇H₁₁N	*Sphingomonas yanoikuyae* B8/36	(8), >98 +	(7), >98	246

C₁₇

a These two products were formed in an inseparable mixture.
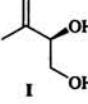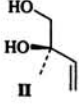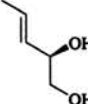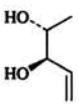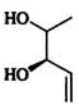
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TABLE 7. MICROBIOLOGICAL OXYGENATIONS OF OLEFINS

	Substrate		Microorganism, Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %	Refs.
C₄		C₄H₆	*Pseudomonas putida* ML 2	(—), 25	84
C₅		C₅H₆	*Pseudomonas putida*, UV4	(*ca.* 30), 20	86
		C₅H₈	*Pseudomonas putida* ML 2; propylene glycol	(—), 34 + (—), 40 I:II = 4:1	84
			Pseudomonas putida UV4; propylene glycol	I (—), 9 + II (—), 45; I:II = 2:1	84
			Pseudomonas putida 8859; propylene glycol	I (—), 12 + II (—), 16; I:II = 3:1	84
		C₅H₈	*Pseudomonas putida* ML 2; propylene glycol	(—), 38 + (—), 33 2 : 1	84
		C₅H₈	*Pseudomonas putida* ML 2; propylene glycol	(—), 74 + (—), 70 1 : 1	84
C₆		C₆H₈	*Pseudomonas putida* UV4	(*ca.* 30), >98	86

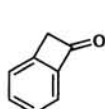TABLE 7. MICROBIOLOGICAL OXYGENATIONS OF OLEFINS (*Continued*)
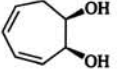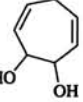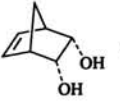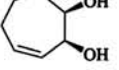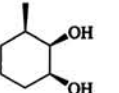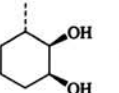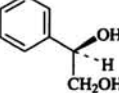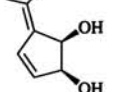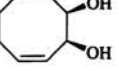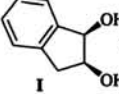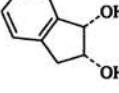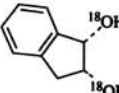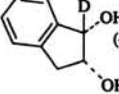
Substrate		Microorganism, Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %	Refs.
C₇				
	C_7H_8	*Pseudomonas putida* UV4	(*ca.* 30, total), >98 + 2:1	86
	C_7H_8	*Pseudomonas* sp. BM2	(35) + (3)	197
	C_7H_{10}	*Pseudomonas putida* UV4	(*ca.* 30), >98	86
R,S	C_7H_{12}	*Pseudomonas putida* UV4	(—), — + (—), —	265, 153
C₈				
	C_8H_8	Purified NDO from *Pseudomonas* sp. strain 9816-4	(—), 78	266
	C_8H_{10}	*Pseudomonas putida* RE213	(95), >98	85
		Pseudomonas putida UV4	" (*ca.* 30), >98	86
	C_8H_{12}	*Pseudomonas putida* UV4	(*ca.* 30), >98	86
C₉				
	C_9H_8	*Pseudomonas putida* 9816-11	**I** (53), 90 + **II** (43), 94	45
		Escherichia coli JM109(DE3)(pDTG141)	**I** (56), 86 + **II** (42), 81	45
		Pseudomonas putida UV4	(47), 20 + **II** (—), >98	82
		Escherichia coli D160-1	" (1.2 g/L), >98	83
		Pseudomonas putida 39/D	" (42 mg/L), 32 + (47 mg/L), 26 + (<1 mg/L)	267
		Pseudomonas putida 39/D; $^{18}O_2$	(—), — + (—), —	267
	C_9H_7D	*Pseudomonas putida* 39/D	(—), — + (—), — + (—), —	267
	C_9H_8O	*Pseudomonas putida* UV4	(10), >98 + (10) + (3) + (2)	268, 255

TABLE 7. MICROBIOLOGICAL OXYGENATIONS OF OLEFINS (*Continued*)
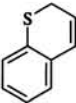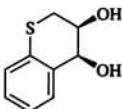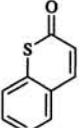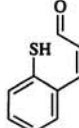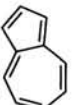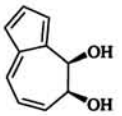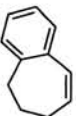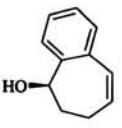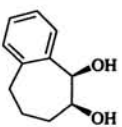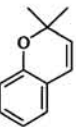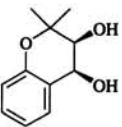
	Substrate	Microorganism, Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %	Refs.
	C₉H₈S	*Pseudomonas putida* UV4	(20), >98 + (—) + (—)	255
C₁₀	C₁₀H₈	*Pseudomonas putida* UV4	(*ca.* 20), >98	86
C₁₁	C₁₁H₁₂	*Pseudomonas putida* UV4	(6), >98 **I** + .OH (0.4), >98 **II**	152, 82
		Pseudomonas putida F39/D	**I** (16), >98 + **II** (1), >98	269
		Pseudomonas sp. 9816/11	(13), >98	269
		Sphingomonas yanoikuyae B8/36	" (13), >98	269
	C₁₁H₁₂O	*Pseudomonas putida* UV4	(18), >98	268, 255
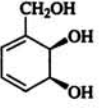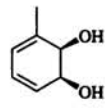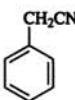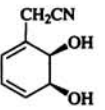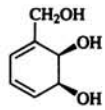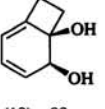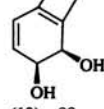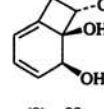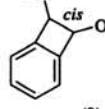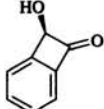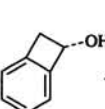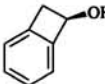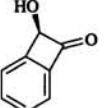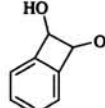
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TABLE 8. MICROBIOLOGICAL BENZYLIC OXYGENATIONS

	Substrate	Microorganism, Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %		Refs.
C₇	C₇H₈	*Pseudomonas putida* UV4	(4), >98 + (*ca.* 60), >98		55
C₈	C₈H₇N	*Pseudomonas putida* UV4	(20), >98 + (15), >98		55
	C₈H₈	*Pseudomonas putida* UV4	(18), >98 + (13), >98 + (9), >98 + (9)		69. 70
			+ (1), 72 + I (33), *ca.* 20 + II (2)		
		Pseudomonas fluorescens 127-68 XVII	I (—), 0 + II (—)		182
	C₈H₈O	*Pseudomonas putida* UV4	(9) + *cis* (35)		69

TABLE 8. MICROBIOLOGICAL BENZYLIC OXYGENATIONS (*Continued*)
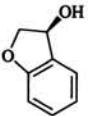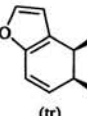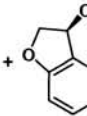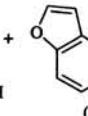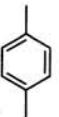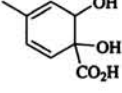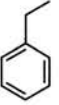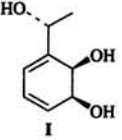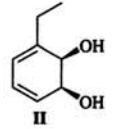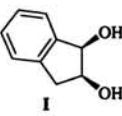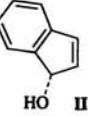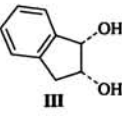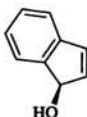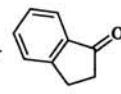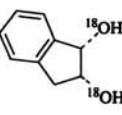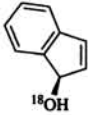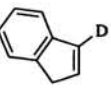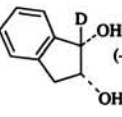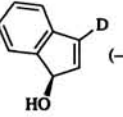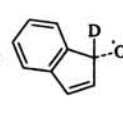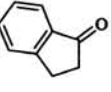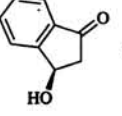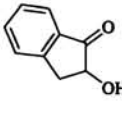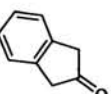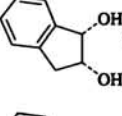
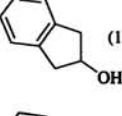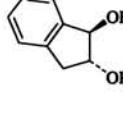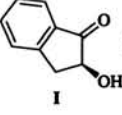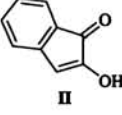| Substrate		Microorganism, Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %	Refs.
	C$_8$H$_8$O	*Pseudomonas putida* UV4		254, 256
	C$_8$H$_{10}$	*Pseudomonas putida* Biotype A strain (ATCC 39119)		188
	C$_8$H$_{10}$	*Pseudomonas putida* 39/D		183
		Pseudomonas putida UV4	**I** (5), >98 + **II** (60), >98	55
	C$_9$H$_8$	*Pseudomonas putida* 9816-11		45
		Escherichia coli JM109 (DE3)(pDTG141)	**I** (56), 86 + **II** (42), 81	45
		Pseudomonas putida UV4	(47), 20 + **II** (—), >98	82
		Pseudomonas putida 39/D	**III** (42 mg/L), 32 + (47 mg/L), 26 + (<1 mg/L)	267
		Pseudomonas putida 39/D; ^{18}O$_2$	(—), — + (—), —	267
D C$_9$H$_7$D		*Pseudomonas putida* 39/D	(—), — + (—), — + (—), —	267
	C$_9$H$_8$O	*Pseudomonas putida* 9816/11	(18), 62 + (2), 0	270
	C$_9$H$_8$O	*Pseudomonas putida* UV4	(28), >98 + (12) + (3), —	87
		Pseudomonas putida 39/D	(26), 76 + (tr)	270
		Pseudomonas putida 9816/11	**I** (23), 6 + **II** (tr)	270
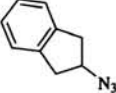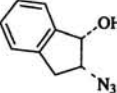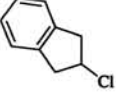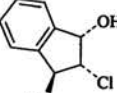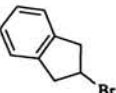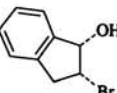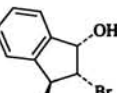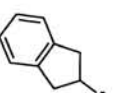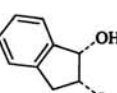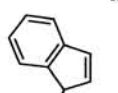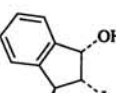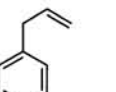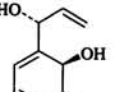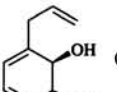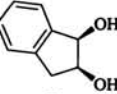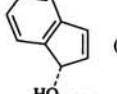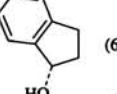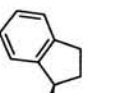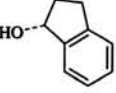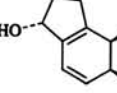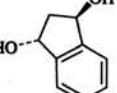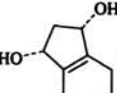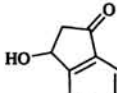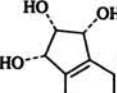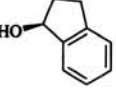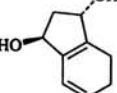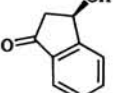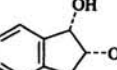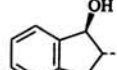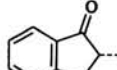
C$_9$

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TABLE 8. MICROBIOLOGICAL BENZYLIC OXYGENATIONS (*Continued*)

Substrate	Microorganism, Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %	Refs.
C₉H₉N₃	*Pseudomonas putida* UV4	(61), >98	87
C₉H₉Cl	*Pseudomonas putida* UV4	(38), >98	87
C₉H₉Br	*Pseudomonas putida* UV4	(35), >98 + (26), >98	87
C₉H₉I	*Pseudomonas putida* UV4	(20), >98 + (13), >98 + (0.5), >98	87
C₉H₁₀	*Pseudomonas putida* UV4	(15), >98 + (18), >98	55
C₉H₁₀	*Pseudomonas putida* 9816-11	**I** (7), 86 + **II** (8), 69 + **III** (64), 79	45
	Escherichia coli JM109 (DE3)(pDTG141)	**I** (18), 91 + **II** (19), 83 + **III** (54), 93	45
	Pseudomonas putida 39/D	(46 mg/L), 80	267
	Pseudomonas putida UV4	" (—), >98	70
	Escherichia coli JM109(DE3)(pDTG141)	" (—), 66	271
C₉H₁₀O	*Pseudomonas putida* UV4	(4), >98 + (13), >98	87
	Escherichia coli JM109(DE3)(pDTG141)	(50) + (12), — + (7)	272
C₉H₁₀O	*Pseudomonas putida* UV4	(9), >98 + (4), 82	87
	Escherichia coli JM109(DE3)(pDTG141)	" (60), 69	272
C₉H₁₀O	*Pseudomonas putida* UV4	(35), >98 + (4), >98 + (1), 26	87
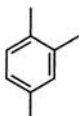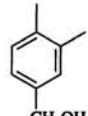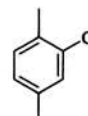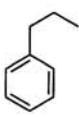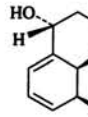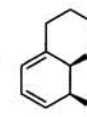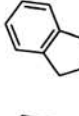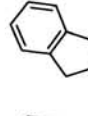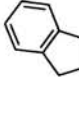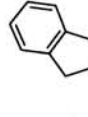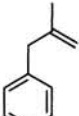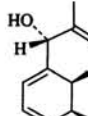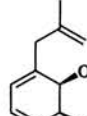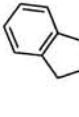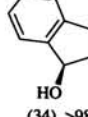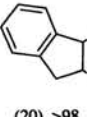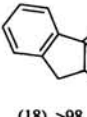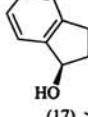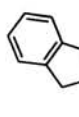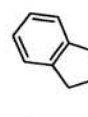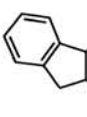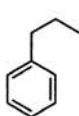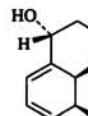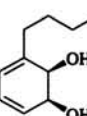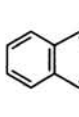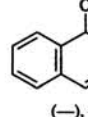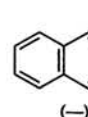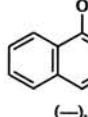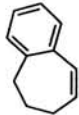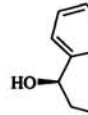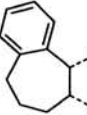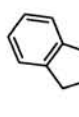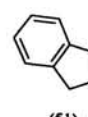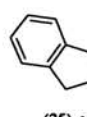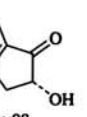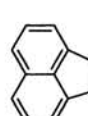
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TABLE 8. MICROBIOLOGICAL BENZYLIC OXYGENATIONS (*Continued*)

Substrate		Microorganism, Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %	Refs.
	C_9H_{12}	*Pseudomonas aeruginosa* PAO1(pRE695)	(—), — + (—), —	236
	C_9H_{12}	*Pseudomonas putida* UV4	(26), >98 + (15), >98	55
	$C_{10}H_9N$	*Pseudomonas putida* UV4	(37), >98	87
	$C_{10}H_{11}NO_2$	*Pseudomonas putida* UV4	(36), >98	87
	$C_{10}H_{12}$	*Psuedomonas putida* UV4	(18), >98 + (9), >98	55
	$C_{10}H_{12}$	*Pseudomonas putida* UV4	+ + + (34), >98 (20), >98 (18), >98 (17), >98	87
	$C_{10}H_{12}O$	*Pseudomonas putida* UV4	(9), >98 + (1), >98	87
	$C_{10}H_{14}$	*Psuedomonas putida* UV4	(9), >98 + (33), >98	55
	$C_{11}H_{10}$	*Sphingomonas paucimobilis* 2322	+ + (—), — (—), — (—), —	273
	$C_{11}H_{12}$	*Pseudomonas putida* UV4	(6), >98 + (0.4), >98	152, 82
		Pseudomonas putida F39/D	**I** (16), >98 + **II** (1), >98	269
	$C_{11}H_{12}O_2$	*Pseudomonas putida* UV4	+ + + (51) (25), >98 (3), >98 (2), >98	87
	$C_{12}H_{10}$	*Beijerinckia* sp. B8/36	(—)	235
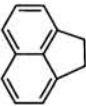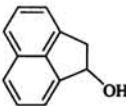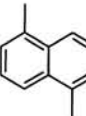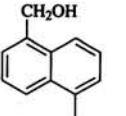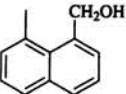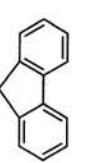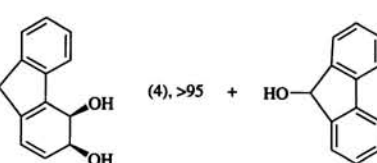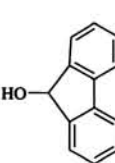
C_{10}

C_{11}

C_{12}

TABLE 8. MICROBIOLOGICAL BENZYLIC OXYGENATIONS (*Continued*)
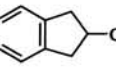
Substrate	Microorganism, Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %	Refs.
$C_{12}H_{10}$	*Pseudomonas aeruginosa* PAO1(pRE695)	(—), —	236
$C_{12}H_{12}$	*Pseudomonas aeruginosa* PAO1(pRE695)	CH₂OH (—)	236
$C_{12}H_{12}$	*Pseudomonas aeruginosa* PAO1(pRE695)	CH₂OH (—)	236
$C_{12}H_{12}$	*Pseudomonas aeruginosa* PAO1(pRE695)	CH₂OH (—)	236
C_{13} $C_{13}H_{10}$	*Pseudomonas* sp. 9816/11	I (4), >95 + II (0.2)	67
	Escherichia coli JM109(pDTG601)	I (57), >95 + II (6)	67
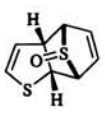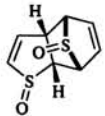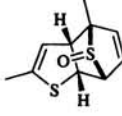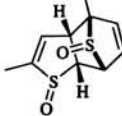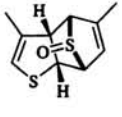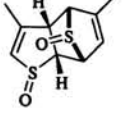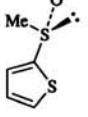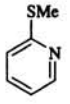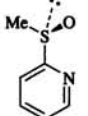
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TABLE 9. MICROBIOLOGICAL OXYGENATION OF THIOLS

	Substrate		Microorganism, Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %	Refs.
C4		C_4H_4S	*Pseudomonas putida* UV4	(11), 77 + (45), —	89
C5		C_5H_6S	*Pseudomonas putida* UV4	(12), 8 + (4), —	89
		C_5H_6S	*Pseudomonas putida* UV4	(4), 51 + (4), —	89
		$C_5H_6S_2$	*Pseudomonas putida* UV4	(41), >98	44
			Pseudomonas putida NCIMB 8859	(4), 69	44
C6		C_6H_7NS	*Pseudomonas putida* UV4	(20), 94	58, 44

TABLE 9. MICROBIOLOGICAL OXYGENATION OF THIOLS (*Continued*)

	Substrate		Microorganism, Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %	Refs.
	(2-SMe pyridine)	C_6H_7NS	*Pseudomonas putida* NCIMB 8859	(18), 35	44
	(4-SMe pyridine)	C_6H_7NS	*Pseudomonas putida* NCIMB 8859	(5), 95	44
C_7	(4-F-phenyl-SMe)	C_7H_7FS	*Pseudomonas putida* UV4	(31), 78	44
			Pseudomonas putida NCIMB 8859	(4), 91	44
	(3-F-phenyl-SMe)	C_7H_7FS	*Pseudomonas putida* UV4	(30), 98	44
			Pseudomonas putida NCIMB 8859	" (53), 97	44
	(4-Cl-phenyl-SMe)	C_7H_7ClS	*Pseudomonas putida* UV4	(2), 72	44
			Pseudomonas putida NCIMB 8859	" (5), >98	44
	(4-Br-phenyl-SMe)	C_7H_7BrS	*Pseudomonas putida* UV4	(2), 73	44
			Pseudomonas putida NCIMB 8859	" (35), >98	44
	(4-I-phenyl-SMe)	C_7H_7IS	*Pseudomonas putida* UV4	(<1), 70	44
			Pseudomonas putida NCIMB 8859	" (3), 90	44
	(4-NO_2-phenyl-SMe)	$C_7H_7NO_2S$	Purified TDO from *Escherichia coli* JM109(pDTG601A)	(—), 86	88
			Purified NDO from *Escherichia coli* JM109(pDTG141)	" (—), >98	88

TABLE 9. MICROBIOLOGICAL OXYGENATION OF THIOLS (*Continued*)
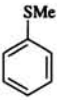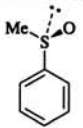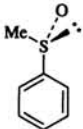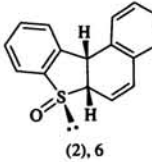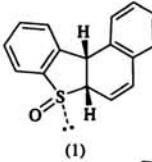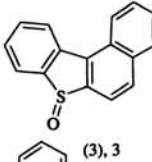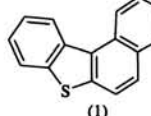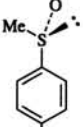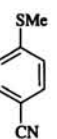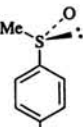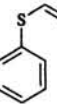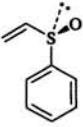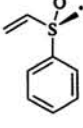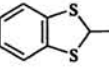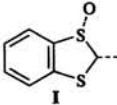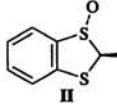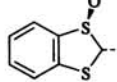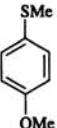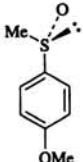
Substrate		Microorganism, Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %	Refs.
(PhSMe)	C₇H₈S	*Pseudomonas putida* UV4	(Me-S(=O)-Ph) (95), >98	58, 44
		Escherichia coli (pKS T11)	" (—), >95	58
		Purified TDO from *Escherichia coli* JM109(pDTG601A)	" (—), >98	88
		Purified NDO from *Escherichia coli* JM109(pDTG141)	(Me-S(O)-Ph sulfoxide) (—), >98	88
		Pseudomonas putida NCIMB 8859	" (33), 91	58, 44
C₈				
(benzothiophene)	C₈H₆S	*Pseudomonas putida* UV4	(2), 6 + (1) + (3), 3 + (1)	89
(4-CF₃-C₆H₄-SMe)	C₈H₇F₃S	*Pseudomonas putida* UV4	(2), 76	44
		Pseudomonas putida NCIMB 8859	" (3), 98	44
(4-CN-C₆H₄-SMe)	C₈H₇NS	*Pseudomonas putida* NCIMB 8859	(<1), 73	44
(PhS-CH=CH₂)	C₈H₈S	*Pseudomonas putida* UV4	(38), >98	58, 44
		Escherichia coli (pKS T11)	" (—), >95	58
		Pseudomonas putida NCIMB 8859	(—), 91	58, 44
(2-methyl-benzodithiole)	C₈H₈S₂	*Pseudomonas putida* UV4	**I** (40), >98 + **II** (5), >98	58
		Escherichia coli (pKS T11)	**I** (—), 97 + **II** (—), 40	58
		Pseudomonas putida NCIMB 8859	(—), 82 + (—), 38	58
(4-OMe-C₆H₄-SMe)	C₈H₁₀OS	Purified TDO from *Escherichia coli* JM109(pDTG601A)	(—), 32	88

TABLE 9. MICROBIOLOGICAL OXYGENATION OF THIOLS (*Continued*)
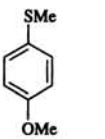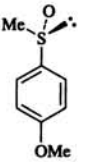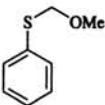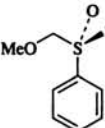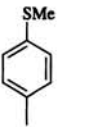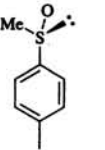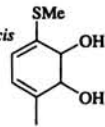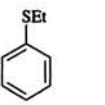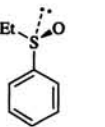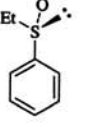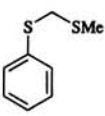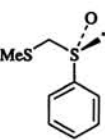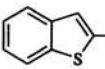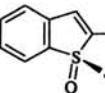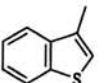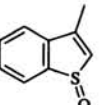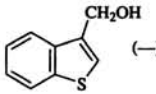
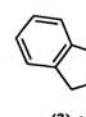| Substrate		Microorganism, Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %		Refs.
	$C_8H_{10}OS$	Purified NDO from *Escherichia coli* JM109(pDTG141)	(—), >98		88
	$C_8H_{10}OS$	*Pseudomonas putida* UV4	(36), >98		44
		Pseudomonas putida NCIMB 8859	" (4), 10		44
	$C_8H_{10}S$	Purified TDO from *Escherichia coli* JM109(pDTG601A)	(—), 38 + (—), —		88
		Purified NDO from *Escherichia coli* JM109(pDTG141)	" (—), >98		88
	$C_8H_{10}S$	*Pseudomonas putida* UV4	(64), >98		58, 44
		Escherichia coli (pKS T11)	" (—), >95		58
		Purified TDO from *Escherichia coli* JM109(pDTG601A)	" (—), >98		88
		Purified NDO from *Escherichia coli* JM109(pDTG141)	(—), 93		88
		Pseudomonas putida NCIMB 8859	" (27), 84		58, 44
	$C_8H_{10}S_2$	*Pseudomonas putida* UV4	(20), 97		58
C₉					
	C_9H_8S	*Pseudomonas putida* UV4	(2), >98		89
		Pseudomonas putida 8859	(26), 56		89
	C_9H_8S	*Pseudomonas aeruginosa* PAO1(pRE695)	(—) + (—)		236

TABLE 9. MICROBIOLOGICAL OXYGENATION OF THIOLS (*Continued*)
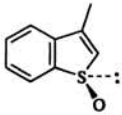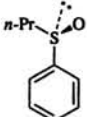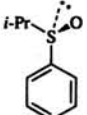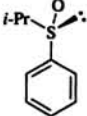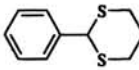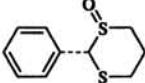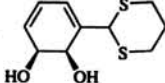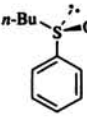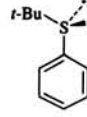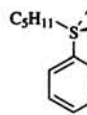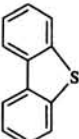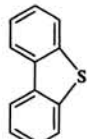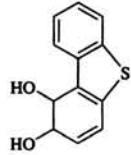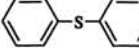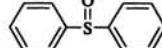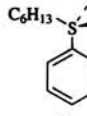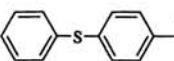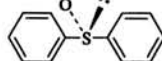
Substrate		Microorganism, Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %		Refs.
	C_9H_8S	*Pseudomonas putida* 8859	(7), 41		89
	$C_9H_{12}S$	*Pseudomonas putida* UV4	(5), >98		58, 44
		Pseudomonas putida NCIMB 8859	" (33), 86		44
	$C_9H_{12}S$	*Pseudomonas putida* UV4	(27), 97		58
		Pseudomonas putida NCIMB 8859	(24), 76		58, 44
C_{10}	$C_{10}H_{12}S_2$	*Pseudomonas putida* UV4	(7), >98 + (18), > 98		58
	$C_{10}H_{14}S$	*Pseudomonas putida* UV4	(7), 98		58
		Pseudomonas putida NCIMB 8859	" (79), >98		44
	$C_{10}H_{14}S$	*Pseudomonas putida* UV4	(2), 62		58
C_{11}	$C_{11}H_{16}S$	*Pseudomonas putida* UV4	(6), 57		44
		Pseudomonas putida NCIMB 8859	" (21), 98		44
C_{12}	$C_{12}H_8S$	*Beijerinckia* B8/38	(7) + (20), —		264
	$C_{12}H_{10}S$	*Pseudomonas putida* UV4	(10)		58
	$C_{12}H_{18}S$	*Pseudomonas putida* UV4	(<1), 78		44
		Pseudomonas putida NCIMB 8859	" (76), >98		44
C_{13}	$C_{13}H_{12}S$	*Pseudomonas putida* UV4	(<1), >98		58
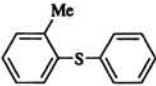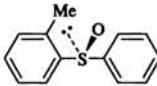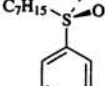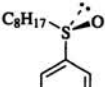
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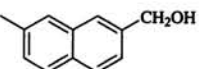TABLE 9. MICROBIOLOGICAL OXYGENATION OF THIOLS (*Continued*)

Substrate	Microorganism, Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %	Refs.
Me C13H12S	*Pseudomonas putida* UV4	Me, O (1), 86	58
SC7H15 C13H20S	*Pseudomonas putida* UV4	C7H15, O (<1), 12	44
	Pseudomonas putida NCIMB 8859	" (43), >98	44
C14 SC8H17 C14H22S	*Pseudomonas putida* UV4	C8H17, O (<1), 22	44
	Pseudomonas putida NCIMB 8859	" (25), 98	44

TABLE 10. DIHYDRODIOLS THAT HAVE NOT BEEN ISOLATED
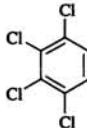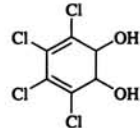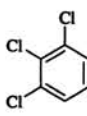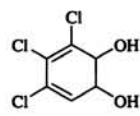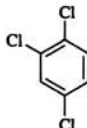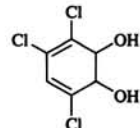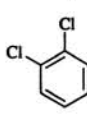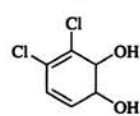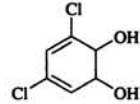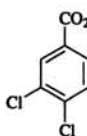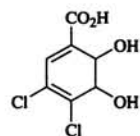
Substrate		Microorganism, Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %		Refs.
C_6					
	$C_6H_2Cl_4$	*Escherichia coli* DH$_\alpha$(pTCB144)		(—)	77
	$C_6H_3Cl_3$	*Escherichia coli* DH$_\alpha$(pTCB144)		(—), —	77
	$C_6H_3Cl_3$	*Escherichia coli* DH$_\alpha$(pTCB144)		(—), —	77
	$C_6H_4Cl_2$	*Pseudomonas* sp.		(—), —	274
	$C_6H_4Cl_2$	*Alcaligenes* sp. OBB65		(—), —	275
C_7					
	$C_7H_4Cl_2O_2$	*Pseudomonas putida* PL-pT-11/43		(—), —	209

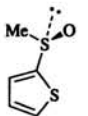TABLE 10. DIHYDRODIOLS THAT HAVE NOT BEEN ISOLATED (*Continued*)
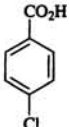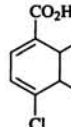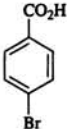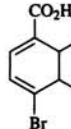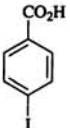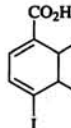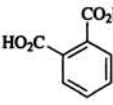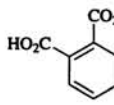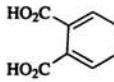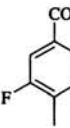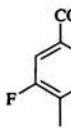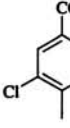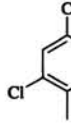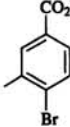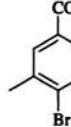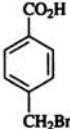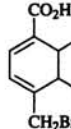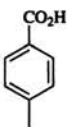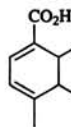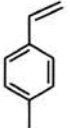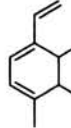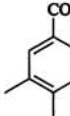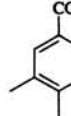
Substrate		Microorganism, Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %		Refs.
	$C_7H_5ClO_2$	*Pseudomonas putida* PL-pT-11/43		(—), —	209
	$C_7H_5BrO_2$	*Pseudomonas putida* PL-pT-11/43		(—), —	209
	$C_7H_5IO_2$	*Pseudomonas putida* PL-pT-11/43		(—), —	209
C_8	$C_8H_6O_4$	*Micrococcus* sp. 12B		(—), —	276
		Burkholderia cepacia DBO1		(—), —	277, 278
	$C_8H_7FO_2$	*Pseudomonas putida* PL-pT-11/43		(—), —	209
	$C_8H_7ClO_2$	*Pseudomonas putida* PL-pT-11/43		(—), —	209
	$C_8H_7BrO_2$	*Pseudomonas putida* PL-pT-11/43		(—), —	209
	$C_8H_7BrO_2$	*Pseudomonas putida* PL-pT-11/43		(—), —	209
	$C_8H_8O_2$	*Pseudomonas putida* PL-pT-11/43		(—), —	209
C_9	C_9H_{10}	*Pseudomonas putida* PL-pT-11/43		(—), —	209
	$C_9H_{10}O_2$	*Pseudomonas putida* PL-pT-11/43		(—), —	209

TABLE 10. DIHYDRODIOLS THAT HAVE NOT BEEN ISOLATED (*Continued*)
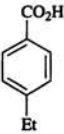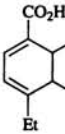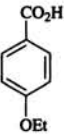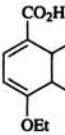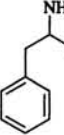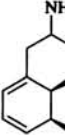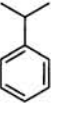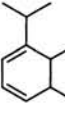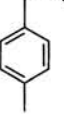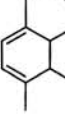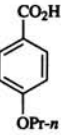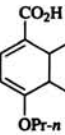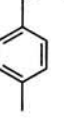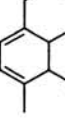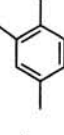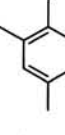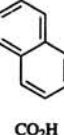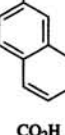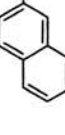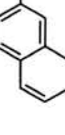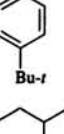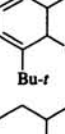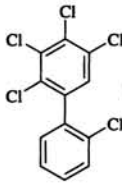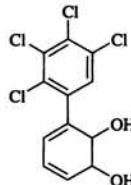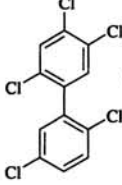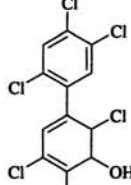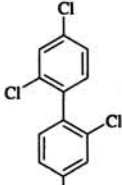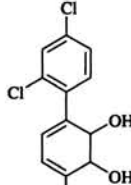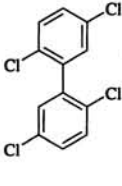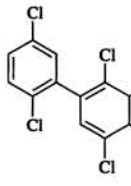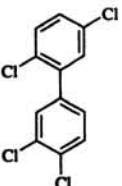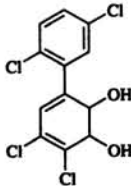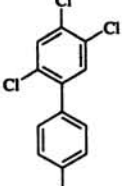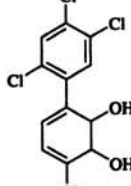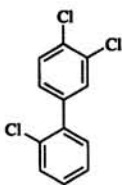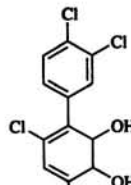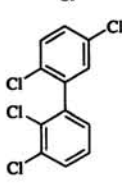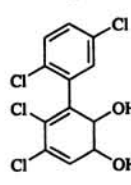
	Substrate		Microorganism, Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %	Refs.
		$C_9H_{10}O_2$	*Pseudomonas putida* PL-pT-11/43	(—), —	209
		$C_9H_{10}O_3$	*Pseudomonas putida* PL-pT-11/43	(—), —	209
		$C_9H_{11}NO_2$	A bacterium	(—), —	279
		C_9H_{12}	*Pseudomonas desmolytica; Pseudomonas convexa*	(—), —	195
C_{10}		$C_{10}H_{12}$	*Pseudomonas putida* PL-pT-11/43	(—), —	209
		$C_{10}H_{12}O_3$	*Pseudomonas putida* PL-pT-11/43	(—), —	209
		$C_{10}H_{14}$	*Pseudomonas putida* PL-pT-11/43	(—), —	209
		$C_{10}H_{14}$	*Pseudomonas putida* PL-pT-11/43	(—), —	209
C_{11}		$C_{11}H_{10}$	*Pseudomonas putida* CSV86	(—), — + (—), — + (—), —	233
		$C_{11}H_{14}O_2$	*Pseudomonas putida* PL-pT-11/43	(—), —	209
		$C_{11}H_{16}$	*Psuedomonas putida, Pseudomonas acidivorans*	(—), —	196
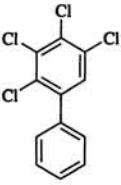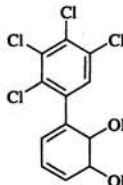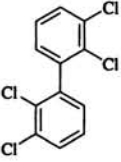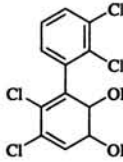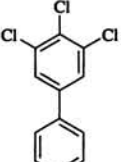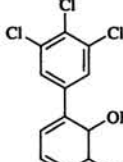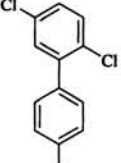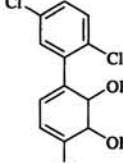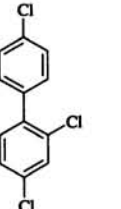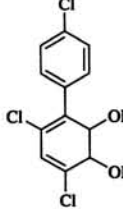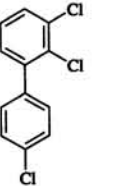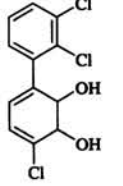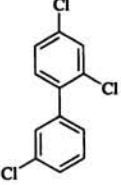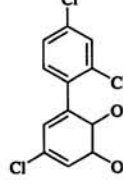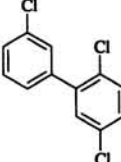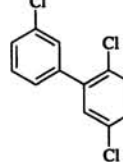
TABLE 10. DIHYDRODIOLS THAT HAVE NOT BEEN ISOLATED (*Continued*)

Substrate	Microorganism, Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %	Refs.
C_{12} $C_{12}H_5Cl_5$	*Burkholderia* sp. LB400	(—), —	52
$C_{12}H_5Cl_5$	*Escherichia coli* JM105(S4.43)	(—), —	280
$C_{12}H_6Cl_4$	*Burkholderia* sp. LB400	(—), —	52
$C_{12}H_6Cl_4$	*Escherichia coli* JM105(S4.43)	(—), —	280
$C_{12}H_6Cl_4$	*Escherichia coli* JM105(S4.43)	(—), —	280
$C_{12}H_6Cl_4$	*Escherichia coli* JM105(S4.43)	(—), —	280
$C_{12}H_6Cl_4$	*Escherichia coli* JM105(S4.43)	(—), —	280
$C_{12}H_6Cl_4$	*Escherichia coli* JM105(S4.43)	(—), —	280
	Burkholderia sp. LB400	" (—), —	281

240

241

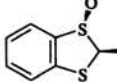TABLE 10. DIHYDRODIOLS THAT HAVE NOT BEEN ISOLATED (*Continued*)

Substrate		Microorganism, Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %		Refs.
	$C_{12}H_6Cl_4$	*Burkholderia* sp. LB400		(—), —	281
	$C_{12}H_6Cl_4$	*Burkholderia* sp. LB400		(—), —	281
	$C_{12}H_7Cl_3$	*Burkholderia* sp. LB400		(—), —	281
	$C_{12}H_7Cl_3$	*Burkholderia* sp. LB400		(—), —	281
	$C_{12}H_7Cl_3$	*Burkholderia* sp. LB400		(—), —	52
	$C_{12}H_7Cl_3$	*Burkholderia* sp. LB400		(—), —	52
	$C_{12}H_7Cl_3$	*Escherichia coli* JM105(S4.43)		(—), —	280
	$C_{12}H_7Cl_3$	*Burkholderia* sp. LB400		(—), —	52, 281
		Biphenyl 2,3-dioxygenase from *Pseudomonas* sp., LB400	"	(—), —	73

TABLE 10. DIHYDRODIOLS THAT HAVE NOT BEEN ISOLATED (*Continued*)
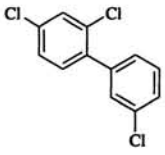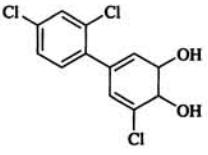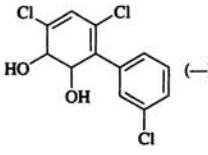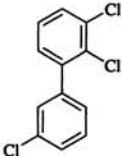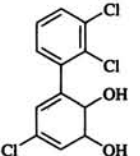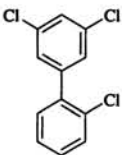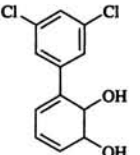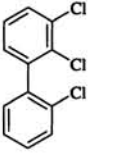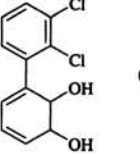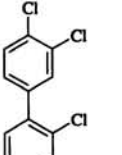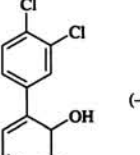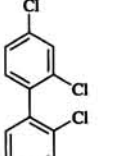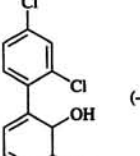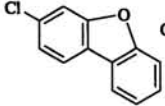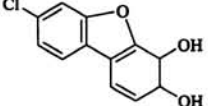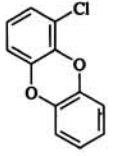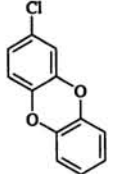
Substrate	Microorganism, Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %	Refs.
$C_{12}H_7Cl_3$	*Burkholderia* sp. LB400	(—), — + (—), —	52
$C_{12}H_7Cl_3$	*Burkholderia* sp. LB400	(—), —	52
$C_{12}H_7Cl_3$	*Burkholderia* sp. LB400	(—), —	52
$C_{12}H_7Cl_3$	*Burkholderia* sp. LB400	(—), —	52
$C_{12}H_7Cl_3$	*Burkholderia* sp. LB400	(—), —	52
$C_{12}H_7Cl_3$	*Burkholderia* sp. LB400	(—), —	52
$C_{12}H_7ClO$	*Escherichia coli* DH5$_\alpha$(pTCB144)	(—), —	77
$C_{12}H_7ClO_2$	*Beijerinckia* sp. B8/36	Dihydrodiol isolated, regiochemistry not determined	263
$C_{12}H_7ClO_2$	*Beijerinckia* sp. B8/36	Dihydrodiol isolated, regiochemistry not determined	263

TABLE 10. DIHYDRODIOLS THAT HAVE NOT BEEN ISOLATED (*Continued*)
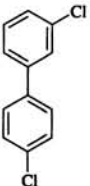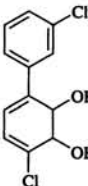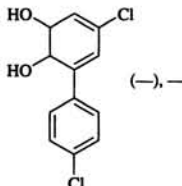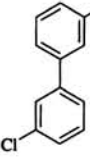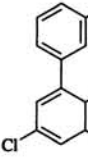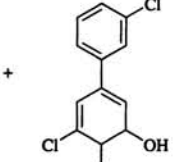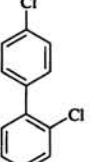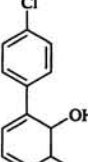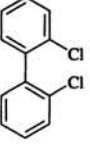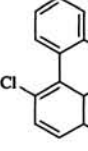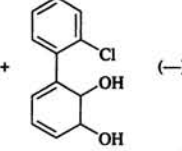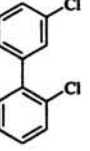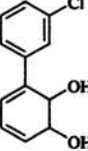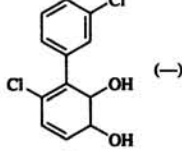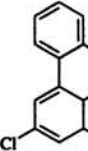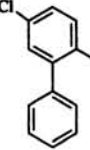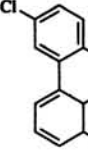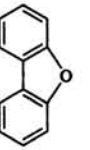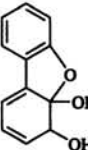
Substrate	Microorganism, Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %	Refs.
$C_{12}H_8Cl_2$	*Burkholderia* sp. LB400	(—), — + (—), —	52
$C_{12}H_8Cl_2$	Biphenyl 2,3-dioxygenase from *Pseudomonas* sp. LB400	(—), — + (—), —	73
	Burkholderia sp. LB400	" (—), —	52
$C_{12}H_8Cl_2$	*Burkholderia* sp. LB400	(—), —	52
$C_{12}H_8Cl_2$	*Burkholderia* sp. LB400	(—), — + (—), —	52
	Biphenyl 2,3-dioxygenase from *Pseudomonas* sp. LB400	" (—), —	73
$C_{12}H_8Cl_2$	*Burkholderia* sp. LB400	(—), — + (—), — I	52
	Biphenyl 2,3-dioxygenase from *Pseudomonas* sp. LB400	(—), — + I (—), —	73
$C_{12}H_8Cl_2$	*Burkholderia* sp. LB400	(—), —	281
$C_{12}H_8O$	*Pseudomonas* sp. HH69	(—), —	282
	Sphingomonas sp. RW1	" (—), —	283
	Escherichia coli DH5$_\alpha$(pTCB144)	" (—), —	77

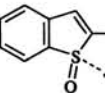TABLE 10. DIHYDRODIOLS THAT HAVE NOT BEEN ISOLATED (*Continued*)
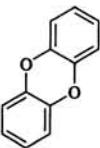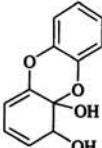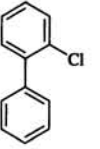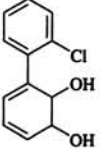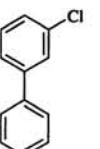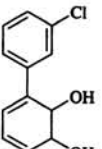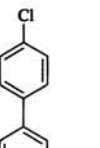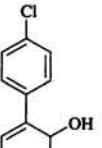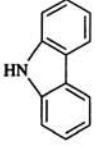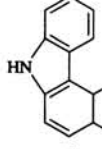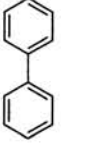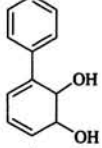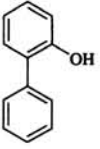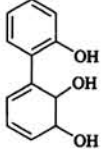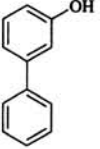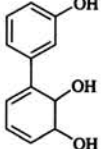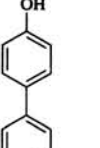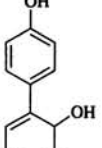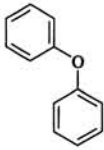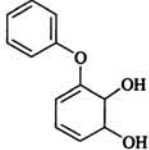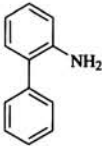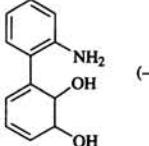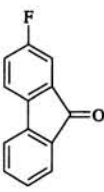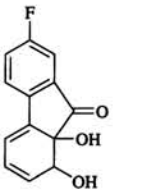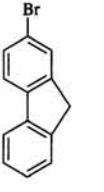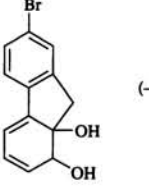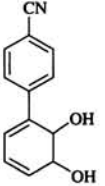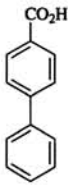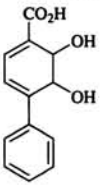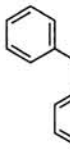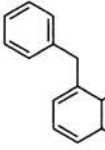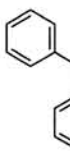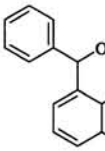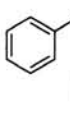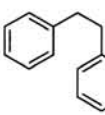
Substrate		Microorganism, Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %	Refs.
	$C_{12}H_8O_2$	*Pseudomonas* sp. HH69	(—), —	284
		Escherichia coli DH5$_\alpha$(pTCB144)	" (—), —	77
	$C_{12}H_9Cl$	*Burkholderia* sp. LB400	(—), —	281
		Purified NDO, nap dox$_{G7}$, from *Pseudomonas putida* G7	" (—), —	285
	$C_{12}H_9Cl$	*Burkholderia* sp. LB400	(—), —	281
		Purified NDO, nap dox$_{G7}$, from *Pseudomonas putida* G7	" (—), —	285
		Pseudomonas pseudoalcaligenes KF707B1	" (—), —	286
	$C_{12}H_9Cl$	Purified NDO, nap dox$_{G7}$, from *Pseudomonas putida* G7	(—), —	285
	$C_{12}H_9N$	*Pseudomonas putida*, F39/D	(—), —	287
		Pseudomonas sp. NCIB 9816-4	"	287
		Escherichia coli JM109(pDTG141)	"	287
	$C_{12}H_{10}$	Purified NDO, Nap dox$_{G7}$ from *Pseudomonas putida* G7	(—), —	285
		Pseudomonas pseudoalcaligenes KF707B1	" (—), —	286
	$C_{12}H_{10}O$	*Escherichia coli* DH5$_\alpha$(pTCB144)	(—), —	77
	$C_{12}H_{10}O$	*Escherichia coli* DH5$_\alpha$(pTCB144)	(—), —	77
	$C_{12}H_{10}O$	*Escherichia coli* DH5$_\alpha$(pTCB144)	(—), —	77

TABLE 10. DIHYDRODIOLS THAT HAVE NOT BEEN ISOLATED (*Continued*)

Substrate		Microorganism, Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %	Refs.
	$C_{12}H_{10}O$	*Escherichia coli* DH5α(pTCB144)	(—), —	77
	$C_{12}H_{11}N$	*Escherichia coli* DH5α(pTCB144)	(—), —	77
C_{13}	$C_{13}H_7FO$	*Pseudomonas* sp. F274	(—), —	288
	$C_{13}H_9Br$	*Pseudomonas* sp. F274	(—), —	288
	$C_{13}H_9N$	*Escherichia coli* DH5α(pTCB144)	(—), —	77
	$C_{13}H_{10}O_2$	*Pseudomonas putida* PL-pT-11/43	(—), —	209
	$C_{13}H_{12}$	*Pseudomonas pseudoalcaligenes* KF707B1	(—), —	286
		Escherichia coli DH5α(pTCB144)	" (—), —	77
	$C_{13}H_{12}O$	*Pseudomonas pseudoalcaligenes* KF707B1	(—), —	286
C_{14}	$C_{14}H_{14}$	*Pseudomonas pseudoalcaligenes* KF707B1	(—), —	286

TABLE 10. DIHYDRODIOLS THAT HAVE NOT BEEN ISOLATED (*Continued*)
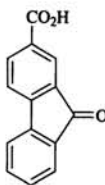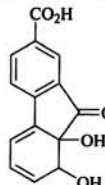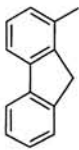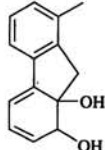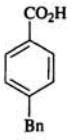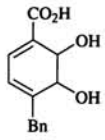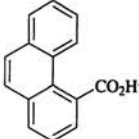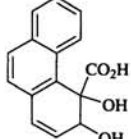
| Substrate		Microorganism, Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %	Refs.
C$_{14}$	C$_{14}$H$_8$O$_3$	*Pseudomonas* sp. F274	(—), —	288
	C$_{14}$H$_{12}$	*Pseudomonas* sp. F274	(—), —	288
	C$_{14}$H$_{12}$O$_2$	*Pseudomonas putida* PL-pT-11/43	(—), —	209
C$_{15}$	C$_{15}$H$_{10}$O$_2$	*Mycobacterium* sp. KR2	(—), —	241

TABLE 11. CHEMICAL TRANSFORMATIONS OF DIHYDRODIOLS
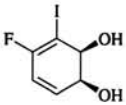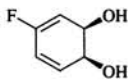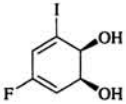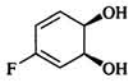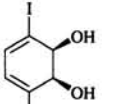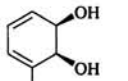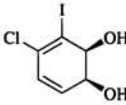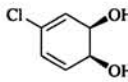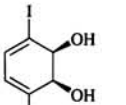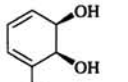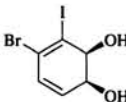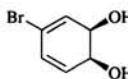
Substrate		Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %		Refs.
C_6					
	$C_6H_6FIO_2$	H_2, Pd/C, MeOH		(75), >98	27
	$C_6H_6FIO_2$	H_2, Pd/C, MeOH		(75), >98	27
	$C_6H_6FIO_2$	H_2, Pd/C, MeOH		(70), 88	27
		1. H_2, Pd/C 2. *P. putida* NCIMB 8859	"	(—), >98	108
	$C_6H_6ClIO_2$	H_2, Pd/C, MeOH		(67), >98	27
	$C_6H_6ClIO_2$	1. H_2, Pd/C 2. *P. putida* NCIMB 8859		(—), >98	108
	$C_6H_6BrIO_2$	H_2, Pd/C, MeOH		(65), >98	27

TABLE 11. CHEMICAL TRANSFORMATIONS OF DIHYDRODIOLS (*Continued*)
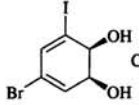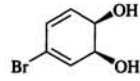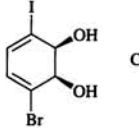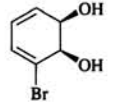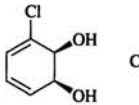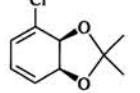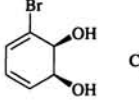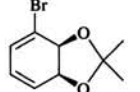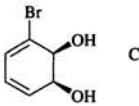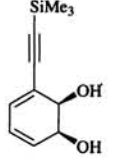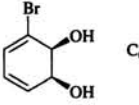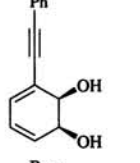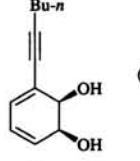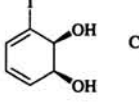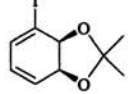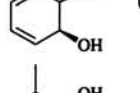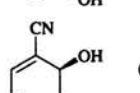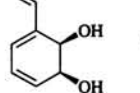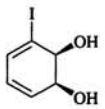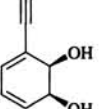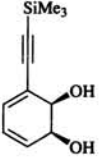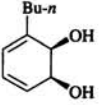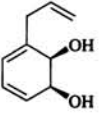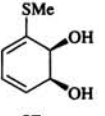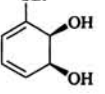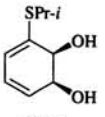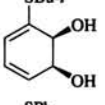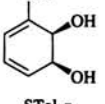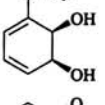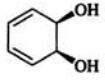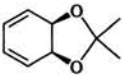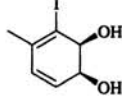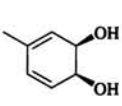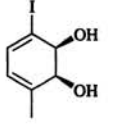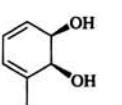
| Substrate	Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %	Refs.
$C_6H_6BrIO_2$	H_2, Pd/C, MeOH	(80), >98	27
$C_6H_6BrIO_2$	1. H_2, Pd/C 2. *P. putida* NCIMB 8859	(—), >98	108
$C_6H_7ClO_2$	$CH_3C(OCH_3)_2CH_3$, acetone, *p*-TsOH	(—), >98	289
$C_6H_7BrO_2$	$CH_3C(OCH_3)_2CH_3$, CH_2Cl_2, *p*-TsOH	(100), >98	290
$C_6H_7BrO_2$	$HC{\equiv}CSiMe_3$, Pd(PPh$_3$)$_4$, CuI, *n*-BuNH$_2$	(78), >98	105
$C_6H_7BrO_2$	$HC{\equiv}CPh$, Pd(PPh$_3$)$_4$, CuI, *n*-BuNH$_2$	(91), >98	106
	$HC{\equiv}CBu$-*n*, Pd(PPh$_3$)$_4$, CuI, *n*-BuNH$_2$	(70), >98	106
$C_6H_7IO_2$	$CH_3C(OCH_3)_2CH_3$, acetone, *p*-TsOH	(—), >98	291
	Bu$_3$SnD, AIBN	(25), >98	25
	Me$_2$CuLi, Et$_2$O, 0°	(38), >98	105
	Bu$_3$SnCN, Pd(PPh$_3$)$_4$, THF	(52), >98	105, 25
	Bu$_3$SnCH=CH$_2$, Pd(PPh$_3$)$_4$, THF	(26), >98	105, 25

TABLE 11. CHEMICAL TRANSFORMATIONS OF DIHYDRODIOLS (*Continued*)

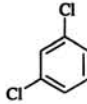| Substrate	Conditions	Product(s), Yield(s) (% or g/L) and Enantiomeric Excess %	Refs.
$C_6H_7IO_2$	$Bu_3SnC\equiv CH$, $Pd(OAc)_2$, PPh_3, THF	(35), >98	25
	$HC\equiv CSiMe_3$, $Pd(OAc)_2$, Ph_3P, Et_3N	(39), >98	105
	Bu_3SnOMe, $Pd(PPh_3)_4$, THF	(11), >98	105, 25
	$Bu_3SnCH_2CH=CH_2$, $Pd(PPh_3)_4$, THF	(31), >98	105, 25
	Bu_3SnSCH_3, $Pd(PPh_3)_4$, THF	(55), >98	25
	Bu_3SnSEt, $Pd(PPh_3)_4$, THF	(61), >98	25
	Bu_3SnSPr-i, $Pd(PPh_3)_4$, THF	(31), >98	25
	Bu_3SnSBu-t, $Pd(PPh_3)_4$, THF	(75), >98	25
	Bu_3SnSPh, $Pd(PPh_3)_4$, THF	(43), >98	25
	$Bu_3SnSTol$-p, $Pd(PPh_3)_4$, THF	(75), >98	25
$C_6H_8O_2$	CH_3COCH_3, $HClO_4$, −82 to −40°	(61), —	292
$C_7H_9IO_2$	H_2, Pd/C, MeOH	(79), >98	27
$C_7H_9IO_2$	*P. putida* UV4; H_2, Pd/C, MeOH	(72), 80	27
	E. coli JM109(pDTG601); H_2, Pd/C, MeOH	" (70), 98	27
	1. H_2, Pd/C 2. *P. putida* NCIMB 8859	" (—), >98	108

Cu, Ni, and Pd Mediated Homocoupling Reactions in Biaryl Syntheses: The Ullmann Reaction

Abstract

The traditional Ullman reaction is the homocoupling of aromatic halides mediated by copper at elevated temperatures. Ullman first reported this reaction in 1901. Although the coupling conditions first reported are still widely used, a host of modifications have been made to these reactions. Some of these modifications include the use of activated and alternative metals, often resulting in much lower coupling temperatures. Nickel and palladium are the most utilized source of alternative metals, Periodic reviews have been published. This chapter covers the literature on copper, nickel, and palladium mediated homocoupling reactions in biaryl synthesis from 1901 to 2000. The focus of this chapter is the scope and limitation of these processes, preparation of the activated metal, and mechanism of the homocoupling process

1. Introduction

The traditional Ullmann reaction is the homocoupling of aromatic halides mediated by copper at elevated temperatures (Eq. 1). Ullmann first reported this reaction in 1901. (1, 2) Although the coupling conditions that were first reported are still widely used, a host of modifications have been made to the reaction. Some of these modifications include the use of activated and alternative metals, often resulting in much lower coupling temperatures. Nickel and palladium are the most utilized source of alternative metals to effect this transformation. Periodic comprehensive reviews have been published, the most recent of which appeared more than 25 years ago. (3-6) In addition, brief overviews of the Ullmann reaction have occurred in review articles on biaryl construction. (7-12) This review covers the literature on Cu-, Ni-, and Pdmediated homocoupling reactions in biaryl synthesis from 1901 through 2000. The focus of this review is on the scope and limitation of these processes, preparation of the activated metal, and mechanism of the homocoupling process. The application and utility of biaryl compounds is beyond the scope of this review.

$$(1)$$
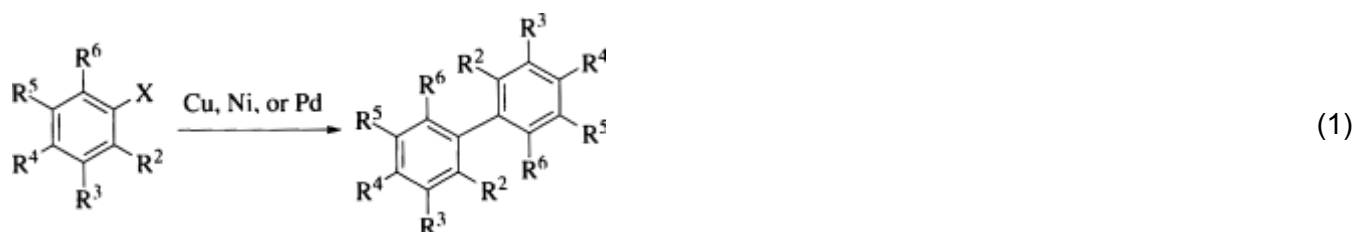
2. Copper-Mediated Homocouplings

2.1. Cu(0) Preparation/Activation
Traditionally, copper bronze is used to dimerize aryl halides. Although there are many reports regarding the capricious nature of the Ullmann homocoupling, the reports are much less frequent when activated copper is used. Therefore, as a matter of course, copper bronze is activated immediately prior to use. The activity of the copper powder may even result in a different product distribution (Eq. 2). (13)

$$(2)$$
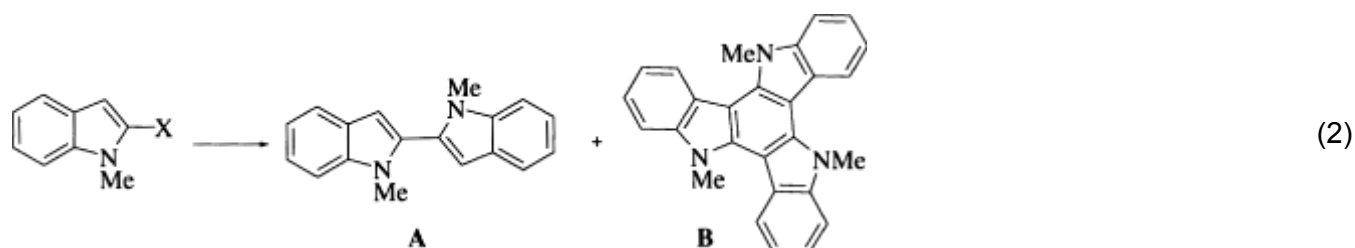
X		A	B
I	Unactivated Cu, neat, 205°	(66%)	(—)
I	Activated Cu, neat, 205°	(—)	(81%)
Cu 200°		(—)	(75%)

The primary surface impurities on copper powder are copper oxides. In fact, the manufacturing process for J. T. Baker purified copper utilizes a method in which molten copper is sprayed into an "oxidizing atmosphere" at 1400°. [14] These copper oxides are relatively insoluble in water and organic solvents, but are much more soluble in acids and bases. One method for cleaning the copper surface is by washing with an acetone solution of iodine followed by a HCl/acetone solution. [15, 16] The activated copper is thoroughly rinsed with acetone or benzene and dried under vacuum prior to use. An alternative procedure is to clean the copper with nitrogen-containing complexing agents (e.g., EDTA, ethylenediamine, biquinolyl, NH_3), which frees the copper surface of cuprous ions. [17] In contrast, ethanolamine can inhibit dimerization by blocking sites on the surface of copper contained on an alumina catalyst. [18]

In addition to cleaning the copper surface, there are alternative methods for the preparation of highly activated copper. Copper powder can also be prepared from the reduction of copper(II) sulfate with zinc metal [19] or with CrO_2Cl_2. [20]

A number of ways are used to prepare highly reactive zero-valent copper. [21-23] Potassium naphthalide can be used to reduce CuI to an activated zero-valent copper slurry, which allows the Ullmann coupling to proceed at lower temperatures. [24] A drawback to this protocol is that the activated copper slurry is prone to sintering upon excessive stirring, which results in decreased reactivity. The reduction of CuI with potassium naphthalide requires an age time of 8 hours; however, a much faster (30 minutes) reduction occurs when CuCl is reduced by lithium naphthalide. [25] The decreased age time necessary for complete copper salt reduction also decreases the amount of slurry sintering. An even more reactive copper slurry can be prepared from the reduction of soluble copper salt complexes [$CuI-PEt_3$ or $CuCl-SMe_2$] with lithium naphthalide. [26]

Sonication is also successful at cleaning the metal surface of copper. The surface morphology of copper dramatically changes upon exposure to ultrasound. For example, a batch of copper powder that contains a coat of 1.2 μm copper oxide (Cu_2O) layer can be activated upon sonication. After 1 hour of sonication, the thickness of the Cu_2O layer is virtually unchanged; however, continued ultrasonic irradiation for an additional 3 hours completely removes the copper oxide layer. After sonication, thin films of carbon and nitrogen are detected on the surface of copper. [27] Sonication of the copper metal prior to and after addition of an aryl halide can increase the rate of biaryl coupling by a factor of more than 50. [28] A four-fold excess of pre-sonicated copper is necessary to obtain such a rate enhancement. When this amount of presonicated copper and 2-iodonitrobenzene are sonicated at 64° for 2 hours, 70% of the biaryl is obtained. A reduced rate of reaction is observed when the amount of pre-sonicated copper is limited to a two-fold excess. Increasing the amount of copper from a four-fold excess to an eight-fold excess gives the same yield of biaryl product (ca. 71%) after a two hour period. In addition to cleaning the metal surface, sonication also reduces the particle size of the copper metal. The direct result of this phenomenon is that the number of active sites is increased, thereby increasing the rate of reaction. The average particle size of the copper powder reaches a constant minimum (25 μm from 87 μm) after 45 minutes of sonication in DMF. [29] This reduction in particle size, however, is dependent on the type of copper being used. [27] Although the use of ultrasound to facilitate the Ullmann reaction is not widely practiced, it seems that it is a convenient method that avoids the high temperatures that are utilized in the traditional Cu(0)-promoted dimerization of aryl halides. In fact, sonication of either a nitromethane or a nitrobenzene solution of picryl bromide and copper forms 2,2′,4,4′,6,6′-hexanitrobiphenyl in a much higher yield than in the absence of ultrasound (Eq. 3). [30] When the nitrated solvents are replaced by xylene, only 16% (^{1}H NMR) of the dimer is observed. [30]

$$(77\%) \qquad (3)$$
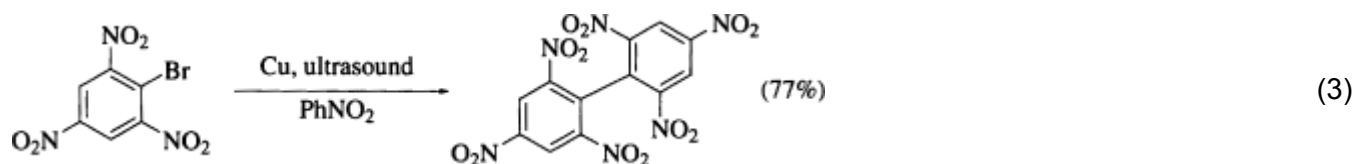
Copper supported on alumina is also effective in this type of homocoupling. (31) The copper is both highly dispersed as well as having a smaller particle size. Copper supported on SiO_2, ZrO_2, TiO_2, and Fe_2O_3 is ineffective.

2.2. Scope and Limitations

Temperatures of >100° are usually necessary to initiate coupling in the traditional Ullmann reaction with copper powder. The Ullmann coupling proceeds most rapidly with aryl halides that are substituted in the ortho position with groups that contain lone pairs of electrons, regardless of whether the groups are electron-donating or withdrawing. (32) Examples of this are illustrated in Eq. 4 (33) and Eq. 5. (34)

$$(61\%) \qquad (4)$$

$$(84\%) \qquad (5)$$
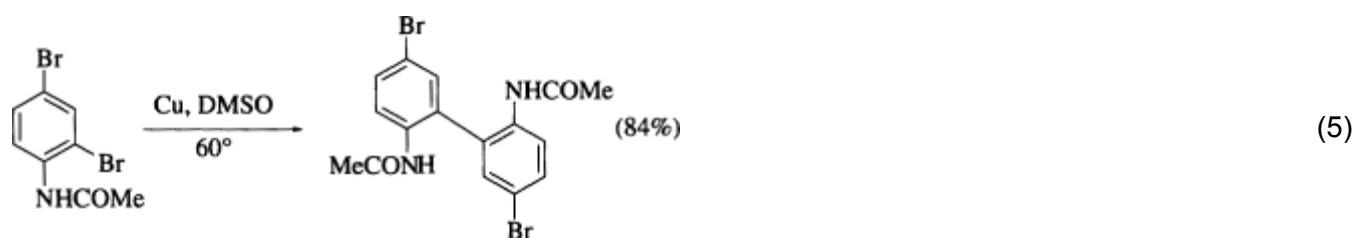
Both 2-iodonitrobenzene and iodoferrocene give near quantitative yields when treated with copper powder at 60°. (35) In contrast, both iodobenzene and 1-iodo-3-nitrobenzene are unreactive under these conditions. Additional electron-withdrawing groups render the aryl halides even more reactive. The admixture of picryl chloride and copper at 135° results in an explosion. (36)

The order of reactivity for halides is I > Br > > Cl, with aromatic fluorides being inert. Aryl sulfonate dimerization does not occur with copper; however, in nickel couplings, aryl bromides are more reactive than aryl sulfonates. (37) In some reactions, aryl mesylates, tosylates, triflates, stannanes, silanes, and sulfonyl halides are also used as participants in biaryl formation via aryl homocoupling with copper, nickel, or palladium. Unless the aromatic ring is sufficiently reactive (e.g., by the attachment of electron-withdrawing groups), aromatic chlorides do not participate in this dimerization under traditional coupling conditions (e.g., copper/bronze). However, these types of couplings smoothly occur when alternative sources of metal are used. Ester, aldehyde, and nitro groups are compatible with the standard reaction conditions. In general, the aryl halide is activated when these groups are ortho to the halide. On occasion, elevated temperatures (>200°) (38) or excess copper (39) can cause reduction of nitro groups. Carboxylic acids, however, are usually protected in some fashion, so as to preclude decarboxylation. (40, 41) Free amino and free hydroxy groups are likewise avoided. In these instances, competition from diarylamine and diaryl ether formation arises, and often predominates. (Although these later types of couplings are also referred to as Ullmann couplings or condensations, and are synthetically useful, these reactions will not be covered by this review since a new carbon-carbon aryl bond is not created.) (42-45)

Although the presence of primary and secondary unprotected amine functional groups in the aryl halide results in poor dimerization under traditional copper-mediated conditions, (46) slightly improved yields are obtained when palladium (47, 48) or nickel (49-52) is used. Similarly, phenolic aryl halides afford the dimerized bisphenols when either nickel (53, 54) or palladium is employed (55) instead of copper as the coupling agent.

The Ullmann coupling between unlike aryl halides occurs when there are sufficient electronic and/or steric differences between the two arene partners. In general, owing to steric hindrance, bulky groups ortho to the aryl halide retard the reaction. However, biaryls that contain four flanking groups about the biaryl axis can often be formed. Although in some cases steric hindrance does inhibit Ullmann couplings, this effect is more pronounced in other biaryl couplings such as the Suzuki reaction. (56) Lower coupling yields are observed as the ortho substituents become prohibitively large.

The most common solvent for the Ullmann reaction is dimethylformamide. (57) Nitrobenzene is also used frequently; when higher temperatures are needed, *p*-nitrotoluene can be used. (58) Other solvents and diluents that can be used include decalin, quinoline, biphenyl, *p*-cymene, tetramethylurea, naphthalene, pyridine, collidine, bitolyl, pseudocumene, xylene, diphenyl ether, tetralin, chlorobenzene, benzene, decane, toluene, anthracene, ethylene dichloride, 2,4-dimethylsulfolane, α -methylnaphthalene, dimethyl sulfoxide, and 1,3-dimethyl-2-imidazolidinone. A wide array of other substituted arenes can also be used as diluents. (46) Of these, 1,2,4-trichlorobenzene and substituted benzaldehydes function well. Phenols, primary amines, and aromatic aldehydes function poorly as diluents.

In a few reactions, improved yields are obtained when acetic acid is added to the reaction mixture (59) or when the copper is contaminated with fatty acids. (60) Benzoic acid promotes the reductive dimerization of iodobenzene. (46) In general, nitrobenzene is used at <200° in order to avoid unwanted nitro reduction. On occasion, the use of DMF promotes dehalogenation. (61, 62) Utilization of *m*-dinitroaryls as solvents results in cross-coupling reactions between the substrate and the solvent. (63, 64) An aqueous solution of copper sulfate is used as the solvent system in the reductive coupling of halogenated aromatic sulfonates (Ar-O scission). In the older literature, sand and salt are often used in the absence of a solvent, especially in large-scale work. In addition to serving as a heat exchanger, these additives aid in the break up of the reaction mixture, which in turn assists in the solubilization of the coupled product upon extraction.

Copper (I) oxide can be used to dimerize aryl halides; however, the yields are typically lower than when copper powder is used. (65) Copper (I) sulfide [Cu_2S] is more reactive than Cu_2O , but less reactive than copper powder. (66) Increased reduction of aryl halides results when these copper salts mediate the reaction. Copper halides are not useful in promoting the homocoupling of haloarenes. (66) Cu(I)-induced homogeneous Ullmann couplings of aryl halides exist. (67-69) Typical conditions for these reactions are Copper(I) triflate (CuOTf) in aqueous NH_3/ CH_3CN . Solvated cuprous ions most likely initiate the coupling process. Couplings under these conditions seem to require the presence of an ortho electron-withdrawing group. Excellent selectivity is observed upon coupling triiodobiphenyls (Eq. 6). (70)

(6)
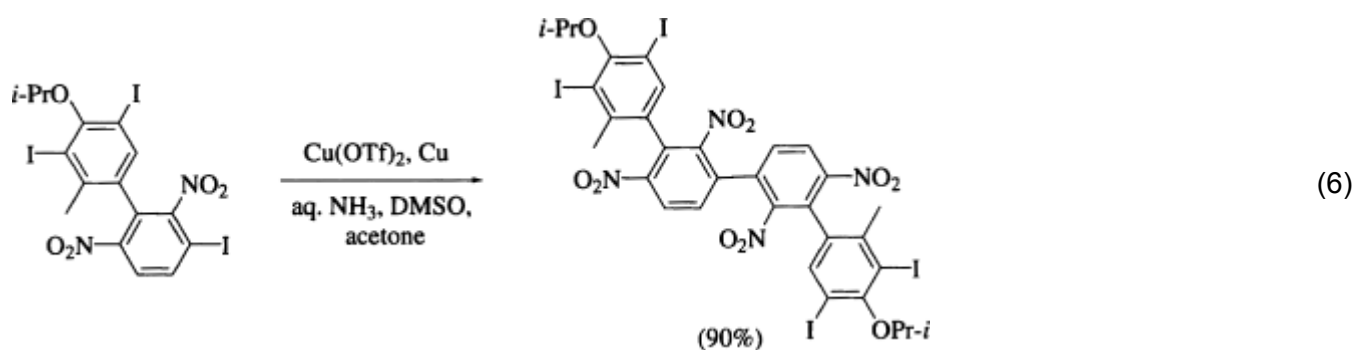
Mild Ullmann couplings of aryl bromides and iodides are also accomplished with Cu(I) thiophene-2-carboxylate (Eq. 7). (71) Low yields of products from Ullmann homocoupling are realized with 2-iodobenzoate and CuCl or CuBr, but not with CuI in *N*-methylpyrrolidinone at room temperature. (71) An ortho ligating group is generally required, but these conditions are tolerated by many functional groups.

(7)
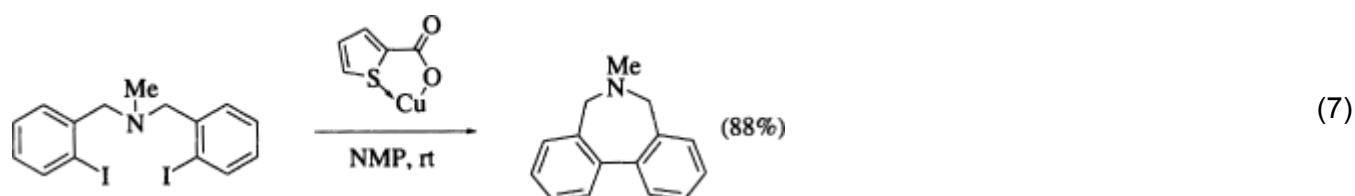
Symmetric biaryls are formed by the homocoupling of aryl chloro- and fluorodi-methylsilanes (Eq. 8). (72) This copper-catalyzed dimerization affords good yields and occurs rapidly at room temperature. In addition to zero-valent copper, nickel, and palladium (*vide infra*), homocouplings of aryl halides occur by using metallic titanium (73) or indium. (74)

$$\text{(8)}$$
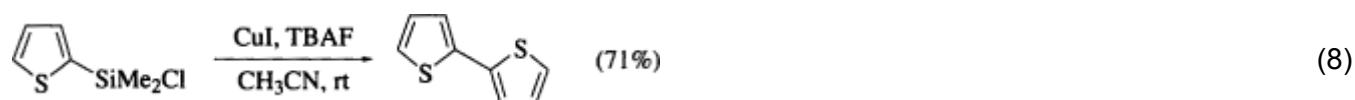
2.3. Mechanism

The actual mechanism of the copper-mediated homocoupling of aryl halides has not been entirely elucidated. The two most likely processes by which coupling may occur involve either formation of aryl radicals or the formation of discrete copper-aryl species. Although neither mechanism may be entirely discounted, and to some extent both may be operative, considerable evidence exists for the intermediacy of discrete aryl copper species.

To a lesser extent, however, there is evidence for a homolytic coupling pathway. An initial step is complexation of solubilized copper atoms with the haloarene. Subsequent outer-sphere single-electron transfer from copper to the aryl halide can then produce an aryl radical. (75) Direct aryl radical dimerization can result in the termination of this sequence. However, an ArCu(II)X species can potentially be generated via this radical intermediate by a net oxidative addition, which is present in the alternative oxidative addition/reductive elimination mechanistic iteration (later in the text).
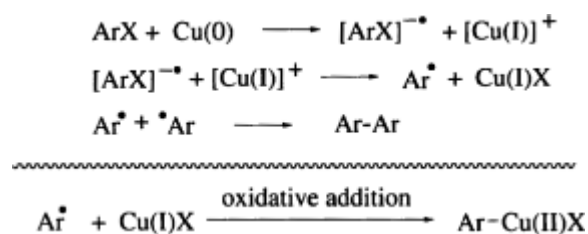
An aryl radical can possibly account for the facile coupling of 2,6-disubstituted aryl halides to form a biaryl with four flanking groups about the biaryl axis. (76, 77) Decreased biaryl formation from the copper powder mediated coupling of 2-iodonitrobenzene, 4-iodonitrobenzene, and 2-bromonitrobenzene occurs upon the addition of radical traps to the reaction mixture. (78) Similar results are obtained in the coupling of aryl halides with copper(I) oxide. (66) Treatment of iodobenzene vapor with copper in the presence of ethyl benzoate results in the partial formation of biphenyl-2-carboxylic acid and biphenyl-4-carboxylic acid (after hydrolysis), which the authors regard as evidence for hydrogen atom abstraction from ethyl benzoate by an aryl radical intermediate. (76)

Cu(111) surface analysis techniques can be used to probe the mechanism of homocoupling on the copper surface, although these ultra-high vacuum conditions are very different from the actual reaction conditions. (79) Two different mechanisms are postulated to be operative on the Cu(111) crystal. A radical mechanism is supported by the fact that the temperature at which carbon-iodide scission occurs is the same as that of the coupling of molecular iodobenzene and phenyl groups adsorbed to Cu(111). (79) Complementary Cu(111) surface work includes variable heating rate temperature-programmed reactions studies. (80) Meta and para electron-withdrawing groups on the phenyl radical, derived from the corresponding iodobenzene, lower the activation barrier to dimerization. Electron-releasing groups raise the activation barrier.

The most widely accepted mechanism for the Ullmann homocoupling involves the formation of an aryl copper intermediate. A direct co-condensation reaction of copper vapors with aryl halides results in the conclusion that an initial oxidative addition step is followed by a disproportionation and reductive elimination sequence. (81) Reaction initiation results from copper atoms on copper clusters or crystallites. Nickel vapors are more reactive than copper vapors. Under ultra-high vacuum conditions, π

-complexation between the aromatic nucleus and copper occurs. ([82]) The resulting species is postulated to exist either as an aryl copper species or as an aryl anion. Regardless of the exact species of the absorbed phenyl group, the aryl π -system is held parallel to the surface plane of copper. ([82])

$$ArX + Cu(0) \longrightarrow ArCu(II)X$$
$$ArCu(II)X + Cu(0) \longrightarrow ArCu(I) + Cu(I)X$$
$$ArCu(I) + ArX \longrightarrow ArCu(III)XAr$$
$$ArCu(III)XAr \longrightarrow Ar\text{-}Ar + Cu(I)X$$
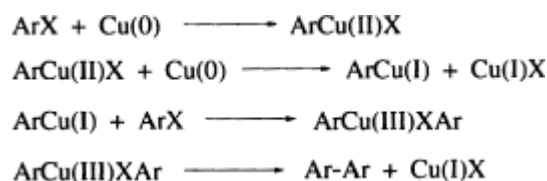
The mechanism for the Cu(I)-induced homogeneous Ullmann coupling invokes the possibility of a Cu(III) intermediate. ([68], [83]) Aryl radicals are not operative in the Cu(I)-mediated homocouplings as shown by the fact that the dimerization of *o*-iodo-*N,N*-dimethylbenzamide occurs without a 1,5-hydrogen atom transfer. ([68]) In analogous couplings initiated by Cu(I), iodomaleate and iodofumarate esters couple stereospecifically, thus discounting the intermediacy of vinyl radicals. ([84])

Highly reactive zero-valent copper, which is prepared by the reduction of soluble copper(I) phosphine complexes with lithium naphthalide, reacts with aryl halides to form organocopper species. ([22], [23], [26]) As in traditional Ullmann couplings, iodoarenes are more active than bromoarenes. Likewise, an activating group in the ortho position enhances the reactivity. ([85]) Other ligating additives can be used to stabilize such aryl copper intermediates. ([86]) Many of these ArCu compounds are stable at room temperature and can be isolated. Moderate heating of these ArCu species results in biaryl formation; ([87], [88]) however, some of the intermediates show a high degree of stability. For example, $4\text{-}MeOC_6H_4Cu$ is stable in refluxing tetrahydrofuran. ([25]) Likewise, pentafluorophenylcopper is formed in a nearly quantitative yield from C_6F_5I and "Rieke copper" as an isolable tan solid. ([24]) Refluxing mesitylene (151°) as solvent is required to effect homocoupling. ([25]) Heating the solid C_6F_5Cu under argon affords the corresponding biaryl along with copper metal. These observations support the premise that an oxidative addition manifold is operative. ([25])

In addition to heat, homocoupling of aryl copper intermediates may be caused by the introduction of molecular oxygen. ([25], [26]) The stable ArCu species can also be quenched with either H_2O or D_2O giving the reduced arenes ArH or ArD, respectively. ([25]) Electrophiles such as alkyl and acyl halides also can react with the ArCu to provide either the alkylated or acylated aromatic systems. ([85])

2.4. Coupling via Cuprates

The oxidation of homocuprates (Ar_2CuLi) results in the coupling of the two organic ligands to form dimers. ([89], [90]) Although oxidation of diaryl cuprates leads to the formation of biaryls, ([91]) a detailed consideration of such couplings is not included in this chapter because the aryl copper species are derived directly from an aryllithium, not an aryl halide. However, the growing significance of this approach to biaryl formation warrants mention.

Although the oxidation of homocuprates to form dimers was initially observed as a side reaction, the intentional introduction of an oxidant into the reaction can be synthetically useful. ([92-96]) More recently, higher order cyanocuprates have been dimerized under oxidative conditions. ([97-99]) The addition of aryllithiums to a solution of a lower order cyanocuprate produces an unsymmetrical diarylcuprate which in turn yields the unsymmetrical biaryl upon treatment with O_2 (Eq. [9]). ([97])

$$ArLi \xrightarrow{CuCN} ArCu(CN)Li \xrightarrow{Ar'Li} (Ar)(Ar')Cu(CN)Li_2 \xrightarrow[-125°]{O_2} Ar\text{-}Ar' \quad (78\text{-}90\%) \tag{9}$$
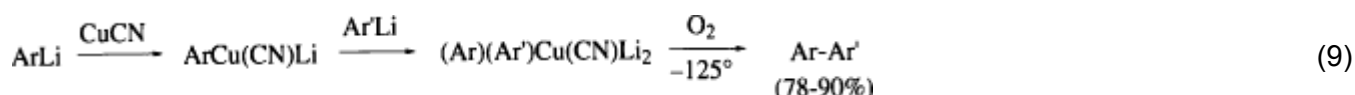
Formation of the higher order cuprate and the subsequent oxidation are very sensitive to temperature with significantly less cross-coupled product being formed at higher temperatures due to increased dimerization. ([99]) Ortho-substituted aryllithium compounds participate in this reaction even when both aryl rings bear such substituents. ([97]) Although coupling to form symmetrical biaryls is possible, the reaction is primarily used for cross-coupling and the products include unsymmetrical biphenyls, ([97-99]) unsymmetrical binaphthyls, ([98], [100]) unsymmetrical bithienyls, ([101]) and thienylnaphthalenes. ([98])

Intramolecular coupling reactions ([101]) allow the use of chiral templates to direct biaryl formation, resulting in asymmetric binaphthyls. ([102], [103]) This asymmetric coupling has been applied toward the synthesis of optically pure biflavones, ([104]) (+)-*o*-permethyltellimagrandin II, ([105]) and (+)-kotanin. ([106])

3. Nickel-Mediated Homocouplings

The introduction of Ni as an agent in the coupling of aryl halides represents a major advance in the field. ([9], [107]) A 1971 report by Semmelhack and co-workers described the use of Ni(cod)$_2$ in DMF as an alternative to copper in the reductive homocoupling of aryl halides (Eq. [10]). ([50]) A major advantage of this new reagent is that the coupling reaction can be accomplished at or near room temperature.

$$(10)$$

3.1. Ni(0) Preparation/Activation

The earliest application of nickel reagents to reductive coupling reactions of aryl halides required their activation prior to use. ([23]) Ni(acac)$_2$ is reduced to Ni(0) by triethylaluminum in the presence of 1,5-cyclooctadiene to form Ni(cod)$_2$, an isolable, though air-sensitive, yellow solid. ([108], [109])

Nickel-Complex Reducing Agents (NiCRA's) are prepared by the reduction of Ni(OAc)$_2$ with alkali metal hydrides and alcohol in THF or THF-benzene. ([54], [110]) Excess NaH is required for the reduction of Ni(II) to Ni(0) with alkoxides and bipyridine serving to stabilize the nickel complex that forms. Catalytic quantities of NiCRA reagents fail to promote dimerization of aryl halides. However, another report describing the use of LiH and Ni(OAc)$_2$ allows for catalytic quantities of the latter in the coupling of aryl chlorides and bromides. ([110])

Rieke and co-workers described a method for the preparation of Ni(0) via the reduction of nickel(II) halides with lithium metal/naphthalene in glyme. ([21], [111], [112]) After the activated nickel forms, the excess of naphthalene remains in the reaction mixture or, alternatively, it is removed by replacing the supernatant. Nickel-aluminum bimetallic clusters can also be prepared by treatment of a mixture of Ni(acac)$_2$, Al(acac)$_3$, and bipyridine with NaH; ([113]) they facilitate the coupling of aryl chlorides and bromides. ([113]) Although not yet applied to reductive biaryl couplings, Ni(0) on carbon is another means of introducing highly dispersed Ni(0) into a reaction. ([114-116]) More recently, Ni(0) on charcoal has been prepared in situ for the coupling of aryl chlorides with organozinc reagents ([117-119]) and other cross-coupling reactions. ([116])

Activated Ni(0) can also be prepared via electrolysis of aqueous NiSO$_4$ with a mercury cathode. ([120]) Mercury is removed from the resulting nickel amalgam by distillation under reduced pressure to yield activated Ni(0), which is used to couple aryl halides. Electrochemically activated Ni powder is vastly superior to commercially available Ni(0) in biaryl couplings. Ni(0) can also be prepared by electrolysis of a DMF solution of Bu$_4$NBF$_4$ using a platinum cathode and a nickel anode, yielding highly activated Ni(0). ([121])

The development of in situ preparations of Ni(PPh$_3$)$_4$ greatly simplifies the use of these reagents, ([122]) leading to catalytic methods. ([123]) Stoichiometric quantities of Ni(PPh$_3$)$_2$Cl$_2$, PPh$_3$, and Zn dust in O$_2$-free DMF react at 50° to form Ni(PPh$_3$)$_4$, which efficiently promotes the reductive homocoupling of aryl halides. ([122]) Although oxygen must be rigorously excluded, no special techniques or equipment are required.

In a catalytic process, Ni(0) that is consumed in reductive biaryl coupling reactions can be regenerated by using a stoichiometric quantity of Zn dust. ([123]) Such catalytic processes often produce higher isolated yields than the stoichiometric version of this reaction. ([123]) Dimerization of slower reacting aryl bromides is accelerated by the addition of an equimolar amount of potassium iodide to the reaction. To form the Ni(0) complex, triphenylphosphine is required in large excess relative to Ni(PPh$_3$)$_2$Cl$_2$, because complexation to zinc is also observed.

An alternative method to generate Ni(0) in situ is electrolysis of NiBr$_2$ or NiCl$_2$ in THF/HMPA, (124) leading to biaryl products. (125) Catalytic amounts of Ni(0) are also prepared in situ from Ni(II)-bpy complexes using electrochemical methods, leading to efficient biaryl coupling reactions. (126-128)

A detailed study of the in situ formation of Ni(0) reagents shows that the ease of reduction of Ni(II) salts by metal reducing agents in *N,N*-dimethylacetamide (DMAc) is NiI$_2$ > NiBr$_2$ > NiCl$_2$. (51) On the basis of this observation, NiI$_2$ would appear to be the choice as the Ni source in these reactions. However, substantial amounts of noncoupled, reduced arene product are obtained when NiI$_2$ is used to generate Ni(0). Fortunately, the rate of reduction of NiCl$_2$ can be accelerated by the addition of halide salts in the sequence I$^-$ > Br$^-$ > Cl$^-$ > no salt. Substantial amounts of reduced, non-coupled aryl halide remain when Ni(OAc)$_2$ or Ni(acac)$_2$ is used as the nickel source. Other nickel sources are ineffective in generating an active Ni species and only starting aryl halide remains upon attempted reductive homocoupling reactions. (51) In addition, Zn, Mn, and Mg are useful as reducing agents for the conversion of Ni(II) into Ni(0), with Zn being the most effective. Fe, Al, Na, and Ca are ineffective. Another report, however, describes a lack of catalytic activity when Cr or Mn powder or Na(Hg) are used in place of Zn in HMPA/DMF. (129) *tert*-Butylmagnesium bromide is also useful in place of these metal reducing agents. (130) The addition of 2,2′-bipyridine also greatly accelerates the reduction of NiCl$_2$ to Ni(0). (51)

3.2. Scope and Limitations

The reactivity of aryl halides in Ni-mediated coupling reactions depends to a large extent on the nature of Ni(0) used and reaction conditions. As with the more traditional copper agents, when Ni(cod)$_2$ or Ni(PPh$_3$)$_4$ are used, the reactivity of aryl halides in homocoupling reactions is I > Br > Cl. (49) When Rieke Nickel is used, the order of reactivity is also I > Br > > Cl. (111) When aryl iodides are coupled using Rieke Nickel, no difference is observed when the source of Ni(0) is NiCl$_2$, NiBr$_2$, or NiI$_2$. However, when aryl bromides are coupled, the best results are obtained when Rieke Ni is generated from NiI$_2$, implying that halogen-halogen exchange facilitates the reaction. (111) Aryl chlorides undergo efficient coupling using Ni(0) generated from NiCl$_2$, PPh$_3$, and excess reducing metal. (51) Similarly, the reactivity of aryl halides using NiCRA is Cl > Br > I, with substantial reduced, non-coupled arene being recovered for aryl iodides. (131)

Homocoupling of aryl triflates using Ni(cod)$_2$ under photolytic conditions has been described, (132) whereas tosylates are generally unreactive toward Ni(cod)$_2$ or Ni(PPh$_3$)$_4$. (49) However, aryl sulfonates dimerize in the presence of Ni(0) generated in situ from Ni(II) halides, triphenylphosphine, zinc, and iodide salts. (133-136) The homocoupling of aryl sulfonates using NiCl$_2$, Zn, PPh$_3$, and NaI in DMF has also been shown to occur under sonication. (135, 136) Although not necessary, (137) sonication effectively doubles the rate of reaction. (136) The highest yields and fastest reactions are achieved with aryl triflates. Aryl tosylates have also been shown to undergo Ni-mediated homocouplings in a variety of solvents including DMF, DMAc, THF, 1,4-dioxane, and acetonitrile. (137) Aryl mesylates also can be effectively coupled using Ni(PPh$_3$)$_2$Cl$_2$ and Zn in NaI with DMF (Eq. 11). (133, 134)

$$\text{(11)}$$
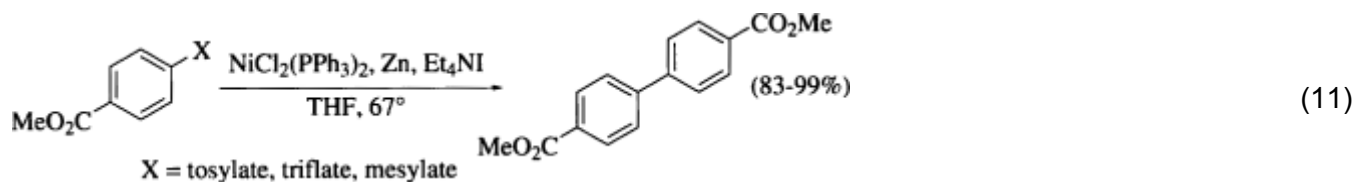
Intramolecular coupling with Ni(cod)$_2$ proves to be a low-yielding reaction. Instead, much higher yields are obtained by the use of Ni(PPh$_3$)$_4$ in DMF as the coupling agent (Eq. 12). (138) It is noteworthy that several intramolecular coupling reactions that are resistant to traditional Ullmann coupling methods can be achieved using Ni(PPh$_3$)$_4$ in DMF. (49)

$$\text{Ni(cod)}_2, \text{ DMF, reflux} \quad (0\text{-}15\%)$$
$$\text{Ni(PPh}_3)_4, \text{ DMF, } 55° \quad (81\%)$$
$$\text{Cu-Bronze, heat} \quad (70\%)$$

(12)
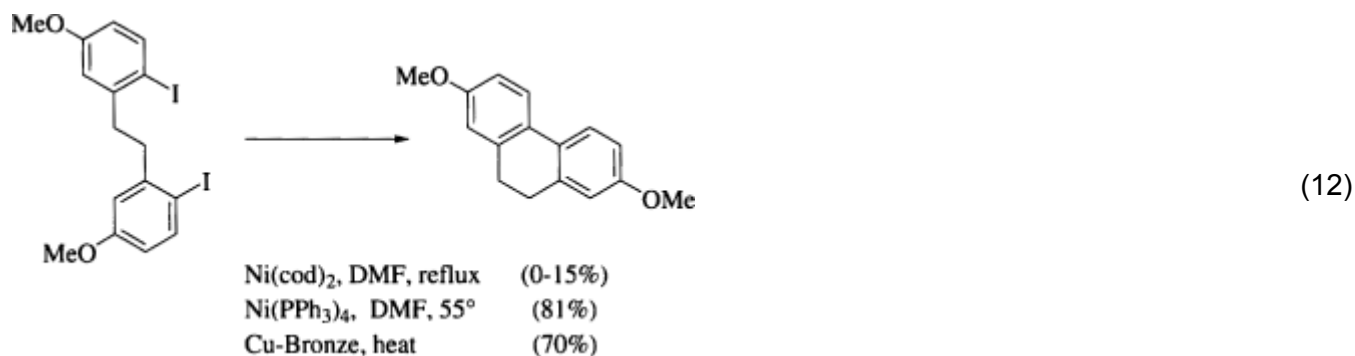
Although ortho substituents typically inhibit nickel-mediated biaryl coupling reactions, (49, 111, 120, 122, 123) increased catalytic quantities of Ni(0) in the presence of stoichiometric amounts of Et$_4$NI produce good yields of biaryls from ortho-substituted aryl bromides. (139) NiCRA-mediated reactions also allow for easy coupling of a number of ortho-substituted aryl halides. (54)

Generally, electron-withdrawing substituents favor coupling (51) whereas electron-donating groups decrease the reactivity of aryl halides, (111) leading to side reactions that can be minimized by the use of appropriately chosen ligands. (51) Many functional groups have proven to be compatible with Ni-mediated reactions including ketones, aldehydes, esters, and nitriles. (49, 111, 139) Acetals and ketals are stable to NiCRA conditions. (54) Other functional groups are stable under some conditions but not others. Amines, for example, are compatible with Ni(cod)$_2$ (49) and NiCRA (54) but not with Ni(0) generated in situ from Ni(II) salts. (51) Similarly, hydroxy groups may prevent coupling using Ni(cod)$_2$, (49) lead to arene reduction as a major by-product when Ni(0) is generated in situ from Ni(II) salts, (51) or couple without complication under NiCRA conditions. (54) However, 2-bromo-3-hydroxypyridine couples to form bipyridyl using Ni(0) generated in situ from NiCl$_2$. (140) Nitro (111) and carboxylic acid groups lead to undesired by-products with no evidence of biaryl formation. (49, 51, 54) The ability of nitro-containing substrates to destroy Ni(0) catalysts is also observed in the coupling of arylzinc halides with aryl halides. (141)

In situ generation of stoichiometric quantities of Ni(0) has been successfully applied to the reductive homocoupling of halopyridines, haloquinolines, and halopyrimidines to form bipyridyls, (142) biquinolines, (142) and bipyrimidines. (143) Although the catalytic method is less successful in a number of cases, (142) Ni(0) reagents are vastly superior to Cu- and Pd-mediated methods in coupling halopyridines. (144) Catalytic Ni(CO)$_2$(PPh$_3$)$_2$ is useful in forming biphenyls and bipyridyls from the corresponding aryl bromide. (145)

Generally, DMF is the solvent of choice, but other solvents also allow efficient coupling. Use of dimethylacetamide results in successful coupling of ketone- and aldehyde-containing aryl halides, a reaction that is unsuccessful in DMF. (146) Co-solvents can drastically improve the usefulness of some solvents. In reactions employing Ni(PPh$_3$)$_4$, toluene or THF are effective only if DMF or PPh$_3$ is added. (49) Reactions utilizing NiCRAs allow the use of nonpolar solvents such as benzene, xylene, hexane, and cyclohexane in combination with THF. (54) DMF is not useful as a solvent in NiCRA-mediated reactions.

Additives are also important in improving yields in nickel-mediated coupling reactions (Eq. 13). Aryl bromides (120, 127) and iodides (120) dimerize in comparable yields using activated Ni(0) in DMF; however, aryl chlorides are unreactive unless KI is added. (120) The addition of Et$_4$NI improves the reaction yields, allows THF to be used in place of DMF, and removes the necessity for an excess of PPh$_3$ in reductive homocoupling of aryl halides. (139) Other iodide salts improve the yield when aryl bromides are used as substrates. (129) Addition of KI to reactions using NiCRA results in higher yields of biaryl product and shorter reaction times. (54) Other promoter salts include alkali, alkali earth, Zn, Mn, and Al halides, with iodides being especially effective. (147) Addition of such promoters accelerates reactions by 20 fold. (147) With such modifications, suitable solvents include DMF, DMAc, DMSO, and other polar aprotic solvents. (147, 148)

$$\text{Ni(PPh}_3)_2\text{Cl}_2 \text{ / Zn / PPh}_3 \text{ (1:1:2), DMF, 50}° \qquad (73\%)^{122}$$
$$\text{Ni(PPh}_3)_2\text{Cl}_2 \text{ / Zn / PPh}_3 \text{ (0.05:1:0.4), DMF, 50}° \qquad (89\%)^{123}$$
$$\text{Ni(PPh}_3)_2\text{Cl}_2 \text{ / Zn / PPh}_3\text{, KI (0.05:1:0.4:1), DMF, rt} \qquad (81\%)^{123}$$
$$\text{Ni(PPh}_3)_2\text{Cl}_2 \text{ / Zn / PPh}_3\text{, KI (0.1:1.5:1), THF, 50}° \qquad (92\%)^{139}$$

(13)

Ligands are also required in reactions employing in situ generation of the Ni(0). Monodentate triaryl phosphines better stabilize Ni(0) than either trialkyl or bidentate aryl phosphines. (51) Triaryl phosphites are effective ligands in biaryl couplings and may be used in lower concentrations than the corresponding phosphines. (149) However, although $\text{Ni(PPh}_3)_2\text{Cl}_2$ is a stable reagent, the Ni(II)/phosphite complex is not isolable and must be formed in situ. The addition of 2,2′-bipyridine minimizes the side reactions that occur through ligand exchange when the aryl chloride bears an electron-donating group. The 2,2′-bipyridine is prepared in situ from 2-chloropyridine. (147, 148) 1,10-Phenanthroline has been used in place of bipyridine (146) and other bidentate ligands are also suitable.

Electrochemical reductive homocoupling of aryl halides using catalytic Ni(0) reagents has been reported. (53, 128, 150-152) Using an iron or duralumin anode, the reactions are conducted using a catalytic amount of $\text{NiBr}_2\text{(bpy)}$ in DMF/EtOH or EtOH/MeOH containing an electrolyte, indicating that polar protic solvents such as alcohols can be used in reductive homocoupling reactions. (53) Additionally, NaBr is used as a less expensive alternative to Bu_4NF, and hydroxy-containing aryl halides are efficiently coupled via this protocol. Aryl chlorides are not reactive under these conditions. The use of 2,2′-dipyridylamine (dpa) as ligand extends electrocatalytic methods to allow EtOH to serve as the sole solvent. (153) Electrocatalyzed couplings require relatively large amounts of nickel halide because of catalyst consumption during each cycle. Turnover is greatly improved through using dibromo[1,2-bis(di-2-propylphosphino)benzene]Ni(II). (154) However, the resulting Ni(0) species is only effective in coupling aryl chlorides. The numerous sources of Ni(0) and the many methods for its generation combined with the variety of reaction conditions allow a wide range of aryl halides and sulfonates to be coupled and permit a multitude of biaryl compounds to be accessible via nickel-mediated methods.

3.3. Mechanism

A number of mechanistic hypotheses have been advanced to explain Ni-mediated reductive biaryl formation. (155) Although the details may differ, two key steps are commonly accepted by the various theories: in an early step, oxidative addition of aryl halide to Ni(0) occurs, forming an ArNi(II) species, and in a final step, reductive elimination of a diaryl nickel species yields the biaryl product. The controversy lies in the intervening steps and in the nature of the diaryl nickel species. Arriving at a single mechanism to explain all Ni-mediated reactions has been complicated by the considerable variability in effective reaction conditions as well as the difficulty in obtaining kinetic data at metal surfaces in heterogeneous reactions. (155)

The earliest proposed mechanisms were based largely on semi-quantitative observations of the coupling reactions. Tsou and Kochi recognized the crucial role played by ArNi(II)X, the product of the oxidative addition of ArX to Ni(0), and an investigation of its fate in these processes provided considerable mechanistic insight. (156) ArNi(II)X can be prepared and isolated and in this study, its reactivity in subsequent reactions is followed. (156)

The possibility that a second molecule of ArX might add to ArNi(II)X to form a $\text{Ar}_2\text{Ni(IV)X}_2$ species which might undergo reductive elimination (49, 50) was considered. (156) Such a reaction would be reversible, meaning that if ArNi(II)X were combined with a different aryl halide, scrambling of aryl groups in the Ni(II) species would be expected. Since aryl scrambling of this nature was not observed when Ar-X was added to ArNi(II)X, it is unlikely that this step is a part of the coupling process. It is also important to note that the existence of the key $\text{Ar}_2\text{Ni(IV)X}_2$ species has never been demonstrated. (139)

$$\text{ArNi(II)X} + \text{Ar}'\text{-X} \rightleftharpoons \underset{\text{Ar}'}{\overset{\text{Ar}}{\text{Ni(IV)X}_2}} \rightleftharpoons \text{Ar}'\text{Ni(II)X} + \text{ArX}$$
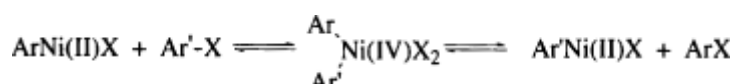
Another possibility that was considered is a metathesis reaction of two ArNi(II)X molecules to form $Ar_2Ni(II)$. (156) For this mechanism to be valid, pre-formed ArNi(II)X should decompose to form biaryl which is also not observed. Thus, it is unlikely that the diarylnickel species is $Ar_2Ni(II)$ under the conditions used in this study. (156) Interestingly, another report described a different outcome for a similar experiment. (157) When PhNi(II)Br was stirred in DMF at room temperature, biphenyl formed in 80% isolated yield. The role of solvent appears critical, as Tsou and Kochi performed their experiments in benzene. (156) A metathesis mechanism has been invoked to explain the formation of biaryl from a stable $Ar_2Ni(II)(bpy)$ complex in the presence of O_2, much like from diarylcuprates. (158)

Under the conditions employed by Tsou and Kochi, aryl radicals were rigorously excluded, rendering their involvement unlikely. (156) However, selective radical inhibition was observed by the addition of electron acceptors such as quinones, suggesting that Ni(I) and/or Ni(III) might be intermediates. ArNi(II)X remains as a key intermediate, indicating that one-electron transfer to ArNi(II)X is required, as demonstrated with electrochemical methods, (159) or two competing reactions are occurring, one producing ArNi(II)X and the other producing $ArNi(III)X_2$ from oxidative addition of ArX to NiX. (160)

The possibility that more than one mechanism may be needed has long been recognized. (51, 161) Arylnickel(II) complexes produce biaryls in high yield in polar solvents without consuming aryl halide. In nonpolar solvents, the same complexes form little biaryl unless additional aryl halide is added. The current theory holds that it is unlikely that one mechanism is in operation for Ni-mediated biaryl couplings given the considerable variation in ligands, (49, 51) the type of aryl halide used, (161) source and quantity of Ni, (51) and reducing agents used to form Ni(0). (51) It has been proposed that a shift in mechanism might occur in the homocoupling of aryl sulfonates as substrate is consumed while the amount of arylnickel species remains constant. (133)

Two mechanisms have emerged that represent opposite ends of a continuum in Ni-mediated biaryl couplings. (125) Their "relative importance is a function of the exact experimental conditions." (125) One mechanism, shown below, is most appropriate when a relatively small amount of Ni is used with a large excess of reductant such as zinc powder. (51) The catalytic cycle begins with oxidative addition of ArX to Ni(0) followed by the one-electron reduction of ArNi(II)X, the key step in the cycle. Oxidative addition of a second molecule of ArX to the resultant ArNi(I)X yields $Ar_2Ni(III)X$, which undergoes reductive elimination to release biaryl. $Ni(I)XL_n$ can then proceed along either of two paths, undergoing oxidative addition of ArX or a one-electron reduction to form Ni(0). (125) A similar mechanism that does not include the competition for Ni(I) has been proposed for reactions using triaryl phosphates in place of triarylphosphines. (149)
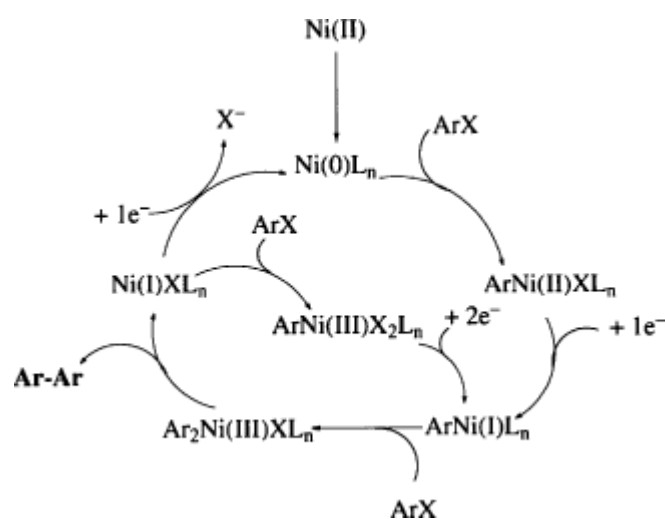
Data on electrocatalytic biaryl couplings are consistent with this mechanism. (162) When aryl sulfonates (X = OTs, OMs, OTf) are used, the Ni(II) species may have an ionic structure. (133) When iodide salts are employed as additives, an additional step includes the substitution of iodide for X^- in ArNi(II)X (123, 129) Iodide has been implicated in bridging between Ni and Zn to aid in electron transfer. (51, 139) Zinc

and other reducing metals (51) provide the electron source for reducing steps and can also be substituted by electrochemical techniques that provide a large reductive driving force. (125) In all cases, however, an excess of reductant must be present for this mechanism to be valid.

Electrochemical methods have been especially useful in gaining a mechanistic insight into the chemistry near the metal surfaces. (155) Based on electrochemically driven reactions, a similar mechanism has been developed which does not include a second competing pathway for Ni(I). (125) In essence, the mechanisms are identical with oxidative addition of ArX to Ni(I) not included in the more recent version. In general, however, the electrochemical data support the mechanism proposed for the coupling of aryl halides in aprotic, polar solvents with an excess of reducing metal.
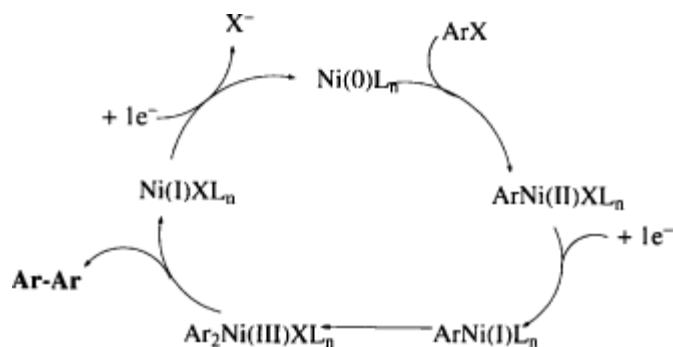
The other catalytic cycle that has emerged is similar to the mechanism proposed by Tsou and Kochi (160) in which ArNi(II)X and ArNi(III)X_2 react to form Ar$_2$Ni(III)X. In the catalytic version, a double chain sequence operates with two interdependent but co-operative catalytic cycles. (125) Unlike the previous mechanism in which the two cycles compete for intermediates, these cycles feed one another and operate cooperatively.
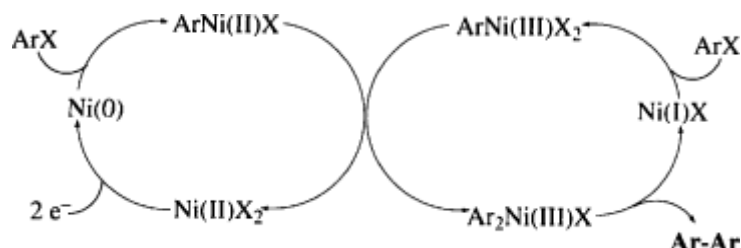
A key aspect of this mechanism is the required interaction of ArNi(II)X and ArNi(III)X_2. Under the reducing environment provided when excess Zn is present, neither of these intermediates would exist in more than trace quantities and their bimolecular reaction would be so slow as to prevent this mechanism from functioning. (125) ArNi(II)X and ArNi(III)X_2 are distinguished by the presence of a second halide atom in the latter. (156) The paramagnetic ArNi(III)X_2 would also be expected to be labile and capable of transferring a ligand. (156) Thus, two competing reactions can be envisioned: aryl and halide transfers. (156) A bridging mechanism explains these transfers and is supported by the observation that aryl iodides are more reactive than aryl bromides which mirrors the bridging capabilities of the two ligands. (156)

$$ArNi(II)X + Ar'Ni(III)X_2 \rightleftharpoons ArNi(III)X_2 + Ar'Ni(II)X$$

$$ArNi(II)X + Ar'Ni(III)X_2 \rightleftharpoons \underset{Ar}{\overset{Ar'}{\diagdown}} Ni(III)X + Ni(II)X_2$$

Only the second possible ligand transfer leads to the diaryl nickel(III) species required for biaryl coupling. The formation of biaryl is an intramolecular process. (156)

4. Palladium-Mediated Homocouplings

4.1. Scope and Limitations
The first reported palladium-mediated dimerizations of aryl halides occurred in the presence of hydrazine. (48) Typically, $PdCO_3$, N_2H_2, NaOH, aqueous MeOH, and bromo, or chloroarene substrates are used to form the biaryl in moderate yields (Eq. 14). (163) Palladium-mercury amalgam can be used to homocouple aryl halides under these conditions (Eq. 15). (164)

$$\text{(14)}$$

$$\text{(15)}$$
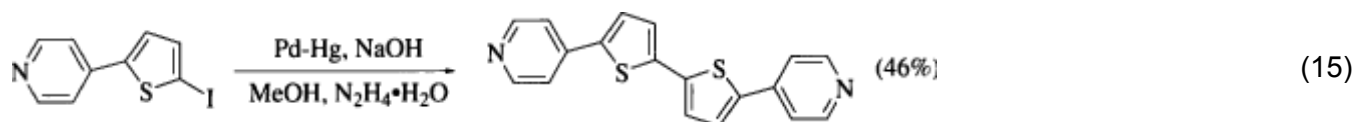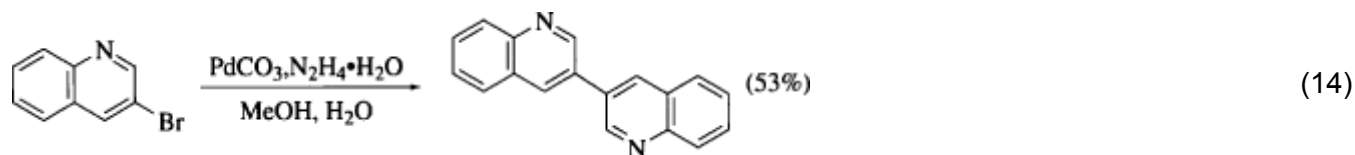
Arylhydrazines may be used in place of hydrazine. (165) The addition of $HgCl_2$ promotes these reactions. A competing side reaction is the heterocoupling between the aryl halide and the aryl hydrazine. The desired products are also contaminated with products resulting from the reductive dimerization of the aryl hydrazine.

Symmetric biaryls can be formed from the palladium-mediated homocoupling of aryl sulfinates. (166) When an aqueous solution of an arenesulfinic acid and 100 mol% of Na_2PdCl_4 is heated an overall reductive desulfinylation occurs, with extrusion of sulfur dioxide, to afford the corresponding biaryl. Although these conditions result in only poor yields of the biaryl, conducting the reaction in the presence of a catalytic amount of $HgCl_2$ increases the product yield two-fold. However, $HgCl_2$ is not necessary to obtain useful yields of biaryls from the desulfonylative homocoupling of arenesulfonic acids. Slightly modified conditions use an aqueous solution of 100 mol% of $PdCl_2$ as the palladium source. (167) This reaction is sensitive to substitution at the ortho position of the aromatic ring. Dechlorination and decarboxylation of the substituted arenesulfonic acid do not occur.

Arylsulfonyl chlorides are dimerized in the presence of Ti(OPr-i)$_4$ with a palladium catalyst loading of 2.5 mol %. (168) Both $PdCl_2(PhCN)_2$ and $Pd(OAc)_2$ perform well as catalysts in this methodology whereas $PdCl_2(PPh_3)_2$ and Pd black function poorly. Decreased yields are obtained when Ti(OPr-i)$_4$ is replaced with Ti(OBu-n)$_4$, while other metal alkoxides [Ti(OBu-t)$_4$, B(OPr-i)$_3$, and Al(OPr-i)$_3$] are completely ineffective. (168) Good dimerization yields are obtained when halogens (Br, Cl, F) are present meta or para to the sulfonyl chloride without competitive dimerization at the halide-bearing carbon. It can be assumed, based on other Pd-mediated desulfonylative couplings, that an ortho substituent hinders biaryl formation. Substituted naphthalenes are poor coupling substrates under these conditions.

Aromatic iodides, when treated with a catalytic amount of $Pd(OAc)_2$ in Et$_3$N at 100°, undergo homocoupling. (169) Homocoupling occurs in the presence of phenylhydrazine upon the in situ generation of Pd(0) from $PdCl_2$ in methanol at reflux. (165) Increased amounts of side products are formed when Bu$_3$N is used in place of Et$_3$N, and the presence of water increases the level of dehalogenated arene that is formed. (169) Steric constraints are much more pronounced than in Ni and Cu homocouplings. The yield of biphenyl product is decreased when ortho substituents are introduced in the aromatic iodide. Homocoupling is not observed when the aryl iodide is 2,6-disubstituted. (169) Slightly modified conditions [$Pd(OAc)_2$, PPh$_3$] have been used to couple 5-iodopyrimidines. (170)

When triphenylarsine is used as the ligand, the $Pd(OAc)_2$-mediated aryl halide dimerization can be extended to the homocoupling of bromobenzenes. (171, 172) Triphenylarsine is preferable to PPh$_3$, NPh$_3$, SbPh$_3$, and BiPh$_3$. Substituted arylbromides form the symmetric biaryl in modest yields. The main side reaction is the reduction of the aryl bromide to the parent arene. The yield of this side reaction is typically 20–30%. The ligand is not necessary in order to couple iodoarenes. (169) Ester, Cl, and F substituents are unaffected under the reaction conditions; however, bromoarenes that contain hydroxy,

cyano, carboxy, or amino substituents do not couple. (172) Interestingly, 4-iodobenzoic acid forms the corresponding dimer in 70% yield (in the absence of AsPh$_3$) whereas the 4-bromobenzoic acid does not form the desired product. Stoichiometric amounts of amines can be used as hydrogen donors to regenerate the catalyst in these coupling reactions.

Similar conditions [5 mol% Pd(OAc)$_2$, n-Bu$_4$NBr, K$_2$CO$_3$, DMF, 100°] can be used to convert iodobenzene into biphenyl in 75% yield. (173) Biphenyl formation from bromobenzene under these conditions occurs in 25% yield. (173) Other substituted aryl bromides readily undergo homocoupling under similar conditions (Eq. 16). (174, 175) Dimerization also occurs in the absence of n-Bu$_4$NBr by using Pd(OAc)$_2$ and diisopropylethylamine in DMF. (176)

$$\text{Pd(OAc)}_2, \, n\text{-Bu}_4\text{NBr} \quad \xrightarrow{} \quad \text{DMF, Et}_3\text{N, } 115° \qquad (60\%) \tag{16}$$
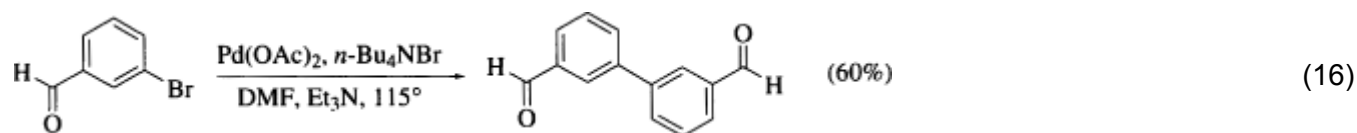
A mixture of a catalytic amount of Pd(OAc)$_2$ and 200 mol% of N-benzyl-1,4-dihydronicotinamide (BNAH) can be used to dimerize 4-iodonitrotoluene. (177) The BNAH may function as an electron-transfer agent. The yield can be substantially improved by adding Et$_3$N to the reaction mixture. It is not known whether this Pd coupling occurs with Et$_3$N and in the absence of BNAH, i.e., conditions that homocouple aryl iodides. (169)

Another interesting Pd(OAc)$_2$-mediated homocoupling of aryl halides uses 50 mol% hydroquinone, Cs$_2$CO$_3$, and 2–4 mol% As(o-tolyl)$_3$. (178) Aryl triflates undergo hydrolysis under the reaction conditions. The couplings proceed more rapidly with As(o-tolyl)$_3$ than with P(o-tolyl)$_3$. Hydroquinone is a requisite reagent; replacement with benzoquinone or catechol results in only unreacted starting material.

Aryl chlorides, bromides, and iodides are coupled upon treatment with Pd/C, sodium formate, NaOH, and a surfactant. (179) The choice of surfactant has only modest effects on the coupling yield; however, biaryl formation is dramatically decreased when the surfactant is eliminated. A more recent investigation of this methodology reports that PEG-400 (180) and CTAB (181) are the preferred phase-transfer catalysts. Polyethers also effectively enhance homocoupling yields under these conditions. (182) This methodology can be applied to the coupling of heterocycles (Eq. 17). (183) As is typically the case, ortho substitution hinders homocoupling. (179) Nitro groups are reduced and the resulting anilines are converted into benzidines. Acetates are inert to the reductive coupling conditions.

$$\text{Pd/C, NaOH, HCO}_2\text{Na} \quad \xrightarrow{} \quad \text{TEBAC, NaOH, H}_2\text{O, reflux} \qquad (67\%) \tag{17}$$
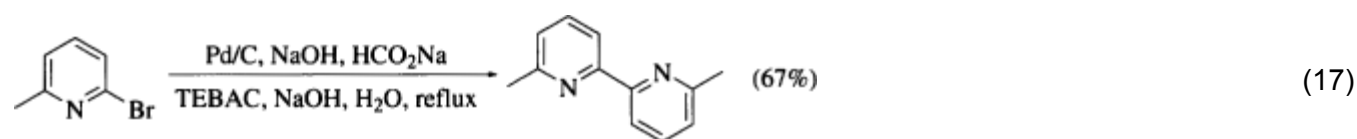
Alternative reducing agents such as carbon monoxide, glycerin, ethylene glycol, alcohols, (184) and formic hydrazide (55) can be used to promote aryl dimerization under biphasic conditions. Water can function as a hydrogen source in these types of dimerizations when zinc is used as a reducing agent. (180, 185) Hydrogen gas can also be used to regenerate the active palladium catalyst. 186, (187) The solid Pd/C catalyst retains >99% of its activity upon recycling. Although the dimerization pathway predominates under the reaction conditions of Pd/C and PEG-400 in water at 90–120°, competitive aryl halide reduction occurs to the extent of 20–40%. In fact, similar conditions can be used for the simple dehalogenation of aryl halides. (188) A heterogeneous trimetallic catalyst (4% Pd, 1% Pt, and 5% Bi on carbon) can be used under similar conditions to dimerize aryl halides. (187) An active carbon-suported palladium iron catalyst can be used with sodium hydroxide and glycerin to achieve aryl halide homocoupling. (189)

Aryl iodides and bromides and pyridyl bromides undergo Pd(0)-catalyzed electro-reductive coupling to form biaryls in excellent yields. (190) Aryl chlorides slowly form arenes under the reaction conditions. This reduction is a competitive process with naphthyl iodides and is the sole pathway for ortho-substituted aryl bromides. Aryl triflates also undergo Pd(0)-catalyzed electro-reductive coupling to

form biaryls. ([191](#), [192](#)) Palladium complexes of monodentate ligands are preferable to those of bidentate ligands in the dimerization of aryl and naphthyl triflates. ([192](#)) When these reactions are performed in the absence of Pd, only the corresponding phenol is formed. ([191](#)) Zinc may also be used as the reducing agent in this reaction. ([193](#))

Palladacycle catalysts with either a tertiary phosphine ([194](#)) or K_2CO_3/Bu_4NBr ([195](#)) also dimerize aryl halides. Homocoupled compounds can also be formed as the predominant products from low-yielding cross-coupling reactions between aryl halides and siloxanes with either catalytic systems of $Pd(OAc)_2$, $P(o\text{-tolyl})_3$, KF, and DMF ([196](#)) or $Pd(dba)_2$, tetrabutylammonium fluoride (TBAF), and DMF. ([197](#)) TBAF is essential in the $[PdCl(\pi\text{-}C_3H_5)]_2$-induced homocoupling of aryl halides in DMSO. ([198](#))

4.2. Mechanism

The mechanism of palladium-catalyzed systems has been studied in great detail. ([192](#), [199-204](#)) In the most widely accepted postulated mechanism, only Pd(0) and Pd(II) intermediates are involved in the catalytic cycle. This mechanism is shown below (X = leaving group, L = ligand). The initial step in this mechanism is a two-electron reduction of the palladium(II) source to either an anionic or neutral Pd(0) species, which is followed by an oxidative addition of this ligated Pd(0) intermediate to an aryl halide.

This results in either the formation of an anionic $Ar[Pd(II)X_2L_2]^-$ intermediate or the corresponding neutral $ArPd(II)XL_2$ intermediate. The latter species can also be arrived at by dissociation of X^- from the former Pd(II) species. Further reductive dissociation provides a ligated anionic Pd(0) complex that undergoes a second oxidative addition to the aryl halide. The palladium reduction is typically accomplished by electrochemical means, Zn, hydrogen gas, or other miscellaneous agents (see above). Once again, halide dissociation occurs to arrive at the penultimate intermediate $Ar_2Pd(II)L_2$. A final reductive elimination step provides the desired biaryl and regenerates the catalytic Pd(0) species to propagate the aryl halide dimerization process.
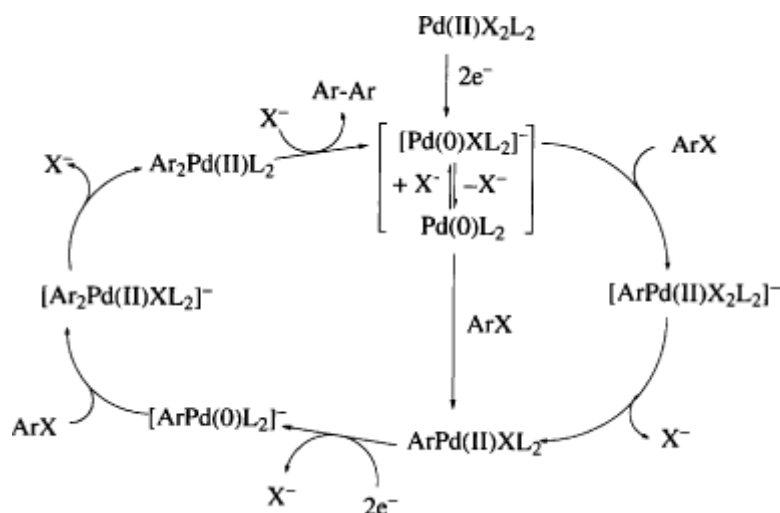
Slightly modified mechanisms have been proposed for palladacycle catalysis ([194](#)) and for the $Pd(OAc)_2$/hydroquinone redox system. ([178](#)) In addition, a single-electron mechanism can be invoked, in which the aryl halide coordinates to the surface of a Pd cluster. ([181](#)), [186](#) Single-electron transfer from the catalyst to the aryl halide occurs, which results in a radical anion. This species decomposes to aryl radicals. In all likelihood, the aryl radicals then dimerize on the palladium surface. Chlorobiphenyls have not been observed during the coupling of chlorobenzene, ([181](#)), [181,186](#) thus negating the direct attack of phenyl radicals on chlorobenzene. Once coupled, the newly formed biphenyl dissociates from the metal surface.

5. Axially Chiral Biaryls

A requisite for successful diastereoselective Ullmann couplings is that rotation about the chiral axis of the newly formed carbon-carbon bond be restricted. This can be accomplished by incorporation of sufficient steric hindrance about the biaryl axis (generally tri-or tetra-substitution in the ortho positions). To date, chiral catalysts have not been reported to promote these types of asymmetric coupling reactions. In successful intramolecular couplings, pre-existing stereochemical elements within the molecule induce asymmetry.

Enantiomerically pure 2,2′-binaphthol has been used in this protocol as a template for the synthesis of chiral biaryl and binaphthyls. (205) 2-Haloaroyl chlorides were converted into the corresponding diesters. These halogenated aromatic rings were then juxtaposed so that only a single diastereomer could be formed upon reductive coupling to form the biaryl (Eq. 18). (206) Hydrolysis of the ester releases the starting chiral binaphthol as well as the newly created chiral biaryl. Nonsymmetric chiral biaryls can also be formed by this method. This is done by monoesterification of 2,2′-binaphthol with one equivalent of an appropriate benzoyl donor. Subsequent esterification with a different benzoyl unit then completes the template construction (207)

(18)
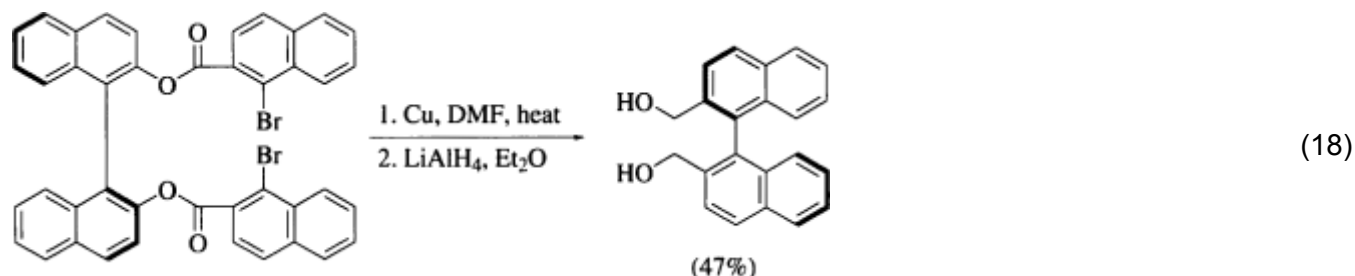
A variety of other chiral scaffolds (**1**,**2**,**3**) have been used to juxtapose aryl halides prior to reductive dimerization. (206) Carbohydrate scaffolds **4–9** have also been used to tether two iodinated galloyl esters and subsequent reductive homocoupling occurred with varying levels of diastereoselectivity. (208) These systems were somewhat flexible, which allowed for a higher degree of conformational freedom. This in turn resulted in lower levels of asymmetric induction.

In another scaffold, the element of chirality was introduced by an asymmetric dihydroxylation of a stilbene precursor. This conformationally flexible system was then locked into a more restricted state (**10**) by carbonate formation. The corresponding axially chiral biaryl was then formed with a high degree of diastereoselectivity via a nickel-mediated reductive homocoupling in 33% yield. (209) No mention was made to account for the remaining 67% of material. This unactivated system did not undergo a copper-mediated reductive homocoupling. Studies on the conformation of the dibromide indicate that a change in twist (from M to P) occurs during the coupling reaction. (210, 211)
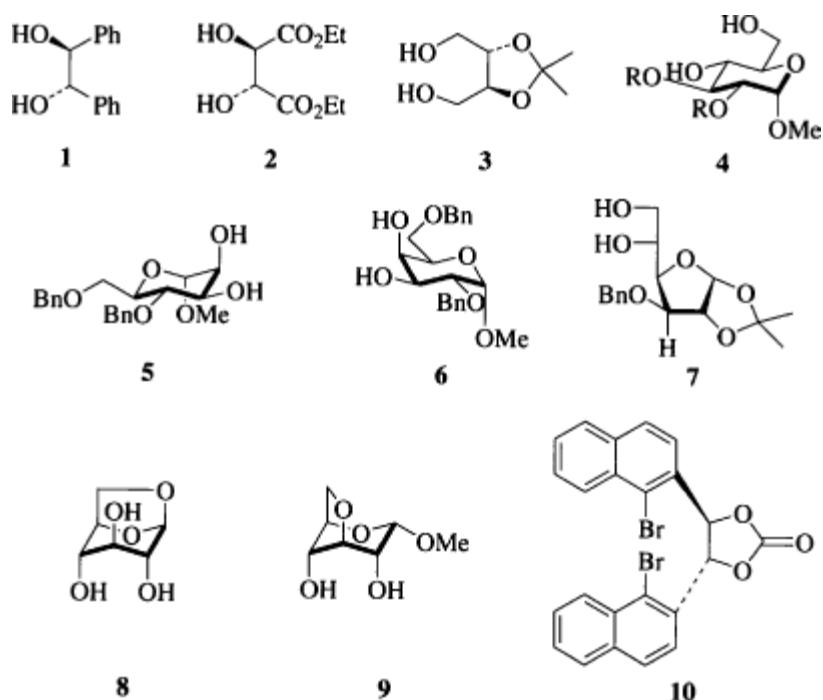
Other intramolecular dimerizations have been accomplished in which the resulting biaryl's chirality has been relayed from an enantiomerically pure scaffold such as **11** (104) or **12**. (102, 106) Coupling in both cases was effected by the initial generation of the higher order cyanocuprate, which was followed by the oxidative release of the desired biaryl. (97-99, 101) It was not mentioned how the intramolecular coupling

proceeded under more traditional conditions [e.g., Cu(0) or Ni(0)]. Other successful couplings with the 1,2-diol linker **1** have been reported. ([105](), [212]()) These types of asymmetric, intramolecular Ullmann couplings have also utilized optically active 1,3-diols **13** and **14** as scaffolds. ([103]())
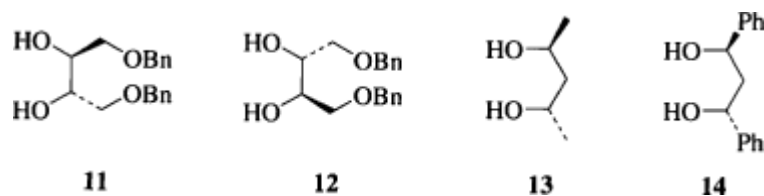
Chiral biaryls can also be formed from intermolecular Ullmann couplings. Initial attempts to induce asymmetry were unsuccessful. The highest level of asymmetric induction was only 13% de when chiral esters such as **15** were used. ([21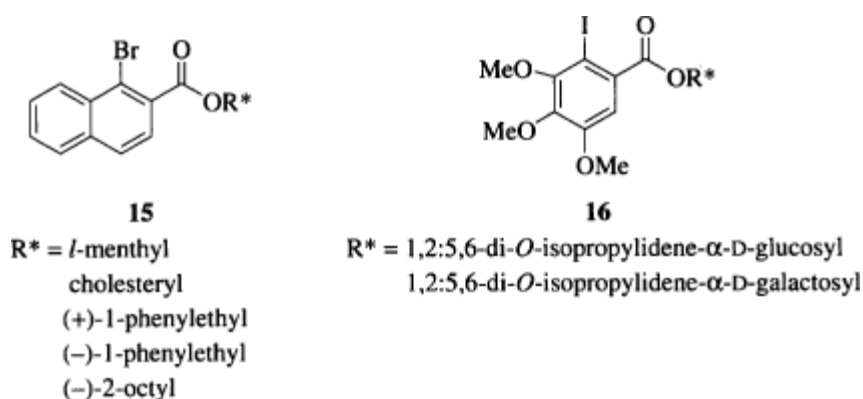3]()) Likewise, carbohydrate esters such as **16** have been poor transmitters of chiral information during the formation of the biaryl axis. ([208]())

15

R* = *l*-menthyl
cholesteryl
(+)-1-phenylethyl
(−)-1-phenylethyl
(−)-2-octyl

16

R* = 1,2:5,6-di-*O*-isopropylidene-α-D-glucosyl
1,2:5,6-di-*O*-isopropylidene-α-D-galactosyl

However, successful stereoselective intermolecular Ullmann reactions have been reported in which an oxazoline is employed as the chiral controller element. ([214-218]()) The rigidity of the oxazoline and the presence of nitrogen atoms are the key structural features that allow this approach to be successful. It is not necessary to have high levels of asymmetric induction during the carbon-carbon bond formation as long as rotation about the chiral biaryl axis can occur under the reaction conditions. In one case, the Ullmann coupling of a bromooxazoline resulted in only a modest 62:38 diastereomeric ratio of atropisomers (*S:R*) after 1 hour. Although the coupling reaction was rapid, a thermodynamically controlled resolution is operative under the reaction conditions (Eq. [19]()). ([214](), [215]()) In this manner, diastereomerically enriched biaryls were formed. After equilibration of the reaction for 40 hours, a steady state diastereomeric mixture of 93:7 (*S:R*) remained. ([214](), [215]()) Interconversion of atropisomers occurred thermally in the absence of metal. This was the first report of a deracemization of chiral biaryls. ([219]()) This phenomenon was later applied to the in situ deracemization of C_2-symmetric bisoxazolines by Cu(I). ([220](), [221]()) Subsequently, other covalent methods have been utilized to deracemize biaryls. ([222](), [223]()) Depending on the nature of the aryl component, increasingly higher levels of diastereoselectivity have been observed as the size of the chiral oxazoline substituent is decreased. ([224]())


(19)
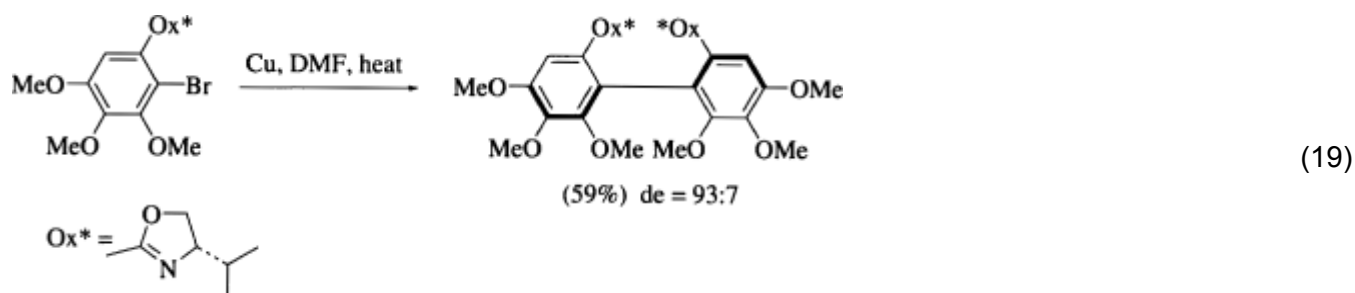
Naturally occurring chiral biaryls have been synthesized by the diastereoselective intermolecular copper-mediated homocoupling of aromatic halides that contain a chiral oxazoline. These couplings usually proceed with high levels of diastereoselectivity; however, a case of poor selectivity has been

reported. (225, 226) This methodology has resulted in the synthesis of chiral biaryl-containing natural products such as (*S*)-gossypol, (227-229) isokotanin A, (230) (–)-herbetenediol, (224) (–)-mastigophorene A, (224) (–)-mastigophorene B, (224) (+)-kotanin, (106) and an ellagitannin. (218)

An extension of this methodology has resulted in the synthesis of *C*₂-symmetric chiral binaphthyls (Eq. 20). (216) Since atropisomerism of the binaphthyl system is precluded under the reaction conditions, the major biaryl stereoisomer was determined on the basis of kinetic preference in the transition state.

R		S:R
Ph	(75%)	2:1
i-Pr	(60%)	4:1
t-Bu	(79%)	32:1

(20)
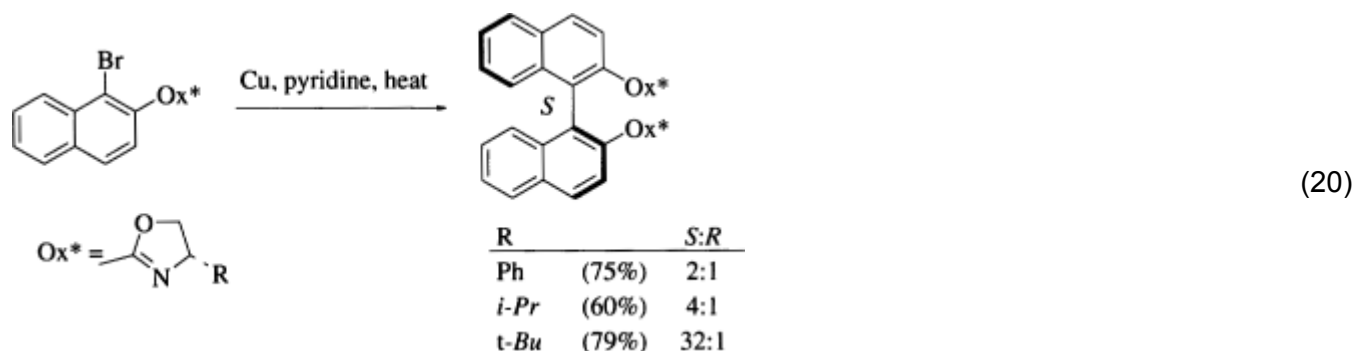
Chiral 1,1′,8,8′-binaphthyls have also been synthesized in this fashion. (220, 231) Interestingly, the subtle change of solvent (pyridine to DMF) completely changed the predominant atropisomer from *S* to *R* about the biaryl axis (Eq. 21). (220)


(21)
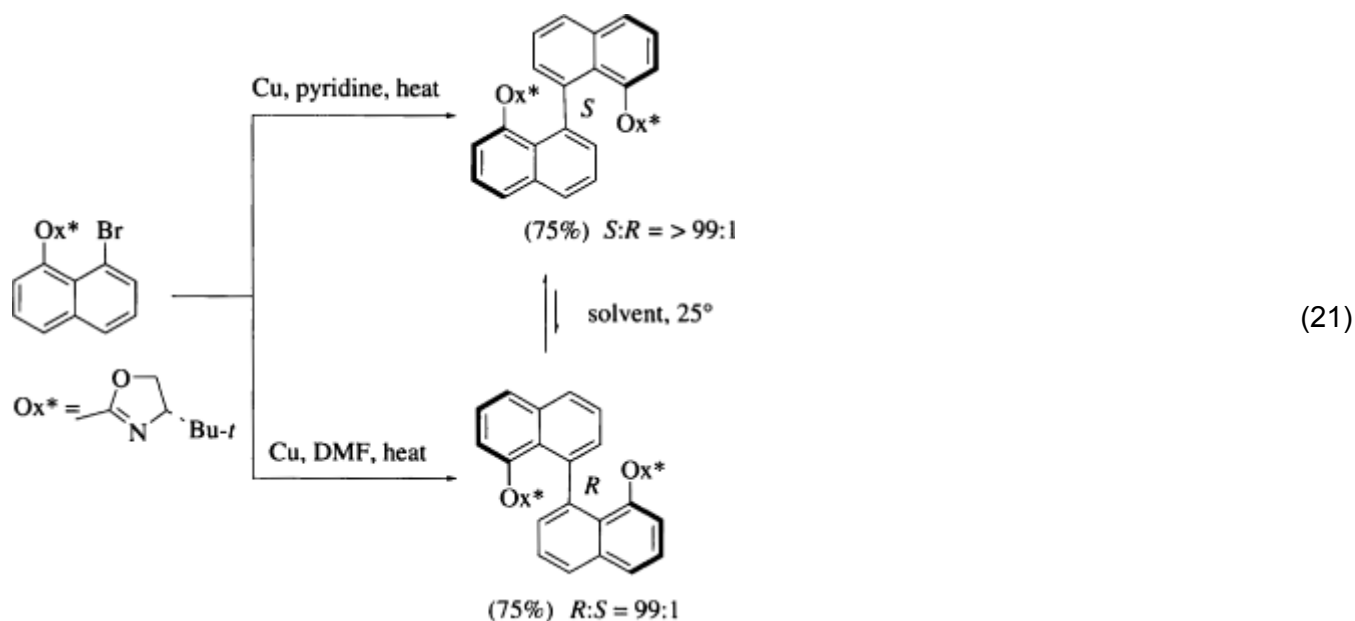
6. Polymerizations

Reductive homocoupling reactions provide the capability of coupling aromatic rings into polymers of arenes and, as such, have received considerable attention from polymer chemists. A logical target for such an application of Ullmann and similar reactions would be poly(*p*-phenylene) (232) and related polymers which exhibit desirable characteristics such as thermal stability and electrical conductivity. (233)

Classic copper-mediated Ullmann couplings of 1,4-dihaloarenes lead to the formation of smaller "oligo(*p*-phenylenes)" (232) such as biphenyls and terphenyls. (234) Often, however, attempts to prepare higher molecular weight poly(*p*-phenylene) derivatives result in the formation of unwanted by-products which decrease the yield of desired product and make purification difficult. The molecular weights of the polymers produced in metal-catalyzed reactions are also frequently limited by the solubility of the polymeric product in the reaction medium. (235)

Some successes with copper-mediated Ullmann methods have been reported. Heating 4,4′-diiodo-3,3′-dimethylbiphenyl with copper powder in α-methylnaphthalene yields a polymeric product with molecular weights ranging from 1000 to 300,000. (236, 237) Biphenyl is also useful as a solvent in the preparation of polymers via copper-mediated reductive homocoupling. Upon heating with activated copper and mercury in biphenyl, poly(3,3′-biphenylylenearylmethane) forms. In both instances, however, side reactions lead to the formation of non-linear products. (234)
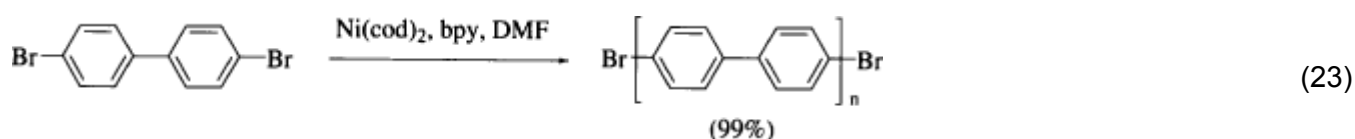
As with simple reductive homocoupling reactions to form biaryls, the use of DMF as a solvent allows milder conditions for polymer formation with fewer side reactions. Treatment of 4,4′-diiodo-3,3′-dinitrobiphenyl with Cu powder in DMF yields a mostly linear, substituted poly(p-phenylene) with an average length of 52 monomer units (Eq. 22). (238)

(22)
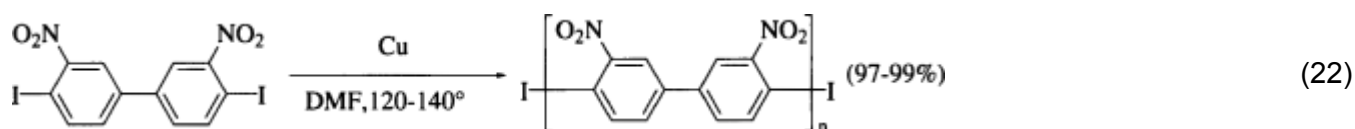
Copper-mediated reductive homocoupling reactions are also useful in the preparation of other poly(arenes), (239, 240) oligo(pyrrole-2,5-diyls), (241) polythiophenes, (242) and pyrrole-derived zwitterionic polymers. (243)

Both traditional copper-mediated Ullmann conditions and Ni(cod)$_2$ are useful in the reductive coupling of substituted p-dihaloarenes to form substituted poly(p-phenylenes). (244) Similarly, copper and nickel-mediated systems have been compared in the preparation of poly(alkyl thiophene-3-carboxylates). (242) Although the polymeric products are of comparable average molecular weights, the polymer obtained from the copper-mediated reaction was of higher quality with narrower polydispersity. (242, 245) A comparison of Rieke Nickel with in situ generated Ni(0) produces polymers of similar molecular weights, but different polydispersity, with Rieke Ni yielding a free flowing powder as opposed to the sticky solid produced when NiBr$_2$, Zn, and PPh$_3$ are used. (245)

The lower reaction temperatures that are required for Ni(0)-mediated reactions have made nickel the preferred catalyst for the polymerization of dihaloarenes. In situ generated Ni(cod)$_2$ has been used in the synthesis of poly(p-phenylenes), (246, 247) poly(9,10-dihydrophenanthrenes), (248) and poly(thiophenes). (246, 249) These reactions produce polymers with regular structure in high yield (Eq. 23). (246, 247)


(23)

Dibromothiophenes may also undergo polymerization in reductive homocoupling reactions as demonstrated by the formation of oligo(3-formyl-2,5-thienyl) in 81% yield from 3-formyl-2,5-dibromothiophene and in situ generated Ni(0). (250) In situ electrochemical generation of Ni(0) is also used to prepare poly(p-phenylenes). (251)

Modifications to the in situ generation of catalytic Ni(0) allow aryl chlorides to be reductively coupled under mild conditions. (51) The use of an excess of reducing metals such as zinc and catalytic NiCl$_2$ has been applied with great success to the preparation of polymers from dichloroarenes. (252) The first description of this methodology is in the synthesis of polyaryl ether sulfones via nickel-mediated reductive homocoupling of the corresponding dichloroarenes. (253, 254) The novelty and versatility of this method is also demonstrated in the polymerization of 2,5-dichlorothiophene (Eq. 24). (253) Poly(thiophene) had previously been prepared from 2,5-dibromothiophene. Although no yield was provided, this represents the first synthesis from 2,5-dichlorothiophene.

Several reaction parameters are critical to the preparation of high polymer. Moisture must be rigorously

excluded as aryl halides are readily reduced in the presence of Ni(0) and water. Oxygen must also be excluded because of its capacity to deactivate the catalyst. The reducing agent, zinc, should have a high surface area but low oxide content. Indeed, the most common cause of failure in these coupling reactions is the use of poor quality zinc metal. Triaryl phosphites can also be used in place of triarylphosphines with good results. (255)
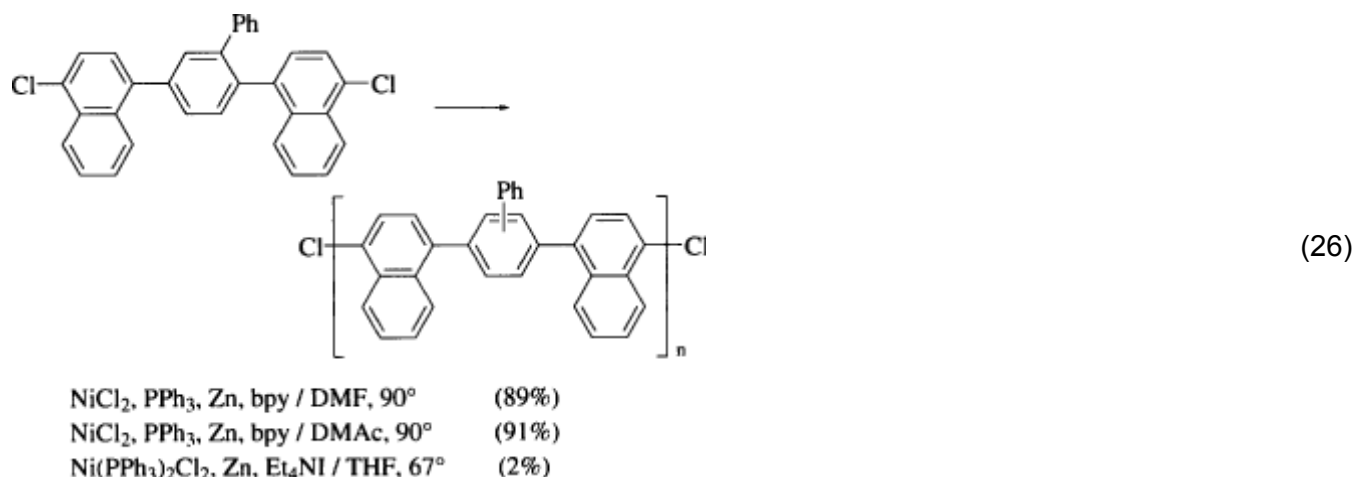

$$\text{(24)}$$
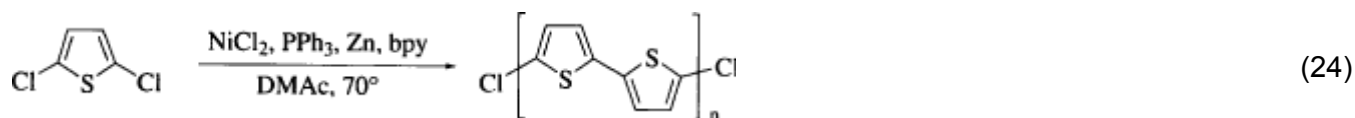
This general method has been applied to the synthesis of substituted poly(p-phenylenes). Poly(3-methoxycarbonylphenylene-1,4-diyl) is prepared from the corresponding dichloroarene with a degree of polymerization of approximately 100. (Eq. 25). (233, 256) The polymer contains a mixture of "head-to-head" and "head-to-tail" units. Substituted poly(m-phenylene) can also be prepared using nickel-catalyzed reductive homocoupling. (257)

$$\text{(25)}$$
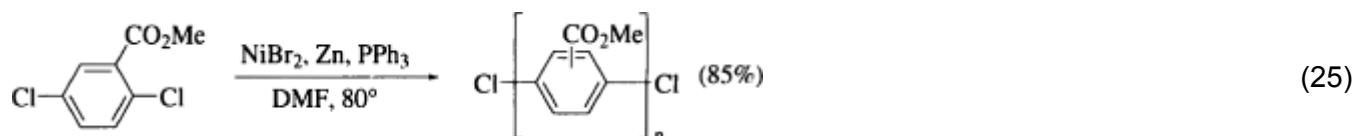
The coordinating ligands of nickel have dramatic effects on the polymerization of 2-benzoyl-1,4-dichlorobenzene. (255) The addition of bipyridyl (bpy) results in shorter reaction times and, apparently, different microstructures of the polymer product.

The wide range of conditions under which high polymer can be prepared has also been noted. (258) Polar aprotic solvents such as DMF, NMP, and HMPA as well as benzene have proven useful. Also, ratios of monomer to NiX_2 can vary from about 10 to nearly 5000 and ratios of PPh_3, and NaI to Ni catalyst may vary from 1.0 to about 10. The zinc to monomer ratio must be at least 1.0. Although the preferred reaction temperature is 50°, reactions have been successful from 25° to about 100°. In studies toward the polymerization of 2,5-bis(4-chloro-1-naphthyl)biphenyl, differences in the conditions for generating the nickel catalyst have been shown to have a profound impact on polymerization reactions. (259) When the catalyst is prepared from $NiCl_2$, PPh_3, Zn, and bpy in DMF or DMAc at 90°, yields range from 89–91%. However, when the catalyst is generated using an alternative method, (139) the yields are considerably lower (Eq. 26). It is not clear whether this difference arises from temperature or solvent effects. However, other work that incorporates similar temperatures produces comparable polymer yields, although unreacted monomer is identified in the reaction using THF as solvent. (260)

$$\text{(26)}$$

$NiCl_2$, PPh_3, Zn, bpy / DMF, 90°	(89%)
$NiCl_2$, PPh_3, Zn, bpy / DMAc, 90°	(91%)
$Ni(PPh_3)_2Cl_2$, Zn, Et_4NI / THF, 67°	(2%)

The ability to couple aryl sulfonates using Ni-mediated reductive homocoupling techniques has been widely applied to the preparation of polymers. (135, 136, 261, 262) Bistriflates of substituted

1,4-arenediols are converted into substituted polyphenylene polymers with unusual solubility in organic solvents. (261, 262) This represents a major advance in the synthesis of poly(*p*-phenylenes) as readily available bisphenols and hydroquinones can enter into polymerization reactions via their sulfonates. (252) The expense of preparing triflates is such that a less expensive alternative is desirable. As a result, aryl tosylates and mesylates have been shown to undergo reductive homocoupling to yield biphenyls, although at slower reaction rates. Polymerization of mesylates allows biphenyls to be prepared in high yield (134) and application of this methodology to mesylates of bisphenols leads to poly(*p*-phenylenes) in good yield. (263)

7. Comparison with Other Biaryl Syntheses

Many other methods have been developed to prepare biaryls via the coupling of aromatic rings (8, 9, 264) but detailed discussions of them are beyond the scope of this review. Broadly speaking, however, these methods can be divided into reductive and oxidative couplings with subcategories of stoichiometric and catalytic quantities of reagent. These methods are most often applied to cross-coupling reactions but many examples of homocoupling reactions are known. Reduction of aryldiazonium salts allows coupling with another arene to form a biaryl. The intermolecular version of the reaction is known as the Gomberg-Bachmann-Hey reaction. (265) When the reaction is carried out intramolecularly, the reaction is known as the Pschorr reaction. (266) Typically, the Pschorr reaction is carried out under acid conditions in the presence of copper powder although variations are known. (8) This reaction is often plagued by low yields and is infrequently used. However, modified conditions allow its successful use in phenanthrene synthesis (9) and diazonium salts of anthranilic acid are coupled using Cu(I) to give diphenic acid in up to 90% yield. (267) The Gomberg-Bachmann-Hey reaction is typically carried out in aqueous base. (265) When phase-transfer conditions and nonaqueous solvents are used, yields are improved considerably. (268) These reactions are most successful on electron-poor substrates. (9) Reductive coupling of hypervalent iodides, which was useful in the formation of biphenylenes, (269) is also useful in forming biaryls. (270-272)

Photochemical coupling reactions to form biaryls have also been described. (8) Photolysis of aryl iodides with aromatic solvents generates unsymmetrical biaryls. (273) Arylthallium bis(trifluoroacetate) couples with an aromatic solvent under photolytic conditions in high yield. (274)

Aryl halides reductively couple using silver powder (275-278) in place of copper but the yields tend to be somewhat lower. (279) Other reductive coupling reactions include the intramolecular coupling of aryl iodides using Al_2O_3, (280, 281) simple heating of naphthyl halides to yield binaphthyls, (282, 283) and the use of $Hg(OAc)_2$ and Ce(IV) to dimerize halobenzenes to biphenyls. (284) 2,6-Diiodophenols dimerize in a buffered two-phase system. (285)

Conversion of aryl halides into aryl metals is another method to form biaryls. Treatment of aryl halides with lithium metal in a Wurtz-type coupling generates biaryls. (286, 287) Preformed pyridyllithium compounds undergo cross-coupling with pyridyl sulfoxides (288) and pyridyl sulfoxides undergo homocoupling upon treatment with CH_3MgBr. (289) Lithiated dibenzofuran couples when treated with Fe(acac) (290) and aryllithium compounds form symmetrical biaryls upon treatment with Co(II) salts (291-293) or Ni(II) salts. (294) Copper (II) salts mediate the coupling of aryllithium compounds. (295, 296)

Treatment of aryllithium with CuI forms arylcopper species that couple with aryl iodides, forming biaryls. (297-299) The aryllithium is formed from an aryl bromide or iodide bearing a ligand at the ortho position, which is required to stabilize the aryl-copper intermediate. Although the requirement of this ligand limits the generality of this ambient temperature method, this methodology allows access to biaryls containing two ortho substituents (297) and has been used in the synthesis of Steganacin (298) and oxygenated phenanthrenes. (300)

Aryl halides are converted into arylmagnesium halides that participate in cross-coupling reactions upon treatment with metal catalysts (Eq. 27). (264)

$$ArMgX \; + \; Ar'X \quad \xrightarrow{\text{Ni(0)}} \quad Ar\text{-}Ar' \tag{27}$$

Ni(II) salts serve as catalysts in preparing heterobiaryls (301, 302) and poly(arenes) (303, 304) via this

method. Ni(II) catalysts bearing chiral ligands are useful in the preparation of enantiomerically pure biaryls. (305-308) Cu(II) salts may also be used in the Kharasch method. (309, 310) Other metal catalysts (264) include Pd(II), Fe(II), Fe(III), Co(II), (292) Ni(0), and Cr(III). (303) Aryl Grignard reagents dimerize upon treatment with triflic anhydride (311) or with 1,4-dichloro-2-butyne. (312) Arylmagnesium bromides form symmetric biaryls upon treatment with $TiCl_4$. (313)

The polar nature of the Grignard reagent required in the Kharasch method precludes the use of potentially reactive groups on the partner aryl halide. However, the method provides some versatility by allowing the replacement of aryl halides with aryl sulfonates, (314) thioethers, carbamates, and ethers. (264) Reactivity differences among these groups also allow for selective coupling at one site of a doubly substituted aromatic compound.

A related method of biaryl synthesis is the Negishi reaction in which arylzinc halides couple with aryl halides in the presence of Ni(0) or Pd(0) (Eq. 28). (264, 315, 316)

$$ArZnX \;+\; Ar'X \;\xrightarrow{\;Ni(0)\ or\ Pd(0)\;}\; Ar\text{-}Ar' \tag{28}$$

Arylzinc halides, prepared from the aryllithium intermediates, cross-couple with aryl bromides and iodides in the presence of Pd(II) and DIBAL-H or Ni(PPh$_3$)$_4$. (317) Catalytic amounts of Pd[P(t-Bu)$_3$]$_2$ couple arylzinc halides with aryl chlorides. (318) Arylzinc halides are also formed using a sacrificial anode process and Co(II) catalyst. (319) This method can be used to couple a pyrimidine and an indole (320) and allow for sulfonates to be used in place of aryl halides as the coupling partner with the arylzinc halide. (264) (Phenylzinc chloride)chromium complexes couple with aryl halides in the presence of a Pd catalyst. (321) Like the reactions involving Grignard reagents, however, the required use of aryllithium compounds limits the nature of substituents that the reaction can tolerate. Highly reactive Rieke zinc allows the conversion of aryl halides into arylzinc halides and subsequent cross-coupling with aryl halides in the presence of Pd(0) to produce biaryls in high yield. (322) Rieke zinc also allows for the homocoupling of dibromothiophenes to form poly(thiophenes) or 1,4-diiodobenzene to form poly(p-phenylenes). (316) The regioregularity of the substituted polymer depends on the catalyst used. Aryl halides may also be converted into arylzinc halides using electrochemical methods, avoiding the troublesome aryllithium intermediate. (323)

Other aryl metals also undergo coupling to form biaryls. (324) Diarylgold(III) complexes produce biaryls upon treatment with NaClO$_4$ and triphenylphosphine. (325) Arylmercuric chloride and diphenylmercury dimerize in the presence of [RhCl(CO)$_2$]$_2$ to yield symmetrical biaryls. (326) Diarylmercury species undergo homocoupling when heated with Ni(0), Pd(0), Cu(0), Pt(0), Ag(0), (327) or Cu/ PdCl$_2$. (328) Aryllead triacetates form biaryls when treated with CuI or Pd$_2$(dba)$_3$-CHCl$_3$. (272) In the presence of Ni(dppe)Cl$_2$ catalyst, 2-(phosphininyl)halogenozirconocene forms 2,2′-biphosphinine. (329) Triarylgallium(III) undergoes homocoupling when reacted with H$_2$O in toluene. (330)

In situ generated hypervalent siloxanes undergo cross-coupling with aryl iodides and electron-deficient aryl bromides in the presence of Pd(dba)$_2$ (Eq. 29). (197) Treatment of phenyl trimethoxysilane with tetrabutylammonium fluoride generates the hypervalent fluorosilicate ion which transmetallates with the arylpalladium halide complex and subsequently couples with aryl iodide. Pd catalysts and fluoride salts (331) or NaOH (332) are also used to cross-couple arylchlorosilanes and aryl halides.

$$ArSi(OMe)_3 \;\xrightarrow{\;F^-\;}\; \left[\begin{array}{c} MeO \quad OMe \\ Ar\!-\!Si\!-\!OMe \\ F \end{array}\right]^{-} \;\xrightarrow[Pd(dba)_2]{\;Ar'X\;}\; Ar\text{-}Ar' \tag{29}$$

In the late 1970's, arylstannanes were shown to couple with aryl halides and triflates in the presence of Pd(0) catalysts in what is now known as the Stille reaction (Eq. 30). (333) A major advantage of the Stille reaction is the compatibility of the reaction conditions with substituents that are not tolerated under conditions involving more reactive main-group metals. (264) Typically, arylstannanes containing tributyltin or trimethyltin are used (264) but the reaction has been expanded to allow the use of arylstannoates in aqueous solution. (334, 335) In general, arylstannanes couple best with aryl bromides and iodides, with

aryl bromides requiring more rigorous conditions. (333) Aryl triflates also undergo coupling with arylstannanes and have reactivities comparable to the aryl bromides. (336) Diazonium salts (337) and hypervalent iodides also serve as coupling partners with the stannanes. Pd(0) is the catalytic species in these reactions, but Pd(II) salts are also useful because they can be reduced to Pd(0) by the organostannane. (336) Although Pd-catalysts are preferred, yields can be improved by the addition of copper salts. (264) Pd(0) coordinated by a bidentate iminophosphine ligand shows remarkable catalytic activity. (338) Steric effects are important in Stille couplings with ortho substituents significantly slowing the reaction rate. (333) The Stille reaction is useful in the preparation of heterobiaryls in which either aryl moiety can be derived from the arylstannane. (264) Poly(arylenes) have also been prepared via the Stille reaction (339) and solid-phase biaryl synthesis using microwave irradiation has been reported. (340)

The Stille reaction can also be used to form symmetrical biaryls. (338) Treatment of iodopyrimidines with hexamethylditin and Pd(0) yields bipyrimidyl. (341) Cu(II) or Mn(II) salts are used to form symmetrical biaryls from arylstannanes in the presence of I_2. (342, 343)

$$ArSnR_3 + Ar'X \xrightarrow{\text{Pd(0)}} Ar\text{-}Ar'$$
$$X = I, Br, OTf$$

(30)

Suzuki couplings in which an arylboronic acid or ester couples with an aryl halide in the presence of Pd(0) and a base have become extensively used (Eq. 31). (264, 344-346) Pd(0) in the form of $Pd(PPh_3)_4$ is most commonly used as a catalyst but the more easily handled $PdCl_2(PPh_3)_2$ and $Pd(OAc)_2$ with triphenylphosphine are readily converted into Pd(0), allowing good yields to be obtained. (344) Phosphine-free Pd(0) is actually more reactive in the Suzuki coupling but is less stable to heat. In a related reaction, $Ni(PPh_3)_2Cl_2$ mediates the cross-coupling of chloronaphthalene with an intramolecularly stabilized arylaluminum reagent. (347) Triflates add to arylboronic acids with the relative reactivity being I > Br > OTf > > Cl. (344) In general, aryl chlorides are inert unless newly developed catalytic systems are employed. (348-355) Aryl triflates give better results when coupled with arylboronate esters. (336) Aryl mesylates and aryl arenesulfonates also participate in the Suzuki reaction using Ni(0) catalysts. (356) The sluggish nature of this reaction can be improved by treating the arylboronate ester with BuLi, forming a more reactive borate that couples with aryl mesylates to form biaryls. (357) The use of a base is required in Suzuki couplings; Na_2CO_3, $NaHCO_3$, Et_3N, and Cs_2CO_3 have proven useful. (344) A variety of fluoride salts have been successfully used as well. (358) For more sterically demanding coupling reactions, strong bases such as NaOH or Ba $(OH)_2$ markedly accelerate the reaction. (344) Strong bases, however, are incompatible with triflates. (345) In all cases, homogenous conditions result in shorter reaction times. (344)

$$Ar\text{-}B\overset{OH}{\underset{OH}{}} + Ar'X \xrightarrow[\text{base}]{\text{Pd(0)}} Ar\text{-}Ar'$$

(31)
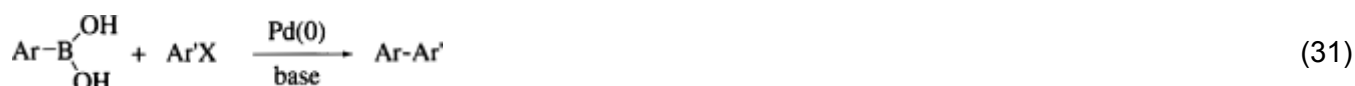
Although more widely used for cross-coupling reactions, the Suzuki reaction has also been applied to the preparation of symmetrical biaryls. Homocoupling was first observed as a competing reaction when cross-coupling was slow. (359) It was subsequently demonstrated that homocoupling can occur as a synthetically useful reaction. In situ formation of arylboronate esters allows for symmetrical biaryl formation in moderate to excellent yield. (360)

Widely used in polymer and natural product synthesis, the Suzuki reaction is applicable to the synthesis of axially chiral biaryls. (264, 344, 345) Planar chiral (haloarene)chromium complexes couple with arylboronic acids in the presence of Pd(0) and base to yield axially chiral biaryls. (321, 361) Chiral ligands also induce asymmetry in binaphthyl products of Suzuki couplings. (362)

Oxidative coupling of phenols dates back to before 1900 (Eq. 32). (363, 364) The variety of conditions available to effect coupling of phenols is so vast that no single mechanism can account for all of the reactions. However, radical processes appear to be at work. A number of metal salts are useful in mediating phenolic coupling including $Fe(ClO_4)_3$, (365) $FeCl_3$, (366) $AlCl_3$, (367) Cu(II), (368) Ru(IV), (369) molten $SbCl_3$, (370) Mn(III), (371) and Tl(III). (372) Catalytic quantities of the CuCl(OH)-TMEDA

complex in the presence of O_2 mediate the intramolecular coupling of naphthols. (373) Naphthols undergo dimerization when treated with Cu(II) on alumina. (374) VOF_3 (375) and $VOCl_3$ (376) are also used in coupling phenolic systems, and electrochemical methods have proven useful in the preparation of poly(2,6-dihydroxynaphthalene). (377) Other metals have also been employed to couple phenols. (8)

(32)

Chiral biaryls can also be prepared by oxidative coupling of naphthols using Cu(II)-chiral amine complexes. (378-380) Chiral biphenanthrols are also prepared using Cu(II)-chiral amine complexes. (381) High enantiomeric excess levels can be achieved using CuCl and chiral 1,5-diaza-cis-decalins. (382) Coupling of chiral tetrahydronaphthols using $K_3Fe(CN)_6$ also leads to chiral biaryls. (383) Electrolysis of 2-naphthol, 2-methoxynaphthalene, and 10-hydroxyphenanthrene on a TEMPO-modified graphite electrode in the presence of (–)-sparteine produces enantiomerically enriched dimers. (384)

Non-phenolic systems also undergo oxidative coupling. (8, 363) Pd(II) is useful in forming symmetrical biaryls by promoting the oxidative homocoupling of toluene or bitolylmercury in acetic acid, (385) monosubstituted benzenes in trifluoroacetic acid, (386) substituted benzenes in acetylacetone and O_2, (387) and substituted benzenes with thallium tris(trifluoroacetate). (388) Pd(II) is also used in a Heck-type reaction to couple iodothiophenes to form poly(thiophenes). (389) Arylmagnesium halides, treated with TlBr, dimerize to form symmetrical biaryls. (390) Arylthallium bis(trifluoroacetate) cross-couples with benzene under photolytic conditions. (274) Thiophenes undergo homocoupling when treated with $Tl(O_2CCF_3)_3$ in trifluoroacetic acid. (391) A mixture of $AlCl_3$ and $CuCl_2$ can be used to couple biphenyl with mesitylene. (392) Raney Nickel dimerizes pyridine but in low yields. (393) Aluminum chloride induces the cross-coupling of chlorothiophenes and substituted benzenes or naphthalenes. (394) NO^+ ions, generated by treatment of sodium nitrite with triflic acid, produce aromatic radical cations which couple to convert benzenes and naphthalenes into biaryls. (395) A number of other systems can also be employed to form biaryls. (8)

8. Experimental Procedures
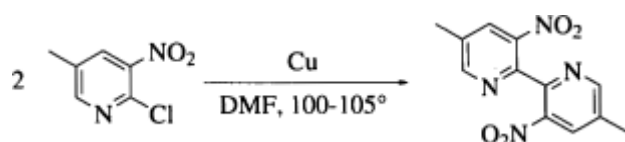
8.1.1.1. 5,5′-Dimethyl-3,3′-dinitro-2,2′-bipyridyl (Preparation Using Copper Powder) (396)
To a stirred mixture of 8.6 g (0.050 mol) of 2-chloro-5-methyl-3-nitropyridine in 50 mL of DMF was added 10 g (0.157 mol) of copper powder. The mixture was heated to 100–105° and maintained at this temperature for 4 hours. After cooling to room temperature, the mixture was filtered and the filter cake was washed with boiling DMF (2 × 20 mL). The collected filtrate was diluted with 200 mL of water and 50 mL of 25% aqueous ammonium hydroxide. The resulting precipitate was collected and washed with water to give 4.3 g (63%) of 5,5′-dimethyl-3,3′-dinitro-2,2′-bipyridyl as yellow crystals, mp 198–200°; ^{1}H NMR (CDCl$_3$) δ 9.0 (s, 4H), 2.8 (s, 6H); Anal. Calcd for $C_{12}H_{10}N_4O_4$: C, 52.55; H, 3.68; N, 20.43. Found: C, 52.68; H, 3.66; N, 20.53.
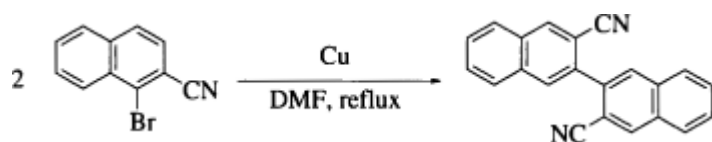
8.1.1.2. 1,1′-Dinaphthalene-2,2′-dicarbonitrile (Preparation Using Copper Bronze) (397)

To 2 g (0.008 mol) of I_2 in 100 mL of acetone was added 10 g (0.157 mol) of copper bronze. After the mixture was stirred for 10 minutes, the residue was filtered and then stirred for 2 minutes with 200 mL of a 1:1 mixture of acetone and concentrated HCl. After filtration by suction, a bright red copper powder was obtained, which was dried in vacuo. 1-Bromo-2-naphthalenecarbonitrile (7.7 g, 0.0332 mol) and 30 mL of DMF were added to the dried metal powder. The mixture was heated to reflux under an argon atmosphere for 36 hours. After cooling to room temperature, the mixture was poured into a beaker containing 300 mL of water and 300 mL of CH_2Cl_2. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic phase was washed with water (3 × 100 mL) and dried with Na_2SO_4. After filtration, the solvent was removed in vacuo and the residue was filtered through silica gel using 1:1 CH_2Cl_2/hexane as the eluent to yield 3.2 g (63%) of

1,1′-binaphthalene-2,2′-dicarbonitrile as white needles, mp 232°; ^{1}H NMR ($CDCl_3$) δ 8.10 (br d, J = 8.4 Hz, 2H), 8.00 (br d, J = 8.1 Hz, 2H), 7.82 (d, J = 8.7 Hz, 2H), 7.63 (ddd, J = 1.4, 7.0, 8.2 Hz, 2H), 7.41 (ddd, J = 1.4, 7.0, 8.4 Hz, 2H), 7.16 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) d 140.5, 134.8, 131.8, 130.4, 129.2, 128.7, 128.5, 126.7, 126.3, 117.5, 111.5; Anal. Calcd for $C_{22}H_{12}N_2$: C, 86.82; H, 3.97; N, 9.20. Found: C, 86.56; H, 3.93; N, 9.14.
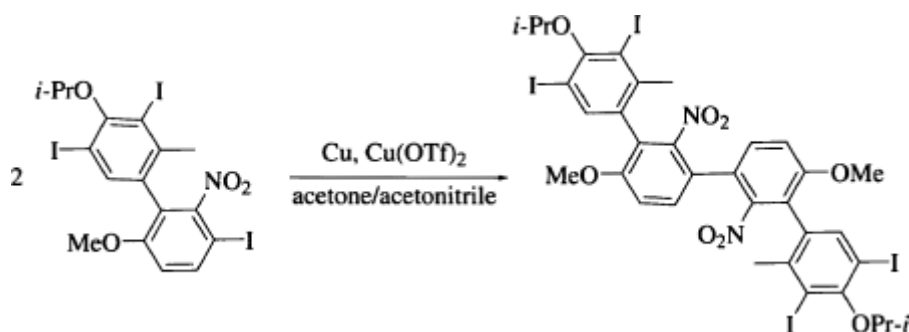
8.1.1.3. 3,3‴,5,5‴-Tetraiodo-4″,6′-dimethoxy-2,2‴-dimethyl-4,4‴-bis(1-methylethoxy)-2′,2″-dinitro-1,1′:3′,1‴ (Preparation Using Copper and Copper(II) Triflate) (70)

A mixture of 9.2 g (25.4 mmol) of hydrated copper (II) trifluoromethanesulfonate, 1.2 g (19 mmol) of Cu powder, 185 mL of acetone, and 11 mL of acetonitrile was heated at reflux under a nitrogen atmosphere for 2.5 hours. The mixture was cooled in an ice bath and a solution of 8.6 g (12.7 mmol) of 3,3′,5′-triiodo-4′-isopropoxy-6-methoxy-2′-methyl-2-nitrobiphenyl in 35 mL of DMSO was added dropwise, followed by 42 mL of ammonium hydroxide. The mixture was stirred at 0° for 8 hours, then at 5° for 12 hours. Water (250 mL) and $CHCl_3$ (250 mL) were added, and the layers were separated. The organic layer was washed with 5% HCl and water, dried over $MgSO_4$, passed through a pad of alumina, and evaporated. The residue was crystallized from MeOH to yield 6.3 g (90%) of a pale yellow solid, mp 282–283°; NMR ($CDCl_3$) δ 1.43 (d, J = 6 Hz, 12 H), 2.28 (br s, 6H), 3.82 (s, 6H), 4.86 (m, 2H), 7.06 (d, J = 9 Hz, 2H), 7.39 (d, J = 9 Hz, 2H); Anal. Calcd for $C_{34}H_{32}I_2N_2O_8$: C, 37.0; H, 2.9; N, 2.5. Found: C, 36.7; H, 3.0; N, 2.5.
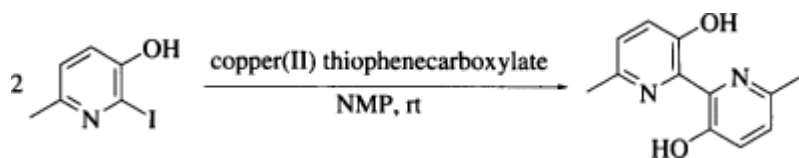
8.1.1.4. 3,3′-Dihydroxy-6,6′-dimethyl-2,2′-bipyridine (Preparation Using Copper(I) thiophenecarboxylate) (71)

8.1.1.4.1. Copper(I) Thiophenecarboxylate (71)

A 500-mL round-bottomed flask was charged with 100 g (0.78 mol) of thiophene-2-carboxylic acid, 28 g (0.196 mol) of CuO, and 300 mL of toluene. The flask was equipped with a Dean-Stark trap, condenser, and magnetic stirring bar, and the mixture was brought to reflux under N_2 and stirred overnight with azeotropic removal of water. The yellow-brown suspension was cooled to 60° and the product was

collected on a medium porosity sintered-glass filter funnel. Under a stream of N_2, the filter cake was washed with 300 mL of de-oxygenated MeOH and then with Et_2O until the eluant was colorless. The filter cake was washed with small amounts of hexanes. The product was dried on the filter under a flow of N_2 for 20 minutes, then transferred to a flask and dried in vacuo. The product was obtained as a tan, air-stable powder that was ground with a mortar and pestle to produce 69.8 g (94%) of a finely divided powder. Elemental analysis was consistent with about 5 mol % of unreacted CuO, which does not affect use. Anal. Calcd for $C_5H_3CuSO_2(CuO)_{0.05}$: C, 30.40; H, 1.50; S, 16.20. Found: C, 30.35; H, 1.55; S, 16.11.

To a stirred solution of 0.470 g (2.00 mmol) of 6-iodo-2-picolin-5-ol in 8 mL of N-methylpyrrolidinone at room temperature was added 1.14 g (6.00 mmol) of copper(I) thiophenecarboxylate under nitrogen. After 4 hours at room temperature, the reaction mixture was diluted with 15 mL of EtOAc and the resulting slurry was filtered through a plug of silica gel using 120 mL of EtOAc as the eluant. The solution was washed with 100 mL of dilute aqueous NH_4OH and the aqueous layer was back extracted with EtOAc (4 × 40 mL). The combined organic layers were washed with 50 mL of water and the resulting aqueous layer was back-extracted with 30 mL of EtOAc. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated at reduced pressure. The crude product was purified by flash chromatography to give 0.15 g (69%) of 3,3′-dihydroxy-6,6′-dimethyl-2,2′-bipyridyl as a green-yellow solid, mp 186.5–188°; ^{1}H NMR (CDCl$_3$) δ 7.29 (d, J = 8.4 Hz, 2H), 7.08 (d, J = 8.4 Hz, 2H), 6.03 (br s, 2H), 2.50 (s, 6H); ^{13}C NMR (CDCl$_3$) δ 153.9, 144.6, 138.5, 126.3, 124.5, 22.7; Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.95. Found: C, 66.74; H, 5.65; N, 12.98.
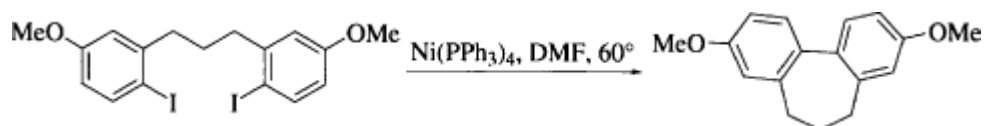
8.1.1.5. 6,7-Dihydro-3,9-dimethoxy-5H-dibenzo[a,c]cycloheptene (Intramolecular Coupling Using Ni(PPh$_3$)$_4$) (49)

To a suspension of 332 mg (0.3 mmol) of Ni(PPh$_3$)$_4$ in 14 mL of DMF at –78° under argon was added, in one portion, 127 mg (0.25 mmol) of α , ω -bis(iodomethoxyphenyl)propane. The reaction mixture was warmed to 60° for 40 hours, during which time the gold-brown starting mixture gradually became green and a black solid appeared. The mixture was cooled to 25°, poured into 50 mL of Et_2O, and washed sequentially with 20 mL of 1 M aqueous HCl and 40 mL of brine. After the ether layer was dried, concentration in vacuo afforded a yellow solid which was purified by preparative TLC (25% CH_2Cl_2 in hexane) to yield 188 mg (74%) of cyclic product, mp 99.5–101°; NMR (CDCl$_3$) δ 7.2 (dd, J = 7, 3 Hz, 2H), 6.9–6.6 (m, 4H), 3.78 (s, 6H), 2.65–1.9 (m, 6H); Anal. Calcd for $C_{17}H_{18}O_2$: C, 79.97; H, 6.71. Found: C, 79.94; H, 6.63.
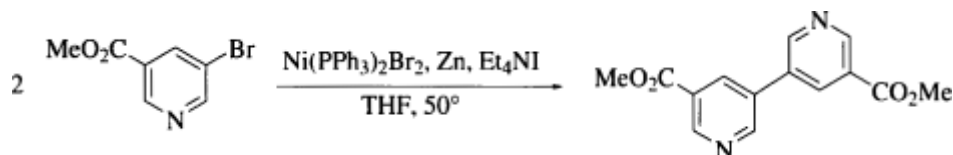
8.1.1.6. 5,5′-Bis(methoxycarbonyl)-3,3′-bipyridyl (Using Catalytic Ni(PPh$_3$)$_2$Br$_2$) (139)

To a dry flask containing a magnetic stirring bar, filled with argon, and stoppered with a rubber septum was added 1.12 g (1.5 mmol) of Ni(PPh$_3$)$_2$Br$_2$, 0.49 g (7.5 mmol) of Zn, and 1.29 g (1.5 mmol) of Et$_4$NI. After the system was purged of air and refilled with argon, 15 mL of THF was added via syringe. After about 30 minutes, a solution of 1.08 g (5 mmol) of methyl 5-bromonicotinate was added, and the mixture was stirred at 50° for 2 hours. The mixture was cooled to room temperature and poured into 30 mL of 2 M aqueous NH_4OH . Chloroform (100 mL) was added and the precipitates were removed by filtration. The layers were separated and the aqueous layer was extracted twice with 50 mL of CHCl$_3$. The combined organic layers were washed with water and brine, dried with $MgSO_4$, and concentrated in vacuo. The residual solid was triturated with CH_2Cl_2 to yield 459 mg (67%) of

5,5′-bis(methoxycarbonyl)-3,3′-bipyridyl, mp 226–226.5°; ^{1}H NMR (CDCl$_3$) δ 9.29 (br s, 2H), 9.05 (br s, 2H), 8.55 (m, 2H), 4.02 (s, 6H); ^{13}C NMR (CDCl$_3$) δ 165.3, 151.6, 150.7, 135.5, 132.5, 126.4, 52.7; Anal. Calcd for C$_{14}$H$_{12}$N$_2$O$_4$: C, 61.54; H, 4.39; N, 10.18. Found: C, 61.76; H, 4.44; N, 10.29.
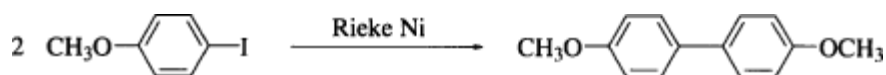
8.1.1.7. 4,4′-Dimethoxybiphenyl (Preparation Using Rieke Ni) (111)
8.1.1.7.1. Rieke Nickel Powder (111)
A 50-mL, two-necked flask was equipped with a magnetic stirring bar, a rubber septum, and a condenser topped with an argon inlet. The flask was charged with 3.82 g (12.22 mmol) of NiI$_2$, 0.195 g (28.1 mmol) of freshly cut lithium wire, 0.16 g (1.25 mmol) of naphthalene, and 30 mL of glyme. The mixture was stirred vigorously at room temperature for 12 hours. The nickel powder precipitated as a black slurry in a colorless, clear solution after the stirring stopped. After the supernatant glyme was removed by syringe, 20 mL of freshly distilled glyme was added and the mixture was stirred for 5 minutes. This procedure was repeated two times to remove the naphthalene. Glyme may be replaced with other solvents such as DMF or DMSO after evaporation of glyme under reduced pressure.

To 12.22 mmol of the activated Ni prepared above in glyme was added 1.88 g (8.02 mmol) of 4-iodomethoxybenzene, and the mixture was stirred at 85° for 2 hours. The reaction mixture changed to a reddish brown color and most of the Ni powder was consumed. The reaction mixture was cooled, poured into 100 mL of Et$_2$O, and filtered. The filtrate was washed with 100 mL of water and dried over MgSO$_4$. The solution was concentrated to 10 mL and 10 mL of EtOH was added to precipitate the product. Crystallization from Et$_2$O/EtOH (1:1) gave 0.58 g (68%) of 4,4′-dimethoxybiphenyl as colorless flakes, mp 176–177°; NMR (CDCl$_3$) δ 7.50 (d, J = 9 Hz, 4H), 6.95 (d, J = 9 Hz, 4H), 3.83 (s, 6H).
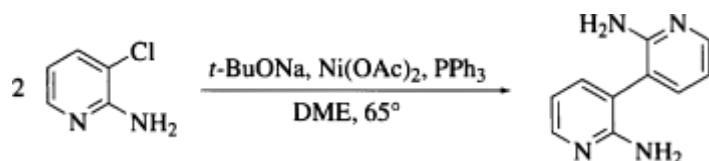
8.1.1.8. 2,2′-Diamino-3,3′-Bipyridyl (Preparation Using Nickel Complex Reducing Agents (NiCRA)) (398)
To a refluxing suspension of 1.44 g (60 mmol) of NaH, 1.77 g (10 mmol) of nickel(II) acetate and 10.48 g (40 mmol) of triphenylphosphine in 30 mL of DME was added 1.48 g (20 mmol) of t-BuOH in 10 mL of DME. After stirring at 65° for 2 hours, 1.29 g (10 mmol) of 2-amino-3-chloropyridine in 20 mL of DME was added and the temperature was maintained at 65° for 17 hours, at which time GC analysis showed the reaction to be complete. The flask was cooled to 25° and excess hydride was carefully destroyed by addition of EtOH until H$_2$ evolution ceased. Water was added, and the organic phase was extracted with Et$_2$O, and the extracts were dried over MgSO$_4$. After removal of solvents under reduced pressure and column chromatography using EtOAc/hexane eluents, 0.744 g (40%) of 2,2′-diamino-3,3′-bipyridyl was isolated, mp 132°; ^{1}H NMR (CDCl$_3$) δ 8.7 (t, 1H), 6.9 (d, 2H), 3.6 (s, 2H); ^{13}C NMR (CDCl$_3$) δ 142.6, 139.6, 137.2, 123.6, 121.3.
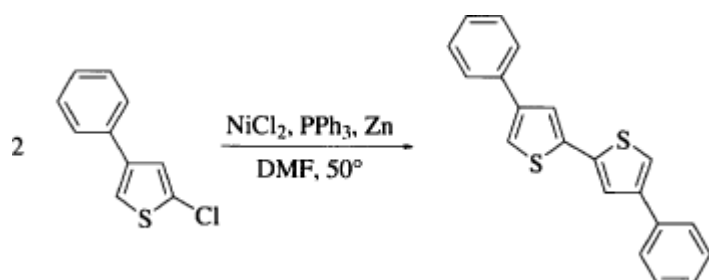
8.1.1.9. 4,4′-Diphenyl-2,2′-bithienyl (Preparation Using NiCl₂) (399)

To a solution of 0.65 g (5 mmol) of NiCl₂ and 5.2 g (20 mmol) of PPh₃ in 25 mL of DMF was added 0.32 g (5 mmol) of Zn powder under N₂. The mixture was stirred for 1 hour at 50° and 0.973 g (5 mmol) of 4-phenyl-2-chlorothiophene was added to the resultant red brown solution. After stirring for 30 minutes, the mixture was poured into 50 mL of H₂O . The resulting precipitate was collected by filtration and washed with H₂O . The dried precipitate was washed with CHCl₃ (2 × 20 mL) then crystallized from CHCl₃ to yield 1.0 g (63%) of 4,4′-diphenyl-2,2′-bithienyl, mp 224–225°; NMR (CDCl₃) δ 7.2–7.7 (m).
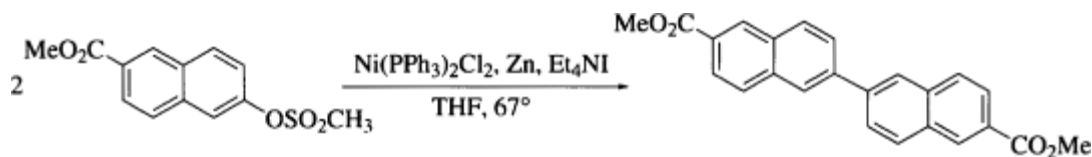
8.1.1.10. 6,6′-Dicarbomethoxy-2,2′-binaphthyl from 6-Carbomethoxy-2-naphthyl Mesylate (Preparation Using Ni(PPh₃)₂Cl₂) (133)

A 125-mL Schlenk tube was charged with 65.2 mg (0.10 mmol) of Ni(PPh₃)₂Cl₂, 111 mg (1.7 mmol) of zinc powder, 385.5 mg (1.5 mmol) of tetraethylammonium iodide, and a magnetic stirring bar. After the tube was sealed with a rubber septum, the contents were dried at 22° at reduced pressure (10^{-3} torr) for 10 hours. The contents of the tube were then placed under an argon atmosphere by filling with Ar followed by three evacuation-filling cycles. Freshly distilled THF (0.50 mL) was added via syringe and the mixture was stirred at room temperature for 5 minutes during which time the color of the mixture became deep red-brown. A solution of 6-carbomethoxy-2-naphthyl mesylate (280 mg, 1.0 mmol) in 0.50 mL of THF was added via syringe. The reaction mixture was heated to reflux and stirred for 10 hours. The mixture was then cooled, filtered, diluted with water, and extracted with CHCl₃. The organic phase was dried with MgSO₄ and concentrated in vacuo. Purification using column chromatography and crystallization from CHCl₃/hexanes yielded 337 mg (91%) of 6,6′-dicarbomethoxy-2,2′-binaphthyl as white crystals, mp 275°; NMR (CDCl₃) δ 8.65 (s, 2H), 8.17–8.09 (m, 4H), 4.03 (s, 6H); Anal. Calcd for C₂₄H₁₈O₄: C, 77.82; H, 4.90. Found: C, 77.16; H, 4.81.
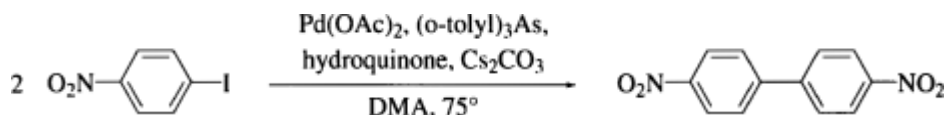
8.1.1.11. 4,4′-Dinitrobiphenyl (Preparation using Pd(OAc)₂) (178)

To a mixture of 299 mg (1.201 mmol) of 4-iodonitrobenzene, 69.8 mg (0.634 mmol) of hydroquinone, and 409.4 mg (1.257 mmol) of Cs₂CO₃ was added a pre-stirred solution of 5.7 mg (0.021 mmol) of Pd(OAc)₂ and 9.0 mg (0.026 mmol) of tri-o-tolylarsine in 3.0 mL of DMA. The mixture was immediately degassed and the flask was refilled with N₂. The reaction mixture was stirred for 1 hour at 75°, then cooled to room temperature. The reaction was quenched with 20 mL of 2 N HCl and the mixture was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with 10% aqueous NaOH solution (4 × 40 mL) and brine (40 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. Column chromatography on silica gel (eluant: 14% Et₂O in hexane) afforded 125.6 mg (86%) of 4,4′-dinitrobiphenyl as a tan crystalline solid, mp 235°; ¹H NMR (DMSO-d₆) δ 8.37 (d, J = 8.8 Hz, 4H), 8.08 (d, J = 8.8 Hz, 4H); ¹³C NMR (DMSO-d₆) δ 147.6, 144.1, 128.7, 124.3.
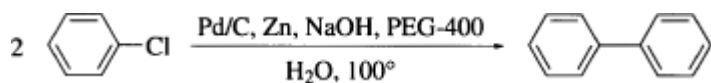
8.1.1.12. Biphenyl (Preparation using Pd/C) (180)

In a 300-mL stainless steel autoclave equipped with a six-blade impeller and an external heating mantle, 5.0 g (44 mmol) of chlorobenzene, 3.3 g (50 mmol) of Zn powder, 5.0 g (125 mmol) of NaOH, 1.5 g

(8.4 mol%) of PEG-400, and 1.0 g of 5% w / w Pd/C (1.0 mol% Pd) were combined and diluted to a total volume of 50 mL with H_2O . The autoclave was heated to 100° and the mixture was stirred at 950 rpm for 2 hours. After cooling, the mixture was extracted with 40 mL of CH_2Cl_2, the organic layer was dried, and the solvent was evaporated. Crystallization from EtOH afforded 2.35 g (68%) of biphenyl, mp 69°; NMR ($CDCl_3$) δ 7.59 (dq, 4H), 7.46 (dt, 4H), 7.39 (tt, 2H); Anal. Calcd for $C_{12}H_{10}$: C, 93.46; H, 6.54. Found: C, 93.26; H, 6.74.

9. Tabular Survey

The tables have been prepared by categorizing biaryls by the nature of the aromatic rings being coupled. Tables 1 through 20 include biphenyls with different substitution patterns while Tables 21 through 33 include examples of biaryls of other non-heterocyclic arenes. Tables 34 through 60 include examples of biheteroarenes. Polymers have been gathered into separate tables. Within each table, entries are listed by increasing number of carbon atoms.

Yields in parentheses are based on isolated products, unless noted otherwise. Examples with unspecified yields have been excluded. For additional pertinent data on polyarenes (beyond chemical yields) for entries in Tables 61-64 (polyarenes), readers are directed to the original publications. The literature has been reviewed through 2000.

The following abbreviations are used in the tables:

acac	acetylacetonate
AcOH	acetic acid
t-AmOH	*tert*-amyl alcohol
BNAH	*N*-benzyl-1,4-dihydronicotinamide
bpy	2,2′-bipyridine
Bs	benzenesulfonyl
cod	1,5-cyclooctadiene
CRA	complex reducing agent
CTA	cetyltrimethylammonium
CTAB	cetyltrimethylammonium bromide
CTBPB	cetyltributylphosphonium bromide
dba	dibenzylideneacetone
DIPEA	diisopropylethylamine
diphos	1,2-bis(diphenylphosphino)ethane
DMAc	*N,N*-dimethylacetamide
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
dmpb	1,4-bis(dimethylphosphino)butane
DMS	dimethylsulfide
DMSO	dimethyl sulfoxide
dpa	2,2′-dipyridylamine
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,3-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
EDTA	ethylenediamine tetraacetic acid
ETOXCA	ethylene oxide/cetyl alcohol condensate
Fs	*p*-fluorobenzenesulfonyl
HMPA	hexamethylphosphoramide
HMPT	hexamethylphosphorous triamide
IPA	isopropyl alcohol
NMP	*N*-methylpyrrolidinone

Ms	methanesulfonyl
PEG	polyethyleneglycol
SDPNS	sodium diisopropylnaphthalene
Tf	trifluoromethanesulfonyl
Ts	*p*-toluenesulfonyl
TBAF	tetrabutylammonium fluoride
TEBAC	triethylbenzylammonium chloride
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethylenediamine
TMS	trimethylsilyl

10. Acknowledgments

End Notes

This chapter is dedicated to Professor Albert I. Meyers on the occasion of his retirement.

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TABLE 1. UNSUBSTITUTED BIPHENYL
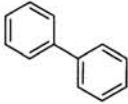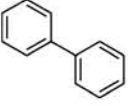
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_6$ Cl			
	Ni(cod)$_2$, DMF, 50°	(14)[a]	49,50
	Ni(CO)$_2$(PPh$_3$)$_2$, DMSO, 70°	(35)[a]	145
	Ni(OAc)$_2$, NaH, t-AmONa, bpy, THF, 63°	(86), (90)[a]	131
	Ni(OAc)$_2$, NaH, t-AmONa, PPh$_3$, THF, 63°	(90)	131
	NiBr$_2$, Zn, KI, HMPA, 50°	(0)	129
	NiCl$_2$, Zn, NaBr, DMF, bpy, 60-80°	(81)	146
	NiBr$_2$, NMP, 2e$^-$, bpy	(90)	128
	Ni(OAc)$_2$, t-BuOLi, LiH, bpy, THF, 63°	(89), (94)[a]	110
	Ni(OAc)$_2$, t-AmONa, NaH, bpy, THF, KI, 63°	(92)	54
	Ni powder, DMF, 130°	(0)	120
	Ni powder, DMF, KI, 130°	(90)[a]	120
	Ni(OAc)$_2$, t-BuONa, LiH, bpy, THF, reflux	(93)[a]	400
	NiCl$_2$(PEt$_3$)$_2$, Zn, HMPA, 80°	(25)[a]	401
	NiCl$_2$(PBu$_3$)$_2$, Zn, HMPA, 80°	(18)[a]	401
	, DMSO, 2e$^-$, 65° R = Pr-i	(80)[a]	154
	NiBr$_2$, Zn, PPh$_3$, DMAc, 80°	(99)[a]	51
	NiI$_2$•6H$_2$O, Zn, PPh$_3$, DMAc, 80°	(58)[a]	51
	Ni(OAc)$_2$•4H$_2$O, Zn, PPh$_3$, DMAc, 80°	(66)[a]	51
	Ni(acac)$_2$•2H$_2$O, Zn, PPh$_3$, DMAc, 80°	(82)[a]	51
	Ni(NO$_3$)$_2$•6H$_2$O, Zn, PPh$_3$, DMAc, 80°	(0)[a]	51
	NiO, Zn, PPh$_3$, DMAc, 80°	(66)[a]	51
	NiF$_2$, Zn, PPh$_3$, DMAc, 80°	(82)[a]	51
	NiCl$_2$, Zn, PPh$_3$, DMAc, 80°	(99)[a]	51,52,148
	NiCl$_2$, Mg, PPh$_3$, DMAc, 80°	(99)[a]	51,52,148
	NiCl$_2$, Mn, PPh$_3$, DMAc, 80°	(99)[a]	52,148
	NiCl$_2$, Zn, P(C$_6$H$_4$OMe-p)$_3$, DMAc, 80°	(89)[a]	52,148
	NiCl$_2$, NaI, PPh$_3$, Zn, bpy, DMAc, 80°	(78)[a]	51,52,148
	NiCl$_2$, NaI, PPh$_3$, Zn, DMAc, 80°	(99)[a]	51,52,148
	NiBr$_2$, NaI, PPh$_3$, Zn, DMAc, 80°	(91)[a]	51,52,148
	NiI$_2$, NaI, PPh$_3$, Zn, DMAc, 80°	(100)[a]	51,52,148
	Ni(acac)$_2$, NaI, PPh$_3$, Zn, DMAc, 80°	(94)[a]	51,52,148
	Ni(OAc)$_2$, NaI, PPh$_3$, Zn, DMAc, 80°	(99)[a]	51,52,148
	Pd/C, Zn, PEG-400, H$_2$O, NaOH, heat	(68)	180
	Pd/C, H$_2$, PEG-400, H$_2$O, NaOH, 110°	(71), (76)[a]	186
	Pd/C, HCO$_2$Na, NaOH, CTAB, H$_2$O, 110°	(83), (87)[a]	181
	Pd/C, HCO$_2$K, NaOH, CTAB, H$_2$O, 110°	(83), (88)[a]	181
	PdCl$_2$, N$_2$H$_4$•H$_2$O, MeOH, reflux	(trace)	47
	Pd(OAc)$_2$, K$_2$CO$_3$, n-Bu$_4$NBr, DMF, 100°	(0)	173
	Pd/C, NaOH, H$_2$O, formic hydrazide, 90°	(54)[a]	55
	Pd/C, HCO$_2$Na, NaOH, H$_2$O, 95°, CTAB	(48)	179
	PdCl$_2$, phenylhydrazine, NaOH, MeOH, reflux	(12)	165
	PdCl$_2$, HgCl$_2$, phenylhydrazine, NaOH, MeOH, reflux	(12)	165
Br			
	Ni(cod)$_2$, DMF, 55°	(82)[a,b]	49,50
	Ni(cod)$_2$, PPh$_3$, bpy, THF	(81)	402
	Ni(cod)$_2$, PPh$_3$, bpy, C$_6$H$_6$	(83)	402
	Ni(OAc)$_2$, NaH, t-AmONa, PPh$_3$, THF, 63°	(70)	131
	Ni(OAc)$_2$, NaH, t-AmONa, bpy, THF, 63°	(70), (76-84)[a]	131
	NiCl$_2$(PEt$_3$)$_2$, Zn, HMPA, 30°	(95)[a]	40

TABLE1. UNSUBSTITUTED BIPHENYL *(Continued)*
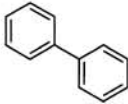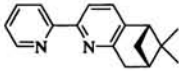
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	NiCl$_2$(PBu$_3$)$_2$, Zn, NMP, 30°	(81)	401
	NiCl$_2$(P(c-C$_6$H$_{11}$)$_3$)$_2$, Zn, NMP, 80°	(75)[a]	401
	NiBr$_2$, Zn, KI, DMF, HMPA	(98)[a]	403
	NiBr$_2$, Zn, KI, PBu$_3$, DMF, 150°	(88)[a]	129
	NiBr$_2$, Zn, KI, PBu$_3$, NMP, 150°	(89)[a]	129
	NiBr$_2$, Zn, KI, HMPA, 50°	(98)	129
	NiCl$_2$, Zn, NaBr, DMF, bpy, 60-80°	(78)	146
	NiBrPh(PBu$_3$)$_2$, PPh$_3$, CH$_3$CN, 2e$^-$	(82)	159
	NiBr$_2$, NMP, bpy, 2e$^-$	(75)	128
	Ni powder, DMF, 140°	(71)	120
	Ni powder, DMSO, 140°	(99)[a]	120
	Ni powder, pyridine, 140°	(71)[a]	120
	Ni powder, mesitylene, 140°	(24)[a]	120
	Ni powder, ethylene glycol, 140°	(0)	120
	Ni powder, neat, 140°	(23)[a]	120
	Ni(OAc)$_2$, t-BuOH, LiH, PPh$_3$, THF, reflux	(95)[a]	400
	Ni(OAc)$_2$, t-BuOH, LiH, bpy, THF, reflux	(98)[a]	400
	NiBr$_2$(PPh$_3$)$_2$, Zn, 50°, THF	(75)	139
	NiCl$_2$(PPh$_3$)$_2$, Zn, Et$_4$NI, 50°, THF	(92)	139,404
	NiI$_2$(PPh$_3$)$_2$, Zn, Et$_4$NI, 50°, THF	(94-99)	139,404
	NiI$_2$(PPh$_3$)$_2$, Zn, Et$_4$NI, 50°, THF	(94)	139,404
	NiBr$_2$(PPh$_3$)$_2$, Zn, Et$_4$NI, 50°, DMF	(84)	139,404
	NiBr$_2$(PPh$_3$)$_2$, Zn, Et$_4$NI, 50°, CH$_3$CN	(88)	139,404
	NiBr$_2$(PPh$_3$)$_2$, Zn, Et$_4$NI, 50°, acetone	(80)	139,404
	Ni(OAc)$_2$, t-BuOLi, LiH, bpy, THF, 63°	(91), (100)[a]	110
	NiCl$_2$(PPh$_3$)$_2$, PPh$_3$, DMF, n-Bu$_4$NBr, 2e$^-$	(80)	127
	Ni(OAc)$_2$, NaH, t-AmONa, bpy, THF, KI, 63°	(82)	54
	NiCl$_2$(PPh$_3$)$_2$, Zn, PPh$_3$, DMF, 50°	(73)	122
	NiCl$_2$(PPh$_3$)$_2$, Zn, PPh$_3$, DMF, 50°	(89)	123
	Ni(OAc)$_2$, bpy, Et$_4$NBr, CH$_3$CN, 2e$^-$	(92)	405
	Ni(CO)$_2$, (PPh$_3$)$_2$, DMSO, 70°	(75)[a]	145
	Ni(CO)$_2$, (PPh$_3$)$_2$, toluene, 70°	(65)[a]	145
	Ni(CO)$_2$, (PPh$_3$)$_2$, hexane, 70°	(25)[a]	145
	NiBr$_2$, EtOH, dpa, H$_2$O, 2e$^-$	(95)	153
	NiBr$_2$, EtOH, MeOH, bpy, 2e$^-$	(84)	153
	NiBr$_2$, bpy, EtOH, DMF, Bu$_4$NBF$_4$, 2e$^-$	(80)	53
	NiBr$_2$, bpy, EtOH, MeOH, NaBr, 2e$^-$	(84)	53
	NiBr$_2$, bpy, NMP, Bu$_4$NBF$_4$, 2e$^-$, 45°	(75)	53
	NiBr$_2$, bpy, DMF, Bu$_4$NBF$_4$, 2e$^-$, 45°	(85)	53
	NiBr$_2$, bpy, MeOH, Bu$_4$NBF$_4$, 2e$^-$	(75)	53
	NiBr$_2$, bpy, MeOH, EtOH, Bu$_4$NBF$_4$, 2e–	(80-84)	53
	NiBr$_2$, bpy, MeOH, EtOH, H$_2$O, Bu$_4$NBF$_4$, 2e$^-$	(40)	53
	NiBr$_2$, bpy, EtOH, H$_2$O, Bu$_4$NBF$_4$, 2e$^-$	(36)	53
	NiCl$_2$, CrCl$_2$, Mn, THF, RT	(88)	406
	Co powder, DMF, heat	(71)	120
	PdCl$_2$, N$_2$H$_4$•H$_2$O, MeOH, reflux	(30)	47
	PdCl$_2$, HgCl$_2$, N$_2$H$_4$•H$_2$O, MeOH, reflux	(4)	47
	Pd(OAc)$_2$, N$_2$H$_4$•H$_2$O, K$_2$CO$_3$, n-Bu$_4$NBr, DMF, 100°	(25)	173
	Pd/CaCO$_3$, MeOH, KOH, heat	(77)	48
	Pd/C, HCO$_2$Na, NaOH, H$_2$O, 95°	(30)	179
	Pd/C, HCO$_2$Na, NaOH, H$_2$O, 95°, CTAB	(65)	179
	Pd/C, HCO$_2$Na, NaOH, H$_2$O, 95°, CTBPB	(60)	179

TABLE 1. UNSUBSTITUTED BIPHENYL (Continued)
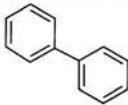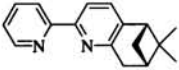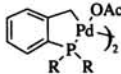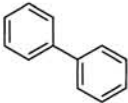
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

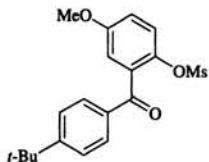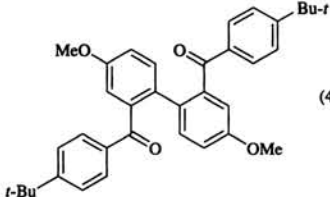| | Pd/C, HCO$_2$Na, NaOH, H$_2$O, 95°, SDPNS | (65) | 179 |
	Pd/C, HCO$_2$Na, NaOH, H$_2$O, 95°, ETOXCA	(51)	179
	Pd/C, Zn, air, H$_2$O, acetone, 25°	(92)[a]	185
	Pd/C, H$_2$, PEG-400, H$_2$O, NaOH, 110°	(73), (79)[a]	186
	Pd(OAc)$_2$, As(o-tol)$_3$, hydroquinone, Cs$_2$CO$_3$, 100°	(56)	178
	Pd(OAc)$_2$, AsPh$_3$, Bu$_3$N, DMF, 140°	(68-78)	171,172
	PdCl$_2$, HgCl$_2$, p-tolylhydrazine hydrochloride, NaOH, MeOH, reflux	(41)	165
	PdCl$_2$, HgCl$_2$, phenylhydrazine, NaOH, MeOH, reflux	(97)	165
	PdCl$_2$, phenylhydrazine, NaOH, MeOH, reflux	(62)	165

	"		
	Cu, DMF, reflux	(80)	407
	Cu, neat, 190°	(30-78)	32
	Cu, neat, 230°	(82)	2
	Cu, neat, 60°	(0)	35
	Cu, neat, heat	(78-80)	46,63
	Cu, neat, 60°	(0)	35
	Cu, diluents, heat	(0-75)	46
	CuI-PEt$_3$, lithium naphthalide, DME, 85°	(66)[a]	25,26
	Ni(OAc)$_2$, NaH, t-AmONa, bpy, THF, 63°	(37), (40-50)[a]	131
	Ni(cod)$_2$, DMF, 40°	(71)[a]	49,50
	Ni (electrogenerated), DMF, 100°	(58)	121
	NiBr$_2$, Zn, HMPA, 50°	(0)[a]	129
	NiBr$_2$, Zn, KI, HMPA, 50°	(94), (98)[a]	129,403
	NiCl$_2$(PEt$_3$)$_2$, Zn, HMPA, 25°	(93)[a]	401
	NiCl$_2$(PEt$_3$)$_2$, Zn, NMP, 25°	(88)[a]	401
	NiBr$_2$, NMP, 2e$^-$, bpy	(70)	128
	NiBr$_2$, EtOH, MeOH, NaBr, 2e$^-$, bpy	(85)	53
	NiBr$_2$, EtOH, dpa, H$_2$O, 2e$^-$	(85)	153
	NiBr$_2$, EtOH, MeOH, bpy, 2e$^-$	(85)	153
	Ni powder, DMF, 120°	(73)	120
	NiI$_2$, lithium naphthalide, DME, 80°	(83)[a]	111
	NiCl$_2$, CrCl$_2$, Mn, THF, rt	(98)	406
	Pd(OAc)$_2$, Et$_3$N, 100°	(54)	169
	Pd(OAc)$_2$, Bu$_3$N, 100°	(38)	169
	Pd(OAc)$_2$, Bu$_3$N, DMF, 140°	(54)	172
	Pd(OAc)$_2$, K$_2$CO$_3$, n-Bu$_4$NBr, DMF, 100°	(75)	173
	Pd(OAc)$_2$, PPh$_3$, K$_2$CO$_3$, 115°	(48)	408
	Pd(OAc)$_2$, DIPEA, DMF, 80°	(96)	176
	[PdCl(π-C$_3$H$_5$)]$_2$, TBAF, DMSO, 120°	(82)	198
	Pd(PPh$_3$)$_4$, Et$_4$NOTs, DMF, 2e$^-$	(94)	190
	PdCl$_2$, N$_2$H$_4$·H$_2$O, MeOH, reflux	(49)	47
	PdCl$_2$, HgCl$_2$, N$_2$H$_4$·H$_2$O, MeOH, reflux	(90)	47
	Pd(OAc)$_2$, As(o-tol)$_3$, hydroquinone, Cs$_2$CO$_3$, 25°	(39)	178
	Pd(OAc)$_2$, As(o-tol)$_3$, hydroquinone, Cs$_2$CO$_3$, 75°	(96)	178
	Pd(OAc)$_2$, P(o-tol)$_3$, hydroquinone, Cs$_2$CO$_3$, 75°	(37)[b]	178
	Pd/C, Zn, air, H$_2$O, acetone, 25°	(94)[a]	185
	PdCl$_2$, p-tolylhydrazine hydrochloride, NaOH, MeOH, reflux	(55)	165
	PdCl$_2$, phenylhydrazine, NaOH, MeOH, reflux	(63)	165
	PdCl$_2$, HgCl$_2$, phenylhydrazine, NaOH, MeOH, reflux	(quantitative)	165
	EtN(i-Pr)$_2$, DMF, 110° R = o-tolyl	(85)	194

TABLE 1. UNSUBSTITUTED BIPHENYL *(Continued)*

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

X			
OTf	PdCl$_2$(PPh$_3$)$_2$, DMF, n-Bu$_4$NBF$_4$, 2e⁻, 90°	(76)	192
OTf	PdCl$_2$(PPh$_3$)$_2$, DMF, Zn, 90°	(30)[b]	192,193
OTf	NiCl$_2$(dppe), KI, DMF, THF, Zn, 67°	(99)	192,193
OTf	Ni(cod)$_2$, hv, toluene, KI, N-methylimidazole	(90)	132
OMs	NiCl$_2$(PPh$_3$)$_2$, Zn, Et$_4$NI, THF, 67°	(91)[a]	133
OBs	NiCl$_2$(PPh$_3$)$_2$, PPh$_3$, NaBr, Zn, DMF, 100°	(80)	137
OFs	NiCl$_2$(PPh$_3$)$_2$, Zn, Et$_4$NI, THF, 67°	(99)[a]	133
SO$_2$Cl	PdCl$_2$(PhCN)$_2$, Ti(OPr-i)$_4$, m-xylene, 140°	(51)	168
SiMe$_2$Cl	CuI, TBAF, CH$_3$CN	(73)	72
SiMe$_2$F	CuI, TBAF, CH$_3$CN	(76)	72

[a] The yield was determined by gas chromatography.

[b] The yield was determined by NMR spectroscopy.

TABLE 2 . 2,2'-DISUBSTITUTED BIARYLS
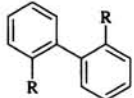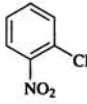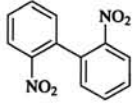
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C₆

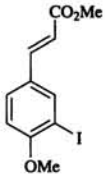| R	X			
F	Cl	Ni(OAc)$_2$, NaH, t-AmONa, bpy, THF, C$_6$H$_6$, KI, 63°	(60)	54
F	Br	NiBr$_2$, bpy, EtOH, MeOH, 2e$^-$	(trace)	153
F	Br	NiBr$_2$, EtOH, 2e$^-$, dpa, H$_2$O	(68)	153
F	Br	Ni(OAc)$_2$, NaH, t-AmONa, bpy, THF, C$_6$H$_6$, KI, 63°	(57)	54
F	Br	Pd(OAc)$_2$, Bu$_3$N, AsPh$_3$, DMF, 140°	(44)	172
F	I	Cu, neat, heat	(65)	409
Cl	I	Cu, neat, 230°	(53)	410
Cl	I	Cu, neat, 190°	(35)	32
Cl	I	Cu, neat, 190-260°	(39)	60
Cl	OTf	PdCl$_2$(PPh$_3$)$_2$, DMF, 2e$^-$, n-Bu$_4$NBF$_4$, 90°	(34)	191,192
Cl	OTf	NiBr$_2$(PPh$_3$)$_2$, THF, Zn, Et$_4$NI, 50°	(56)	139
Cl	OTf	NiCl$_2$, Zn, KI, HMPA, 20-50°	(25-84) [a]	129,403
Br	I	Cu, neat, 220°	(7)	411

	Cu, neat, heat	(32) after reduction to diamine	412
	Cu, neat, 215-225°	(61-66)	291,413

TABLE 2. 2,2'-DISUBSTITUTED BIARYLS *(Continued)*
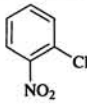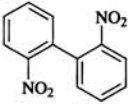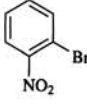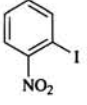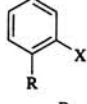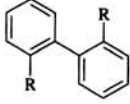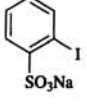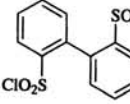
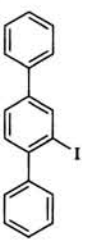| Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Cu, neat, 240-250°	(71)	414
	Cu, sand, 215-225°	(52-61)	15,415
	Cu, sand, 260-265°	(52-61)	416
	Cu, sand, 200-240°	(43)	417
	Cu, neat, 200-220°	(40)	418
	Cu, sand, 200-245°	(60)	1
	Cu, sand, 240-245°	(41)	419
	Cu, nitrobenzene, reflux	(0)	418
	Cu, nitrobenzene, 210°	(77)	58
	Cu, DMF, reflux	(80)	57
	Cu, neat, 210-220°	(76)	1
	Cu, neat, 190°	(75)	32
	Cu, neat, 200-220°	(64)	418
	Cu, nitrobenzene, reflux	(45)	418
	Cu, methyl benzoate, 190°	(71)	46
	Cu, 1,2,4-trichlorobenzene, 190°	(71)	46
	$Ni(cod)_2$, DMF, 36°	(0)	49,50
	Cu(I) thiophene-2-carboxylate, NMP, 70°	(86)	71
	CuCl•DMS, dioxane, lithium naphthalide, 101°	(87)[a]	25
	$Cu(OTf)_2$, Cu, CH_3CN, acetone, aq. NH_3	(79),(90)[a]	68,83
	Cu, neat, heat	(23) after reduction to diamine	413
	Cu, neat, 200-220°	(65)	418
	Cu, neat, 190-240°	(96)	19
	Cu, neat, 60°	(99)	35
	Cu, nitrobenzene, reflux	(43)	418
	Cu, xylene, 120-140°	(93-97)	238
	CuCl•DMS, dioxane, lithium naphthalide, 101°	(87)	25,26
	$CuI-PEt_3$, lithium naphthalide, DME, 85°	(87)[a]	26
	Cu(I) thiophene-2-carboxylate, NMP, 23°	(92)	71
	Cu_2O, pyridine, 115°	(81)	66
	Cu(OTf), CH_3CN	(0)	67
	Cu(OTf), CH_3CN, sulfolane	(0)	67
	Cu(OTf), CH_3CN, IPA	(0)	67
	Cu(OTf), CH_3CN, acetone	(0)	67
	Cu(OTf), CH_3CN, acetone, aq. NH_3	(92)[a]	67
	Cu, acetone, CH_3CN, aq. NH_3	(82)	420
	Cu, $CuSO_4$, acetone, CH_3CN, aq. NH_3	(83)	420
	NiI_2, DME, lithium naphthalide, 80°	(<1)[a]	111

R	X				
OH	Br	$Ni(OAc)_2$, NaH, t-AmONa, bpy, THF, C_6H_6, KI, 63°	(63)		54
$PO(OH)_2$	Br	1. $Pd/CaCO_3$, NaOH, MeOH, reflux	(0)		420
		2. HCl			
NH_2	I	$Pd/CaCO_3$, N_2H_4•H_2O, KOH, MeOH, 135-140°	(20)		48

	1. Cu, $CuSO_4$, H_2O, reflux	(12)	421
	2. PCl_5		
	1. Cu, $CuSO_4$, H_2O, reflux	(75)	422
	2. PCl_5		

TABLE 2. 2,2'-DISUBSTITUTED BIPHENYL *(Continued)*

	Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C$_7$
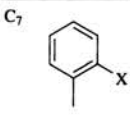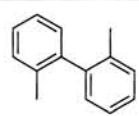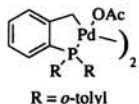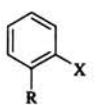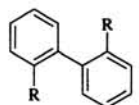
	X			
	Cl	Ni(OAc)$_2$, NaH, *t*-AmONa, THF, 63°	(82),(84)^a	131
	Cl	Ni(OAc)$_2$, NaH, *t*-AmONa, bpy, THF, KI, 63°	(90)	54
	Cl	Ni(OAc)$_2$, NaH, *t*-AmONa, bpy, THF, C$_6$H$_6$, KI, 63°	(80)	54
	Cl	NiBr$_2$, bpy, PPh$_3$, THF, *t*-BuMgCl, reflux	(85)^a	130
	Cl	Pd/C, H$_2$, PEG-400, H$_2$O, NaOH, 100-110°	(33)^a	186
	Cl	Pd/C, Zn, PEG-400, H$_2$O, NaOH, heat	(27)	180
	Br	Ni powder, DMF, 140°	(27)^a	120
	Br	NiBr$_2$(PPh$_3$)$_2$, Zn, THF, Et$_4$NI, 50°	(83)	139
	Br	Ni(OAc)$_2$, NaH, *t*-AmONa, bpy, THF, KI, 63°	(75)	54
	Br	Ni(OAc)$_2$, NaH, *t*-AmONa, bpy, THF, C$_6$H$_6$, KI, 63°	(80)	54
	Br	Ni(OAc)$_2$, *t*-BuOLi, LiH, bpy, THF, 63°	(61),(76)^a	110
	Br	NiCl$_2$(PPh$_3$)$_2$, Zn, PPh$_3$, DMF, 40°	(12)^a	123
	Br	NiBr$_2$, EtOH, 2e$^-$, dpa, H$_2$O	(43)	153
	Br	NiBr$_2$, bpy, EtOH, MeOH, 2e$^-$	(trace)	153
	Br	Ni(cod)$_2$, DMF, 34°	(41)	49, 50
	Br	Pd(OAc)$_2$, Et$_3$N, DMF, 115°	(60)	175
	Br	Pd(OAc)$_2$, Bu$_3$N, DMF, AsPh$_3$, 140°	(0)	172
	Br	Pd/C, HCO$_2$Na, SDPNS, NaOH, H$_2$O, 95°	(33)	179
	Br	PdCl$_2$, *o*-tolylhydrazine hydrochloride, NaOH, MeOH, reflux	(99)	165
	I	Cu, neat, sealed tube, 230°	(63)	2
	I	Cu, neat, 190°	(25)	32
	I	Cu, neat, 260°	(65)	423
	I	Cu, neat, sealed tube, 230-240°	(75)	424
	I	NiBr$_2$, Zn, KI, HMPA, 50°	(83)	129, 403
	I	PdCl$_2$, N$_2$H$_4$•H$_2$O, MeOH, reflux	(17-54)	47
	I	PdCl$_2$, N$_2$H$_4$•H$_2$O, MeOH, reflux, HgCl$_2$	(67-77)	47
	I	Pd(OAc)$_2$, Bu$_3$N, DMF, 140°	(0)	172
	I	Pd(OAc)$_2$, Et$_3$N, 100°	(10)	169
	I	Pd(OAc)$_2$, *n*-Bu$_3$N, 100°	(1)	169
	I	Pd/C, Zn, air, H$_2$O, acetone, 25°	(84)^a	185
	I	EtN(*i*-Pr)$_2$, DMF, 110°	(74)	194
		R = *o*-tolyl		
	OTf	NiCl$_2$, Zn, PPh$_3$, NaI, DMF, sonication, 60°	(82)^a	135
	OTf	PdCl$_2$(PPh$_3$)$_2$, Zn, DMF, 90°	(0)^b	192
	OFs	NiCl$_2$(PPh$_3$)$_2$, Zn, THF, Et$_4$NI, 67°	(72)^a	133

R	X			
CH$_2$OH	I	Cu(I) thiophene-2-carboxylate, NMP, 70°	(48) based on 62% conversion	71
CH$_2$OH	I	In, DMF, reflux	(78)	74
CF$_3$	Cl	Ni(OAc)$_2$, NaH, *t*-AmONa, bpy, THF, 63°	(71)	54
CF$_3$	Cl	Ni(OAc)$_2$, NaH, *t*-AmONa, bpy, THF, C$_6$H$_6$, KI, 63°	(70)	54
CF$_3$	Br	Ni(OAc)$_2$, NaH, *t*-AmONa, bpy, THF, 63°	(42)	54
CF$_3$	Br	Ni(OAc)$_2$, NaH, *t*-AmONa, bpy, THF, C$_6$H$_6$, KI, 63°	(62)	54

TABLE 2. 2,2'-DISUBSTITUTED BIARYLS (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

R	X			
CF₃	I	Cu, neat, reflux	(75)	425
CF₃	I	NiBr₂, Zn, KI, HMPA, 35°	(75)[a]	129
CN	Br	Cu, neat, 190°	(3)	32
CN	Br	Pd(OAc)₂, EtN(i-Pr)₂, DMF, 115°	(86), (89)[a]	175

X			
Br	Cu, neat, 190°	(0)	32
Br	Pd(OAc)₂, EtN(Pr-i)₂, DMF, 115°	(62), (69)[a]	175
Br	Ni(cod)₂, bpy, DMF, 60°	(96 overall) I:II 84:16	426
Br	1.2 eq Ni(cod)₂	(100 overall) I:II 8:92	426
I	Cu, neat, 220°	(70)	427
I	Cu, DMF, reflux	(65)	428

R	X			
H	I	Indium, DMF, reflux	(75)	74
K	Br	1. Cu, H₂O, reflux	(76)	429
		2. acid		

X			
Cl	Ni(OAc)₂, NaH, t-AmONa, bpy, THF, 63°	(91)	54
Cl	Ni(OAc)₂, NaH, t-AmONa, bpy, THF, C₆H₆, KI, 63°	(74)	54
Br	Ni(OAc)₂, NaH, t-AmONa, bpy, THF, 63°	(66-77), (69-79)[a]	131
Br	NiBr₂, EtOH, MeOH, NaBr, bpy, 2e⁻	(28)	53
Br	NiBr₂(PPh₃)₂, Zn, THF, Et₄NI, 50°	(81)	139
Br	Cu, neat, reflux	(0)	32
Br	Pd(OAc)₂, Bu₃N, DMF, AsPh₃, 140°	(0)	172
Br	Ni(OAc)₂, NaH, t-AmONa, bpy, THF, 63°	(74)	54
Br	Ni(OAc)₂, NaH, t-AmONa, bpy, THF, C₆H₆, KI, 63°	(68)	54
I	Cu, neat, 210-260°	(88)	2
I	Cu, neat, 190°	(70)	32
I	Indium, DMF, reflux	(88)	74
I	Pd(OAc)₂, hydroquinone, As(o-tol)₃, Cs₂CO₃, 100°	(82)	178
I	Pd/C, Zn, air, H₂O, acetone, 25°	(73)[a]	185
I	NiI₂, lithium naphthalide, DME, 80°	(<1)[a]	111

	Cu, neat, 200-250°	(81)	430

TABLE 2. 2,2'-DISUBSTITUTED BIARYLS *(Continued)*
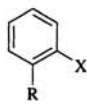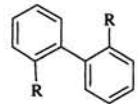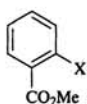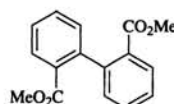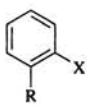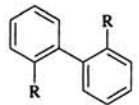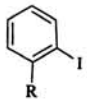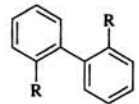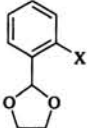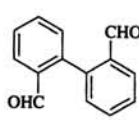
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C₈

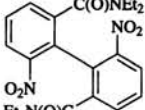| R	X			
Et	I	Cu, neat, 240°	(60)	431
COMe	Br	[PdCl(π-C₃H₅)]₂, Bu₄NF, DMSO, 120°	(0)	198
COMe	I	Cu, neat, heat	(45)	432
COMe	I	Cu, DMF, reflux	(59)	432
COMe	I	NiBr₂, KI, Zn, HMPA, 20°	(68), (96)[a]	129

X			
Cl	Cu, neat, 190°	(0)	32
Br	Cu, neat, 190°	(80)	32
Br	NiBr₂(PPh₃)₂, Zn, THF, 67°	(68)	139
Br	NiBr₂(PPh₃)₂, Zn, Et₄NI, THF, 67°	(79-90)	139
Br	Ni(cod)₂, DMF, 41-54°	(81)	49
Br	NiCl₂(PPh₃)₂, Zn, PPh₃, DMF, 40°	(33)[a]	123

C₈₋₉

R	X			
NHCOCF₃	I	Cu(I) thiophene-2-carboxylate, NMP, 23°	(79) based on 89% conversion	71
(N-acetyl-N-methyl)	I	Cu(I) thiophene-2-carboxylate, NMP, 23°	(90)	71
CH₂NHMe	Br	Cu(I) thiophene-2-carboxylate, NMP, 23°	(99)	71

C₉

R			
CH₂NMe₂	Cu(I) thiophene-2-carboxylate, NMP, 23°	(97)	71
(N-acetyl-N-methyl)	Cu(I) thiophene-2-carboxylate, NMP, 70°	(83)	71
H₂C–NHMe (amide)	Cu(I) thiophene-2-carboxylate, NMP, 23°	(51) based on 82% conversion	71
(C(=S)NMe₂)	Cu(I) thiophene-2-carboxylate, NMP, 23°	(94)	71
(O–C(=O)NMe₂)	Cu(I) thiophene-2-carboxylate, NMP, 23°	(41) based on 50% conversion	71

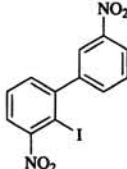| X			
Cl	1. Ni(OAc)₂, NaH, *t*-AmONa, bpy, THF, C₆H₆, KI, 63° 2. acid	(64)	54
Br	1. Ni(OAc)₂, NaH, *t*-AmONa, bpy, THF, C₆H₆, KI, 63° 2. acid	(57)	54

TABLE 2. 2,2'-DISUBSTITUTED BIARYLS (Continued)
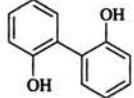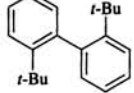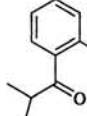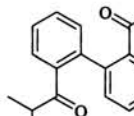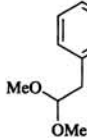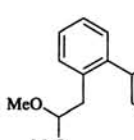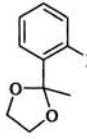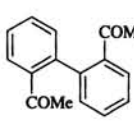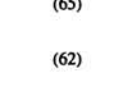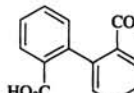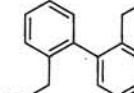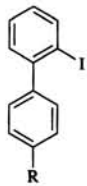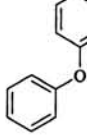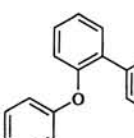
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. Cu, quinoline, 240° 2. HCl	(25)	433
C_{10}	PdCl$_2$(PPh$_3$)$_2$, DMF, Et$_4$NOTs, 2e$^-$	(0)	190
	Cu, DMF, reflux	(66)	432
	Cu, neat, 235-260°	(82)	434
X			
Cl	1. Ni(OAc)$_2$, NaH, t-AmOH, bpy, THF, C$_6$H$_6$, KI, 63° 2. acid	(65)	54
Br	1.Ni(OAc)$_2$, NaH, t-AmOH, bpy, THF, C$_6$H$_6$, KI, 63° 2. acid	(62)	54
	1. Cu, quinoline, 200° 2. NaOH/HCl	(70)	433
	1. Cu, quinoline, 240° 2. HCl	(35)	433
C_{12}			
R			
H	Cu, neat, heat	(69)	435
H	Cu, neat, 260°	(72)	436
H	Cu, neat, 300°	(52)	437
NO$_2$	Cu, neat, 220-225°	(50)^c	39
NO$_2$	Cu, neat, 225-235°	(51)	438
	Cu, neat, 210-270°	(75)	410

322

323

TABLE 2. 2,2'-DISUBSTITUTED BIARYLS (Continued)
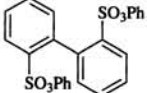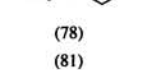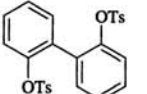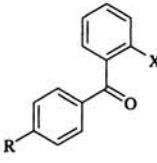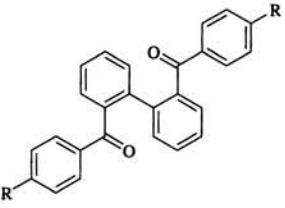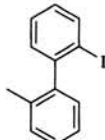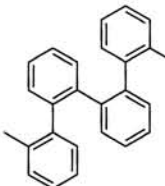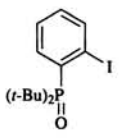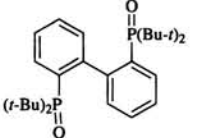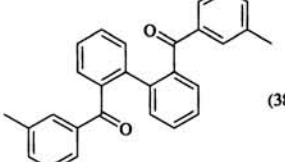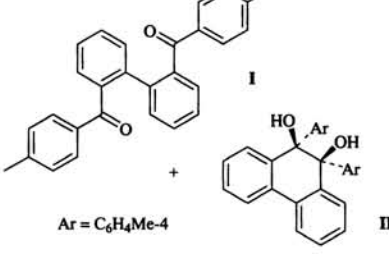
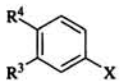| Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Cu, neat, 195°	(78)	439
	Cu, neat, 180-210°	(81)	421
C₁₃	Cu, neat, 260°	(50)	2

R	X			
H	Cl	NiCl₂, NaI, triphenyl phosphite, NMP, Zn, 70°	(76)ᵃ	149
H	Cl	NiCl₂, NaI, tris(2-methylphenyl) phosphite, NMP, ZnCl₂, 60°	(100)ᵃ	149
H	Cl	NiCl₂, NaI, tris(phenylphenyl) phosphite, NMP, Zn, 60°	(99)ᵃ	149
H	Cl	NiCl₂, NaI, tris(2-methoxyphenyl) phosphite, NMP, Zn, 60°	(97)ᵃ	432
H	I	Cu, DMF, reflux	(76)	432
H	I	NiCl₂(PEt₃)₂, Zn, NMP, 30°	(67)	401
F	Cl	NiBr₂, Zn, DMAc, PPh₃, 80-90°	(82)	440
F	Br	Cu, neat, 200°	(30)	441
Cl	Br	Cu, neat, 200°	(0)	441

	Cu, neat, 265-285°	(70)	442
C₁₄	Cu, DMF, heat	(96)	443
	Cu, neat, 250°	(38)	441

I

Ar = C₆H₄Me-4   II

| | Ni(cod)₂ (2 eq), bpy, DMF, 60° | (96 overall)   I:II 76 : 24 | 426 |
| | Ni(cod)₂ (2 eq), bpy, DMF, 60°, H⁺ | (99 overall)   I:II 0 : 100 | 426 |

TABLE 2. 2,2'-DISUBSTITUTED BIARYLS *(Continued)*
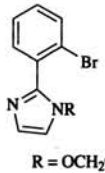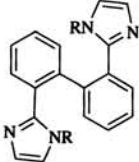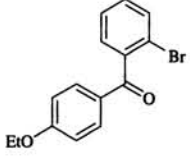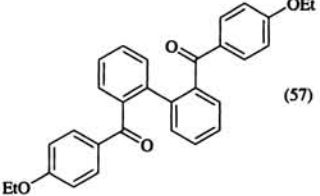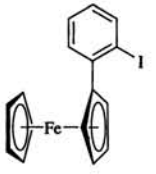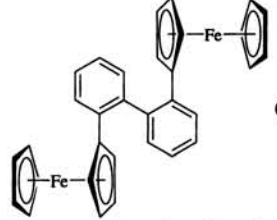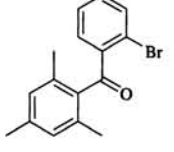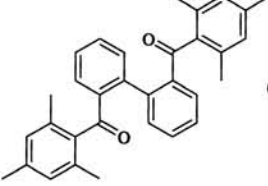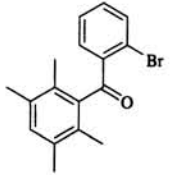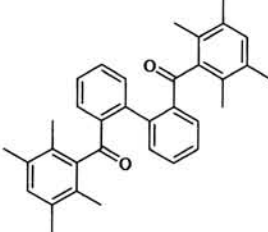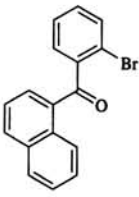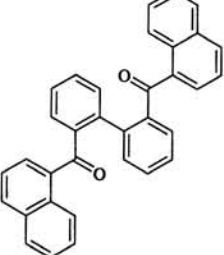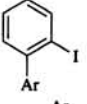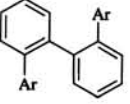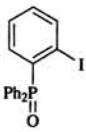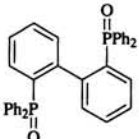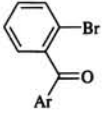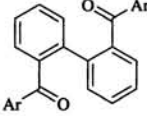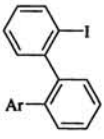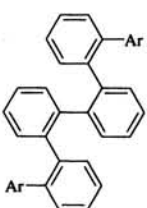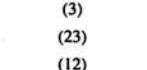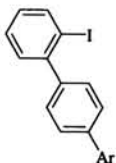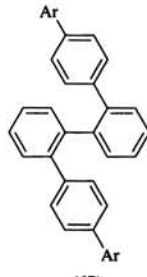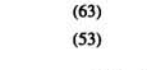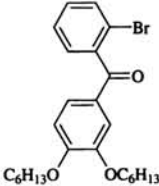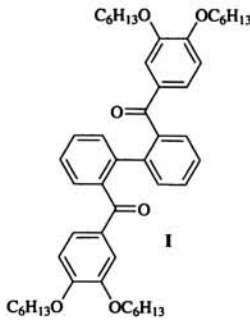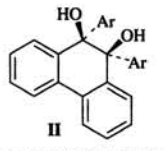
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₁₄			
R = OCH₂CH₂OSiMe₃	Ni(cod)₂, *hv*, toluene	(66)	132
	Cu, neat, 250°	(57)	441
C₁₆			
	Cu, neat, 147°	(11)	444
	Cu, neat, 210°	(80)	445
C₁₇			
	Cu, sand, 220-250°	(67)	446
	Cu, neat, 200°	(66)	441
C₁₈			

Ar			
biphenyl-2-yl	Cu, neat, 275-280°	(21)	447
biphenyl-3-yl	Cu, neat, 255-260°	(40)	447
biphenyl-4-yl	Cu, neat, 230-290°	(50)	291
biphenyl-4-yl	Cu, neat, 255-260°	(49)	447

TABLE 2. 2,2'-DISUBSTITUTED BIARYLS *(Continued)*

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Cu, DMF, reflux	(78)	448
C$_{19}$ Ar = biphenyl-4-yl	Cu, neat, 200°	(22)	441
C$_{24}$			
Ar			
biphenyl-2-yl	Cu, neat, 255–265°	(3)	449
biphenyl-3-yl	Cu, neat, 275–285°	(23)	449
biphenyl-4-yl	Cu, neat, 225–235°	(12)	449
Ar			
biphenyl-2-yl	Cu, neat, 265–275°	(67)	438
biphenyl-3-yl	Cu, neat, 265–275°	(63)	438
biphenyl-4-yl	Cu, neat, 225–235°	(53)	438
C$_{25}$	Ni(cod)$_2$ (2 eq), bpy, DMF, 60°,	(92 overall) I:II 78:22	426
	Ni(cod)$_2$ (2 eq), bpy, DMF, 60°, H$^+$	(97 overall) I:II 0:100	426

Ar = C$_6$H$_3$(OC$_6$H$_{13}$)-3,4

[a] The yield was determined by gas chromatography.

[b] The yield was determined by NMR spectroscopy.

[c] Excess Cu powder (>1.4 eq) reduced nitro to amine.

TABLE 3. 3,3'-DISUBSTITUTED BIARYLS

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C₆

X			
Cl	Ni(OAc)₂, NaH, *t*-AmONa, bpy, THF, C₆H₆, KI, 63°	(84)	54
Br	Ni(OAc)₂, NaH, *t*-AmONa, bpy, THF, C₆H₆, KI, 63°	(74)	54
Br	Ni(OAc)₂, *t*-BuOLi, bpy, THF, 63°	(87), (100)[a]	110
Br	Pd(OAc)₂, *n*-Bu₄NBr, H₂O, IPA, K₂CO₃, DMF, 115°	(86)	174
Br	NiBr₂, bpy, 2e⁻, EtOH, DMF, Bu₄NBF₄	(53)	53
Br	NiBr₂, bpy, 2e⁻, EtOH, MeOH, NaBr	(46)	53
Br	Pd(OAc)₂, H₂O, IPA, K₂CO₃, DMF, 115°	(86), (97)[a]	175
I	Cu, neat, heat	(23)	409
I	[PdCl(π-C₃H₅)]₂, TBAF, DMSO, 120°	(68)	198

X			
Br	Pd(OAc)₂, *n*-Bu₄NBr, H₂O, K₂CO₃, DMF, 115°	(42), (83)[a]	174, 175
I	Cu, neat, 180-260°	(55)	59
I	Cu, neat, 230-250°	(64)	410
I	Cu, neat, 250°	(96)	450
I	Cu, neat, 250°	(67)	2
I	Cu, neat, 190°	(40)	32
I	Pd(OAc)₂, K₂CO₃, DMF, H₂O, IPA, 115°	(82), (94)[a]	175
I	Cu, neat, 190-260°	(55)	59
SO₂Cl	PdCl₂(PhCN)₂, Ti(OPr-*i*)₄, *m*-xylene, 140°	(67)	168

X			
Cl	Pd/CaCO₃, N₂H₄•H₂O, MeOH, KOH, 135-140°	(47)	48
Br	Pd/CaCO₃, N₂H₄•H₂O, MeOH, KOH, 135-140°	(54)	48

X			
Cl	Cu, neat, 200-220°	(0)	418
Cl	Cu, nitrobenzene, reflux	(0)	418
Br	Cu, neat, 190°	(3)	32
Br	Cu, neat, 200-220°	(15)	418
Br	Cu, nitrobenzene, reflux	(0)	418
I	Cu, neat, 190°	(30)	32
I	Cu, neat, heat	(26)	417
I	Cu, nitrobenzene, 210°	(48)	58
I	Cu, neat, 200-220°	(0)	418
I	Cu, nitrobenzene, reflux	(36)	418
I	Cu, neat, 60°	(0)	35
I	Cu, DMF, 210°	(82)	451
I	Pd(OAc)₂, As(tol-*o*)₃, hydroquinone, Cs₂CO₃, 75°	(86)	178
I	Cu, neat, 200-225°	(52)	1

X	R			
I	SO₂F	Cu, neat, 200-230°	(54)	452
Br	PO(OH)₂	1. Pd/CaCO₃, NaOH, MeOH, reflux 2. HCl	(23)	453
Cl	OH	Ni(OAc)₂, NaH, *t*-AmOH, bpy, THF, C₆H₆, KI, 63°	(70)	54
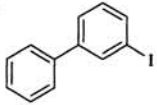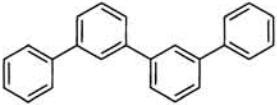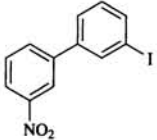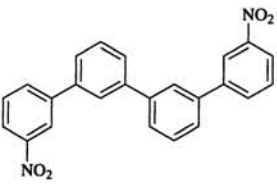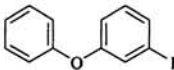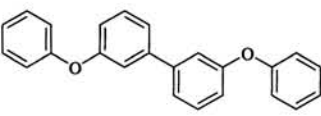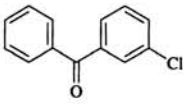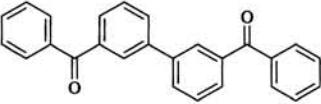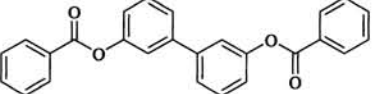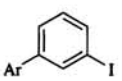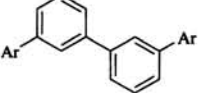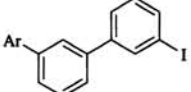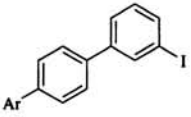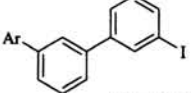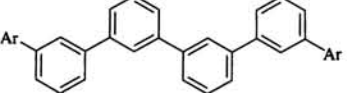
TABLE 3. 3,3'-DISUBSTITUTED BIARYLS (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C₇

X			
Cl	NiBr₂, bpy, 2e⁻, NMP	(80)	128
Cl	Ni powder, KI, DMF, 140°	(72)	120
Cl	Pd/C, HCO₂Na, NaOH, H₂O, CTAB, 95°	(36)	179
Cl	Ni(OAc)₂, NaH, t-AmONa, THF, bpy, 63°	(75), (80)[a]	131
Cl	Ni(OAc)₂, NaH, t-AmONa, bpy, THF, KI, 63°	(85)	54
Cl	Ni(OAc)₂, NaH, t-AmONa, bpy, THF, C₆H₆, KI, 63°	(77)	54
Br	Ni(OAc)₂, NaH, t-AmONa, bpy, THF, 63°	(88)	54
Br	Ni(OAc)₂, NaH, t-AmONa, bpy, THF, C₆H₆, KI, 63°	(83)	54
Br	Pd/CaCO₃, N₂H₄•H₂O, MeOH, KOH, 135-140°	(52)	48
Br	Ni powder, DMF, 140°	(68)	120
Br	Ni(OAc)₂, LiH, t-BuOLi, bpy, THF, 63°	(92), (100)[a]	110
Br	PdCl₂, m-tolylhydrazine hydrochloride, NaOH, MeOH, HgCl₂, reflux	(quantitative)	165
I	Cu, neat, 205-240°	(35)	2
I	Cu, neat, 190°	(50)	32
I	Cu, DMF, reflux	(55)	57
I	PdCl₂, N₂H₄•H₂O, MeOH, reflux	(28)	47
I	Pd/C, Zn, air, H₂O, acetone, 25°	(89)[a]	185
OTf	NiCl₂, Zn, PPh₃, NaI, DMF, sonication, 60°	(82)[a]	135

X			
Cl	Ni(OAc)₂, NaH, t-AmONa, bpy, KI, 63°	(93)	54
Cl	Ni(OAc)₂, NaH, t-AmONa, bpy, THF, C₆H₆, KI, 63°	(77)	54
Br	Ni(OAc)₂, NaH, t-AmONa, bpy, THF, 63°	(87)	54
Br	Ni(OAc)₂, NaH, t-AmONa, bpy, THF, C₆H₆, KI, 63°	(80)	54
Br	Pd(OAc)₂, Bu₃N, DMF, AsPh₃, 140°	(0)	172
I	Cu, neat, reflux	(72)	425
I	NiCl₂(PPh₃)₂, PPh₃, Zn, NaBr, DMF, 100°	(69)	137

	Pd(OAc)₂, n-Bu₄NBr, DMF, IPA, Et₃N, 115°	(57), (64)[a]	174
	Pd(OAc)₂, DMF, IPA, Et₃N, 115°	(57), (64)[a]	175

C₇₋₁₄

X			
Cl	Pd(OAc)₂, n-Bu₄NBr, DMF, Et₃N, 115°	(60), (67)[a]	174
Br	Pd(OAc)₂, DMF, Et₃N, 115°	(53), (67)[a]	175
OTs	NiCl₂(PPh₃)₂, PPh₃, Zn, NaBr, DMF, 100°	(62)	137

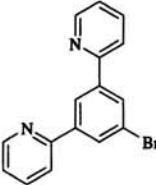|			
	1. Pd/CaCO₃, N₂H₄•H₂O, MeOH, KOH, 135-140° 2. acid	(57)	48
	1. Pd/C, NaOH, H₂O, formic hydrazide, 85° 2. acid	(88)[b]	55

TABLE 3. 3,3'-DISUBSTITUTED BIARYLS (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C₇

X			
Cl	Ni(OAc)$_2$, NaH, t-AmONa, bpy, THF, 63°	(82)	54
Cl	Ni(OAc)$_2$, NaH, t-AmONa, bpy, THF, C$_6$H$_6$, KI, 63°	(73)	54
Cl	Ni(OAc)$_2$, LiH, t-BuOLi, bpy, THF, 63°	(70), (79)[a]	110
Br	Ni(OAc)$_2$, NaH, t-AmONa, bpy, THF, 63°	(82)	54
Br	Ni(OAc)$_2$, NaH, t-AmONa, bpy, THF, C$_6$H$_6$, KI, 63°	(82)	54
Br	Ni(OAc)$_2$, LiH, t-BuOLi, bpy, THF, 63°	(93), (100)[a]	110
Br	Pd(OAc)$_2$, Bu$_3$N, DMF, AsPh$_3$, 140°	(57)	172
Br	Ni(OAc)$_2$, NaH, t-AmONa, THF, bpy, 63°	(71), (75)[a]	131
Br	NiCl$_2$(PEt$_3$)$_2$, Zn, NMP, 30°	(91)	401
I	Cu, neat, 190°	(65)	32
I	Pd(OAc)$_2$, As(o-tol)$_3$, hydroquinone, Cs$_2$CO$_3$, 75°	(96)	178
I	Pd/C, Zn, air, H$_2$O, acetone	(79)[a]	185

C₈

	Pd(PPh$_3$)$_4$, DME, n-Bu$_3$N, reflux	(23)	454

X			
Br	NiCl$_2$(PPh$_3$)$_2$, Zn, Et$_4$NI, THF, 50°	(75)	455
I	Cu, neat, 240-260°	(36)	456

C₈₋₉

X			
Cl	NiBr$_2$(PPh$_3$)$_2$, Zn, Et$_4$NI, THF, 50°	(81)	139
Br	NiBr$_2$(PPh$_3$)$_2$, Zn, Et$_4$NI, THF, 50°	(85)	139
Br	NiBr$_2$(PPh$_3$)$_2$, Zn, PPh$_3$, DMF, 50°	(85)	122
I	NiBr$_2$, Zn, KI, HMPA, 50°	(96)	129, 403
I	NiCl$_2$(PPh$_3$)$_2$, PPh$_3$, Zn, DMF, 54°	(65)	457
I	Cu, neat, 260°	(58)	2
I	Cu, neat, 240°	(32)	458
I	Cu, neat, 190°	(25)	32
I	Cu, DMF, reflux	(89)	57
OMs	NiBr$_2$(PPh$_3$)$_2$, Zn, Et$_4$NI, THF, 67°	(93)[a]	133

C₉₋₁₀

R	X			
H	Cl	Ni(OAc)$_2$, NaH, t-AmONa, bpy, THF, C$_6$H$_6$, KI, 63°	(75)	54
H	Br	Ni(OAc)$_2$, NaH, t-AmONa, bpy, THF, C$_6$H$_6$, KI, 63°	(71)	54
Me	Cl	Ni(OAc)$_2$, NaH, t-AmONa, bpy, THF, C$_6$H$_6$, KI, 63°	(73)	54
Me	Br	Ni(OAc)$_2$, NaH, t-AmONa, bpy, THF, C$_6$H$_6$, KI, 63°	(68)	54

C₁₀

	NiCl$_2$(PPh$_3$)$_2$, Zn, pyridine	(65)	459

TABLE 3. 3,3'-DISUBSTITUTED BIARYLS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{12}$			
	Cu, neat, 225-312°	(16)	437
	Cu, sand, 250-260°	(83) crude	460
	Cu, neat, 225-235°	(62)	449
	Cu, neat, 210-270°	(68)	410
C$_{13}$	NiCl$_2$, tris(2-phenylphenyl) phosphite, NMP, Zn, NaI, 60°	(97)^a	149
	Cu, neat, 215-260°	(41)	2
C$_{18}$ Ar = biphenyl-2-yl	Cu, neat, 260-265°	Ar (60)	447
C$_{24}$ Ar			
biphenyl-2-yl	Cu, neat, 260-265°	(60)	449
biphenyl-3-yl	Cu, neat, 225-235°	(54)	449
  Ar			
biphenyl-2-yl	Cu, neat, 225-235°	(64)	438
biphenyl-3-yl	Cu, neat, 225-235°	(50)	438
  Ar = biphenyl-4-yl	Cu, neat, 265-270°	Ar (63)	449

^{a} The yield was determined by gas chromatography.
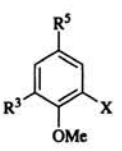^{b} The yield was determined by HPLC.

TABLE 4. 4,4'-DISUBSTITUTED BIARYLS
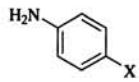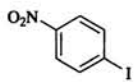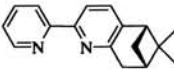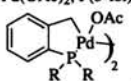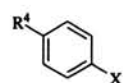
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C₆

X			
I	PdCl₂, HgCl₂, N₂H₄•H₂O, MeOH, reflux	(26)	47
Br	Pd(OAc)₂, Bu₃N, AsPh₃, DMF, 140°	(0)	172
Br	Pd/CaCO₃, N₂H₄•H₂O, KOH, MeOH, 135-140°	(60) derivative	48
Br	Ni(cod)₂, DMF, 35-45°	(30), (54)[a]	49, 50
Cl	Pd/CaCO₃, N₂H₄•H₂O, KOH, MeOH, 135-140°	(47)	48
Cl	NiCl₂, PPh₃, Zn, DMAc, 80°	(31)[b]	51, 52

Conditions	Product(s) and Yield(s) (%)	Refs.
Cu, neat, 220-235°	(52)	1
Cu, neat, 190°	(25)	32
Cu, neat, 200-220°	(54)	418
Cu, neat, 140°	(<8)	238
Cu, nitrobenzene, 210°	(61)	58
Cu, nitrobenzene, reflux	(25)	418
Cu, xylene, 140°	(92)	238
Cu, biphenyl, 200°	(58)	238
CuI, potassium naphthalide, DME, 85°	(3)	24
Cu, DMF, reflux	(75)	407
NiBr₂, KI, Zn, HMPA, 50°	(0)	129
NiCl₂, CrCl₂, Mn, THF, rt	(0)	406
Pd(OAc)₂, Et₃N, 100°	(54)	169
Pd(OAc)₂, n-Bu₃N, 100°	(0)	169
Pd(OAc)₂, Et₃N, CH₃CN, BNAH, 100°	(77)	177
Pd(OAc)₂, n-Bu₃N, DMF, 140°	(47)	172
Pd(OAc)₂, PPh₃, NaOAc, DMF, 110-115°	(46)	461
[PdCl(p-C₃H₅)]₂, TBAF, DMSO, 120°	(77)	198
Pd(OAc)₂, As(o-tol)₃, hydroquinone, Cs₂CO₃, 75°	(86)	178
Pd(OAc)₂, P(o-tol)₃, hydroquinone, Cs₂CO₃, 75°	(89)	178
[structure] EtN(i-Pr)₂, DMF, 110° R = o-tolyl	(80)	194

R⁴	X	Conditions	Product(s) and Yield(s) (%)	Refs.
NO₂	Br	Cu, neat, 190°	(3)	32
NO₂	Br	Cu, neat, 200-220°	(36)	418
NO₂	Br	Cu, nitrobenzene, reflux	(15)	418
NO₂	Br	Ni powder, DMF, 140°	(0)	120
NO₂	Br	Ni(CO)₂(PPh₃)₂, DMSO, 70°	(0)[b]	145
NO₂	Br	Ni(cod)₂, DMF, 40°	(0)	49, 50
NO₂	Br	Pd(OAc)₂, n-Bu₃N, DMF, AsPh₃, 140°	(30)	172
NO₂	Br	Pd(OAc)₂, DMF, K₂CO₃, H₂O, IPA, 115°	(31), (74)[b]	175
NO₂	Br	Pd(OAc)₂, DMF, K₂CO₃, H₂O, IPA, n-Bu₄NBr, 115°	(85)	174
NO₂	Br	Pd(OAc)₂, As(o-tol)₃, hydroquinone, Cs₂CO₃, 100°	(88)	178
NO₂	Cl	Cu, neat, 200-220°	(0)	418
NO₂	Cl	Cu, nitrobenzene, reflux	(0)	418
NO₂	Cl	NiCl₂, PPh₃, Zn, DMAc, 80°	(0)[b]	51
NO₂	Cl	NiBr₂, bpy, NMP, 2e⁻	(0)	128
NO₂	Cl	Pd(OAc)₂, Et₃N, DMF, 115°	(17),(20)[b]	175

TABLE 4. 4,4'-DISUBSTITUTED BIARYLS *(Continued)*

	Substrate		Conditions	Product(s) and Yield(s) (%)	Refs.

C_{6-7}
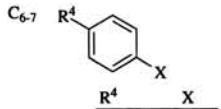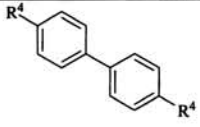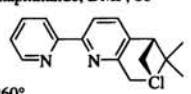
R^4	X	Conditions	Product(s) and Yield(s) (%)	Refs.
NO_2	OMs	$NiCl_2(PPh_3)_2$, Zn, Et_4NI, THF, 67°	(0)	133
OH	Br	$NiBr_2$, bpy, 2e⁻, EtOH, MeOH, NaBr	(86)	53
OH	Br	$NiBr_2$, bpy, 2e⁻, EtOH, DMF, Bu_4NBF_4	(84)	53
OH	Br	$Ni(OAc)_2$, NaH, *t*-AmONa, bpy, THF, 63°	(68)	54
OH	Br	$Ni(OAc)_2$, NaH, *t*-AmONa, bpy, KI, C_6H_6, THF, 63°	(76)	54
OH	Br	$NiBr_2$, bpy, NMP, 2e⁻	(0)	128
OH	Br	$Ni(cod)_2$, DMF, 40°	(0)	49, 50
O⁻Na⁺	Br	$Ni(cod)_2$, DMF, 37-60°	(3)	49, 50
O⁻Na	Br	$Pd/CaCO_3$, $N_2H_4 \cdot H_2O$, MeOH, KOH, 135-140°	(13)	48
O⁻Na	Br	$Pd(OAc)_2$, *n*-Bu_3N, DMF, $AsPh_3$, 140°	(0)	172
O⁻Na⁺	Br	$Pd/BaSO_4$, NaOH, H_2O, formic hydrazide, 80°	(79)[b]	55
OH	Cl	$NiCl_2$, PPh_3, Zn, DMAc, 80°	(25)[b]	51
F	Br	$NiBr_2$, bpy, 2e⁻, EtOH, MeOH, NaBr	(82)	53
F	Br	$NiBr_2$, bpy, 2e⁻, EtOH, DMF, Bu_4NBF_4	(63)	53
F	Br	$NiCl_2$, bpy, DMF, NaBr, Zn, 60-80°	(78)	146
F	Br	$NiBr_2$, dpa, H_2O, 2e⁻, EtOH	(90)	153
F	Br	$NiBr_2$, bpy, 2e⁻, EtOH, MeOH	(82)	153
F	Br	$Ni(OAc)_2$, NaH, *t*-AmONa, bpy, THF, 63°	(85)	54
F	Br	$Ni(OAc)_2$, NaH, *t*-AmONa, bpy, THF, KI, C_6H_6, 63°	(64)	54
F	Br	Pd/C, NaOH, diethylene glycol dimethyl ether, polyethylene glycol dimethyl ether, ethylene glycol, 100°	(74-89)[b]	462
F	Cl	$Ni(OAc)_2$, NaH, *t*-AmONa, bpy, THF, KI, C_6H_6, 63°	(75)	54
F	Cl	Pd/C, NaOH, diethylene glycol dimethyl ether, polyethylene glycol dimethyl ether, ethylene glycol, 100°	(66)[b]	462
F	I	Cu, neat, heat	(60)	409
F	I	Pd/C, Zn, air, H_2O, acetone, 25°	(96)[b]	185
F	OMs	$NiCl_2(PPh_3)_2$, Zn, Et_4NI, THF, 67°	(54)	133
F	OTf	$NiCl_2(dppe)$, Zn, KI, DMF, THF, 67°	(85)	192
F	SO_2Cl	$PdCl_2(PhCN)_2$, $Ti(OPr-i)_4$, *m*-xylene, N_2, 140°	(74)	168
$PO(OH)_2$	Br	1. $Pd/CaCO_3$, MeOH, NaOH, reflux 2. HCl	(28)	453
Cl	Br	$Pd(OAc)_2$, *n*-Bu_3N, DMF, $AsPh_3$, 140°	(48)	172
Cl	Br	$Ni(OAc)_2$, NaH, *t*-AmONa, bpy, THF, 63°	(60)	54
Cl	Br	$NiBr_2$, lithium naphthalide, DME, 80°	(36)[b]	111
Cl	Br	NiI_2, lithium naphthalide, DME, 80°	(61)[b]	111
Cl	Br	$NiBr_2$, lithium naphthalide, DMSO, 80°	(41)[b]	111
Cl	Br	$NiBr_2$, lithium naphthalide, DMF, 80°	(<1)[b]	111
Cl	Br	$NiCl_2$, $CrCl_2$, Mn, THF, rt	(25)	406
Cl	I	Cu, neat, 180-260°	(63)	60
Cl	I	Cu, neat, 230-250°	(48)	410
Cl	I	Cu, neat, 200-250°	(82)	2
Cl	I	Cu, neat, 190°	(40)	32
Cl	I	Cu, methyl benzoate, 190°	(15)	46
Cl	I	Cu, 1,2,4-trichlorobenzene, 190°	(30)	46
Cl	I	$Pd(OAc)_2$, Et_3N, 100°	(57)	169
Cl	I	$Pd(OAc)_2$, *n*-Bu_3N, 100°	(67)	169
Cl	I	Pd/C, Zn, air, H_2O, acetone, 25°	(94)[b]	185
Cl	I	NiI_2, lithium naphthalide, DME, 80°	(75)[b]	111
Cl	I	$NiBr_2$, lithium naphthalide, DME, 80°	(77)[b]	111
Cl	I	$NiCl_2$, lithium naphthalide, DME, 80°	(74)[b]	111
Cl	OTf	$PdCl_2(PPh_3)_2$, DMF, 2e⁻, *n*-Bu_4NBF_4 90°	(57)	191, 19
Cl	OTf	$PdCl_2(PPh_3)_2$, DMF, Zn, 90°	(17)[a]	191, 19
Cl	OTf	$NiCl_2(dppe)$, KI, DMF, THF, Zn, 67°	(0)	191, 19
Cl	SO_2Cl	$PdCl_2(PhCN)_2$, $Ti(OPr-i)_4$, *m*-xylene, N_2, 140°	(74), (76)[b]	168
Cl	SO_2Cl	$Pd(OAc)_2$, $Ti(OPr-i)_4$, *m*-xylene, N_2, 140°	(71)[b]	168
Cl	SO_2Na	$PdCl_2$, H_2O, 90°	(73)	167

TABLE 4. 4,4'-DISUBSTITUTED BIARYLS (Continued)
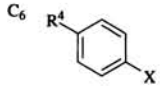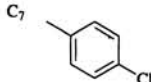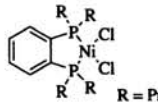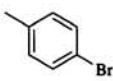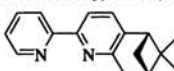
	Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C6

R^4	X			
Br	I	Pd(OAc)$_2$, n-Bu$_3$N, DMF, 140°	(41)	172
Br	SO$_2$Cl	PdCl$_2$(PhCN)$_2$, Ti(OPr-i)$_4$, m-xylene, N$_2$, 140°	(56)	168

C7

Conditions	Product(s) and Yield(s) (%)	Refs.
NiBr$_2$(PPh$_3$)$_2$, Zn, Et$_4$NI, THF, 50°	(81)	139
NiCl$_2$(quinoline)$_2$, Zn, pyridine, 80°	(4)^b	463
NiCl$_2$, PPh$_3$, DMAc, Zn, 80°	(90)^b	51
Ni(OAc)$_2$, NaH, t-AmONa, THF, 63°, PPh$_3$	(63)	131
Ni(OAc)$_2$, NaH, t-AmONa, THF, 63°, bpy	(75), (80)^b	131
NiCl$_2$, NaI, Zn, NMP, 60-80°, tris(2-methylphenyl) phosphite	(97)^b	149
NiCl$_2$, NaI, Zn, NMP, 60°, tris(2-phenylphenyl) phosphite	(99)^b	149
NiCl$_2$, NaI, Zn, NMP, 60-80°, tris(2-methoxyphenyl) phosphite	(99)^b	149
NiCl$_2$, NaI, Zn, NMP, 60-65°, tris(2-t-butylphenyl) phosphite	(99)^b	149
Ni(OAc)$_2$, t-BuOLi, LiH, bpy, THF, 63°	(91), (94)^b	110
Ni(OAc)$_2$, NaH, t-AmONa, bpy, THF, 63°	(90)	54
Ni(OAc)$_2$, NaH, t-AmONa, bpy, KI, C$_6$H$_6$, THF, 63°	(74)	54
Ni powder, DMF, 140°	(<2)^b	120
Ni powder, DMF, KI, 140°	(83)	120
Pd/C, HCO$_2$Na, NaOH, H$_2$O, CTAB, 95°	(55)	179
Pd/C, HCO$_2$Na, NaOH, H$_2$O, CTAB, 110°	(60), (67)^b	181
Pd/C, H$_2$, PEG-400, H$_2$O, NaOH, 100-110°	(51), (56)^b	186
Pd/C, NaOH, H$_2$O, formic hydrazide, 80°	(59)^b	55
Pd/C, Zn, PEG-400, H$_2$O, NaOH, heat	(51)	180

DMSO, 2e⁻, 65°	(91)^b	154
THF, 2e⁻, 65°	(96)^b	154

R = Pr-i

Conditions	Product(s) and Yield(s) (%)	Refs.
Ni powder, DMF, 140°	(71)	120
Ni(CO)$_2$(PPh$_3$)$_2$, DMSO, 70°	(70)^b	145
NiCl$_2$, bpy, NaBr, DMF, Zn, 60-80°	(80)	146
NiBr$_2$, bpy, 2e⁻, NaBr, EtOH, MeOH	(90)	53
NiBr$_2$(PPh$_3$)$_2$, Zn, Et$_4$NI, THF, 50°	(89)	139
Ni(OAc)$_2$, NaH, bpy, t-AmONa, THF, 63°	(70-80)	131
NiCl$_2$(PPh$_3$)$_2$, Zn, PPh$_3$, DMF, 50°	(73)^b	123
NiCl$_2$(PPh$_3$)$_2$, Zn, PPh$_3$, DMF, 50°	(60)	122
NiCl$_2$(PPh$_3$)$_2$, PPh$_3$, DMF, n-Bu$_4$NBr, 2e⁻	(75)	127
Ni(OAc)$_2$, t-BuOLi, LiH, bpy, THF, 63°	(74), (93)^b	110
Ni(OAc)$_2$, NaH, t-AmONa, bpy, THF, KI, 63°	(84)	54
Ni(OAc)$_2$, NaH, t-AmONa, bpy, KI, C$_6$H$_6$, THF, 63°	(82)	54
NiCl$_2$, CrCl$_2$, Mn, THF, rt	(90)	406
Pd/C, NaOH, H$_2$O, formic hydrazide, 95°	(97)^b	55
Pd(OAc)$_2$, n-Bu$_3$N, DMF, AsPh$_3$, 140°	(58-60)	171, 17
Pd/CaCO$_3$, N$_2$H$_4$•H$_2$O, NaOH, MeOH, 135-140°	(66)	48
PdCl$_2$, HgCl$_2$, p-tolylhydrazine hydrochloride, NaOH, MeOH, reflux	(quantitative)	165
PdCl$_2$, HgCl$_2$, phenylhydrazine, NaOH, MeOH, reflux	(76)	165
PdCl$_2$, phenylhydrazine, NaOH, MeOH, reflux	(27)	165

TABLE 4. 4,4'-DISUBSTITUTED BIARYLS (Continued)
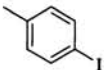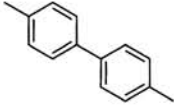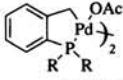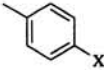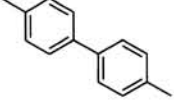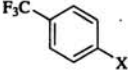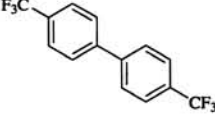
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

	Cu, neat, 210-260°	(54)	2
	Cu, neat, 260°	(60)	464
	Cu, neat, 190°	(45)	32
	Cu, methyl benzoate, 190°	(4)	46
	Cu, 1,2,4-trichlorobenzene, 190°	(14)	46
	Cu, DMF, reflux	(68)	57
	Ni(cod)$_2$, DMF, 40°	(63)	49, 50
	NiCl$_2$, KI, Zn, HMPA, 50°	(92)	129, 403
	NiCl$_2$(PEt$_3$)$_2$, Zn, NMP, 30°	(87)	401
	NiCl$_2$(quinoline)$_2$, Zn, pyridine, 80°	(4)	463
	Pd(OAc)$_2$, n-Bu$_3$N, 100°	(34)	169
	Pd(OAc)$_2$, Et$_3$N, 100°	(50)	169
	Pd(OAc)$_2$, n-Bu$_3$N, DMF, 140°	(54)	172
	Pd(dba)$_2$, TBAF, DMF, PhSi(OMe)$_3$	(40)	197
	PdCl$_2$, HgCl$_2$, phenylhydrazine, NaOH, MeOH, reflux	(77)	165
	PdCl$_2$, phenylhydrazine, NaOH, MeOH, reflux	(44)	165
	PdCl$_2$, N$_2$H$_4$•H$_2$O, MeOH, reflux	(48)	47
	PdCl$_2$, HgCl$_2$, N$_2$H$_4$•H$_2$O, MeOH, reflux	(quantitative)	47
	Pd/C, Zn, air, H$_2$O, acetone, 25°	(92)[b]	185
	EtN(Pr-i)$_2$, DMF, 110° (R = o-tolyl)	(87)	194

X			
OTf	NiCl$_2$(dppe), KI, Zn, DMF, 90°	(94)	192, 193
OTf	NiCl$_2$(dppe), KI, Zn, THF, DMF, 67°	(59)[a]	193
OTf	NiCl$_2$, Zn, PPh$_3$, NaI, DMF, sonication, 60°	(85)[b]	135
OTf	NiCl$_2$, Zn, PPh$_3$, NaI, DMF, sonication, 60°	(7)[a]	192, 193
OTf	PdCl$_2$(PPh$_3$)$_2$, Zn, DMF, 90°	(84)[b]	133
OMs	NiCl$_2$(PPh$_3$)$_2$, Zn, Et$_4$NI, THF, 67°	(90)[b]	133
OBs	NiCl$_2$(PPh$_3$)$_2$, Zn, Et$_4$NI, THF, 67°	(80), (93)[b]	133
OFs	NiCl$_2$(PPh$_3$)$_2$, Zn, Et$_4$NI, THF, 67°	(40)	168
SO$_2$Cl	PdCl$_2$(PhCN)$_2$, Ti(OPr-i)$_4$, N$_2$, m-xylene, 140°	(71)	167
SO$_2$Na	PdCl$_2$, H$_2$O, 90°	(63)	166
SO$_2$Na	Na$_2$PdCl$_4$, HgCl$_2$, H$_2$O, reflux		

X			
Cl	NiBr$_2$, bpy, 2e$^-$, Bu$_4$NBF$_4$, EtOH, DMF	(80)	53
Cl	NiCl$_2$(quinoline)$_2$, Zn, pyridine, 80°	(65), (68)[b]	463
Cl	Ni(OAc)$_2$, t-BuOLi, LiH, bpy, THF, 63°	(84), (86)[b]	110
Cl	Ni(OAc)$_2$, NaH, t-AmONa, bpy, THF, KI, 63°	(88)	54
Cl	Ni(OAc)$_2$, NaH, t-AmONa, bpy, C$_6$H$_6$, KI, THF, 63°	(77)	54
Cl	Pd/C, HCO$_2$Na, NaOH, H$_2$O, CTAB, 100°	(75), (82)[b]	181
Cl	Pd/C, H$_2$, PEG-400, H$_2$O, NaOH, 110°	(69), (77)[b]	186
Cl	Pd/C, Zn, PEG-400, H$_2$O, NaOH, heat	(69)	180
Br	Ni(OAc)$_2$, NaH, t-AmONa, bpy, THF, 63°	(93)	54
Br	Ni(OAc)$_2$, NaH, t-AmONa, bpy, C$_6$H$_6$, KI, THF, 63°	(87)	54
Br	NiBr$_2$, EtOH, 2e$^-$, dpa, H$_2$O	(90)	153
Br	NiBr$_2$, EtOH, MeOH, 2e$^-$, bpy	(36)	153

TABLE 4. 4,4'-DISUBSTITUTED BIARYLS (Continued)

Substrate		Conditions	Product(s) and Yield(s) (%)	Refs.

C$_{7-8}$

F$_3$C—C$_6$H$_4$—X → F$_3$C—C$_6$H$_4$—C$_6$H$_4$—CF$_3$
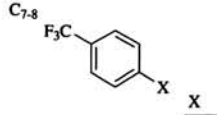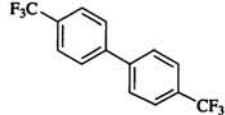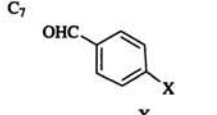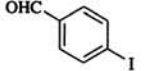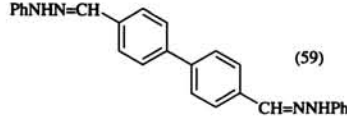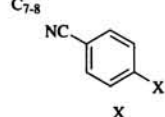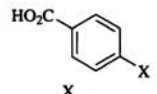
X		Conditions	Product(s) and Yield(s) (%)	Refs.
I		Cu, neat, reflux	(41)	425
OTf		NiCl$_2$(dppe), KI, Zn, THF, DMF, 67°	(93)	192, 193
OTf		PdCl$_2$(PPh$_3$)$_2$, Zn, DMF, 90°	(76)	192, 193
OTf		PdCl$_2$(PPh$_3$)$_2$, 2e⁻, DMF, n-Bu$_4$NBF$_4$, 90°	(45),(68)[a]	191, 192

C$_7$

OHC—C$_6$H$_4$—X → OHC—C$_6$H$_4$—C$_6$H$_4$—CHO

X		Conditions	Product(s) and Yield(s) (%)	Refs.
Cl		NiBr$_2$(PPh$_3$)$_2$, Zn, Et$_4$NI, THF, 50°	(70)	139
Cl		NiCl$_2$, Zn, PPh$_3$, DMAc, 80°	(62), (94)[b]	51
Cl		NiCl$_2$, Zn, pyridine, 80°	(84-85)[b]	463
Cl		NiCl$_2$(quinoline)$_2$, Zn, pyridine, 80°	(84), (90)[b]	463
Cl		NiCl$_2$(pyridine)$_2$, Zn, pyridine, 80°	(88)[b]	463
Br		NiCl$_2$(PPh$_3$)$_2$, Zn, PPh$_3$, DMF, 50°	(70)	122
Br		NiBr$_2$(PPh$_3$)$_2$, Zn, Et$_4$NI, THF, 50°	(75)	139
Br		NiCl$_2$, Zn, bpy, NaBr, DMAc, 60-80°	(80)	146
Br		Ni(CO)$_2$(PPh$_3$)$_2$, DMSO, 70°	(75)[b]	145
Br		Ni(CO)$_2$(PPh$_3$)$_2$, toluene, 70°	(65)[b]	145
Br		Ni(CO)$_2$(PPh$_3$)$_2$, hexane, 70°	(40)[b]	145
Br		Ni(cod)$_2$, DMF, 35°	(79)	49, 50

OHC—C$_6$H$_4$—I → PhNHN=CH—C$_6$H$_4$—C$_6$H$_4$—CH=NNHPh

		Conditions	Product(s) and Yield(s) (%)	Refs.
		1. Cu, neat, 260°	(59)	2
		2. PhNHNH$_2$		

C$_{7-8}$

NC—C$_6$H$_4$—X → NC—C$_6$H$_4$—C$_6$H$_4$—CN

X		Conditions	Product(s) and Yield(s) (%)	Refs.
Cl		NiCl$_2$, Zn, PPh$_3$, DMAc, 80°	(98)[b]	51
Cl		NiCl$_2$(quinoline)$_2$, Zn, pyridine, 80°	(80), (85)[b]	463
Cl		Ni(OAc)$_2$, NaH, t-AmONa, bpy, THF, C$_6$H$_6$, KI, 63°	(80)	54
Cl		Pd/C, NaOH, H$_2$O, formic hydrazide, 85°	(86)[b]	55
Br		Ni (electrogenerated), DMF, 130°	(77)	121
Br		Ni(cod)$_2$, DMF, 36°	(81)	49,
Br		NiI$_2$, naphthalene, Li, DME, 80°	(71)	111
Br		Ni(OAc)$_2$, NaH, t-AmONa, bpy, THF, C$_6$H$_6$, KI, 63°	(72)	54
Br		NiBr$_2$, lithium naphthalide, DME, 80°	(55)	111
Br		Pd(OAc)$_2$, n-Bu$_3$N, DMF, AsPh$_3$, 140°	(0)	172
I		Ni (electrogenerated), DMF, 100°	(68)	121
I		NiI$_2$, lithium naphthalide, DME, 80°	(85)	111
I		NiI$_2$, lithium naphthalide, 20°	(85)[b]	112
OMs		NiCl$_2$(PPh$_3$)$_2$, Zn, Et$_4$NI, THF, 67°	(94)[b]	133
OTf		PdCl$_2$(PPh$_3$)$_2$, 2e⁻, DMF, n-Bu$_4$NBF$_4$, 90°	(55), (70)	191
OTf		PdCl$_2$(PPh$_3$)$_2$, Zn, DMF, 90°	(85)[a]	192
OTf		NiCl$_2$(dppe), KI, Zn, DMF, THF, 67°	(45), (70)[a]	192

HO$_2$C—C$_6$H$_4$—X → HO$_2$C—C$_6$H$_4$—C$_6$H$_4$—CO$_2$H

X		Conditions	Product(s) and Yield(s) (%)	Refs.
I		Pd(OAc)$_2$, n-Bu$_3$N, DMF, 140°	(70)	172
Br		Pd(OAc)$_2$, n-Bu$_3$N, DMF, AsPh$_3$, 140°	(0)	172
Br		Ni(cod)$_2$, DMF, 40-60°	(0)	49,
Br		Pd/CaCO$_3$, N$_2$H$_4$·H$_2$O, KOH, MeOH, 135-140°	(40)	48
Br		Pd/C, NaOH, H$_2$O, formic hydrazide, 85°	(64)[c]	55

TABLE 4. 4,4'-DISUBSTITUTED BIARYLS (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
X Br	1. Ni(cod)$_2$, DMF, 30-65° 2. acid	(0)	49,50
SO$_2$Na	1. PdCl$_2$, H$_2$O, 90° 2. acid	(70)	167
	NiCl$_2$, Zn, PPh$_3$, DMAc, 80°	(69)[b]	51
	NiCl$_2$, Zn, PPh$_3$, DMAc, bpy, 80°	(96)	51
	Ni(OAc)$_2$, NaH, t-AmONa, bpy, THF, 63°	(73), (79)[b]	131
	NiBr$_2$(PPh$_3$)$_2$, Zn, Et$_4$NI, THF, 50°	(67)	139
	Ni(OAc)$_2$, t-BuOLi, LiH, bpy, THF, 63°	(63), (68)[b]	110
	Ni(OAc)$_2$, NaH, t-AmONa, bpy, THF, 63°	(87)	54
	Ni(OAc)$_2$, NaH, t-AmONa, bpy, C$_6$H$_6$, KI, THF, 63°	(71)	54
	NiBr$_2$(PPh$_3$)$_2$, Zn, Et$_4$NI, THF, 50°	(67)	139
	Ni(OAc)$_2$, t-BuOLi, LiH, bpy, THF, 63°	(63), (68)[b]	110
	NiCl$_2$, Zn, PPh$_3$, NaI, bpy, DMAc, 80°	(80)[b]	52
	NiCl$_2$, Zn, PPh$_3$, bpy, DMAc, 70°	(96)[b]	52
	NiCl$_2$, Zn, PPh$_3$, NaBr, DMF, 2-methylaminopyridine, 70°	(63)[b]	52
	NiCl$_2$, Zn, PPh$_3$, NaBr, DMAc, 2-chloropyridine, 70°	(92)[b]	52
	Pd/C, HCO$_2$Na, NaOH, H$_2$O, CTAB, 110°	(20), (21)[b]	181
	Pd/C, H$_2$, PEG-400, H$_2$O, NaOH, 110°	(36)[b]	186
	Pd(OAc)$_2$, DMF, H$_2$O, K$_2$CO$_3$, 115°	(48), (95)[b]	175
	Pd/C, HCO$_2$Na, NaOH, H$_2$O, CTAB, 95°	(49)	179
	Pd(OAc)$_2$, n-Bu$_3$N, DMF, AsPh$_3$, 140°	(50-57)	171, 17
	Pd/CaCO$_3$, N$_2$H$_4$•H$_2$O, MeOH, KOH, 135-140°	(35)	48
	Pd(OAc)$_2$, As(o-tol)$_3$, hydroquinone, Cs$_2$CO$_3$, 100°	(54)	178
	Pd(dba)$_2$, TBAF, DMF, PhSi(OMe)$_3$	(34)[b]	197
	Pd/C, NaOH, H$_2$O, formic hydrazide, 95°	(87)[b]	55
	Cu, neat, 190°	(0)	32
	Ni(cod)$_2$, DMF, 40°	(83)	49, 50
	NiCl$_2$(PPh$_3$)$_2$, Zn, PPh$_3$, DMF, 50°	(42)	122
	NiCl$_2$(PPh$_3$)$_2$, PPh$_3$, DMF, n-Bu$_4$NBr, 2e$^-$	(36)	127
	NiCl$_2$, Zn, bpy, NaBr, DMF, 60-80°	(65)	146
	Ni(OAc)$_2$, NaH, THF, t-AmONa, PPh$_3$, 63°	(60)	131
	Ni(OAc)$_2$, NaH, THF, t-AmONa, bpy, 63°	(75), (78)[b]	131
	NiBr$_2$, bpy, 2e$^-$, Bu$_4$NBF$_4$, EtOH, DMF	(80)	53
	NiBr$_2$, bpy, 2e$^-$, NaBr, EtOH, MeOH	(46)	53
	NiBr$_2$, 2e$^-$, dpa, H$_2$O, EtOH	(32)	153
	NiBr$_2$, 2e$^-$, bpy, MeOH, EtOH	(46)	153
	NiCl$_2$(PPh$_3$)$_2$, Zn, PPh$_3$, DMF, 40°	(73)[b]	123
	NiBr$_2$, lithium naphthalide, DME, 80°	(0)[b]	111
	NiBr$_2$(PPh$_3$)$_2$, Zn, THF, Et$_4$NI, 50°	(66-72)	139
	NiBr$_2$(PPh$_3$)$_2$, Zn, THF, 50°	(61)	139
	Ni powder, DMF, 140°	(68)	120
	Ni(OAc)$_2$, NaH, t-AmONa, bpy, THF, 63°	(70)	54
	Ni(OAc)$_2$, NaH, t-AmONa, bpy, C$_6$H$_6$, KI, THF, 63°	(70)	54
	Ni(OAc)$_2$, t-BuOLi, LiH, bpy, THF, 63°	(39), (47)[b]	110

TABLE 4. 4,4'-DISUBSTITUTED BIARYLS *(Continued)*
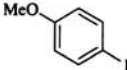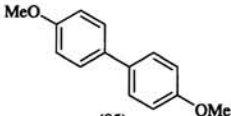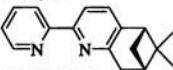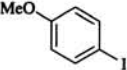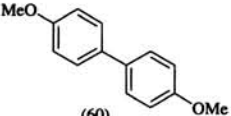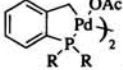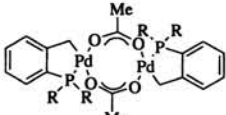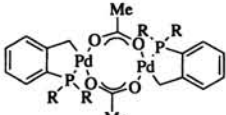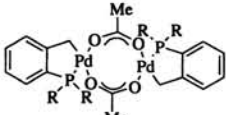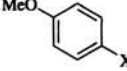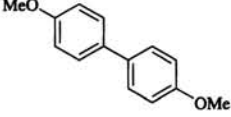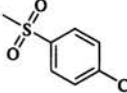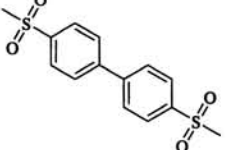
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

	Cu, neat, 230–240°	(85)	2
	Cu, neat, 190°	(70)	32
	Cu, methyl benzoate, 190°	(8)	46
	Cu, 1,2,4-trichlorobenzene, 190°	(45)	46
	Ni (electrogenerated), DMF, 80°	(75)	121
	NiI$_2$, lithium naphthalide, DME, 80°	(68), (85)[b]	111
	NiBr$_2$, bpy, 2e$^-$, Bu$_4$NBF$_4$, EtOH, DMF	(58)	53
	NiBr$_2$, KI, Zn, HMPA, 50°	(87)	129, 403
	NiCl$_2$, CrCl$_2$, Mn, THF, rt	(96)	406
	Pd(PPh$_3$)$_4$, 2e$^-$, DMF, Et$_4$NOTs	(87)	190
	Pd(OAc)$_2$, Et$_3$N, 100°	(39)	169
	Pd(OAc)$_2$, n-Bu$_3$N, 100°	(25)	169
	Pd(OAc)$_2$, n-Bu$_3$N, DMF, 140°	(58)	172
	Pd(OAc)$_2$, n-Bu$_4$NBr, DMF, H$_2$O, IPA, K$_2$CO$_3$, 115°	(81)	174
	Pd(OAc)$_2$, DMF, H$_2$O, IPA, K$_2$CO$_3$, 115°	(80)	175
	Pd(OAc)$_2$, As(o-tol)$_3$, hydroquinone, Cs$_2$CO$_3$, 75°	(95)	178
	Pd(OAc)$_2$, P(o-tol)$_3$, hydroquinone, Cs$_2$CO$_3$, 50°	(94)	178
	Pd(OAc)$_2$, P(o-tol)$_3$, Cs$_2$CO$_3$, 50°	(0)	178

	Pd/C, n-Bu$_4$NBr, DMF, K$_2$CO$_3$, 135°	(60)	195
	Pd(OAc)$_2$, n-Bu$_4$NBr, DMF, K$_2$CO$_3$, 135°	(60)	195
	Pd/C, Zn, air, H$_2$O, acetone, 25°	(92)[b]	185

| | EtN(i-Pr)$_2$, DMF, 110° | (70) | 194 |

	n-Bu$_4$NBr, DMF, K$_2$CO$_3$, 135°	(67)	195
	n-Bu$_4$NBr, DMAc, K$_2$CO$_3$, 135°	(47)	195
	Cs$_2$CO$_3$, P(o-tol)$_3$, DMAc, 50°	(88)[b]	178

X			
OTf	PdCl$_2$(PPh$_3$)$_2$, 2e$^-$, n-Bu$_4$NBF$_4$, DMF, 90°	(15)	192
OTf	PdCl$_2$(PPh$_3$)$_2$, Zn, DMF, 90°	(0)	192, 193
OTf	NiCl$_2$(dppe), KI, Zn, DMF, THF, 67°	(98)	192, 193
OTf	NiCl$_2$, Zn, PPh$_3$, NaI, DMF, sonication, 60°	(95)[b]	135
OMs	NiCl$_2$(PPh$_3$)$_2$, Zn, Et$_4$NI, THF, 67°	(83)[b]	133
OBs	NiCl$_2$(PPh$_3$)$_2$, Zn, Et$_4$NI, THF, 67°	(94)[b]	133
OFs	NiCl$_2$(PPh$_3$)$_2$, Zn, Et$_4$NI, THF, 67°	(71), (85)[b]	133

| | NiCl$_2$, PPh$_3$, bpy, Zn, DMAc, 90° | (99) | 465 |

TABLE 4. 4,4'-DISUBSTITUTED BIARYLS (Continued)
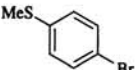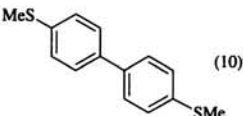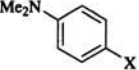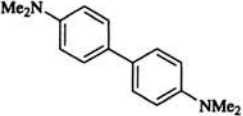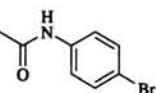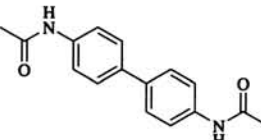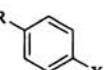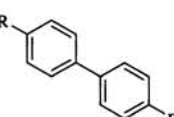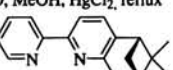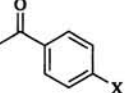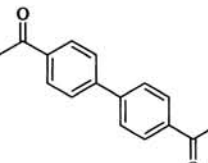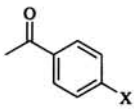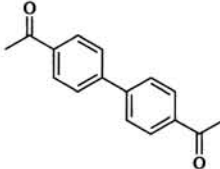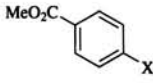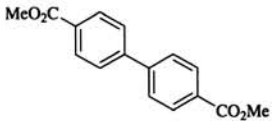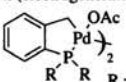
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

| | Ni(OAc)$_2$, t-BuOLi, LiH, bpy, THF, 63° | (10)[b] | 110 |

C$_8$

X			
Br	NiBr$_2$, bpy, EtOH, MeOH	(trace)	153
Br	NiBr$_2$, EtOH, 2e⁻, dpa, H$_2$O	(30)	153
Br	Ni(OAc)$_2$, NaH, t-AmONa, bpy, THF, C$_6$H$_6$, KI, 63°	(81)	54
Br	Pd/CaCO$_3$, N$_2$H$_4$•H$_2$O, MeOH, KOH, 135-140°	(60)	48
Br	Pd(OAc)$_2$, n-Bu$_3$N, DMF, AsPh$_3$, 140°	(45)	172
I	Pd(PPh$_3$)$_4$, 2e⁻, Et$_4$NOTs, DMF	(93)	190

| | NiCl$_2$(PPh$_3$)$_2$, Zn, PPh$_3$, DMF, 40° | (37) | 123 |
| | Ni(cod)$_2$, DMF, 50-60° | (0) | 49 |

R	X			
Et	I	Cu, neat, heat	(53)	466
			(82)	47
Et	I	PdCl$_2$, N$_2$H$_4$•H$_2$O, MeOH, HgCl$_2$, reflux		
CH=CH$_2$	Br	NiCl$_2$, CrCl$_2$, Mn, THF, rt	(84)	406

CH$_2$CN	Br	Ni(cod)$_2$, DMF, 33°	(79)	49, 50
OEt	I	Cu, neat, 230-240°	(75)	2
OEt	I	Cu, DMF, reflux	(77)	57
OAc	Cl	NiCl$_2$, PPh$_3$, DMAc, Zn, 80°	(66)[b]	51
OAc	Cl	NiCl$_2$, PPh$_3$, DMAc, Zn, bpy, 80°	(75), (90)[b]	51
OAc	Cl	NiCl$_2$, PPh$_3$, DMAc, Zn, NaBr, 80°	(66)[b]	147

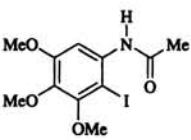| X			
Cl	NiCl$_2$, PPh$_3$, DMAc, Zn, 80°	(100)[b]	51
Cl	Ni powder, DMF, KI, 140°	(85)	120
Cl	NiBr$_2$(PPh$_3$)$_2$, Zn, Et$_4$NI, THF, 50°	(73)	139
Cl	NiCl$_2$, bpy, NaBr, DMAc, Zn, 60-80°	(75)	146
Cl	NiCl$_2$(quinoline)$_2$, Zn, pyridine, 80°	(80), (84)[b]	463
Br	NiCl$_2$(PPh$_3$)$_2$, PPh$_3$, DMF, n-Bu$_4$NBr, 2e⁻	(47)	127
Br	NiBr$_2$, lithium naphthalide, DME, 80°	(57)[b]	111
Br	NiI$_2$, lithium naphthalide, DME, 80°	(46)	111
Br	NiCl$_2$(PPh$_3$)$_2$, PPh$_3$, Zn, DMF, 50°	(68)	122
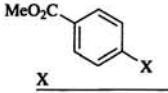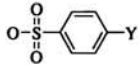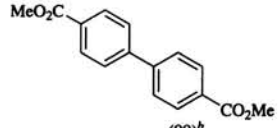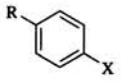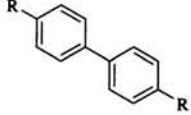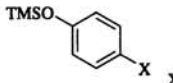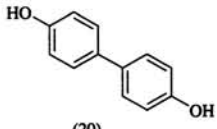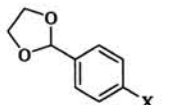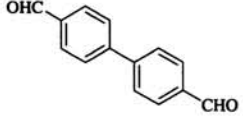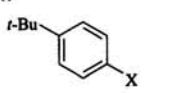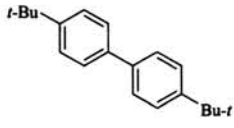
TABLE 4. 4,4'-DISUBSTITUTED BIARYLS *(Continued)*

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

X

X			
Br	NiBr$_2$, EtOH, 2e$^-$, dpa, H$_2$O	(63)	153
Br	Ni powder, DMF, 140°	(77)	120
Br	NiI$_2$, lithium naphthalide, DME, 20°	(46)	112
Br	NiBr$_2$(PPh$_3$)$_2$, Zn, Et$_4$NI, THF, 50°	(71)	139
Br	NiCl$_2$(PPh$_3$)$_2$, Zn, PPh$_3$, DMF, 50°	(58)	123
Br	NiBr$_2$, bpy, EtOH, MeOH, 2e$^-$	(trace)	153
Br	Ni(cod)$_2$, DMF, 45°	(93)	49, 50
Br	[PdCl(π-C$_3$H$_5$)]$_2$, TBAF, DMSO, 120°	(75)	198
Br	Pd/C, HCO$_2$Na, NaOH, H$_2$O, SDPNS, 95°	(41)	179
I	Cu, neat, 235-260°	(26)	467
I	NiBr$_2$, Zn, KI, HMPA, 50°	(98)	129, 403
OTs	NiCl$_2$(PPh$_3$)$_2$, Zn, NaBr, DMF, PPh$_3$, 100°	(67)	137
OMs	NiCl$_2$(PPh$_3$)$_2$, Zn, Et$_4$NI, THF, 67°	(73)^b	133
OMs	NiCl$_2$(PPh$_3$)$_2$, Zn, Et$_4$NI, DMAc, 100°	(85)^b	133
OMs	NiCl$_2$(PPh$_3$)$_2$, Zn, KI, DMAc, 67°	(93)^b	133
OMs	NiCl$_2$(PPh$_3$)$_2$, Zn, NaI, DMAc, 100°	(91)^b	133
OMs	NiCl$_2$(PPh$_3$)$_2$, Zn, NaBr, DMAc, 100°	(96)^b	133
OMs	NiCl$_2$(PPh$_3$)$_2$, Zn, NaBr, NMP, 100°	(trace)^b	133
OMs	NiCl$_2$(PPh$_3$)$_2$, Zn, NaBr, DMF, PPh$_3$, 100°	(83)	137
OFs	NiCl$_2$(PPh$_3$)$_2$, Zn, Et$_4$NI, THF, 67°	(98)^b	133

X

X			
Cl	NiBr$_2$(PPh$_3$)$_2$, Zn, Et$_4$NI, THF, 50°	(85)	139
Cl	NiCl$_2$, PPh$_3$, Zn, pyridine, heat	(92)	468
Cl	NiCl$_2$, PPh$_3$, Zn, 4-methylpyridine, heat	(60)	468
Cl	NiCl$_2$, PPh$_3$, Zn, DMAc, heat	(82)	468
Cl	NiCl$_2$, Zn, pyridine, 85°	(78)^b	463
Cl	NiCl$_2$, Zn, 4-methylpyridine, 85°	(83)^b	463
Cl	NiCl$_2$(pyridine)$_2$, Zn, pyridine, 85°	(81)^b	463
Cl	NiCl$_2$(quinoline)$_2$, Zn, pyridine, 85°	(88), (89)^b	463
Cl	NiCl$_2$(PPh$_3$)$_2$, PPh$_3$, DMF, n-Bu$_4$NBr, 2e$^-$	(51)	127
Br	Ni (electrogenerated), DMF, 100°	(5)	121
Br	Ni (electrogenerated), DMF, 130°	(37)	121
Br	NiCl$_2$(PPh$_3$)$_2$, Zn, PPh$_3$, DMF, 50°	(83)	123
Br	NiCl$_2$(PPh$_3$)$_2$, Zn, PPh$_3$, DMF, 50°	(76)	122
I	Cu, neat, 190°	(15)	32
I	Cu, DMF, reflux	(74)	57
I	Cu, neat, 220-260°	(70)	2
I	Pd(OAc)$_2$, As(o-tol)$_3$, hydroquinone, Cs$_2$CO$_3$, 75°	(99)	178
I	Pd(OAc)$_2$, P(o-tol)$_3$, hydroquinone, Cs$_2$CO$_3$, 75°	(95)	178
I	NiBr$_2$(PPh$_3$)$_2$, Zn, Et$_4$NI, THF, 50°	(86-90)	139
I	NiBr$_2$(PPh$_3$)$_2$, Zn, THF, 50°	(85)	139
I	Ni, DMF, 100°	(0)	121
I	Ni (electrogenerated), DMF, 25°	(20)	121
I	Ni (electrogenerated), DMF, 50°	(60)	121
I	Ni (electrogenerated), DMF, 100°	(90)	121
I	EtN(i-Pr)$_2$, DMF, 110°	(76)	194

TABLE 4. 4,4'-DISUBSTITUTED BIARYLS (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C8-14

MeO2C—⟨ ⟩—X

MeO2C—⟨ ⟩—⟨ ⟩—CO2Me

X			
OMs	NiCl2(PPh3)2, Zn, Et4NI, THF, reflux	(99)[b]	133
OMs	NiCl2(PPh3)2, Zn, Et4NI, DMAc	(73)[b]	133
OMs	NiCl2(PPh3)2, Zn, KI, THF	(93)[b]	133
OMs	NiCl2(PPh3)2, Zn, KBr, THF	(86)[b]	133
OMs	NiCl2(PPh3)2, Zn, NaBr, DMAc	(78)[b]	133
OMs	NiCl2(PPh3)2, Zn, KBr, DMAc	(79)[b]	133
OTf	NiCl2(PPh3)2, Zn, Et4NI, THF, reflux	(99)[b]	133

O=S(O)(O)—⟨ ⟩—Y

Y			
H	NiCl2(PPh3)2, Zn, Et4NI, THF, reflux	(83), (97)[b]	133
Me	NiCl2(PPh3)2, Zn, Et4NI, THF, reflux	(99)[b]	133
F	NiCl2(PPh3)2, Zn, Et4NI, THF, reflux	(85), (99)	133
Cl	NiCl2(PPh3)2, Zn, Et4NI, THF, reflux	(79)[b]	133

C9

R—⟨ ⟩—X

R—⟨ ⟩—⟨ ⟩—R

R	X			
i-Pr	I	Cu, neat, 260-270°	(79)	431
CO2Et	Br	Ni(cod)2, DMF, 40°	(81)	49, 50
CO2Et	OTf	PdCl2(PPh3)2, Zn, DMF, 90°	(69)[a]	192, 193
CO2Et	OTf	NiCl2(dppe), Zn, DMF, THF, KI, 67°	(63), (86)[a]	192, 193
CO2Et	I	Ni(cod)2, hv, toluene, N-methylimidazole	(90)	132
CO2Et	I	CuI-P(Et)3, lithium naphthalide, DME or THF, heat	(52)[b]	85
i-PrO	Br	Pd/C, NaOH, H2O, formic hydrazide, 95°	(78)[b]	55

TMSO—⟨ ⟩—X

HO—⟨ ⟩—⟨ ⟩—OH

X			
Br	1. Cu, quinoline, 240°	(20)	433
	2. HCl		
I	1. Cu, quinoline, 240°	(55)	433
	2. HCl		

(1,3-dioxolan-2-yl)—⟨ ⟩—X

OHC—⟨ ⟩—⟨ ⟩—CHO

X			
Cl	Ni(OAc)2, NaH, t-AmONa, bpy, THF, 63°	(78)	54
Cl	Ni(OAc)2, NaH, t-AmONa, bpy, THF, C6H6, KI, 63°	(76)	54
Br	Ni(OAc)2, NaH, t-AmONa, bpy, THF, C6H6, KI, 63°	(63)	54

C10-11

t-Bu—⟨ ⟩—X

t-Bu—⟨ ⟩—⟨ ⟩—Bu-t

X			
I	PdCl2(PPh3)2, 2e⁻, Et4NOTs, DMF, 90	(97)	190
I	Pd(PPh3)4, 2e⁻, Et4NOTs, DMF, 90°	(98)	190
I	2e⁻, Et4NOTs, DMF, 90°	(0)	190
I	Cu, neat, 325°	(29)	469
Br	Pd(PPh3)4, 2e⁻, Et4NOTs, DMF, 90°	(99)	190
Br	NiCl2, Zn, bpy, NaBr, DMF, 60-80°	(76)	146
Cl	Pd(PPh3)4, 2e⁻, Et4NOTs, DMF, 90°	(0)	190
OTf	NiCl2(dppe), Zn, KI, DMF, 90°	(36)	192

TABLE 4. 4,4'-DISUBSTITUTED BIARYLS (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
X			
Br	1. Ni(OAc)$_2$, NaH, t-AmONa, bpy, THF, C$_6$H$_6$, KI, 63° 2. acid	(64)	54
Cl	1. Ni(OAc)$_2$, NaH, t-AmONa, bpy, THF, C$_6$H$_6$, KI, 63° 2. acid	(72)	54
C$_{11}$ 	Cu, neat, 300°	(40)	470
C$_{12}$ 	Cu, quinoline, 240°	(60)	433
  X			
Cl	NiCl$_2$, bpy, LiBF$_4$, DMAc, 2e$^-$	(22)	471
Br	Pd/C, HCO$_2$Na, NaOH, H$_2$O, CTAB, 95°	(48)	179
I	Cu, neat, 250-270°	(66)	472
I	Cu, neat, 290°	(42)	473
I	Cu, neat, 300°	(97)	437
I	Cu, neat, 250-270°	(82)	2
OMs	NiCl$_2$(PPh$_3$)$_2$, Zn, Et$_4$NI, THF, 67°	(99)^b	133
OFs	NiCl$_2$(PPh$_3$)$_2$, Zn, Et$_4$NI, THF, 67°	(60)	133
	Cu, neat, 225-235°	(42)	438
	Cu, neat, 200-220°	(47)	238
	Cu, neat, 200-220°	(50)	238
  R X			
NO$_2$ I	Cu, neat, heat	(14)	474
OH Br	Pd/C, Na$_2$CO$_3$, H$_2$O, MeOH, formic hydrazide, 70°	(75)	55

TABLE 4. 4,4'-DISUBSTITUTED BIARYLS (Continued)
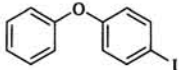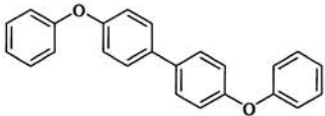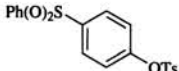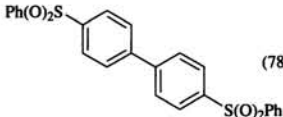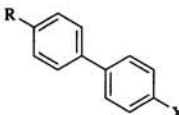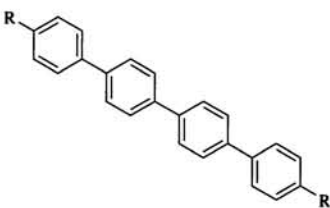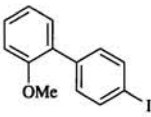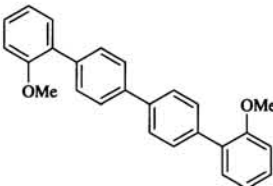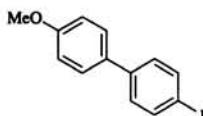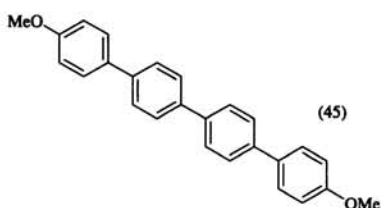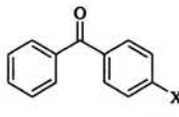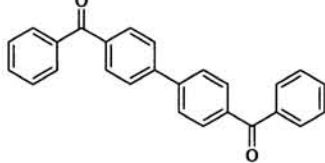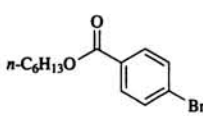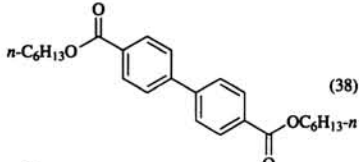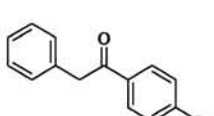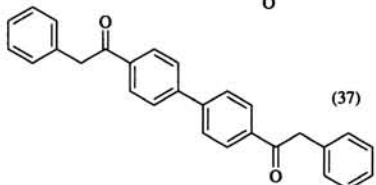
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Cu, DMF, reflux	(45)	410
	NiCl₂(PPh₃)₂, PPh₃, NaBr, Zn, DMF, 100°	(78)	137

R	X			
F	Cl	NiBr₂, Zn, DMAc, PPh₃, 50-90°	(82)	475
F	Br	Cu, neat, 200°	(30)	55
Cl	Br	Cu, neat, 200°	(0)	405

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₁₃	Cu, neat, 280°	(70)	474
	Cu, neat, 280°	(45)	474

X			
Br	Pd/C, Zn, air, acetone, H₂O, 25°	(0)	185
I	Cu, neat, 250°	(55)	2
OTs	NiCl₂(PEt₃)₂, PPh₃, NaBr, Zn, DMF, 100°	(—)	137

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd(OAc)₂, n-Bu₃N, DMF, AsPh₃, 140°	(38)	172
C₁₄	Ni(cod)₂, DMF, 40°	(37)	475

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TABLE 4. 4,4'-DISUBSTITUTED BIARYLS (Continued)
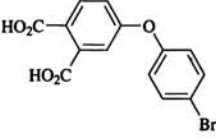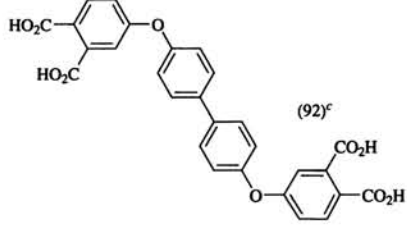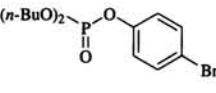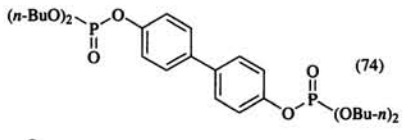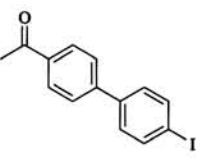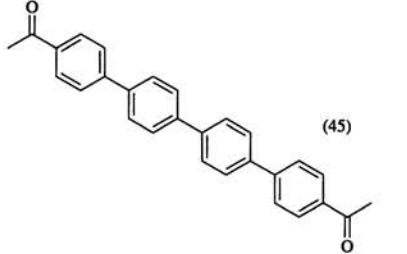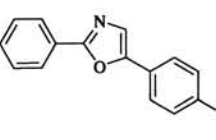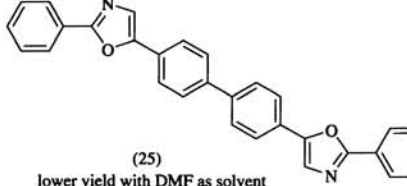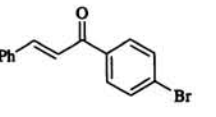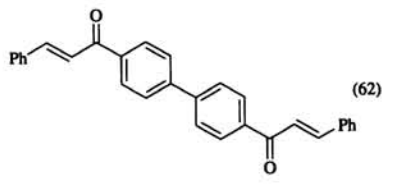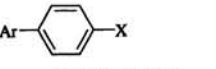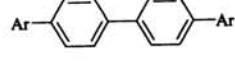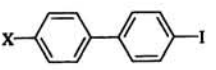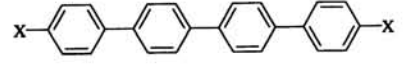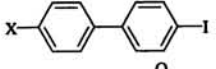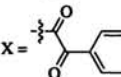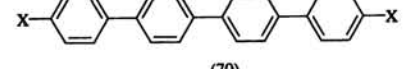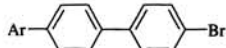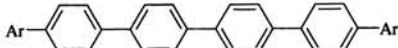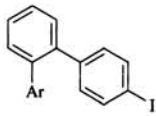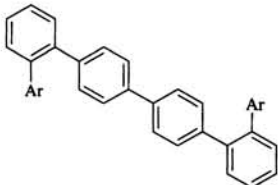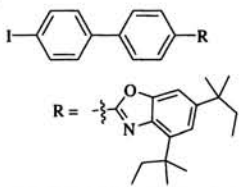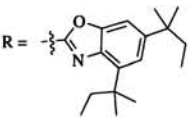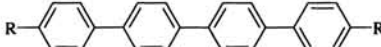
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd/C, NaOH, H₂O, formic hydrazide, 80°	(92)ᶜ	55
	Ni(OAc)₂, bpy, Et₄NBr, 2e⁻, CH₃CN	(74)	405
	Ni(cod)₂, DMF, 42°	(45)	475
C₁₅	Cu, neat, 120-250°	(25) lower yield with DMF as solvent	476
	Ni(cod)₂, DMF, 50-65°	(62)	49

$$\text{HO}_2\text{C-} \quad \text{Pd/C, NaOH, H}_2\text{O, formic hydrazide, 80°}$$

C₁₈

Ar—⬡—X

Ar = biphenyl-4-yl

Ar—⬡—⬡—Ar

X			
I	Cu, neat, 280°	(40)	62
OMs	NiCl₂(PPh₃)₂, Zn, Et₄NI, THF, 67°	(60)	133

C₁₉₋₂₅

X—⬡—⬡—I   Cu, biphenyl, 255-260°   X—⬡—⬡—⬡—⬡—X   477

$$X = (CH_2)_5\overset{O}{\overset{\|}{C}}OR$$

R	
Me	(11)
Et	(13)
n-Pr	(12)
n-Heptyl	(7)

C₂₀

X—⬡—⬡—I   PdCl₂, Bu₃N, 220°   X—⬡—⬡—⬡—⬡—X   478

(70)

$$X = \overset{O}{\overset{\|}{C}}\overset{O}{\overset{\|}{C}}\text{-Ph}$$
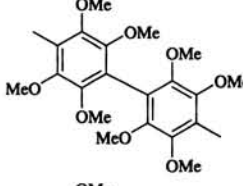
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TABLE 4. 4,4'-DISUBSTITUTED BIARYLS *(Continued)*

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
Ar—⟨⟩—⟨⟩—Br Ar = biphenyl-4-yl	NiCl₂, bpy, LiBF₄, DMAc, 2e⁻	Ar—⟨⟩—⟨⟩—⟨⟩—⟨⟩—Ar (35)	471
Ar = biphenyl-2-yl	Cu, neat, 225–235°	(61)	438
C₂₉ I—⟨⟩—⟨⟩—R R =	Cu, neat, 270–280°	R—⟨⟩—⟨⟩—⟨⟩—⟨⟩—R (27)	479

a The yield was determined by NMR spectroscopy.

b The yield was determined by gas chromatography.

c The yield was determined by HPLC.

TABLE 5. 2,2',3,3'-TETRASUBSTITUTED BIARYLS
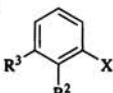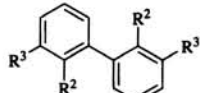
Substrate			Conditions	Product(s) and Yield(s) (%)	Refs.

C$_{6-18}$

R^2	R^3	X			
NO$_2$	NO$_2$	I	Cu, p-nitrotoluene, heat	(53)	58
Cl	Cl	I	Cu	(63)	480
OMe	F	I	Cu, heat	(67)	481
Me	Me	I	Cu, neat, 150°	(45)	482
Me	Me	I	PdCl$_2$, HgCl$_2$, N$_2$H$_4$•H$_2$O, MeOH, reflux	(64)	47
Me	OMe	I	Cu, neat, 270°	(92)	483
OMe	OMe	I	Cu, neat, 250°	(70-83)	484
(CH$_2$)$_2$CO$_2$Et	Cl	I	Cu, neat, 240°	(20)	485
				yield includes iodide preparation and subsequent ester hydrolysis	
Ph	Ph	I	Cu, neat, 260-270°	(64)	486

TABLE 6. 2,2',4,4'-TETRASUBSTITUTED BIARYLS

Substrate			Conditions	Product(s) and Yield(s) (%)	Refs.
C$_6$					
R^2	R^4	X			
Cl	NO$_2$	I	Cu, neat, 210°	(44)	487
Br	NO$_2$	I	Cu, neat, 210°	(23)	487
Cl	Cl	I	Cu, neat, 220-270°	(53)	2
F	F	Br	Pd/C, NaOH, diethylene glycol dimethyl ether, polyethylene glycol dimethyl ether, glycerol, 100°	(87)[a]	462
		X			
		I	Cu, xylene, 110-140°	(94)	238
		Br	Cu, nitrobenzene, reflux	(65)	1
		Cl	Cu, nitrobenzene, reflux	(60)	1
		Cl	Cu, methyl benzoate, 190°	(18)	46
		Cl	Cu, 1,2,4-trichlorobenzene, 190°	(16)	46
		Cl	Cu, neat, 190°	(0)	32
	R^4	X			
	F	Br	Cu, neat, 240-250°	(46)	488
	Br	Br	Cu, neat, 190-250°	(65)	1
	Br	Br	Cu, DMF, reflux	(76)	489
	Br	Br	Cu, DMF, 120°	(70)	490
	Cl	Cl	Cu, neat, 240°	(42)	1
	Cl	Cl	Cu, DMF, reflux	(75)	57
C$_7$					
R^2	R^4	X			
NO$_2$	Me	I	Cu, sand, 180°	(46)	491
NO$_2$	CF$_3$	Cl	Cu, neat, reflux	(30)	492
NO$_2$	CF$_3$	Cl	Cu, neat, reflux	(24)	493
NO$_2$	OMe	I	Cu, neat, 130-170°	(82)	494
Me	NO$_2$	I	Cu, sand, 205-210°	(10)	495
Me	NO$_2$	I	Cu, neat, 280°	(25)	491
Me	F	Br	Pd/C, NaOH, diethylene glycol dimethyl ether, polyethylene glycol dimethyl ether, glycerol, 100°	(73)[a]	462
CF$_3$	NO$_2$	I	Cu, neat, 250-300°	(17)	496
CF$_3$	F	I	Cu, heat	(63)	497
CF$_3$	Cl	I	Cu, heat	(56)	497
OMe	F	I	Cu, sand, 200°	(43)	498
OMe	NO$_2$	I	Cu, neat, 230°	(50)	499
OMe	NO$_2$	I	Cu, heat	(<10)	238
OMe	NO$_2$	I	Cu, biphenyl, 200°	(54)	238
OMe	NO$_2$	I	Cu, xylene, 200°	(91)	238
OMe	NO$_2$	I	Cu, nitrobenzene, 210-220°	(83)	500

TABLE 6. 2,2',4,4'-TETRASUBSTITUTED BIARYLS *(Continued)*

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C_8

R^2	R^4	X			
NO_2	CO_2Me	Br	Cu, neat, 185°	(81)	1
NO_2	CO_2Me	I	Cu, neat, 170-190°	(78)	501
NO_2	OAc	I	Cu, neat, 140-180°	(77)	502
Me	Me	I	Cu, neat, sealed tube, 230-260°	(86)	2
Me	Me	I	Ni powder, DMF, 140°	(54)	120
Me	Me	I	$NiCl_2$, NaBr, Zn, bpy, DMF, 60-80°	(79)	146
Me	OMe	I	Cu, neat, 260-290°	(62)	503
CF_3	CF_3	I	Cu, heat	(32)	504
CO_2Me	NO_2	Br	Cu, neat, 200-205°	(51)	505
CO_2Me	Cl	Br	Cu, neat, 200°	(61)	505
CO_2Me	Br	I	Cu, neat, 180-230°	(75)	506
OMe	OMe	I	Cu, neat, 260°	(71)	507
OMe	OMe	I	Cu, neat, 190°	(65)	32
OMe	OMe	I	Cu_2O, heat	(47)	65
OMe	OMe	I	Cu, heat	(72-73)	65

C_{9-12}

R^2	R^4	X			
NO_2	CO_2Et	I	Cu, nitrobenzene, reflux	(69)	508
CO_2Me	Me	I	$NiCl_2$, KI, Zn, HMPA, 20°	(98)	129
CO_2Me	OMe	Br	Cu, neat, 220-250°	(100)	509
OMe	CO_2Me	I	Cu, neat, 210-220°	(91)	510
OMe	CO_2Me	Br	Cu, neat, 210-220°	(<30)	510
OMe	CO_2Me	Br	Cu, neat, 255-260°	(34)	511
NHCOMe	NHCOMe	Br	Cu, DMF, 100-120°	(95)	34
SO_3Ph	NO_2	I	Cu, neat, 205°	(68)	512

C_{12}

Cu, xylene, 110-140°	(92-98)	238
Cu, neat, 190-205°	(83)	513

Cu, biphenyl, 180°	(48)	238

Cu, neat, 215-225°	(70)	514

TABLE 6. 2,2',4,4'-TETRASUBSTITUTED BIARYLS *(Continued)*

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₁₃			
R²			
Me	Cu, 200-270°	(45)	515
OMe	Cu, neat, 190-210°	(54)	513
	Cu, neat, 180-210°	(92)	421
C₁₄			
	Cu, neat, 230°	(77)	516
C₁₅			
R⁴'			
H	NiCl₂(PPh₃)₂, PPh₃, Zn, Et₄NI, THF, 67°	(65)	134
F	NiCl₂(PPh₃)₂, PPh₃, Zn, Et₄NI, THF, 67°	(62)	134
C₁₈			
	Cu, neat, 270-275°	(45)	447
	Cu, neat, 320°	(10)	291
C₁₉			
	NiCl₂(PPh₃)₂, PPh₃, Zn, Et₄NI, THF, 67°	(45)	134
C₂₈			
Ar = 1-(3,3'-dimethylbiphenyl-4-yl)	Cu, 230°	(20)	517

ᵃ The yield was determined by gas chromatography.

TABLE 7. 2,2',5,5'-TETRASUBSTITUTED BIARYLS

	Substrate			Conditions	Product(s) and Yield(s) (%)	Refs.

C$_{7-8}$

R^2	R^5	X	Conditions	Product(s) and Yield(s) (%)	Refs.
NO$_2$	Me	Br	Cu, neat, 215-235°	(73)	518
NO$_2$	OMe	I	Cu, neat, 140-170°	(80)	502
NHCHO	Cl	Br	Cu, DMSO, 70°	(97)	34
NHCHO	NO$_2$	Br	Cu, DMF, 100°	(44)	34
Me	NO$_2$	I	Cu, neat, 220-270°	(22)	519
Me	SO$_2$F	I	Cu, neat, 220°	(41)	452
Me	Cl	I	Cu, neat, 280-290°	(50)	520
CHO	NO$_2$	I	Cu, DMF, reflux	(65)	428
CHO	Cl	I	Cu, DMF, reflux	(42)	521
SMe	Cl	I	Cu, neat, 200-280°	(25-30)	522
NO$_2$	CO$_2$Me	Br	Cu, nitrobenzene, reflux	(81)	518
NHCOMe	NO$_2$	Br	Cu, DMF, 110°	(94)	34
NHCOMe	Cl	Br	Cu, DMF, 100°	(76)	34
NHCOMe	Cl	Br	Cu, DMSO, 50°	(88)	34
NHCOMe	Br	Br	Cu, DMSO, 60°	(84)	34
Me	Me	I	Cu, neat, 265-300°	(46)	2
Me	Me	I	Ni powder, DMF, 140°	(42)	120
Me	Me	I	Pd(OAc)$_2$, Et$_3$N, 100°	(3)	169
Me	Me	I	Pd(OAc)$_2$, n-Bu$_3$N, 100°	(trace)	169
Me	Me	I	PdCl$_2$, HgCl$_2$, N$_2$H$_4$•H$_2$O, MeOH, reflux	(74)	47
Me	Me	I	PdCl$_2$, N$_2$H$_4$•H$_2$O, MeOH, reflux	(19)	47
Me	Me	Br	NiCl$_2$, bpy, NaBr, Zn, DMF, 60-80°	(76)	146

C$_9$

Cu, DMF, reflux   (45)   523

C$_{8-9}$

R^2	R^5	X	Conditions	Product(s) and Yield(s) (%)	Refs.
Me	Me	Br	NiCl$_2$, bpy, NaBr, Zn, DMF, 60-80°	(76)	146
Me	Me	I	PdCl$_2$, HgCl$_2$, N$_2$H$_4$• H$_2$O, MeOH, reflux	(74)	47
Me	Me	I	PdCl$_2$, N$_2$H$_4$• H$_2$O, MeOH, reflux	(19)	47
CF$_3$	CF$_3$	I	Cu, sand, reflux	(42)	524
CO$_2$Me	NO$_2$	I	Cu, neat, 200°	(75)	525
OMe	Me	Br	PdCl$_2$(PPh$_3$)$_2$, 2e$^-$, Et$_4$NOTs, DMF	(0)	190
OMe	OMe	I	Cu, neat, 215-260°	(93)	2
OMe	OMe	I	Cu, neat, heat	(80-90)	526
OMe	OMe	Br	NiBr$_2$, bpy, NaBr, 2e$^-$, EtOH, MeOH	(29)	53
OMe	CHO	I	NiCl$_2$(PPh$_3$)$_2$, PPh$_3$, Zn, DMF, 54°	(16)	457
OMe	CO$_2$Me	Br	Cu, neat, sealed tube, 240-250°	(7)	527
NO$_2$	CH$_2$CO$_2$Me	Br	Cu, neat, 175°	(38)	37
Me	CO$_2$Me	I	Cu, neat, 260-310°	(65) crude	528

TABLE 7. 2,2',5,5'-TETRASUBSTITUTED BIARYLS (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C$_{10}$

R^2	X			
OMe	I	Cu, neat, 175°	(17)	37
OMe	I	Cu, neat, 230°	(26)	523
OSO$_2$Me	Br	Cu, neat, 230°	(48)	37

R^2	R^5	X			
Me	CO$_2$Et	I	Cu, neat, 260-310°	(55)	528
CO$_2$Me	CO$_2$Me	I	Cu, neat, 260-310°	(70)	528

C$_{11}$

Cu, neat, 300° (68) 529

Cu, neat, 225-285° (58) 530

Cu, heat, 270-275° (81) 431

Cu, heat (60-70) 531

C$_{12}$

Cu, neat, 235° (62) 532

TABLE 7. 2,2',5,5'-TETRASUBSTITUTED BIARYLS *(Continued)*

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{13}$	NiBr$_2$, PPh$_3$, Zn, DMAc, 80-90°	(88)	440
	Cu, neat, 260°	(59)	533
C$_{14}$	NiCl$_2$(PPh$_3$)$_2$, PPh$_3$, Zn, DMF, 54°	(16)	457
C$_{16}$	Cu, neat, 200-220°	(75)	37
C$_{18}$	Cu, neat, 270-275°	(64)	447
C$_{20}$	Cu, neat, 300°	(60)	529

TABLE 8. 2,2',6,6'-TETRASUBSTITUTED BIARYLS

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C$_{6-7}$

R^2	R^6	X			
NO$_2$	NO$_2$	Cl	Cu, DMF, 145°	(51)	534
NO$_2$	NO$_2$	Cl	Cu, nitrobenzene, heat	(54)	58
NO$_2$	NO$_2$	Cl	Cu, DMF, reflux	(0)	61
NO$_2$	Br	Br	Cu, neat, 140-160°	(72)	535
NO$_2$	I	I	Cu, neat, 150-160°	(75)	536
Cl	Cl	I	Cu, sealed tube, 230°	(59)	537
Cl	Cl	I	Cu, sealed tube, 200°	(quantitative) crude	538
NO$_2$	Me	I	Cu, neat, 180-235°	(81)	539
NO$_2$	Me	I	Cu, neat, 200°	(79)	491
NO$_2$	Me	I	Cu, neat, 200-235°	(80)	540
NO$_2$	Me	I	Cu, neat, 240-280°	(68)	541
NO$_2$	Me	I	Cu, neat, 180-230°	(67), yield includes preparation of precursor	542
NO$_2$	Me	I	Cu, DMF, reflux	(>66)	543
NO$_2$	OMe	I	Cu, DMF, reflux	(>66)	543
NO$_2$	OMe	Cl	Cu, nitrobenzene, 180-210°	(70)	544
NO$_2$	OMe	Cl	Cu, DMF, reflux	(84)	57
F	OMe	I	Cu, neat, 180-200°	(65)	545

C$_8$

R^2	R^6	X			
NO$_2$	CO$_2$Me	I	Cu, neat, 165°	(79)	546
NO$_2$	CO$_2$Me	I	Cu, neat, 165-175°	(83)	547
NO$_2$	CO$_2$Me	I	Cu, neat, 100-180°	(91)	548
NO$_2$	CO$_2$Me	Br	Cu, heat	(50)	549
NO$_2$	CO$_2$Me	Cl	Cu, neat, 225-235°	(60)	550
I	CO$_2$Me	I	Cu, neat, 110-115°	(61) and 31% recovered starting material	33
Br	CO$_2$Me	I	Cu, neat, 160-170°	(81)	542
F	CO$_2$Me	I	Cu, neat, 180-240°	(57)	551
Me	Me	I	Cu, neat, 240-265°	(21)	552
Me	Me	Br	Ni(cod)$_2$, DMF, 54°	(0)	49, 50
Me	Me	Br	NiCl$_2$, CrCl$_2$, Mn, THF, rt	(0)	406
Me	CHO	I	Cu, neat, 190-220°	(50)	428
Me	OMe	I	Cu, neat, heat	(70)	553
OMe	OMe	I	Cu, neat, 170-210°	(85-90)	554
OMe	OMe	Br	Cu, neat, 240-260°	(48)	555
CF$_3$	CF$_3$	I	Cu, neat, 270°	(33)	556

C$_{10}$

Cu, neat, 100-160°	(88)	548

TABLE 8. 2,2',6,6'-TETRASUBSTITUTED BIARYLS *(Continued)*
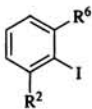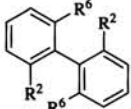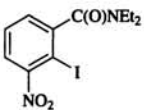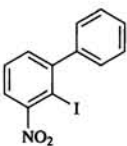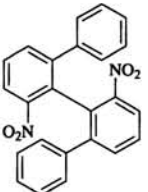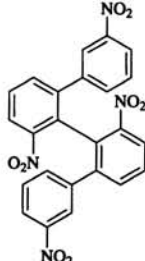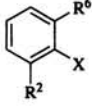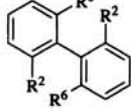
	Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C$_{9-10}$

R^2	R^6			
NO$_2$	CO$_2$Et	Cu, neat, 155-235°	(80)	557
Me	CO$_2$Me	Cu, neat, 260-270°	(74)	558
Me	CO$_2$Me	Cu, DMF, heat	(80)	559
Me	CO$_2$Me	Cu, neat, 270°	(90) after saponification to diacid	560
OMe	CO$_2$Me	Cu, neat, 205-215°	(81)	551
Et	CO$_2$Me	Cu, DMF, reflux	(41)	33

C$_{11}$

Cu, neat, 160°   (51)   561

C$_{12}$

Cu, neat, 210-215°   (95)   562

Cu, neat, 190-195°   (91)   563

C$_{18-19}$

R^2	R^6	X		
F	POPh$_2$	Cl	Cu, DMF, 140°	(71)	564
Ph	Ph	I	Cu, neat, 260-270°	(3)	486
OMe	POPh$_2$	Br	Cu, DMF, 140°	(91)	565
OMe	POPh$_2$	I	Cu, DMF, 140°	(91)	565

TABLE 9. 3,3',4,4'-TETRASUBSTITUTED BIARYLS

	Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C₆₋₇

R³	R⁴	X			
F	OH	Br	NiBr₂, EtOH, MeOH, 2e⁻, bpy, NaBr	(75)	53
NO₂	NO₂	I	Cu, neat, 250°	(47)	1
Cl	Cl	SO₂Cl	PdCl₂(PhCN)₂, Ti(OPr-i)₄, m-xylene, 140°	(70)	168
NO₂	Me	I	Cu, nitrobenzene, reflux	(39)	566
Cl	Me	I	Cu, neat, 220°	(90)	567
Br	OMe	Br	Pd(OAc)₂, Bu₃N, DMF, AsPh₃, 140°	(46)	172
Me	Cl	SO₂Cl	PdCl₂(PhCN)₂, Ti(i-PrO)₄, m-xylene, 140°	(75)	168
CF₃	NO₂	I	Cu, neat, 265-300°	(35)	496

C₇

X			
I	Cu, neat, 200°	(21)	568
Br	NiBr₂, EtOH, DMF, 2e⁻, bpy, Bu₄NBF₄	(48)	53
Br	NiBr₂, EtOH, MeOH, 2e⁻, NaBr, bpy	(36)	53

C₈

X			
I	Cu, neat, 270°	(23)	569
I	Cu, neat, heat	(60)	570
I	Ni powder, DMF, 140°	(70)	120
I	PdCl₂, N₂H₄•H₂O, MeOH, reflux	(56)	47
I	PdCl₂, HgCl₂, N₂H₄•H₂O, MeOH, reflux	(78)	47
Br	Pd(PPh₃)₄, 2e⁻, Et₄NOTs, DMF	(78)	190
Br	NiCl₂, Zn, bpy, NaBr, DMF, 60-80°	(75)	146
Br	PdCl₂, HgCl₂, 3,4-xylylhydrazine hydrochloride, NaOH, MeOH, reflux 60-80°	(88)	165
Cl	Pd/C, H₂, PEG-400, H₂O, NaOH, 110°	(39)ᵃ	186
Cl	Pd/C, HCO₂Na, CTAB, H₂O, NaOH, 110°	(20), (25)ᵃ	181

R³	R⁴	X			
CN	CN	I	NiI₂, lithium naphthalide, DME, 30-35°	(78)	571
Me	OMe	Cl	NiBr₂(PPh₃)₂, Zn, Et₄NI, THF, 50°	(57)	139
CO₂H	CO₂H	Cl	Pd/C, NaOH, H₂O, formic hydrazide, 80-85°	(52)ᵃ	55
CO₂H	CO₂H	Br	Pd/C, NaOH, H₂O, formic hydrazide, 85°	(86-93)ᵇ	55

X			
I	Cu, neat, heat	(51)	572
I	Cu, neat, 260-270°	(86)	507
I	Cu, neat, 260-280°	(87)	490
I	Cu, neat, 190°	(55)	32
I	Cu, neat, CO₂, 235°	(77)	573
I	PdCl₂, HgCl₂, N₂H₄•H₂O, MeOH, reflux	(51)	47
Br	NiBr₂(PPh₃)₂, Zn, Et₄NI, THF, 50°	(70)	574
Br	Ni(OAc)₂, t-BuOLi, LiH, bpy, THF, 63°	(75), (91)ᵃ	110

TABLE 9. 3,3',4,4'-TETRASUBSTITUTED BIARYLS *(Continued)*

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{10}	Cu, neat, 250°	(3)	575
	NiCl$_2$(PPh$_3$)$_2$, Zn, NaBr, DMAc, 80°	(>97)	576
X = Cl	NiCl$_2$(PPh$_3$)$_2$, Zn, KI, NMP, 80°	(67)	576
Cl	NiCl$_2$(PEt$_3$)$_2$, Zn, KI, NMP, 80°	(>64)	576
Cl	NiCl$_2$(PBu$_3$)$_2$, Zn, NaBr, DMAc, 70°	(71)[a]	576
Cl	NiCl$_2$, PBu$_3$, Zn, NaBr, DMAc, 70°	(>21)	576
Cl	NiCl$_2$(PEt$_3$)$_2$, Zn, NaCl, DMF, 80°	(87)[a]	576
Cl	NiCl$_2$, PEt$_3$, Zn, NaCl, DMF, 77-80°	(13)[a]	576
Br	NiCl$_2$(PPh$_3$)$_2$, Zn, NaBr, DMAc, 80°	(>84)	576
C_{11}	Ni(OAc)$_2$, NaH, *t*-AmOH, bpy, THF, reflux	(50)	577
C_{13} R^3 = OMe, R^4 = OC$_6$H$_{13}$, X = I	Cu, neat, 270°	(66)	578
R^3 = OC$_6$H$_{13}$, R^4 = OMe, X = I	Cu, neat, 270°	(48)	578
	Ni(cod)$_2$, DMF, 42°	(50)	475
	Cu, neat, 260-300°	(43)	579
	Cu, neat, 290°	(36)	580
C_{16}	NiCl$_2$(PBu$_3$)$_2$, Zn, NaBr, DMF, 50-70°	(87)[a]	576
C_{17}	NiCl$_2$, NaI, tris(2-methylphenyl) phosphite, NMP, Zn, 60-80°	(82)	149

TABLE 9. 3,3',4,4'-TETRASUBSTITUTED BIARYLS *(Continued)*

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{18}$			
	Cu, neat, 260°	(67)	447
	Cu, neat, 270-310°	(50)	581

[a] The yield was determined by gas chromatography.

[b] The yield was determined by HPLC.

TABLE 10. 3,3',5,5'-TETRASUBSTITUTED BIARYLS
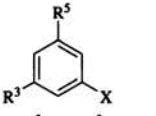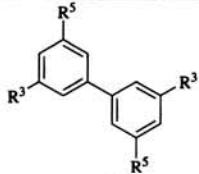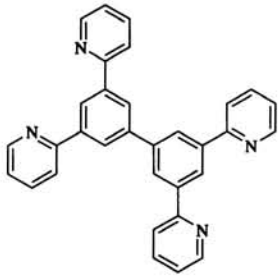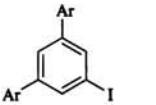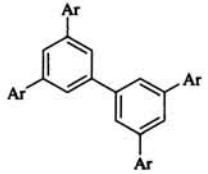
	Substrate		Conditions	Product(s) and Yield(s) (%)	Refs.

C$_{6-8}$

R^3	R^5	X			
F	F	Br	NiBr$_2$, EtOH, DMF, 2e$^-$, Bu$_4$NBF$_4$, bpy	(54)	53
NO$_2$	NO$_2$	I	Cu, neat, 270°	(15)	582
Me	NO$_2$	I	Cu, DMF, reflux	(71)	583
CF$_3$	CF$_3$	I	Cu, sand, reflux	(30)	524
CO$_2$Me	Cl	I	Cu, neat, 265-270°	(25)	584
OMe	OMe	I	Cu, neat, 200-275°	(62-70)	585
OMe	OMe	I	Cu, neat, 230°	(37)	586

C$_{16}$

NiCl$_2$(PPh$_3$)$_2$, Zn, DMF, 50°   (70)   584, 587

C$_{30}$

Ar = biphenyl-2-yl

Cu, neat, heat   (35)   588

TABLE 11. 2,2',3,3',4,4'-HEXASUBSTITUTED BIARYLS
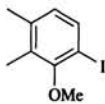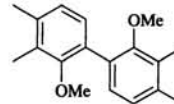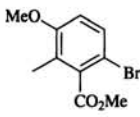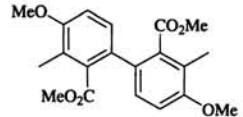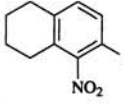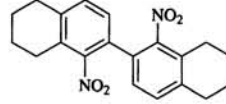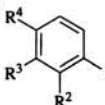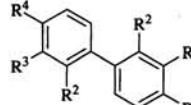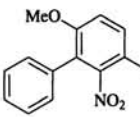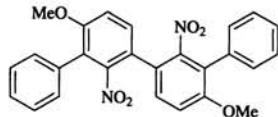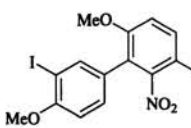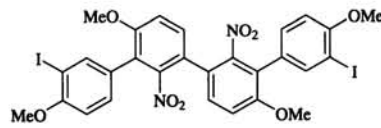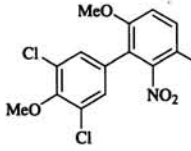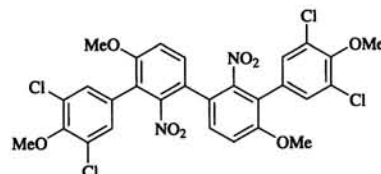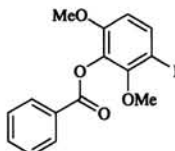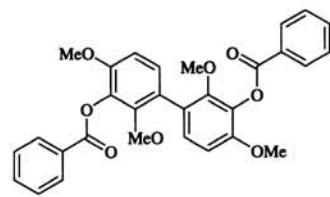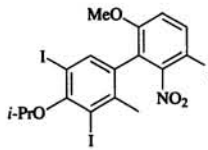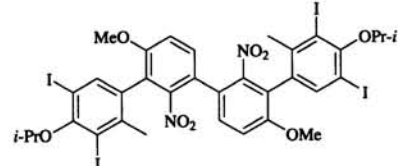
	Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₉		Cu, neat, heat	(59)	589
C₁₀		Cu, 2,4-dimethylsulfolane, 250°	(85)	590
		Cu, neat, 135-190°	(20)	591

C₁₁₋₁₂

R²	R³	R⁴			
CO₂Me	CO₂Me	OMe	Cu, neat, 220-250°	(56)	592
OMe	CO₂Me	CO₂Me	Cu, neat, 220-250°	(92)	592
OMe	Et	OEt	Cu, neat, 260°	(67)	593
OEt	Et	OMe	Cu, neat, 260°	(49)	593
OEt	Et	OEt	Cu, neat, 200°	(62)	593

C₁₃	Cu, neat, 150-200°	(73)	594	
	CuOTf, DMSO, acetone, CH₃CN, aq. NH₃	(62)	420	
C₁₄	Cu, neat, 170-180°	(5)	594	
	CuOTf, DMSO, acetone, CH₃CN, aq. NH₃	(54)	420	
	Cu, neat, 200-210°	(78)	594	
C₁₅	Cu, neat, 245-260°	(89)	595	
C₁₇	Cu(OTf)₂, Cu, acetone, CH₃CN, DMSO, aq. NH₃, 0°	(90)	70	

TABLE 11. 2,2',3,3',4,4'-HEXASUBSTITUTED BIARYLS *(Continued)*
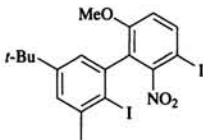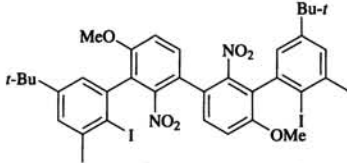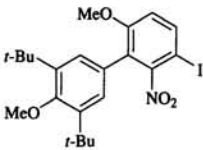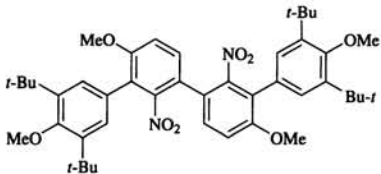
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{18}$	Cu(OTf)$_2$, Cu, acetone, CH$_3$CN, DMSO, aq. NH$_3$, 0°	(84)	70
C$_{22}$	Cu, neat, 180-200°	(87)	594

TABLE 12. 2,2',3,3',5,5'-HEXASUBSTITUTED BIARYLS
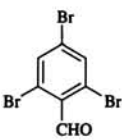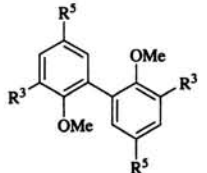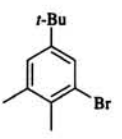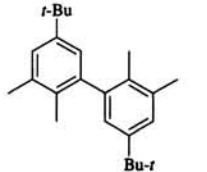
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₇	Cu, DMF, reflux	(42)	596
C₇₋₉			

R^3	R^5	X			
NO₂	NO₂	I	Cu, nitrobenzene, reflux	(13)	597, 598
OMe	Me	Br	Cu, neat, 230-290°	(19)	599
OMe	Me	Br	Cu, neat, 300°	(19-20)	484
OMe	CHO	I	Cu, neat, 250°	(65)	600
OMe	CHO	I	NiCl₂(PPh₃)₂ PPh₃, Zn, DMF, 54°	(8)	457
OMe	CHO	Br	Cu, nitrobenzene, reflux	(0)	601
OMe	CHO	Br	Cu, methyl benzoate, reflux	(0)	601
OMe	CHO	Br	Cu, DMF, reflux	(0)	601
OMe	CHO	Br	Cu, neat, heat	(0)	601

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₁₂	Cu, neat, 300°	(56)	529

TABLE 12. 2,2',3,3',5,5'-HEXASUBSTITUTED BIARYLS *(Continued)*
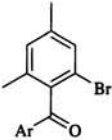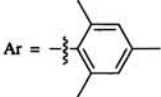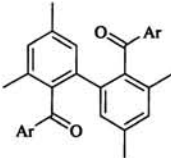
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{18}$			
	Cu, neat, 200°	(63)	602

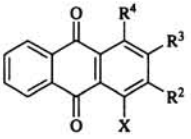TABLE 13. 2,2',3,3',6,6'-HEXASUBSTITUTED BIARYLS
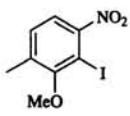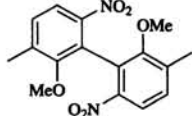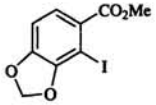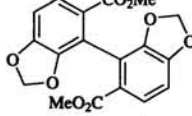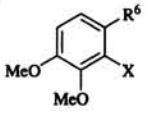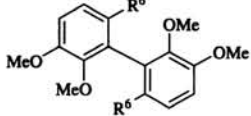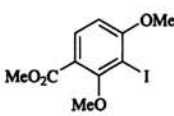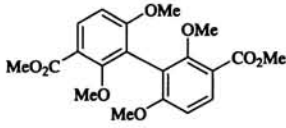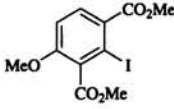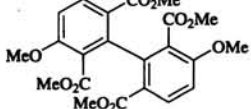
	Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_8$		Cu, DMF, reflux	(81)	603
C$_9$		Cu, DMF, heat	(>64 but <73)	604
C$_{9-10}$				

R^6	X			
CHO	Br	Cu, neat, 220-240°	(60)	605
CHO	I	Cu, DMF, reflux	(63)	601
CHO	I	Cu, neat, 250°	(45)	600
OMe	I	Cu, neat, 180-215°	(76)	606
CO$_2$Me	Br	Cu, neat, heat	(70)	605

	Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{10}$		Cu, neat, 200-235°	(47)	607
C$_{11}$		Cu, neat, sealed tube, 205-210°	(13)	608

TABLE 13. 2,2',3,3',6,6'-HEXASUBSTITUTED BIARYLS *(Continued)*

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{13}	Cu, DMF, reflux	(66)	56
C_{15-16}			
R^6: CHO	Cu, neat, 220-240°	(56)	609
CO$_2$Me	Cu, neat, 220-240°	(65)	609
C_{20}	Cu, DMF, reflux	(85)	610
	Cu, DMF, 140°	(82)	565

394

TABLE 14. 2,2',4,4',5,5'-HEXASUBSTITUTED BIARYLS
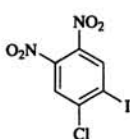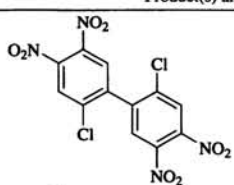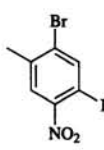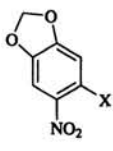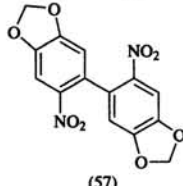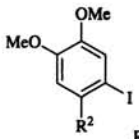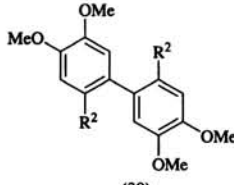
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₆	Cu, nitrobenzene, reflux	(41)	598
C₇	Cu, DMF, 70°	(77)	611
$\underline{X}$			
I	Cu, nitrobenzene, 160°	(57)	568
Br	Cu, nitrobenzene, 160°	(79)	568
C₈ $\underline{R^2}$			
Br	Cu, nitrobenzene, 220-230°	(30)	612
Cl	Cu neat, 230-250°	(31-36)	484
NO₂	Cu, neat, 210-240°	(70)	613

TABLE 14. 2,2',4,4',5,5'-HEXASUBSTITUTED BIARYLS (Continued)
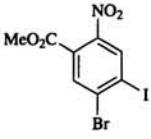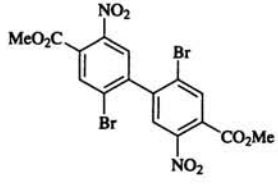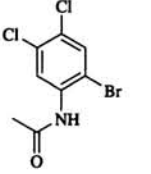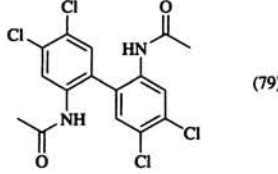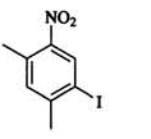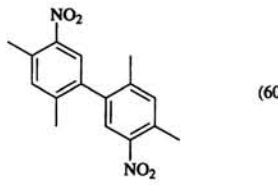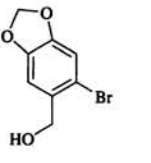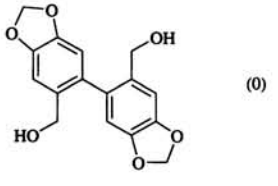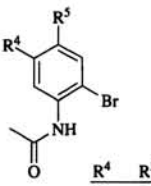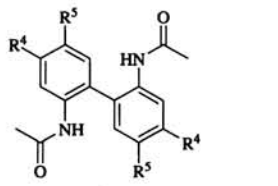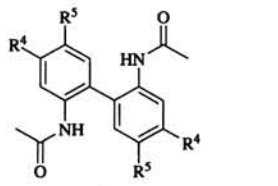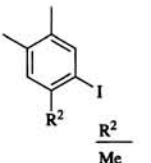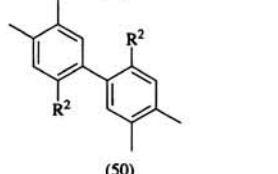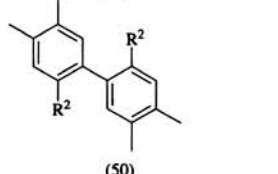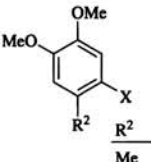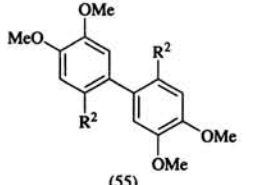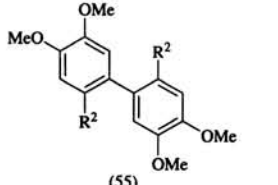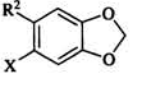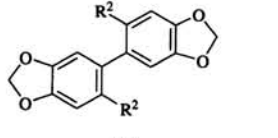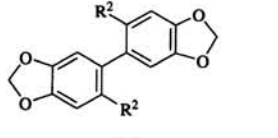
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C₈

Cu, neat, 150-225°

(40)

611

Cu, DMSO, 90°

(79)

34

Cu, DMF, reflux

(60)

583

Ni(cod)₂, 34°

(0)

49, 50

C₉

R⁴	R⁵		
Me	Cl	Cu, DMSO, 50°	(61)	34
OMe	Br	Cu, DMF, 80°	(95)	34

R²			
Me	Cu, neat, 230-250°	(50)	2
OMe	Cu, neat, 200-260°	(69)	589

R²	X		
Me	I	Cu, neat, 200-210°	(55)	614
CHO	Br	Cu, neat, sealed tube, 200-220°	(68)	615

R₂	X		
CH₂OMe	Br	Ni(cod)₂, 40-60°	(67)	49, 50
CO₂Me	I/Br (not defined)	Cu, DMF, reflux	(>64 but <73)	604

396

397

TABLE 14. 2,2',4,4',5,5'-HEXASUBSTITUTED BIARYLS (Continued)
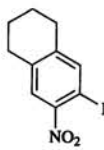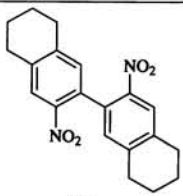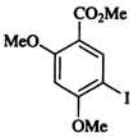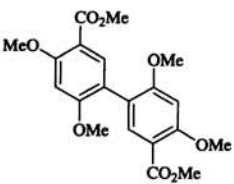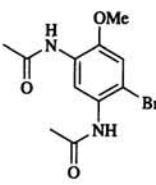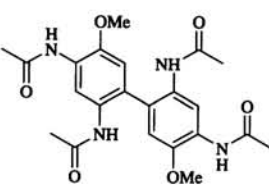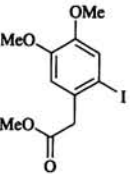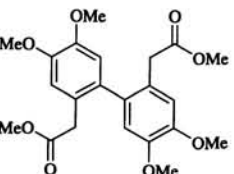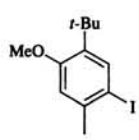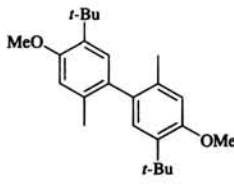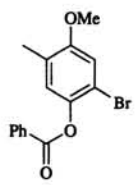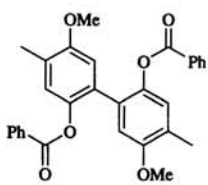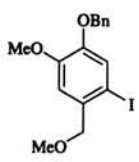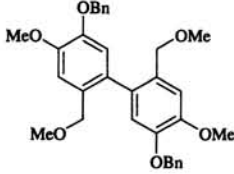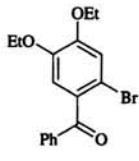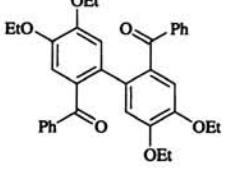
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{10}$			
	Cu, neat, 110-140°	(75)	591
	Cu, neat, <140°	(73)	616
	Cu, DMF, reflux	(23)	61
	Cu, neat, 210-220°	(75)	607
C$_{11}$			
	Cu, DMSO, 90°	(86)	34
	Cu, neat, 200-220°	(38)	614
C$_{12}$			
	Cu, neat, 240-250°	(78)	617
C$_{15}$			
	Cu, neat, 230°	(38)	618
C$_{16}$			
	NiCl$_2$(PPh$_3$)$_2$, Zn, PPh$_3$, DMF, 50°	(68)	122
C$_{17}$			
	Cu, DMF, reflux	(29)	575

TABLE 15. 2,2',4,4',6,6'-HEXASUBSTITUTED BIARYLS
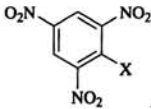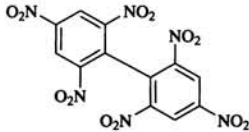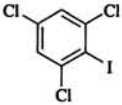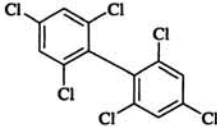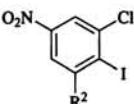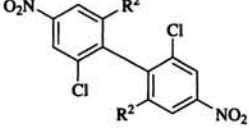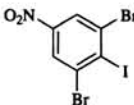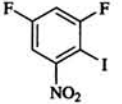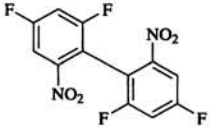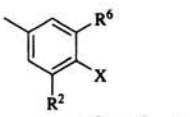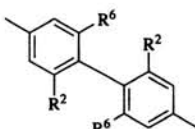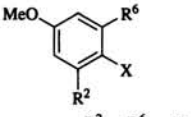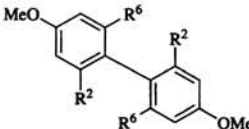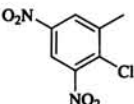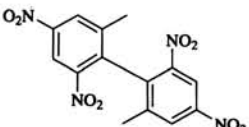
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₆ (2,4,6-trinitro, X)			
X = Cl	Cu, nitrobenzene, heat	(55)	1
Cl	Cu, ethylene dichloride, 84°	(71)	619
Cl	Cu, nitrobenzene, heat	(58)	620
Cl	Ti, neat, 140-150°	(11)	73
Br	Cu, nitrobenzene, ultrasound	(77)[a]	30
(2,4,6-trichloro, I)	Cu, neat, 220-230°	(53)	2
(2,4,6-tribromo, I)	Cu, neat, sealed tube, 200°	(75) crude	538
R²			
R² = Cl	Cu, neat, 240-260°	(37)	621
NO₂	Cu, neat, 240°	(46)	598
(dibromo nitro iodo)	Cu, sand, 180-200°	(30)	460
(difluoro nitro iodo)	Cu, neat, 115-260°	(75)	622

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₇ R² R⁶ X			
NO₂ Br I	Cu, DMF, reflux	(58)	623
NO₂ NO₂ Cl	Cu, nitrobenzene, heat	(40)	624
(MeO) R² R⁶ X			
NO₂ NO₂ Cl	Cu, nitrobenzene, heat	(90)	624
Cl Cl I	Cu, neat, heat	(79)	625
(O₂N methyl Cl NO₂)	Cu, neat, 205-230°	(52)	626

TABLE 15. 2,2',4,4',6,6'-HEXASUBSTITUTED BIARYLS *(Continued)*

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C$_8$
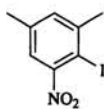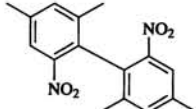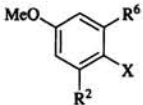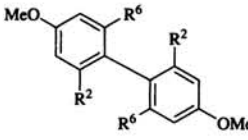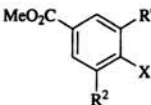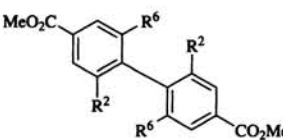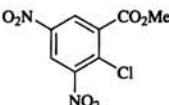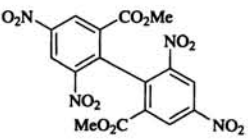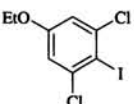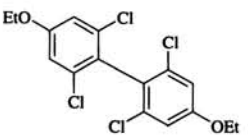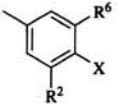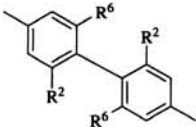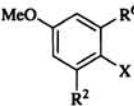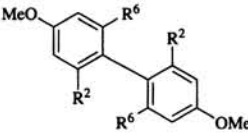
| | Cu, neat, 190-230° | (50) | 542 |

R^2	R^6	X			
NO$_2$	Me	Br	Cu, nitrobenzene, 190°	(59)	627
NO$_2$	Me	Br	Cu, neat, 200-230°	(65)	627
OMe	Cl	I	Cu, neat, 190°	(85-89)	625

R^2	R^6	X			
NO$_2$	NO$_2$	Br	Cu, *p*-xylene, heat	(90) crude	624
NO$_2$	NO$_2$	Cl	Cu, nitrobenzene, heat	(54)	1
Cl	Cl	I	Cu, neat, 280°	(40)	628

| | Cu, neat, 160° | (62) | 629 |

| | Cu, neat, 190° | (60-63) | 625 |

C$_9$

R^2	R^6	X			
Me	Me	I	Cu, neat, 260-270°	(13)	2
Me	Me	I	PdCl$_2$, N$_2$H$_4$•H$_2$O, MeOH, reflux	(0)	47
Me	Me	I	PdCl$_2$, HgCl$_2$, N$_2$H$_4$•H$_2$O, MeOH, reflux	(0)	47
Me	Me	I	Pd(OAc)$_2$, Et$_3$N, 100°	(0)	169
Me	Me	I	Pd(OAc)$_2$, *n*-Bu$_3$N, 100°	(0)	169
Me	Me	OTf	NiCl$_2$, Zn, PPh$_3$, NaI, DMF, sonication, 60°	(0)[b]	135
OMe	OMe	I	Cu, neat, 170-210°	(74)	630
OMe	OMe	Br	Cu, neat, 290°	(88)	631

R^2	R^6	X			
NO$_2$	CO$_2$Me	I	Cu, DMF, reflux	(72)	632
Me	Me	I	Cu, heat	(18)	633
Me	OMe	I	Cu, neat, 200°	(90)	634
OMe	OMe	I	Cu, neat, 230-270°	(64)	635
OMe	OMe	Br	Cu, neat, 270-305°	(24)	635
CHO	OMe	I	Cu, neat, 270°	(64)	636

TABLE 15. 2,2',4,4',6,6'-HEXASUBSTITUTED BIARYLS (Continued)
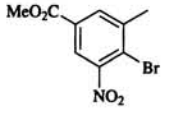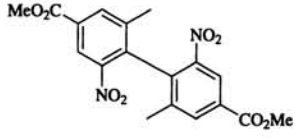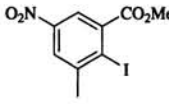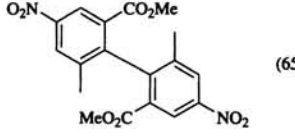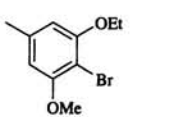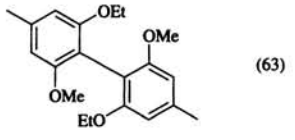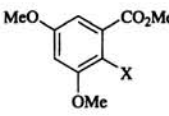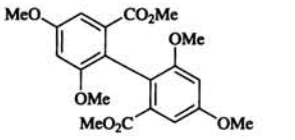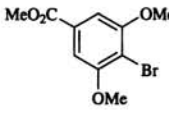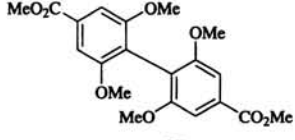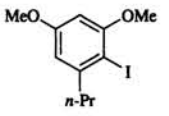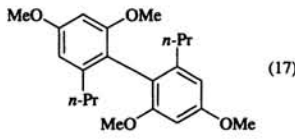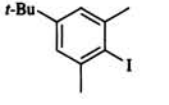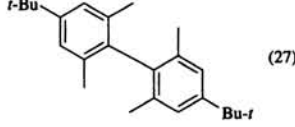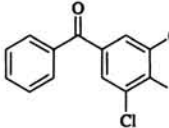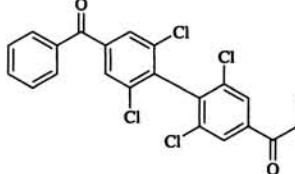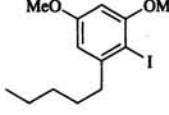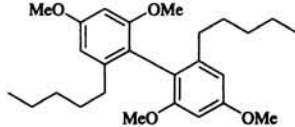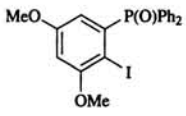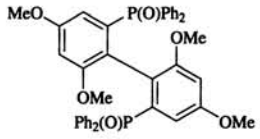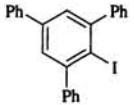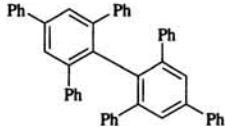
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_8	Cu, neat, 170–220°	(70)	637
C_9	Cu, DMF, reflux	(65)	638
C_{10}	Cu, neat, 290°	(63)	631

X
Br	Cu, neat, 250–260°	(64), (80)[b]	639
Br	Cu, neat, 230–240°	(84)	640
I	Cu, neat, 220–225°	(89)	640

	Cu, neat, 250–270°	(37)	641
	Cu, neat, 250–260°	(31), (49)[b]	639
C_{11}	Cu, neat, 210–220°	(17)	642
C_{12}	Cu, neat, 300°	(27)	529
C_{13}	Cu, neat, 280°	(75)	643
	Cu, neat, 220–230°	(66)	644

TABLE 15. 2,2',4,4',6,6'-HEXASUBSTITUTED BIARYLS *(Continued)*

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C_{13-14}
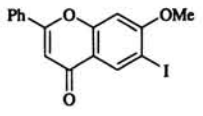
R			
H	Cu, neat, AcOH, 175-190°	(65)	59
H	Cu, nitrobenzene, heat	(21)	59
Me	Cu, neat, AcOH, 130-150°	(63)	59
NO_2	Cu, neat, AcOH, 150-170°	(54)	59
OMe	Cu, neat, AcOH, 155°	(29)	59

C_{14}

Cu, neat, 170-180°   (80)   645

Cu, neat, heat   (trace)   515

Cu, DMF, reflux $(>60)^c$ dr 95 : 5, prior to purification   230

Cu, DMF, reflux   (43) *RSS* + (31) *SSS*   225, 22

C_{16}

X			
I	Cu, neat, 240°	(66)	646
Br	Cu, neat, 240°ʸ	(0)	646

C_{17}

Cu, DMF, reflux $(>51)^c$ dr 91.5 : 8.5, prior to purification   230

TABLE 15. 2,2',4,4',6,6'-HEXASUBSTITUTED BIARYLS *(Continued)*

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{20}$			
	Cu, DMF, 140°	(66)	565
C$_{24}$			
	Cu, neat, 270-280°	(50)	647

[a] The yield was determined by NMR spectroscopy.

[b] The yield was determined by gas chromatography.

[c] The yield includes oxazoline opening and acetylization.

TABLE 16. 3,3',4,4',5,5'-HEXASUBSTITUTED BIARYLS
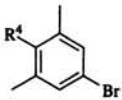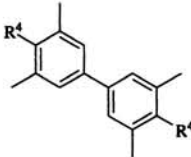
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C_{8-9}

R^4			
OH	Pd/C, formic hydrazide, NaOH, H_2O, MeOH, 70°	(86)	55, 648
OMe	$NiCl_2$, Zn, PPh_3, DMF, 50-60°	(58)	490

TABLE 17. 2,2',3,3',4,4',5,5'-Octasubstituted Biaryls
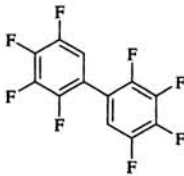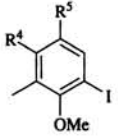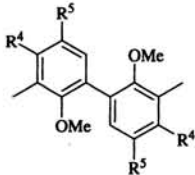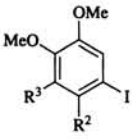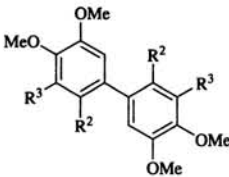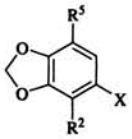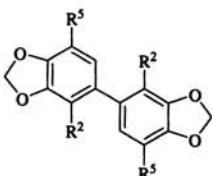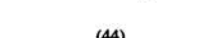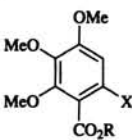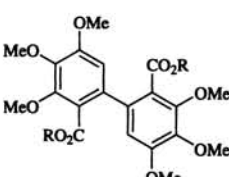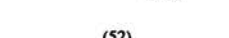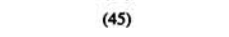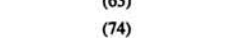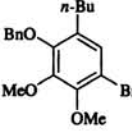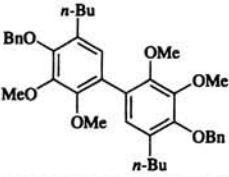
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C₆

| | Cu, DMF, reflux | (73) | 649 |

C₁₀

R⁴	R⁵			
Me	OMe	Cu, neat, >220°	(76)	650
Me	OMe	Cu, neat, 235°	(36)	651
OMe	Me	Cu, neat, 220°	(86)	652

R²	R³			
CHO	OMe	Cu, DMF, heat	(77)	653
OMe	OMe	Cu, neat, 220°	(69)	654

X	R²	R⁵			
I	CO₂Me	OMe	Cu, DMF, reflux	(44)	655
Br	OMe	CO₂Me	Cu, DMF, reflux	(10)	655

C₁₁ ₋ ₁₄

R	X			
Me	I	Cu, neat, 210°	(52)	458
Me	I	Cu, neat, 240-250°	(45)	617
Me	Br	Cu, neat, 240-250°	(63)	617
n-Bu	I	Cu, neat, 250°	(74)	617

C₁₉

| | NiCl₂(PPh₃)₂, PPh₃, Zn, DMF, 54° | (5) | 457 |

410

411

TABLE 18. 2,2',3,3',4,4',6,6'-OCTASUBSTITUTED BIARYLS

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₇			
R³ = Me, X = Br	Cu, nitrobenzene, 160-183°	(70)	656
Me, Br	Cu, nitrobenzene, heat	(80)	657
OMe, Br	Cu, 1,2-dichloroethane, 84°	(77) as derivative	619
OMe, Br	Cu, toluene, reflux	(83)	658
OMe, Br	Cu, toluene, reflux	(83)	659
OMe, Cl	Cu, xylene, reflux	(71) as derivative	658
C₁₀	Cu, neat, 200°	(75)	660
	Cu, neat, 250°	(81)	661
	Cu, DMF, heat	(92)	653
C₉₋₁₀			
R³ = OMe, R⁴ = OMe	Cu, neat, 220°	(63)	652
NO₂, Me	Cu, neat, 200-300°	(0)	662
C₁₀	Cu, neat, 240°	(88)	663
X = I/Br (not defined)	Cu, DMF, heat	(>64 but <73)	604
Br	Cu, DMF, reflux	(51)	664
C₁₁	Cu(I) thiophene-2-carboxylate, NMP, 23°	(86)	71
	Cu, neat, 200°	(81)	665

TABLE 18. 2,2',3,3',4,4',6,6'-OCTASUBSTITUTED BIARYLS *(Continued)*
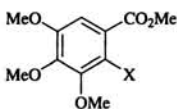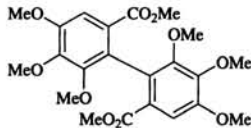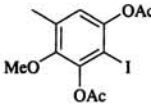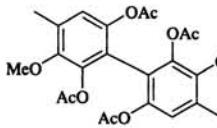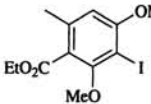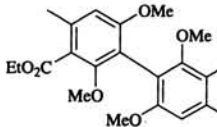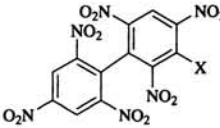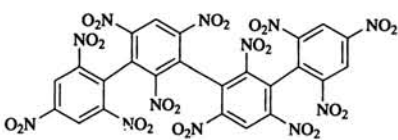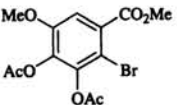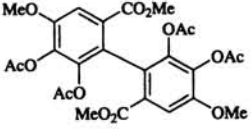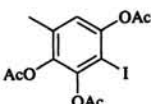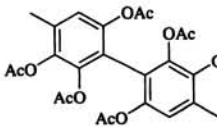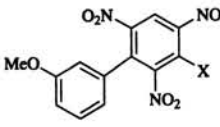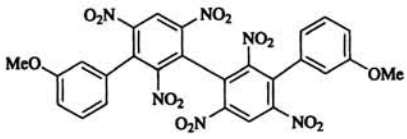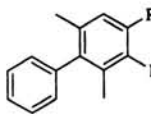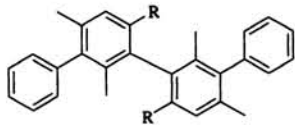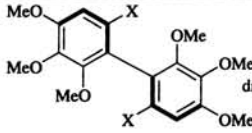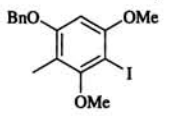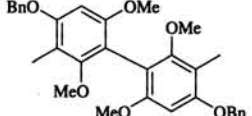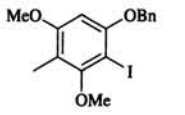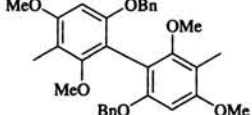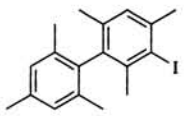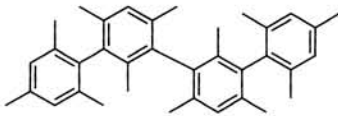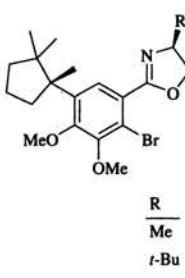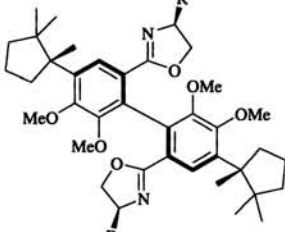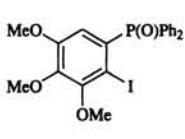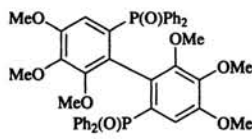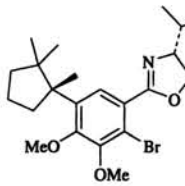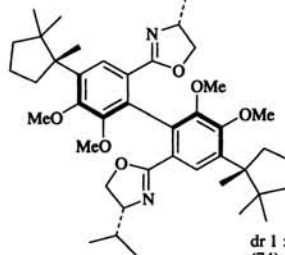
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

X			
I/Br (not defined)	Cu, DMF, heat	(>64 but <73)	604
Br	Cu, neat, 240°	(36)	458
Br	Cu, DMF, reflux	(40)	666
Br	Cu, neat, 210-220°	(60)	667
Br	Cu, heat	(47)	640

C_{12}

	Cu, neat, heat	(41)	630

	Cu, 210-220°	(72)	668

X			
Cl	Cu, nitrobenzene, 200°	(84)	659
Br	Cu, nitrobenzene, 200°	(67)[a]	659

C_{13}

	Cu, DMF, heat	(>64 but <73)	604

	Cu, neat, heat	(51)	630

X			
Cl	Cu, toluene, reflux	(74)	659
Br	Cu, toluene, relux	(80)	659

C_{15}

R			
Me	Cu, neat, 200-250°	(9)	669
OMe	Cu, neat, 125-285°	(10)	670

TABLE 18. 2,2',3,3',4,4',6,6'-OCTASUBSTITUTED BIARYLS *(Continued)*

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Cu, DMF, reflux	(58) dr 93 : 7, prior to purification	214, 215, 218
C16	Cu, neat, 180°	(56)	671
	Cu, neat, 180°	(42)	671
C18	Cu, neat, 250-270°	(48)	669
C20-23			
R			
Me	Cu, DMF, reflux	(66) of S atropisomer dr 7.2 : 1 (S/R biaryl axis)	224
t-Bu	Cu, DMF, reflux	(64) of S atropisomer dr 3 : 1 (S/R biaryl axis)	224
C21	Cu, DMF, 140°	(79-90)	565
C22	Cu, DMF, reflux	dr 1 : 6.7 (S/R biaryl axis) (74) of R atropisomer	224

[a] The yield was determined by NMR spectroscopy.

416

417

TABLE 19. 2,2',3,3',5,5',6,6'-OCTASUBSTITUTED BIARYLS
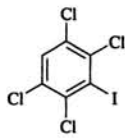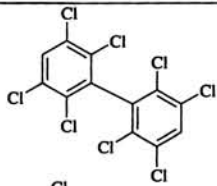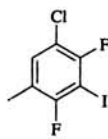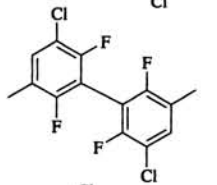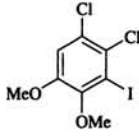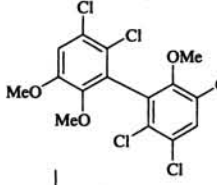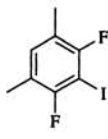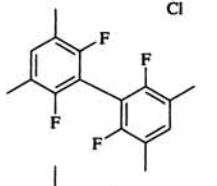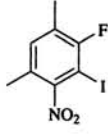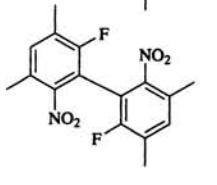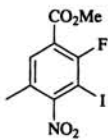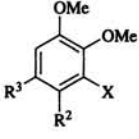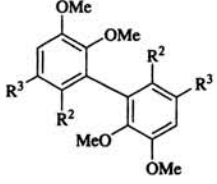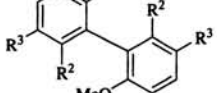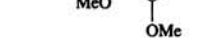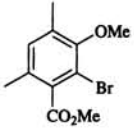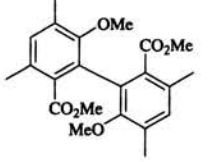
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_6$	Cu, neat, sealed tube, 190°	(65)	672
C$_7$	Cu, neat, 200°	(34)	16
C$_8$	Cu, heat	(30)	673
	Cu, neat, 200°	(60)	16
	Cu, nitrobenzene, 200°	(75)	674
C$_9$	Cu, 220-225°	(65)	674, 67

C$_{9-10}$

R^2	R^3	X			
OMe	NO$_2$	I	Cu, neat, 210-230°	(16)	606
Me	Me	Br	Cu, neat, 280-300°	(17-20)	146
OMe	OMe	I	Cu, neat, 250-260°	(60)	676

| C$_{11}$ | Cu, DMF, reflux | (83) | 677 |

TABLE 20. 2,2',3,3',4,4',5,5',6,6'-DECASUBSTITUTED BIARYLS
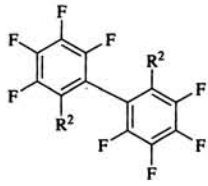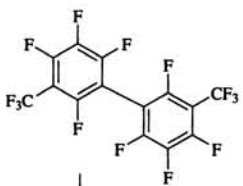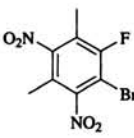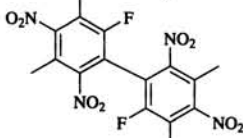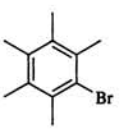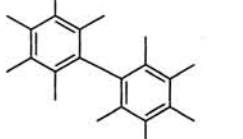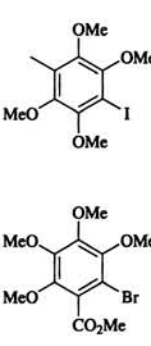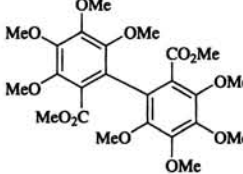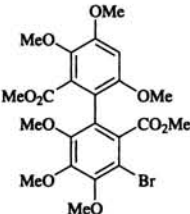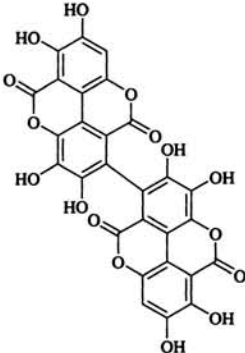
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C_{6-7}

R^2	X			
NO_2	Br	Cu, DMF, reflux	(57)	649
F	I	Cu, neat, sealed tube, 300°	(72)	678
F	I	CuI, potassium naphthalide, DME, 85°	(83)	24, 25
F	I	CuCl, lithium naphthalide, dioxane, 101°	(91)[a]	26
F	I	NiI_2, lithium naphthalide, DME, 20°	(100)[a]	112
F	I	Cu, neat, sealed tube, 180-290°	(87)	679
F	I	NiI_2, lithium naphthalide, DME, 80°	(100)[a]	111
F	I	CuI-PEt₃, lithium naphthalide, THF, mesitylene, 151°	(91)	25
F	I	CuCl, lithium naphthalide, DME, 85°	(92)[a]	25
F	Br	Cu, neat, sealed tube, 200°	(91)	680
F	Br	Cu, neat, sealed tube, 180-240°	(87)	681
F	Br	Cu, DMF, reflux	(96)	682
F	Br	NiI_2, lithium naphthalide, DME, 80°	(49)[a]	111
F	Br	$NiBr_2$, lithium naphthalide, DME, 80°	(37)[a]	111
F	Cl	Cu, neat, 320-360°	(73)	683
F	Cl	Cu, neat, sealed tube, 230°	(68)	684
F	OMs	$NiCl_2(PPh_3)_2$, Zn, Et₄NI, THF, 67°	(0)[a]	133
Me	Br	Cu, DMF, reflux	(61)	649
CN	Br	Cu, DMF, reflux	(77)	649

C_7

Cu, neat, 270-290°   (73)   685

C_8

Cu, nitrobenzene, 190°   (69)   674

C_{11}

$NiCl_2$, bpy, NaBr, Zn, DMF, 60-80°   (65)   146

Cu, neat, 250°   (19)   676

C_{12}

Cu, neat, 250-260°   (29)   677

TABLE 20. 2,2',3,3',4,4',5,5',6,6'-DECASUBSTITUTED BIARYLS *(Continued)*

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C$_{22}$

1. Cu, neat, 220°

2. HI, Ac$_2$O

(88)

667

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^{a} The yield was determined by gas chromatography.

422

TABLE 21. 1,1'-BINAPHTHYLS
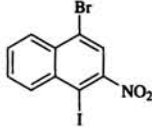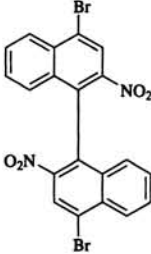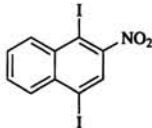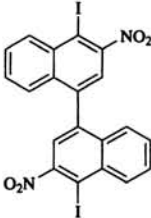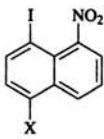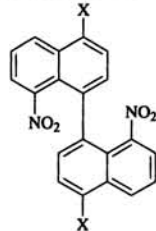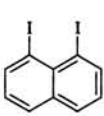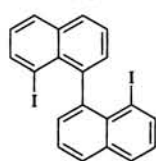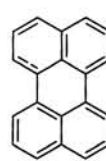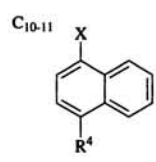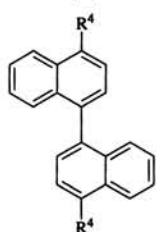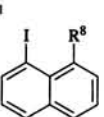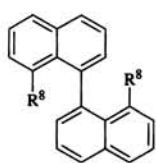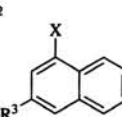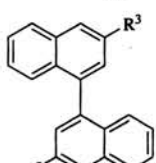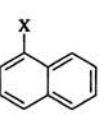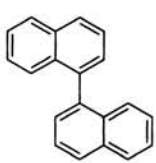
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{10}$	Cu, 200°	(80)	686
	Cu, DMF, 150-160°	(8)	61
	Cu, PhNO$_2$, reflux	(11)	687

TABLE 21. 1,1'-BINAPHTHYLS *(Continued)*

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

X			
NO$_2$	Cu, nitrobenzene, reflux	(36)	688
Br	Cu, nitrobenzene, reflux	(29)	688

| | Pd(OAc)$_2$, K$_2$CO$_3$, Bu$_4$NBr, DMF, 100° | (39) + (42) | 173 |

C$_{10\text{-}11}$

R^4	X			
NO$_2$	I	Cu, naphthalene, 220-230°	(52)	689
Me	Br	Cu, I$_2$, 1-methylnaphthalene, 230-270°	(3)	690
OMe	I	Cu, 220-230°	(15-20)	691

C$_{10\text{-}11}$

R^8	X			
I	I	Pd(OAc)$_2$, K$_2$CO$_3$, Bu$_4$NBr, DMF, 100°	(39)	173
NO$_2$	I	Cu, nitrobenzene, reflux	(44)	688
CO$_2$K	Br	Cu, H$_2$O, 100°	(8)	411

C$_{10\text{-}12}$

R^3	X			
NO$_2$	I	Cu, 215-280°	(7-20)	591, 692
CO$_2$Me	Br	Ni(cod)$_2$, DMF, 60°	(50)	693

C$_{10\text{-}11}$

X			
Cl	Ni(OAc)$_2$, NaH, *t*-AmOH, bpy, THF, 63°	(88-90)	131
Cl	Ni(OAc)$_2$, LiH, *t*-BuOH, bpy, THF, 63°	(87)	110
Br	Cu, I$_2$, 180-285°	(50)	689
Br	Ni(bpy)Br$_2$, bpy, NMP, –1.3 V	(75)	128
Br	Ni(OAc)$_2$, LiH, *t*-BuOH, bpy, THF, 65°	(88-94)	110, 400
Br	Ni(OAc)$_2$, NaH, *t*-AmOH, bpy, THF, 63°	(70-74)	131
Br	Ni(OAc)$_2$, NaH, *t*-AmOH, PPh$_3$, THF, 63°	(85)	131

TABLE 21. 1,1'-BINAPHTHYLS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
Br	NiCl$_2$, CrCl$_2$, Mn, bpy-like ligand, THF, 25°	(98)	406
Br	Pd(OAc)$_2$, Et$_3$N, DMF, 115°	(40)	175
Br	Pd(OAc)$_2$, As(o-tolyl)$_3$, hydroquinone, DMA, 100°	(80)	178
Br	PdCl$_2$, HgCl$_2$, PhNHNH$_2$, NaOH, MeOH, reflux	(71)	165
Br	[PdCl(π-C$_3$H$_5$)]$_2$, TBAF, DMSO, 120°	(48)	198
Br	Pd/CaCO$_3$, N$_2$H$_4$, KOH, MeOH, heat	(14)	48
I	Cu, 260-285°	(74-92)	1, 694
I	Cu, DMF, reflux	(76)	57
I	NiCl$_2$, Ph$_3$P, Zn, NaI, DMF, 60°, ultrasound	(80)	135
I	Ni(OAc)$_2$, NaH, t-AmOH, bpy, THF, 63°	(62-66)	131
I	Pd/C, Zn, acetone, H$_2$O, rt	(70)	185
I	Pd/C, Zn, H$_2$O, 18-crown-6, rt	(40)	695
I	In, DMF, reflux	(80)	74
SO$_2$Cl	PdCl$_2$(PhCN)$_2$, Ti(OPr-i)$_4$, m-xylene, 140°	(26)	168
OTf	NiCl$_2$, Ph$_3$P, Zn, NaI, DMF, 60°, ultrasound	(80)	135
OTf	NiCl$_2$(dppe), Zn, KI, DMF, THF, 90°	(3-85)	192
OTf	NiCl$_2$(PPh$_3$)$_2$, Zn, KI, DMF, 90°	(92)	192
OTf	NiCl$_2$(dppf), Zn, KI, DMF, THF, 90°	(93)	192
OTf	PdCl$_2$(PPh$_3$)$_2$, DMF, 20°, 2e$^-$	(20)	191
OTf	PdCl$_2$(PPh$_3$)$_2$, DMF, 60°, 2e$^-$	(40)	191
OTf	PdCl$_2$(PPh$_3$)$_2$, DMF, 90°, 2e$^-$	(50)	191
OTf	PdCl$_2$(PPh$_3$)$_2$, Bu$_4$NBF$_4$, DMF, 2e$^-$	(7-50)	191
OTf	PdCl$_2$(MePPh$_2$)$_2$, Bu$_4$NBF$_4$, DMF, 2e$^-$	(30)	192
OTf	PdCl$_2$(dppm), Bu$_4$NBF$_4$, DMF, 2e$^-$	(35)	192
OTf	PdCl$_2$(dppe), Bu$_4$NBF$_4$, DMF, 2e$^-$	(33)	192
OTf	PdCl$_2$(dppp), Bu$_4$NBF$_4$, DMF, 2e$^-$	(31)	192
OTf	PdCl$_2$(dppb), Bu$_4$NBF$_4$, DMF, 2e$^-$	(40)	192
OTf	NiCl$_2$(PPh$_3$)$_2$, Zn, KI, THF, 67°	(92)	193
OTf	NiCl$_2$(dppe), Zn, KI, THF, DMF, 67°	(82)	193
OTf	PdCl$_2$(PPh$_3$)$_2$, Zn, DMF, 90°	(59)	192, 193

C$_{11-17}$
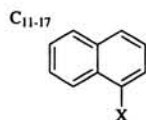
X			
OTf	Pd(OAc)$_2$, Zn, BINAP, DMF, 90°	(61-98)	192
OTf	Pd(OAc)$_2$, Zn, PPh$_3$, DMF, 90°	(51-67)	192
OTf	Pd(OAc)$_2$, Zn, dppe, DMF, 90°	(58)	192
OTf	Pd(OAc)$_2$, Zn, dppf, DMF, 90°	(64)	192
OTf	Pd(OAc)$_2$, Zn, DIOP, DMF, 90°	(13)	192
OTs	NiCl$_2$(dppe), Zn, KI, DMF, 140°	(88)	192, 193
OTs	NiCl$_2$(PPh$_3$)$_2$, Zn, KI, DMF, 140°	(70)	192, 193
OTs	NiCl$_2$(PPh$_3$)$_2$, Zn, PPh$_3$, NaBr, DMF, 100°	(79)	137

C$_{10-16}$
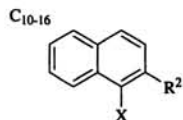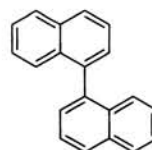
R^2	X			
NO$_2$	I	Cu, 120-130°	(17-70)	591, 692
NO$_2$	I	Cu, DMF, reflux	(77)	61
OH	Br	PdCl$_2$(PPh$_3$)$_2$, Et$_4$NOTs, DMF, 2e$^-$	(16)	190
CN	Br	Cu, DMF, reflux	(63)	397
OMe	Br	PdCl$_2$(PPh$_3$)$_2$, Et$_4$NOTs, DMF, 2e$^-$	(53)	190
OMe	Br	Pd(OAc)$_2$, K$_2$CO$_3$, i-PrOH, DMF, 115°	(3)	74
OMe	I	Pd(OAc)$_2$, As(o-tolyl)$_3$, hydroquinone, DMA, 125°	(91)	178
Me	OTf	NiCl$_2$(dppf), Zn, KI, DMF, 100°	(66)	192
Me	OTf	Pd(OAc)$_2$, Zn, BINAP, DMF, 100°	(16)	192
CO$_2$Me	Cl	Cu, I$_2$, 250-300°	(25-48)	696
CO$_2$Me	Br	Cu, 190°	(61-87)	697-700
CO$_2$Me	Br	Cu, 270-290°	(46-78)	701-703
CO$_2$Me	Br	Cu, DMF, reflux	(75-85)	704-706
SO$_3$Ph	I	Cu, <300°	(83)	707
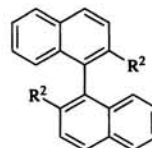
TABLE 21. 1,1'-BINAPHTHYLS (Continued)
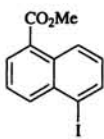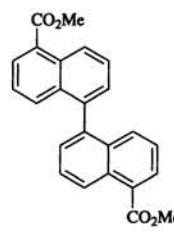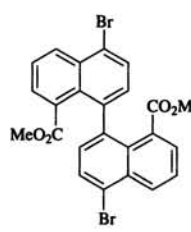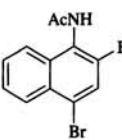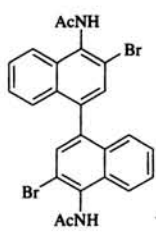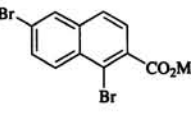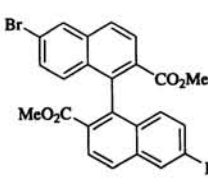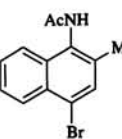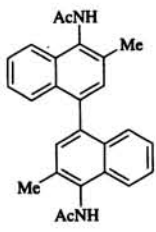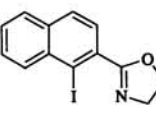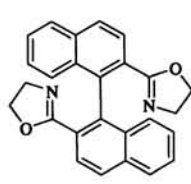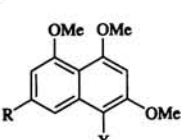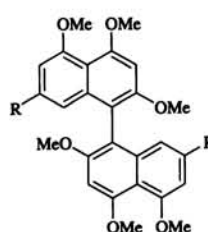
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₁₂			
	Cu, CO₂, 220-240°	(75)	708
	Cu, CO₂, heat	(>50)	709
	Cu, 210-220°	(55)	36
	Cu, DMSO, 65°	(96)	34
	Cu, 160-170°	(41)	36
C₁₃	Cu, tetralin, reflux	(39)	710
	Cu, pyridine, 120°	(69)	711
C₁₄₋₁₅			
R = OMe, X = Br	Cu, 260-280°	(14)	712
R = CO₂Me, X = I	Cu, 120°	(80)	713

428

429

TABLE 21. 1,1'-BINAPHTHYLS (Continued)
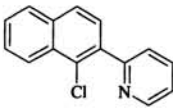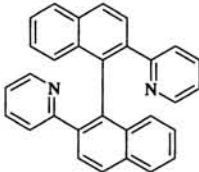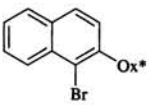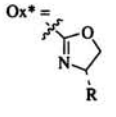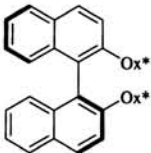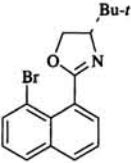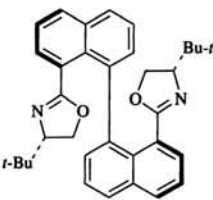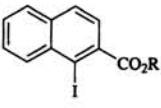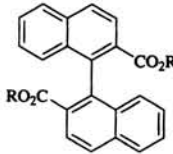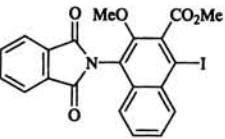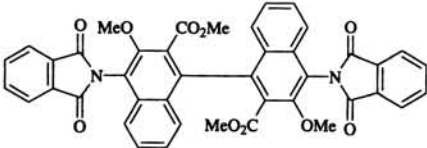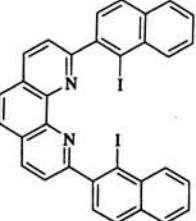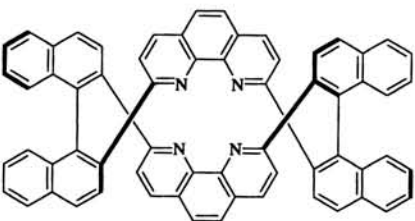
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₁₅	Ni(PPh₃)₂Cl₂, Zn, Et₄NI, THF, rt	(69)	714
C₁₆₋₁₉ Ox*	Cu, pyridine, reflux		
Ox* =		R	
		i-Pr (60)	216
		t-Bu (77-79)	212, 216, 220
		Ph (75)	216
C₁₇	Cu, DMF, reflux	(91)	220
C₁₉₋₃₈ CO₂R	Cu, DMF, reflux		
		R	
		(+)-1-phenethyl (80-95)	213
		(–)-1-phenethyl (80-95)	213
		(–)-2-octyl (80-95)	213
		(–)-menthyl (89)	213
		cholesteryl (80-95)	213
C₂₁	Cu, 220-230°	(45-50)	715
C₃₂	Cu, biphenyl, 255°	(41)	716

430

431

TABLE 21. 1,1'-BINAPHTHYLS *(Continued)*
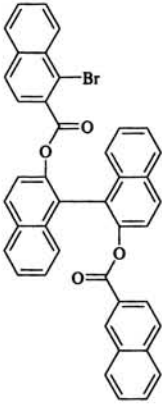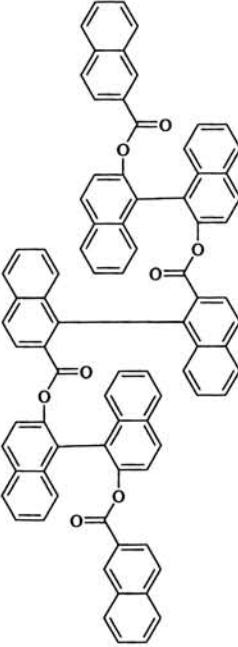
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C₄₂

R

Cu, DMF, reflux

(66)

R,R,R

717

TABLE 22. 2,2'-BINAPHTHYLS

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₁₀			
	Cu, 250-280°	(65)	686
X			
Br	Pd/CaCO₃, N₂H₄, KOH, MeOH, heat	(50)	48
Br	PdCl₂, HgCl₂, PhNHNH₂, NaOH, MeOH, reflux	(50)	165
I	Cu, 225-260°	(68)	2
I	[PdCl(π-C₃H₅)]₂, TBAF, DMSO, 120°	(58)	19
	Cu, nitrobenzene, reflux	(32)	687
C₁₀₋₁₂			
R³ X			
NO₂ I	Cu, 135-190°	(31)	718
CO₂Me Br	Cu, 190°	(90)	698

TABLE 22. 2,2'-BINAPHTHYLS (Continued)
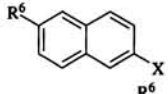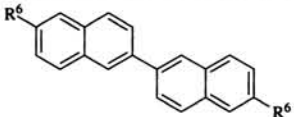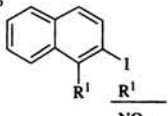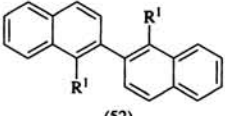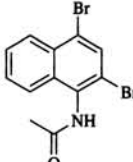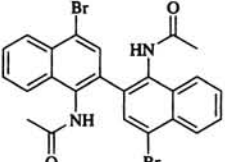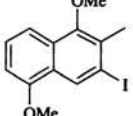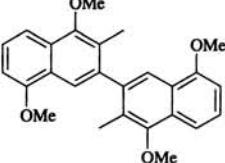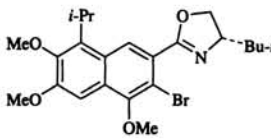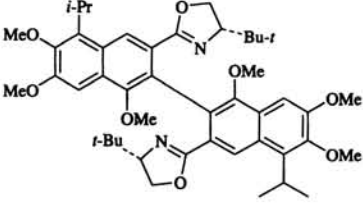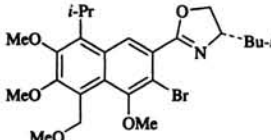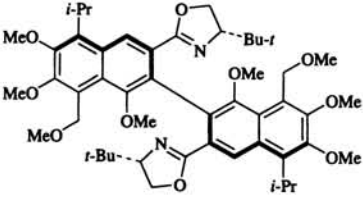
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C$_{10-13}$

R^6	X			
OH	Br	Pd, SrCO$_3$, N$_2$H$_4$, EtOCH$_2$CH$_2$OH, 135-140°	(10)	719
OH	Br	Pd/CaCO$_3$, NaOH, H$_2$O, HCONHNH$_2$, 80°	(63)	55
OMe	Br	Pd, SrCO$_3$, N$_2$H$_4$, EtOCH$_2$CH$_2$OH, 135-140°	(10)	719
CO$_2$Me	OMs	NiCl$_2$(PPh$_3$)$_2$, Zn, Et$_4$NI, THF, 67°	(91)	133

C$_{10-16}$

R^1			
NO$_2$	Cu, 135-190°	(52)	591
NO$_2$	Cu, nitrobenzene, reflux	(35-84)	692, 720
NO$_2$	Cu, DMF, reflux	(78)	61
OMe	Cu, I$_2$, 200-210°	(36)	721
SO$_3$Ph	Cu, 170-175°	(95)	722

C$_{12}$

Cu, DMSO, 60° — (96) — 34

C$_{13}$

Cu, 210° — (46) — 723

C$_{23}$

Cu, pyridine, reflux — (81) — 227, 229

C$_{25}$

Cu, DMF, reflux — (80) — 227, 228

TABLE 23. BISTETRAHYDRONAPHTHYLS
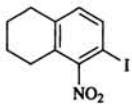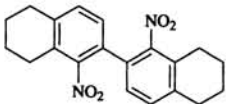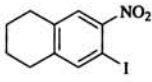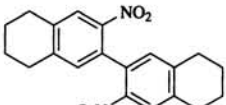
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{10}$	Cu, 135-190°	(20)	591
	Cu, 110-140°	(75)	591
	Cu, 140°	(73)	616
	Cu, DMF, reflux	(23)	61

TABLE 24. MISCELLANEOUS BIARYLS
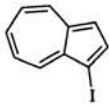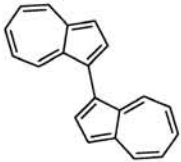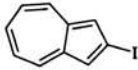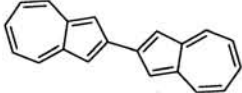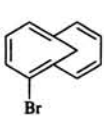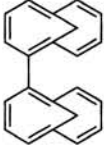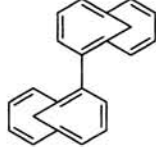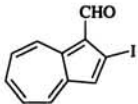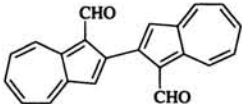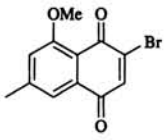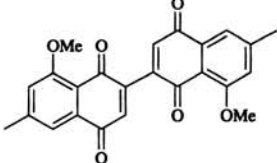
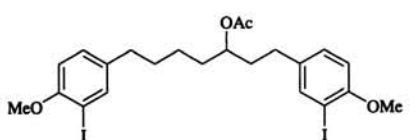| Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{10}$	Cu, 200°	(83)	724
	Cu, 180°	(54)	724
C$_{11}$	Ni(PPh$_3$)$_2$Br$_2$, Zn, Et$_4$NI, 50°	+ (45) (43)	404, 725
	Cu, 220°	(40)	724
C$_{12}$	Cu, (Ph$_3$P)$_4$Pd, DMF, 130°	(>43)	726

TABLE 24. MISCELLANEOUS BIARYLS (Continued)
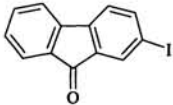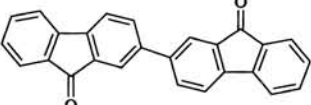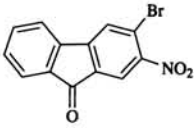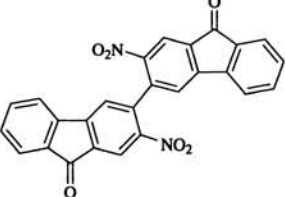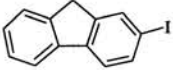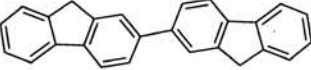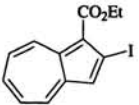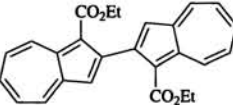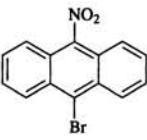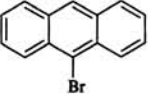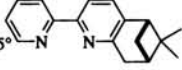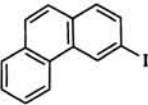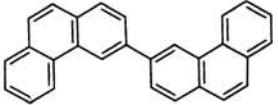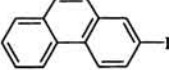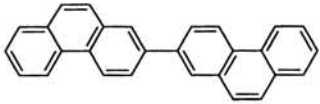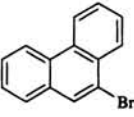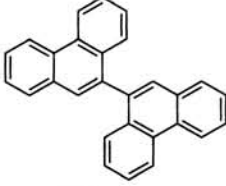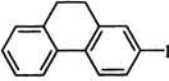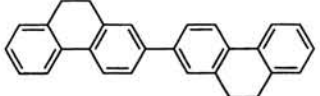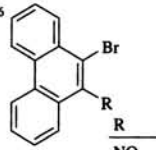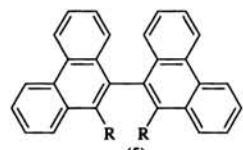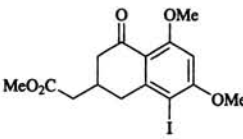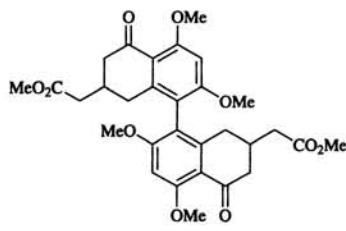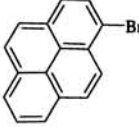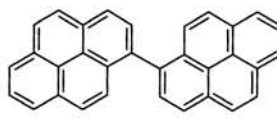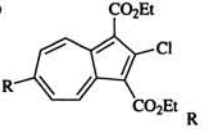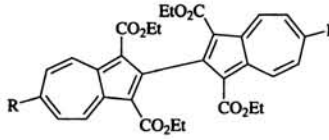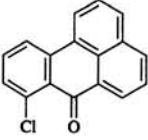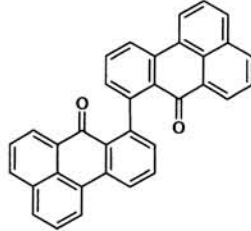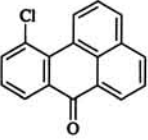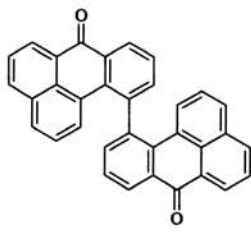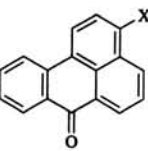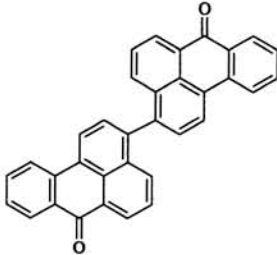
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₁₃	Cu, 225-230°	(31)	727
	Cu, xylene, reflux	(6)	728
	Cu, biphenyl, 190-220°	(44)	729
	Cu, 220°	(82)	724
C₁₄	Cu, 220-235°	(41)	730
	NiBr₂, Ph₃P, Zn, THF, 60-100°	(38-52)	731
	Ni(cod)₂, bpy	(16)	731
	NiCl₂, CrCl₂, Mn, THF, 25°	(0)	406
	Cu, biphenyl, 250°	(11)	732
	Cu, 190°	(65)	733
	Cu, 330-350°	(15)	734
	Cu, 190°	(63)	733
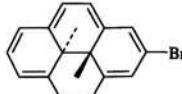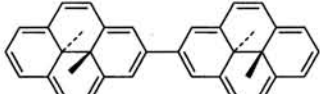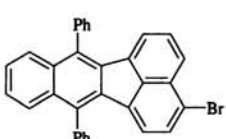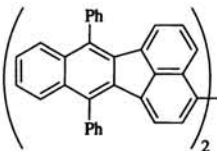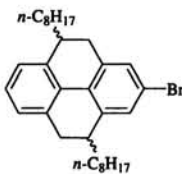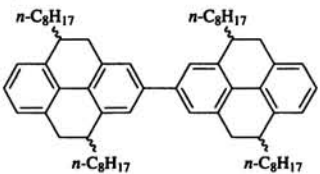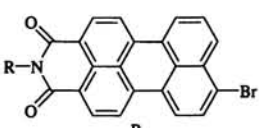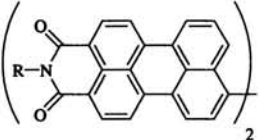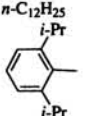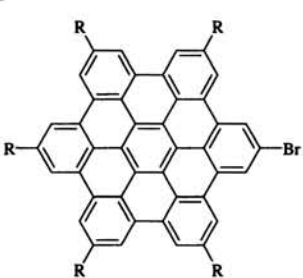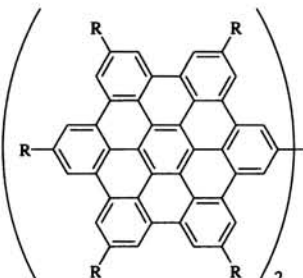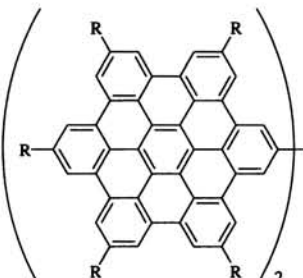
TABLE 24. MISCELLANEOUS BIARYLS *(Continued)*

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C14-16			
R			
NO2	Cu, 200°	(5)	61
NO2	Cu, DMF, reflux	(0)	61
CO2Me	Cu, 265°	(80)	735
CO2Me	Cu, DMF, reflux	(70)	736
C15	Cu, 280-300°	(26)	737
C16	Cu, 280-290°	(30)	738
C16-19			
R			
H	Cu, 220°	(83)	724
Me	Cu, 220°	(53)	724
i-Pr	Cu, 235°	(11)	724
C17	Cu, naphthalene, heat	(95)	739
	Cu, naphthalene, heat	(8)	739
X			
Cl	Cu, 280-300°	(5)	740
Br	Cu, 280-300°	(13)	740

TABLE 24. MISCELLANEOUS BIARYLS *(Continued)*

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{18}$	Ni(PPh$_3$)$_2$Cl$_2$, Ph$_3$P, Zn, DMF, 50°	(41)	741
C$_{20}$	Cu, 250°	(4)	742
C$_{32}$	NiCl$_2$, Ph$_3$P, Zn, NaBr, DMAc, 80°	(40)	743
	Ni(cod)$_2$, cod, bpy, toluene, DMF, 75°	(95 - 99)	247, 744

C$_{34}$

R			
n-C$_{12}$H$_{25}$	Ni(cod)$_2$, DMF 60°	(89)	745
	Ni(cod)$_2$, DMF 60°	(83)	745

C$_{62-102}$

R			
t-C$_4$H$_9$	Ni(cod)$_2$, cod, bpy, toluene, 60°	(75)	746
n-C$_{12}$H$_{25}$	Ni(cod)$_2$, cod, bpy, toluene, 60°	(85)	746

TABLE 25. 1,1'-BIANTHRAQUINONES
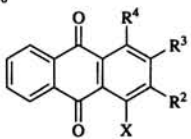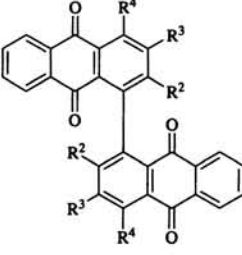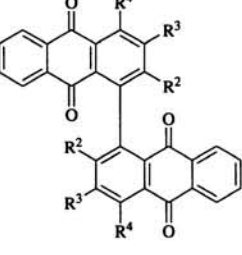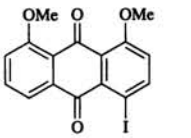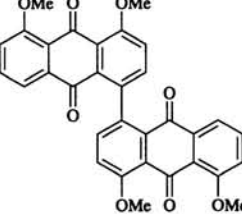
Substrate				Conditions	Product(s) and Yield(s) (%)	Refs.

C_{14-16}

R^2	R^3	R^4	X			
Br	H	H	Br	Cu, $PhNO_2$, 200-210°	(68)	747
H	Br	H	Br	Cu, $PhNO_2$, reflux	(65)	748
H	Cl	H	Cl	Cu, $PhNO_2$, reflux	(86)	749
H	H	H	Cl	Cu	(77)	750
H	H	H	Cl	Cu, $PhNO_2$, reflux	(70-80)	751
H	H	H	I	Cu, CO_2, 210-275°	(20)	752
H	SO_3H	NH_2	Br	Cu, H_2O	(78)	753
Me	H	H	I	Cu, $PhNO_2$, reflux	(50)	754
Me	H	H	I	Cu, 210-290°	(50)	755
Me	H	H	I	Cu	(30-45)	706, 756
H	Me	H	Br	Cu, $PhNO_2$, reflux	(50-70)	757
H	H	Me	Cl	Cu, 290-300°	(77)	758
H	H	Me	Cl	Cu, $PhNO_2$, reflux	(70)	758
OMe	H	H	Cl	Cu, $PhNO_2$, reflux	(0)	759
OMe	H	H	I	Cu, 360°	(20)	760
OMe	H	H	I	Cu	(80)	761
Et	H	H	I	Cu, 240°	(50)	762
CO_2Me	H	H	Br	Cu, DMF, reflux	(75)	706
H	H	CO_2Me	Cl	Cu, 265-300°	(>62)	763
OMe	H	OMe	Br	Cu, naphthalene, 225°	(59)	764
Me	H	OMe	Cl	Cu, CO_2, 300°	(10-40)	765

C_{14-22}

R^2	R^3	R^4	X			
H	OMe	OMe	I	Cu, 310°	(53)	766
Me	H	Me	I	Cu, 210-250°	(35)	767
i-Pr	H	H	I	Cu, 200°	(75)	762
CO_2Et	H	H	Cl	Cu, $PhNO_2$, reflux	(75)	768
N=CHPh	Br	H	Br	Cu, naphthalene, 220-260°	(66)	769
H	OMe	OCOPh	Br	Cu, $PhNO_2$, reflux	(69)	770
H	OMe	OCOPh	Br	Cu, naphthalene, reflux	(83)	770
H	H	NHCOPh	Cl	Cu, DMF, reflux	(90)	771

C_{16}

Cu, CO_2, 310°

(87)

772

TABLE 25. 1,1'-BIANTHRAQUINONES *(Continued)*
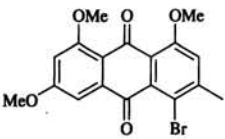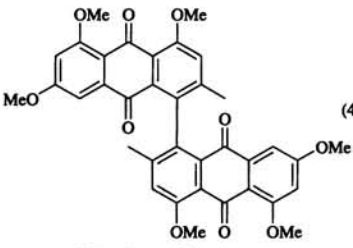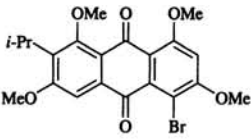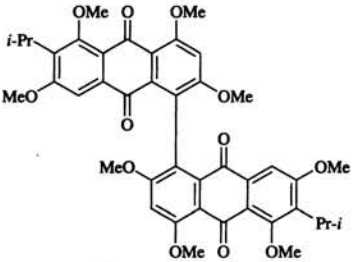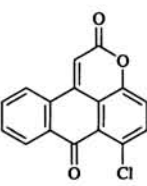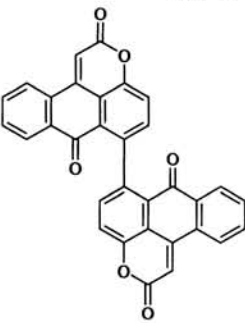
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₁₈	Cu, naphthalene, 230-240°	(40-90)	773-775
C₂₁	Cu, naphthalene, 240°	(83)	776
C₁₆	Cu, PhNO₂, reflux	(37)	777

TABLE 26. 2,2'-BIANTHRAQUINONES
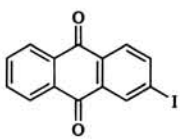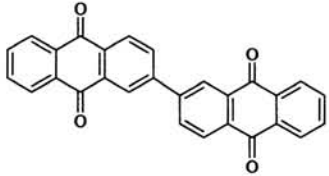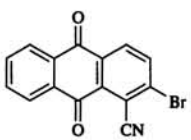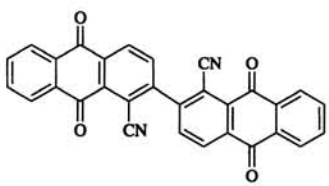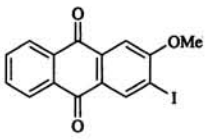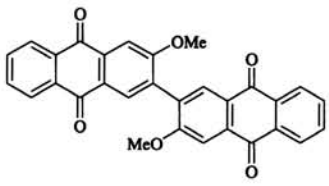
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{14}$	Cu, 230-330°	(49)	778
C$_{15}$	Cu, PhNO$_2$, reflux	(58)	779
	Cu, 360°	(2)	760

TABLE 27. BICOUMARINS, BICHROMONES, AND BIFLAVONES
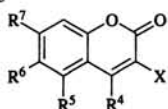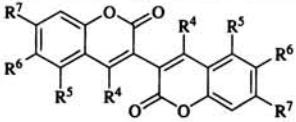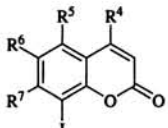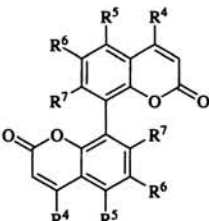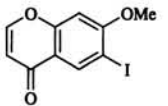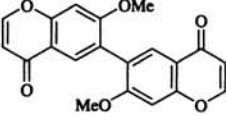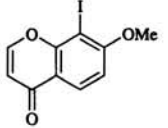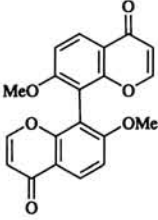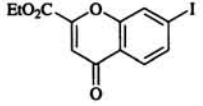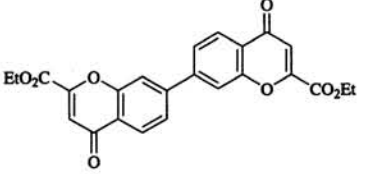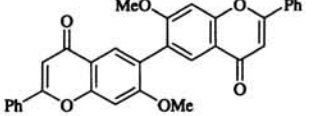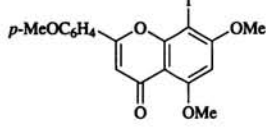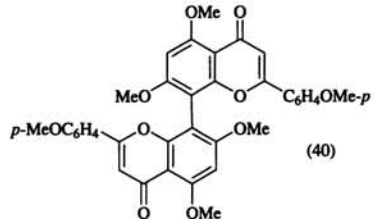
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C_{10-13}

R^4	R^5	R^6	R^7	X			
OMe	H	H	H	Br	Cu, 210°	(35)	780
H	H	H	OMe	I	Cu, Ph$_2$O, reflux	(25)	781
Me	H	H	OMe	I	Cu, Ph$_2$O, reflux	(17)	781
H	H	CO$_2$Me	OMe	I	Cu, Ph$_2$O, reflux	(16)	781
Me	H	CO$_2$Me	OMe	I	Cu, Ph$_2$O, reflux	(20)	781

R^4	R^5	R^6	R^7			
H	H	H	OMe	Cu, Ph$_2$O, reflux	(48)	781
Me	OMe	H	H	Cu, Ph$_2$O, reflux	(8)	781
Me	H	H	OMe	Cu, Ph$_2$O, reflux	(68)	781
H	H	CO$_2$Me	OMe	Cu, Ph$_2$O, reflux	(63)	781
Me	OMe	CO$_2$Me	H	Cu, Ph$_2$O, reflux	(12)	781
Me	H	CO$_2$Me	OMe	Cu, Ph$_2$O, reflux	(64)	781

C_{10}

Cu   (<15)   782

Cu   (<15)   782

C_{12}

Cu, DMF, 155–160°   (14)   783

C_{16}

Cu   (<15)   782

C_{18}

Cu, DMF, reflux   (40)   784

TABLE 27. BICOUMARINS, BICHROMONES, AND BIFLAVONES *(Continued)*
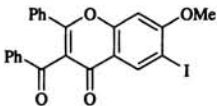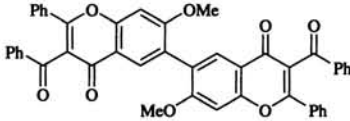
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{23}$	Cu, heat	(<15)	782

TABLE 28. BIPHENYLENES VIA INTERMOLECULAR COUPLING
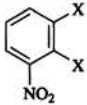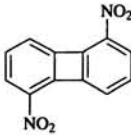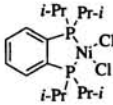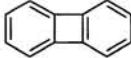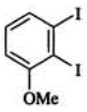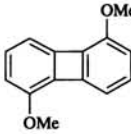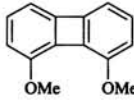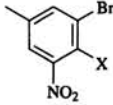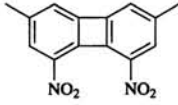
Substrate		Conditions	Product(s) and Yield(s) (%)	Refs.
C6				
	X			
	Cl	Cu, DMF, reflux	(1)	785
	I	Cu, DMF, 152°	(22–43)	536
		, DMSO, 2 e⁻, 65°	(0)	154
C7		Cu, DMF, reflux	(9) (2)	603
	X			
	Cl	Cu, DMF, reflux	(7)	623
	Br	Cu, DMF, reflux	(48)	623
	I	Cu, DMF, reflux	(3)	623

TABLE 28. BIPHENYLENES VIA INTERMOLECULAR COUPLING *(Continued)*
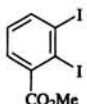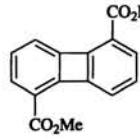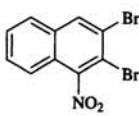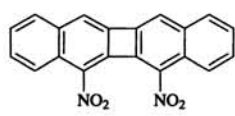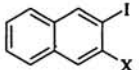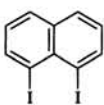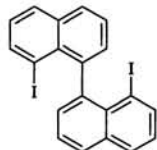
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_8$ (structure: benzene with two I groups and CO$_2$Me)	Cu, DMF, 55°	(structure: biphenylene with CO$_2$Me groups) (75)	33
C$_{10}$ (naphthalene with Br, Br, NO$_2$)	Cu, DMF, reflux	(structure with NO$_2$ NO$_2$) (2)	786
(naphthalene with I, X)		(fused ring structure)	

X			
Br	Cu, DMF, reflux	(1)	787
I	Cu, DMF, reflux	(1)	786

| (naphthalene with two I) | Pd(OAc)$_2$, K$_2$CO$_3$, Bu$_4$NBr, DMF, 100° | (perylene structure) (42) + (binaphthyl with I, I structure) (39) | 173 |

TABLE 29. TRIARYLENES
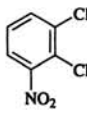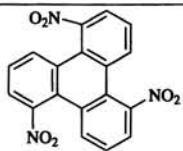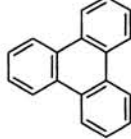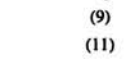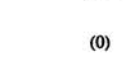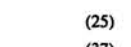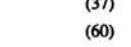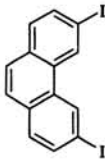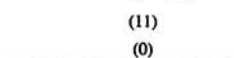
Substrate		Conditions	Product(s) and Yield(s) (%)	Refs.
C$_6$		Cu$_2$O, DMF, reflux	(2)	785
	$\dfrac{X}{Cl}$	Ni(cod)$_2$, bpy, DMF, 70°	(9)	731
	Cl	Ni(cod)$_2$, bpy, THF, reflux	(11)	731
	Cl	, DMSO, –2.2 V, 65°	(0)	154
	Br	Ni(0), DMF, 140°	(25)	120
	Br	Ni(cod)$_2$, bpy, THF, reflux	(37)	731
	Br	Ni(cod)$_2$, PPh$_3$, DMF, 70°	(60)	731
C$_{14}$		Cu, biphenyl, 250°	(11)	732,788
		Cu, DMF, reflux	(0)	788

TABLE 30. TETRAARYLENES
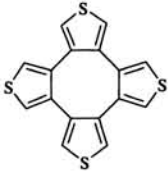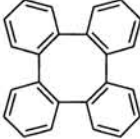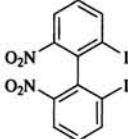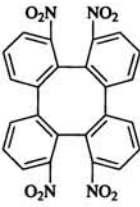
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_4$			
	Ni(cod)$_2$, PPh$_3$, DMF, 70°	(64)	731
	Ni(cod)$_2$, bpy, DMF, 70°	(70)	731
C$_6$	Ni(0), DMF, 140°	(25)	120
C$_{12}$	Cu$_2$O, DMF, 152°	(4-20)	536

TABLE 31. INTRAMOLECULAR COUPLINGS FORMING SYMMETRIC BIPHENYLS AND BINAPHTHYLS
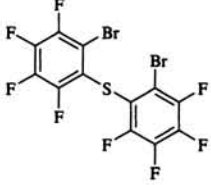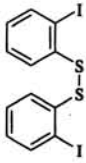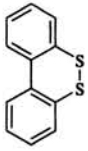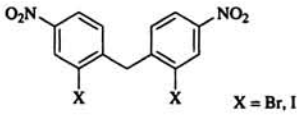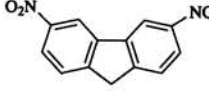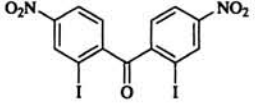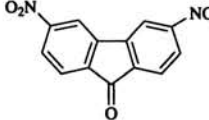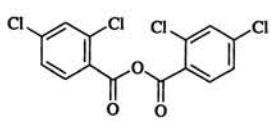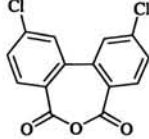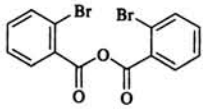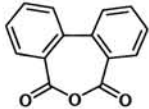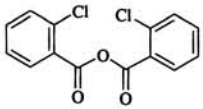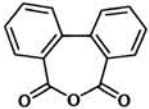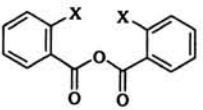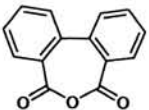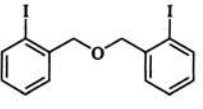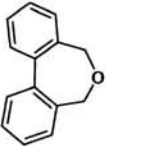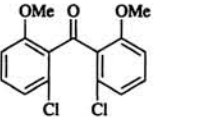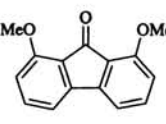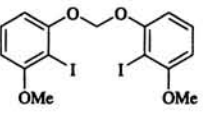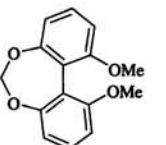
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{12}$	Cu, 200° Cu, DMF, 150°	 (100) (0)	789 789
	Cu, 180°	(60)	422
C$_{13}$ X = Br, I	Cu, sand, PhNO$_2$, DMF, heat	(0)	790
	Cu, DMF, reflux	(0)	790

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C₁₄

| | Cu, pyridine, 60-70° | (89) | 791 |
| | Cu, DMF, 60-70° | (88) | 791 |

Cu, complexing agent, benzene, reflux

complexing agent		
DMF, heat	(85)	791
HMPA	(87)	791
TMED	(28)	791
4,5-phenanthroline	(95)	791
bpy	(98)	791

| | Cu, TMED, 60-70° | (36) | 791 |
| | Cu, DMF, 60-70° | (34) | 791 |

Cu, solvent, 60-70°

X	solvent		
Br	TMED	(22)	791
Br	NMP	(65)	791
Br	HMPA	(61)	791
Br	DMF	(90)	791
Br	pyridine	(98)	791
I	TMED	(18)	791
I	NMP	(65)	791
I	HMPA	(58)	791
I	DMF	(56)	791
I	pyridine	(98)	791

| | Pd(OAc)₂, As(*o*-tolyl)₃, hydroquinone, Cs₂CO₃, DMA, 100° | (61) | 178 |

C₁₅

| | Cu, heat | (0) | 577 |

| | Cu, 200° | (15) | 792 |

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	$\underset{\text{S}}{\bigotimes}\overset{\text{O}}{\underset{\text{C}}{\text{C}}}\text{OCu}$, NMP, rt	(88)	71

C$_{16}$

| | Cu, 210° | (8) | 432 |

C$_{16-20}$

n			
2	Ni(PPh$_3$)$_2$Cl$_2$, Ph$_3$P, Zn, DMF, 50°	(98)	793
2	(Ph$_3$P)$_4$Ni, DMF, 55°	(81)	49, 138
3	Cu, 240°	(74)	49
3	(Ph$_3$P)$_4$Ni, DMF, 55°	(83)	49, 138
4	(Ph$_3$P)$_4$Ni, DMF, 55°	(76)	49, 138
5	(Ph$_3$P)$_4$Ni, DMF, 55°	(85)	49, 138
6	(Ph$_3$P)$_4$Ni, DMF, 55°	(38)	49, 138

C$_{16-20}$

	Cu, DMF, reflux		

n			
2		(21)	794
3		(86)	794
4		(41)	794
5		(26)	794
6		(19)	794

C$_{17}$

	Ni(OAc)$_2$, NaH, *t*-AmOH, bpy, THF, reflux	(52), including accompanying rearrangements	577
	Cu	(0)	577

	(Ph$_3$P)$_4$Ni, DMF, 55°	(80-85)	49, 138

C$_{18}$

	Cu, DMF, reflux	(90)	33
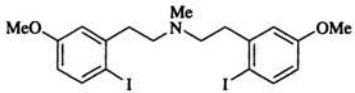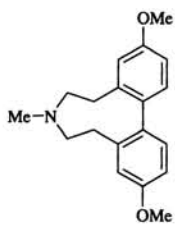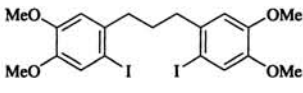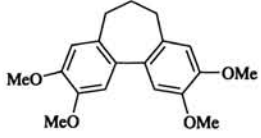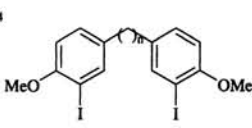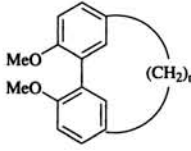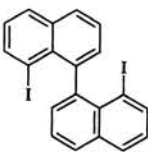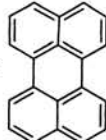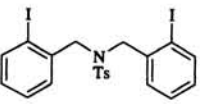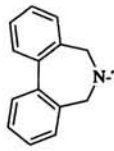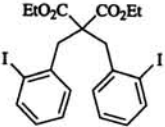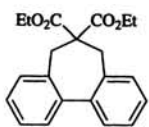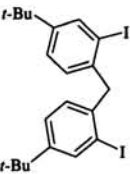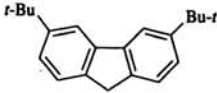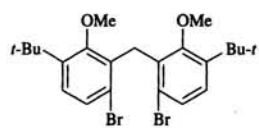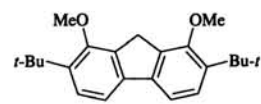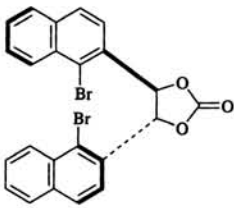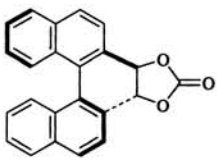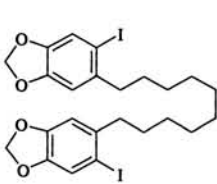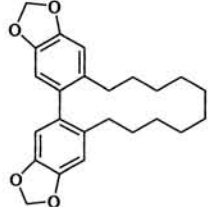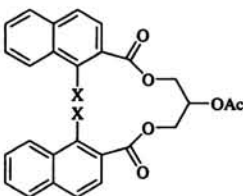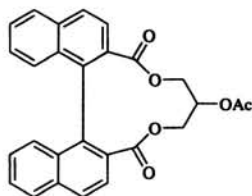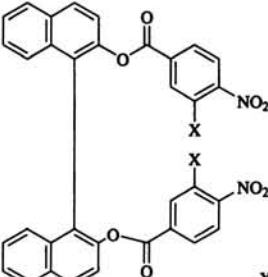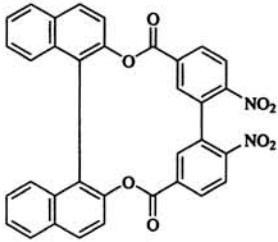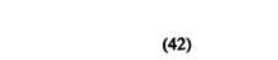
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{19}$			
	(Ph$_3$P)$_4$Ni, DMF, 55°	(60)	795
	Cu, Hg, 250°	(23)	796
C$_{19-24}$	Ni(PPh$_3$)$_2$Cl$_2$, Ph$_3$P, Zn, DMF, 50°		
n			
5		(0)	793
6		(7)	793
7		(10)	793
8		(7)	793
9		(11)	793
10		(9)	793
C$_{20}$	Pd(OAc)$_2$, K$_2$CO$_3$, Bu$_4$NBr, DMF, 100°	(85)	173
C$_{21}$	Pd(OAc)$_2$, As(o-tolyl)$_3$, hydroquinone, Cs$_2$CO$_3$, DMA, 100°	(82)	178
	Pd(OAc)$_2$, As(o-tolyl)$_3$, hydroquinone, Cs$_2$CO$_3$, DMA, 100°	(65)	178
	Cu, 230°	(95)	797
	Ni(PPh$_3$)$_2$Cl$_2$, Ph$_3$P, Zn, DMF, 70-75°	(85)	798
	NiCl$_2$•6H$_2$O, PPh$_3$, Zn, DMF, 70-75°	(76)	798

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C$_{22}$

Ni(PPh$_3$)$_2$Cl$_2$, Ph$_3$P, Zn,
NaBr, DMF, 80°

 (62)

577

C$_{23}$

NiCl$_2$, Ph$_3$P, Zn, NaI, DMF, 70-80°

 (33)

209

C$_{24}$

(Ph$_3$P)$_4$Ni, DMF, 45°

 (58)

49, 138

C$_{27}$

X			
Br	Cu, DMF, reflux	(9)	799
I	Cu, DMF, reflux	(67)	799

C$_{34}$

X			
Cl	Cu, DMF, reflux	(42)	206
I	Cu, DMF, reflux	(70)	206

TABLE 31. INTRAMOLECULAR COUPLINGS FORMING SYMMETRIC BIPHENYLS AND BINAPHTHYLS *(Continued)*

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C$_{38}$

Ni(PPh$_3$)$_2$Cl$_2$, Ph$_3$P, Zn, DMF, 50°

(55)

800

C$_{38}$

Ni(PPh$_3$)$_2$Cl$_2$, Ph$_3$P, Zn, DMF, 54°

(6)

457

C$_{42}$

Cu, DMF, reflux

(36-98)

206, 801, 802

Cu, DMF, reflux

(11)

803
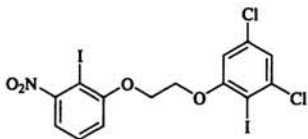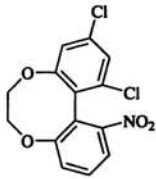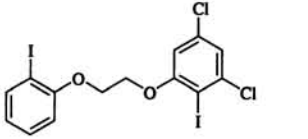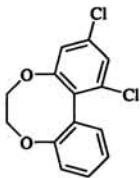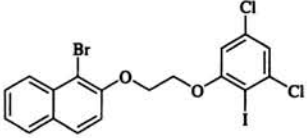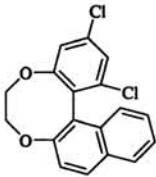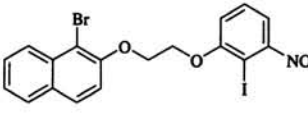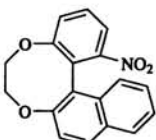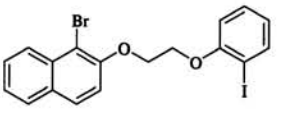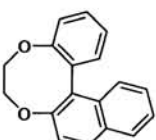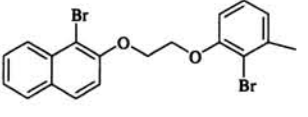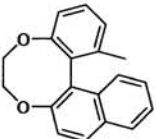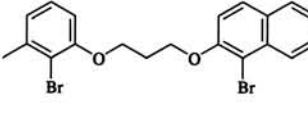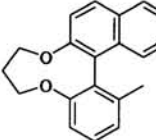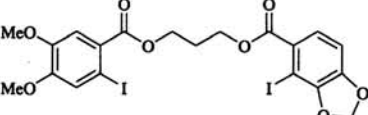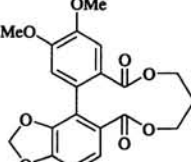
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{14}$	Cu, DMF, reflux	(56)	207
	Cu, DMF, reflux	(51)	207
C$_{18}$	Cu, DMF, reflux	(61)	207
	Cu, DMF, reflux	(38)	207
	Cu, DMF, reflux	(43)	207
C$_{19}$	Cu, DMF, reflux	(28)	207
C$_{20}$	Cu, DMF, reflux	(31)	207
	Cu, DMF, reflux	(84)	604
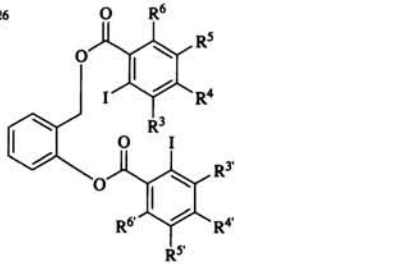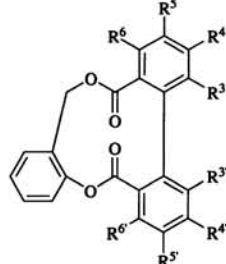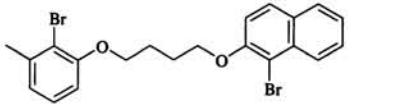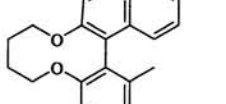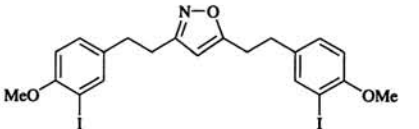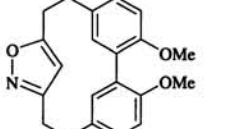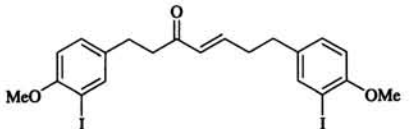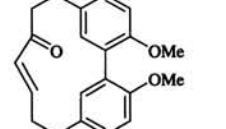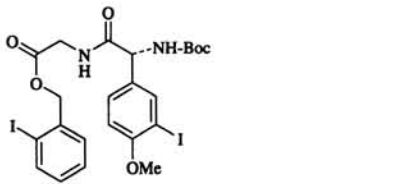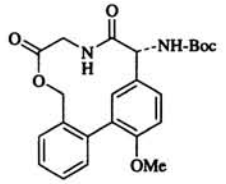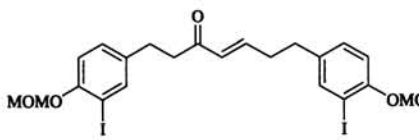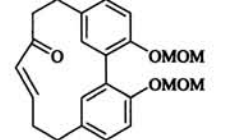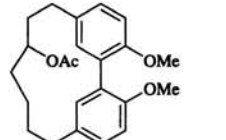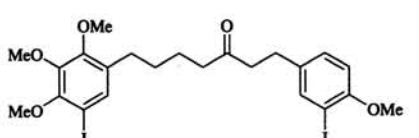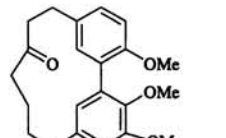
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C$_{21-26}$

R³	R⁴	R⁵	R⁶	R³'	R⁴'	R⁵'	R⁶'	Conditions	Yield	Refs.
H	H	H	NO₂	H	Cl	H	Cl	Cu, DMF, reflux	(84)	804
H	OMe	OMe	H	H	H	H	NO₂	Cu, DMF, reflux	(90)	804
H	OMe	OMe	H	H	H	H	H	Cu, DMF, reflux	(71)	805
-OCH₂O-		H	H	H	-OCH₂O-		H	Cu, DMF, reflux	(75)	805
H	OMe	OMe	OMe	H	H	H	NO₂	Cu, DMF, reflux	(87)	804
H	Cl	H	Cl	H	OMe	OMe	OMe	Cu, DMF, reflux	(89)	804
-OCH₂O-		H	H		OMe	OMe	H	Cu, DMF, reflux	(89)	805
H	-OCH₂O-		H	OMe	OMe	OMe	H	Cu, DMF, reflux	(78)	805
H	OMe	OMe	H	OMe	OMe	OMe	H	Cu, DMF, reflux	(83)	805

C$_{21}$

| | Cu, DMF, reflux | (49) | 207 |

| | Ni(PPh₃)₂Cl₂, Ph₃P, Zn, DMF | (31) | 766 |

| | (PPh₃)₄Ni, DMF, 50° | (52) | 49,138 |

C$_{23}$

| | Ni(PPh₃)₂Cl₂, Ph₃P, Zn, DMF, 55° | (57) | 807 |

| | (PPh₃)₄Ni, DMF, 50° | (46) | 49 |

| | Ni(PPh₃)₂Cl₂, Ph₃P, Zn, DMF, 50° | (49) | 806 |

| | Ni(PPh₃)₂Cl₂, Ph₃P, Zn, DMF, 54° | (8) | 457 |

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C25

Ni(PPh₃)₂Cl₂, Ph₃P, Zn, DMF, 54°

(9)   457

C32

Cu, DMF, reflux

(80)   207

C33

X			
Br	Ni(cod)₂	(0)	808
I	Ni(cod)₂	(0)	808

C35

Ni(PPh₃)₂Cl₂, Ph₃P, Zn, DMF, 54°

(10)   457, 809

C36

Cu, DMF, reflux

(44)   207

Cu, DMF, reflux

(33)   207

(Ph₃P)₄Ni, DMF, 55°

(20)   810

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{37}$	Ni(PPh$_3$)$_2$Cl$_2$, Ph$_3$P, Zn, DMF, 54°	(7)	457, 809
C$_{41}$	Cu, DMF, reflux	(77)	208
C$_{41-47}$			
R PhCH$_2$	Cu, DMF, reflux	(50)	208
MeO, MeO, MeO	Cu, DMF, reflux	(50)	208
C$_{43}$	Cu, DMF, reflux	(69)	208

TABLE 33. BIPHENYLENES VIA INTRAMOLECULAR COUPLING
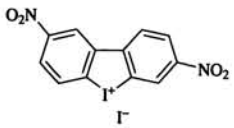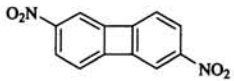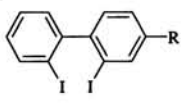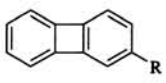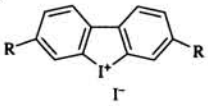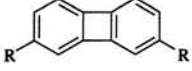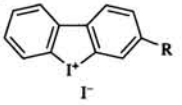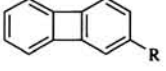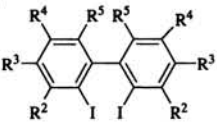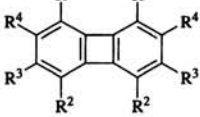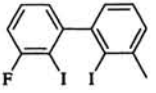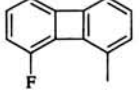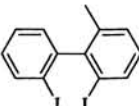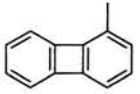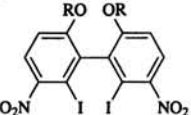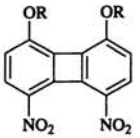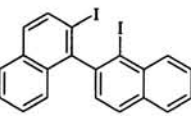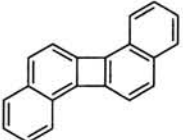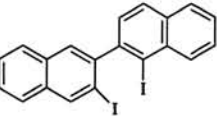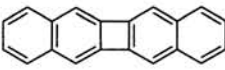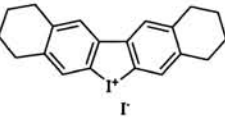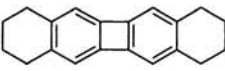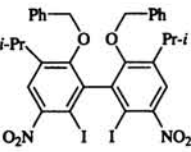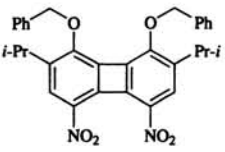
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{12}$	Cu$_2$O, 350°	(< 1)	456
C$_{12-13}$			
R: NO$_2$	Cu$_2$O, 350°	(17)	456
R: OMe	Cu$_2$O, 350°	(23)	456
C$_{12-14}$			
R: H	Cu$_2$O, heat	(15)	811
H	Cu$_2$O, 350-360°	(21-28)	415, 812
Me	Cu$_2$O, heat	(5)	811
Me	Cu$_2$O, CuC$_2$O$_4$, heat	(35)	813
C$_{12-18}$			
R: NO$_2$	Cu$_2$O, heat	(16-17)	456
Ph	Cu$_2$O, 450°	(17)	813

C$_{12-20}$

R^2	R^3	R^4	R^5			
F	F	F	F	Cu$_2$, 200°	(5)	814
H	H	H	H	Cu, heat	(38-44)	65
H	H	H	H	Cu$_2$O, heat	(31)	65
H	H	OMe	H	Cu$_2$O, 330-360°	(42)	612
H	H	H	CO$_2$Me	Cu, pyridine, reflux	(11)	33
H	Me	Me	H	Cu$_2$O, 380-400°	(5)	813
H	H	Me	OMe	Cu$_2$O, 350°	(31)	603
H	OMe	OMe	H	Cu$_2$O, 330-360°	(31)	612
Me	H	OMe	OMe	Cu$_2$O, 340°	(27)	654
Me	OMe	Me	H	Cu$_2$O, 330-360°	(28)	612
Me	OMe	OMe	H	Cu$_2$O, CuC$_2$O$_4$, 360-400°	(18)	651
H	OMe	OMe	OMe	Cu$_2$O, 350°	(18)	654
H	OMe	OMe	OMe	Cu, heat	(46)	65, 654
OMe	OMe	OMe	H	Cu$_2$O, 340°	(22)	654
OMe	H	OMe	OMe	Cu$_2$O, 330-350°	(30)	654
Me	OMe	Me	Me	Cu$_2$O, CuC$_2$O$_4$, 360-400°	(7)	651

C$_{13}$	Cu$_2$O, heat	(27)	815
	Cu$_2$O, heat	(74)	815

TABLE 33. BIPHENYLENES VIA INTRAMOLECULAR COUPLING (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{13}$	Cu$_2$O, 350°	(41)	456
C$_{14-26}$			

R			
Me	Cu, DMF, reflux	(79)	816
Me	Cu$_2$O, 270°	(28)	816
PhCH$_2$	Cu, DMF, reflux	(42)	816

C$_{20}$	Cu, 250-350°	(9)	817
	Cu$_2$O, 230-330°	(6)	818
	Cu$_2$O, 340°	(3-5)	616
C$_{32}$	Cu, DMF, reflux	(76)	819

TABLE 34. BIPYRROLES

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₉ [pyrrole structure]	Cu, DMF, reflux	(25)	820
[2-iodo-1-methylindole]	Cu, 205°	(66)	13

C₉₋₂₁ [pyrrole with R³, R⁴, R⁵, I substituents] → [bipyrrole product]

R³	R⁴	R⁵	Conditions	Product(s) and Yield(s) (%)	Refs.
CO₂Me	Me	CO₂Me	Cu, DMF, rt	(60)	821
Me	Me	CO₂Et	Cu, 240°	(15)	822
Me	Me	CO₂Et	Cu, DMF, 100°	(35)	823
Me	CO₂Et	Me	Cu, DMF, rt	(32)	823
Me	CO₂Et	CO₂Me	Cu, DMF, rt	(21)	821
Et	Me	CO₂Et	Cu, DMF, 100-140°	(29-50)	823-825
Me	Et	CO₂Et	Cu, DMF, 110°	(45-50)	824, 826, 827
Et	Et	CO₂Et	Cu, DMF, 110°	(35-40)	827
CO₂Et	Me	CO₂Et	Cu, DMF, rt	(61-63)	821, 823
CO₂Et	Me	CO₂Et	Cu, benzene, 80°	(77)	821
CO₂Et	Me	CO₂Et	Cu, PhNO₂, 100°	(38)	821
CO₂Et	Me	CO₂Et	Cu, 210°	(54)	828
CO₂Et	Et	CO₂Et	Cu, DMF, reflux	(65)	823
CO₂Et	n-C₃H₇	CO₂Et	Cu, DMF, 20°	(62-71)	829
CH₂CH₂CO₂Et	Me	CO₂Et	Cu, DMF, rt	(30)	823
CO₂Et	CH₂CH₂OMe	CO₂Et	Cu, 1,3-dimethyl-2-imidazolidinone, rt	(67)	830
Me	Me	CO₂CH₂Ph	Cu, DMF, rt	(57)	821
Me	CO₂CH₂Ph	Me	Cu, DMF, rt	(18)	821
CO₂Et	Me	CO₂CH₂Ph	Cu, DMF, 100°	(77)	821
CO₂Et	Ph	CO₂Et	Cu, DMF, reflux	(44)	831
CO₂CH₂Ph	Me	CO₂Et	Cu, DMF, rt	(27)	821
CO₂CH₂Ph	Me	CO₂CH₂Ph	Cu, DMF, rt	(56)	821

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₁₀ [pyrrole structure]	Cu, 220°	(59)	820
C₁₁ [2-iodo-N-CO₂Et indole]	[thiophene-2-carboxylate OCu], NMP, rt	(69)	71
C₁₂ [pyrrole structure]	Cu, I₂, DMF, reflux	(35)	832
C₁₉ [bipyrrole structure]	Cu, DMF, 140°	(69)	833

478

479

TABLE 35. UNSUBSTITUTED 2,2'-BIPYRIDYL
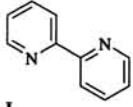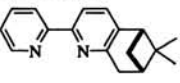
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₅ 	NaH, Ni(OAc)₂, t-BuOH, Ph₃P, DME, 65°	(51) **I**	398
		I	
	NaH, Ni(OAc)₂, t-BuOH, Ph₃P, DME, 45°	(66)	398, 834
	NiCl₂, Ph₃P, Zn, DMAc, 50-80°	(70)	51
	NiBr₂(PPh₃)₂, Zn, Et₄NI, THF, 50°	(60)	139
	HCO₂Na, Pd/C, TEBAC, NaOH(aq)	(52)	179
		I	
	Cu, cymene, reflux	(60-63)	835-837
	Cu, biphenyl, 230°	(72)	835, 838
	Cu, DMF, reflux	(87)	6, 835
	Cu, tetralin, reflux	(26)	6, 835
	Cu, decane, reflux	(51)	6, 835
	Cu, decalin, reflux	(61)	6, 835
	Cu, pseudocymene, reflux	(63)	6, 835
	NiCl₂, Ph₃P, Zn, DMF, 50°	(68)	142, 839
	Ni(bpy)₂(OAc)₂, Et₄NBr, CH₃CN, 2 e⁻	(88)	405
	NiBr₂(PPh₃)₂, Zn, Et₄NI, THF, 50°	(72)	139
	NaH, Ni(OAc)₂, t-BuOH, Ph₃P, DME, 30-45°	(65-70)	398, 834
	Ni(CO)₂(PPh₃)₂, toluene, DMF, 70°	(75)	145
	NiCl₂, CrCl₂, Mn, THF, 25°	(0)	406
	Pd(OAc)₂, P(o-tol)₃, KF, DMF, 120°	(63)	196
	Pd(OAc)₂, As(o-tolyl)₃, hydroquinone, Cs₂CO₃, DMAc, 100°	(72)	178
	PdCl₂(PPh₃)₂, Et₄NOTs, DMF, 2e⁻	(91)	190
	Pd(OAc)₂, Bu₄NBr, DMF, H₂O, i-PrOH, K₂CO₃, 50°	(92)	174, 175
	PdCl₂, HgCl₂, PhNHNH₂, NaOH, MeOH, reflux	(42)	165
		I	
	Cu, cymene, 220°	(20)	836
	NiCl₂(PEt₃)₂, Zn, KI, HMPA, 40°	(0)	401
	Pd(OAc)₂, Ph₃P, styrene, Et₃N, 100°	(66-71)	840
	Pd(OAc)₂, styrene, Et₃N, 100°	(68)	840
C₆	PdCl₂(PPh₃)₂, Bu₄NBF₄, DMF, 2e⁻	**I** (78)	192

TABLE 36. 3,3'-DISUBSTITUTED-2,2'-BIPYRIDYLS

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C₅₋₇

R	X			
OH	I	Cu, DMF, reflux	(25)	841
OH	Br	NiCl₂•6 H₂O, Zn, PPh₃, DMF, 50°	(55)	140
NO₂	Cl	Cu, DMF, 100-150°	(51-85)	842-845
OMe	I	Cu, DMF, reflux	(39)	841
OMe	I	NiCl₂, Zn, DMF, 50°	(60)	841
OMe	I	NiCl₂, Zn, PPh₃, DMF, 50°	(65)	841
OMe	Br	NiCl₂•6 H₂O, PPh₃, Zn, DMF, 50°	(75)	142, 839
Me	Br	Cu, neat, 240°	(40)	846
Me	Br	Cu, NaCl, p-cymene, reflux	(19)	847
CF₃	Cl	Ni(PPh₃)₂Cl₂, Zn, Et₄NI, THF, 60°	(0)	848
CF₃	Cl	HCO₂Na, PhCH₂NEt₃Cl, Pd/C, NaOH,	(trace)	849
CF₃	Cl	ethylene glycol, H₂O, toluene, reflux		
CN	Br	Cu, DMF, 150°	(39)	850
CO₂Me	Cl	NiBr₂(PPh₃)₂, Zn, Et₄NI, THF, 50°	(53)	139
NHAc	Br	Cu, DMF, 100°	(34)	842

C₁₀

NiCl₂•6 H₂O, Zn, PPh₃, DMF, 50-60°   (79)   851

TABLE 37. 4,4'-DISUBSTITUTED-2,2'-BIPYRIDYLS

Substrate			Conditions	Product(s) and Yield(s) (%)	Refs.
C_{6-12}					

R	X				
CF_3	Cl	$NiCl_2(PPh_3)_2$, Zn, Et_4NI, THF, 60°	(34)		848
Me	Br	Cu, neat, 240°	(33)		846
OMe	Cl	$NiCl_2 \cdot 6H_2O$, PPh_3, Zn, DMF, 50°	(88)		852
Et	Br	Cu, neat, 220°	(25)		853
Ph	Br	Cu, neat, 250°	(18)		853
p-Tol	Br	$Ni(PPh_3)_2Cl_2$, PPh_3, Zn, DMF, 50°	(27)		854

TABLE 38. 5,5'-DISUBSTITUTED-2,2'-BIPYRIDYLS

Substrate			Conditions	Product(s) and Yield(s) (%)	Refs.

C_{5-12}

R	X	Conditions	Product(s) and Yield(s) (%)	Refs.
NO_2	Br	Pd(OAc)$_2$, K$_2$CO$_3$, toluene, DMF, i-PrOH, 105°	(8-19)	175
NO_2	Br	Pd(OAc)$_2$, K$_2$CO$_3$, toluene, DMF, 115°	(8)	175
NO_2	I	Cu, neat, 180°	(2)	846
NH_2	Cl	NiCl$_2$•6 H$_2$O, Zn, Ph$_3$P, DMF, 50°	(60)	855-856
Cl	Br	Cu, neat, 225°	(8)	846
Br	Br	Cu, neat, 225°	(1)	846
CF_3	Cl	NaH, Ni(OAc)$_2$, t-AmOH, bpy, THF, reflux	(57)	398
CF_3	Cl	Ni(PPh$_3$)$_2$Cl$_2$, Zn, Et$_4$NI, THF, 60°	(32)	848
CF_3	Cl	HCO$_2$Na, Pd/C, Et$_3$NCH$_2$PhCl, H$_2$O, reflux	(32)	848
Me	Br	Pd(OAc)$_2$, Bu$_4$NBr, DMF, H$_2$O, i-PrOH, K$_2$CO$_3$, 115°	(95)	174, 175
Me_2N	Br	NiCl$_2$•6 H$_2$O, Zn, Ph$_3$P, DMF, 50°	(64)	855
(pyrrolidinyl-Me)	Cl	Pd(PPh$_3$)$_4$, (n-Bu$_3$Sn)$_2$, Et$_3$N, DMF, 100°	(58)	857
PhN=CH	Cl	Ni(PPh$_3$)$_2$Br$_2$, Zn, Et$_4$NI, THF, 50-80°	(83)	858

TABLE 39. 6,6'-DISUBSTITUTED-2,2'-BIPYRIDYLS
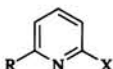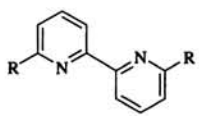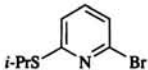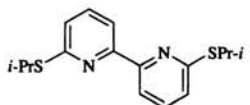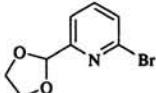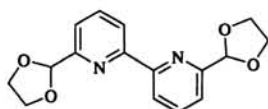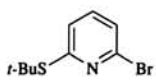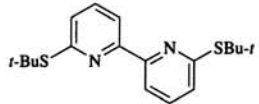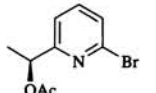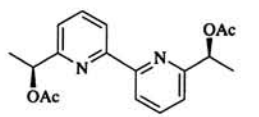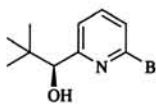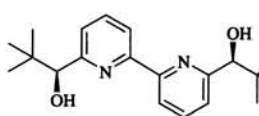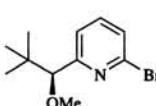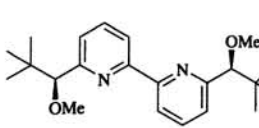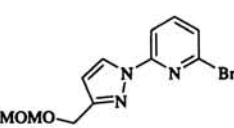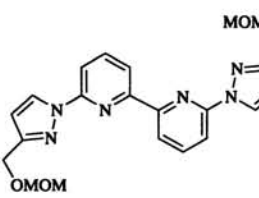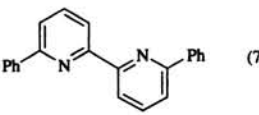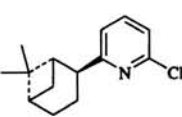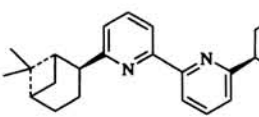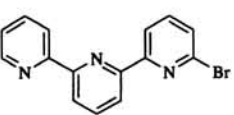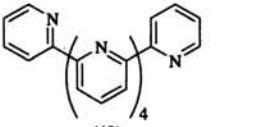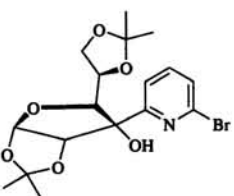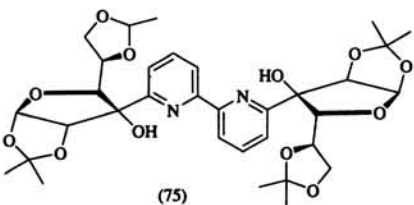
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C$_{5-7}$

R	X			
NO$_2$	Cl	Cu, DMF, 100°	(51)	844
CF$_3$	Cl	Ni(PPh$_3$)$_2$Cl$_2$, Zn, Et$_4$NI, THF, 60°	(29)	848
CF$_3$	Cl	Pd/C, HCO$_2$Na, TEBAC, NaOH, H$_2$O, reflux	(9)	848
Me	Br	NaH, Ni(OAc)$_2$, t-BuOH, PPh$_3$, DME, 45°	(73)	398
Me	Br	Raney Ni, toluene, reflux	(64-68)	859, 860
Me	Br	Ni(cod)$_2$, DMF	(95)	861
Me	Br	Ni(dmpb)Cl$_2$, Zn, Bu$_4$NBF$_4$, DMF, 2e⁻	(67)	862
Me	Br	Pd/C, HCO$_2$Na, TEBAC, NaOH, H$_2$O, reflux	(50-67)	183, 863, 864
Me	Br	Pd(OAc)$_2$, K$_2$CO$_3$, Bu$_4$NBr, i-PrOH, H$_2$O, 110°	(74)	862
MeO	Br	NiCl$_2$, PPh$_3$, Zn, DMF, 50°	(70-87)	142, 839, 852
MeO	Cl	NaH, Ni(OAc)$_2$, t-BuOH, PPh$_3$, DME, 45°	(79-80)	398, 834
CO$_2$Me	Cl	NiBr$_2$(PPh$_3$)$_2$, Zn, Et$_4$NI, THF, 50°	(90)	139

C$_8$

NiCl$_2$•6 H$_2$O, PPh$_3$, Zn, KI, DMF, 50°	(50)	865
NiCl$_2$•6 H$_2$O, PPh$_3$, Zn, DMF, 50°	(45)	865

Ni(PPh$_3$)$_2$Cl$_2$, Zn, Et$_4$NI, THF, 50°	(65)	866

TABLE 39. 6,6'-DISUBSTITUTED-2,2'-BIPYRIDYLS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₉			
	NiCl₂•6 H₂O, PPh₃, Zn, KI, DMF, 50°	(60)	865
	NiCl₂•6 H₂O, PPh₃, Zn, DMF, 50°	(40)	865
	NiCl₂, Zn, PPh₃, DMF, 72°	(39)	867
C₁₀	NiCl₂, Zn, PPh₃, DMF, 72°	(50-60)	867, 868
	$\underline{X}$		
	Br — Cu, biphenyl, 230°	(30)	838
	Br — NiCl₂•6 H₂O, PPh₃, Zn, DMF 50°	(43)	866
	Br — Ni(CO)₂(PPh₃)₂, toluene, DMF, 70°	(70)	145
	Cl — Ni(PPh₃)₂Cl₂, PPh₃, Zn, DMF, 50°	(27-38)	866, 867
C₁₁	NiCl₂, Zn, PPh₃, DMF, 72°	(65)	868, 869
	NiCl₂•6 H₂O, Zn, PPh₃, DMF, 50°	(40)	870, 871
	Ni(CO)₂(PPh₃)₂, toluene, DMF, 70°	(70)	145
C₁₄	NiCl₂•6 H₂O, PPh₃, Zn, NaI, DMF, 70°	(60)	872
C₁₅			
	Cu, biphenyl, 230°	(40)	870
	NiCl₂•6 H₂O, PPh₃, Zn, DMF, reflux	(48)	873
C₁₇	NiCl₂•6 H₂O, PPh₃, Zn, DMF, 80°	(75)	874

TABLE 39. 6,6'-DISUBSTITUTED-2,2'-BIPYRIDYLS (*Continued*)
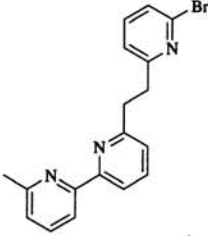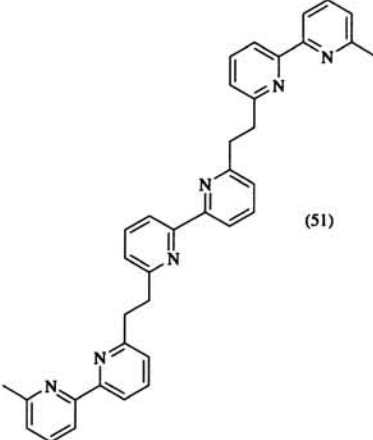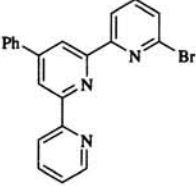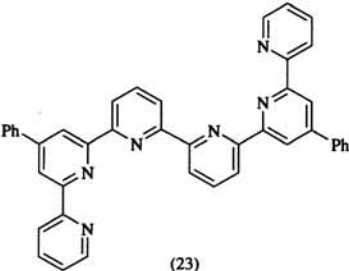
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C₁₈

NiCl₂•6 H₂O, PPh₃, Zn, DMF, 60°

(51)

875

C₂₁

NiCl₂•6 H₂O, PPh₃, Zn, DMF, reflux

(23)
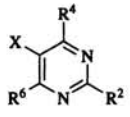
873

TABLE 40. POLYSUBSTITUTED-2,2'-BIPYRIDYLS
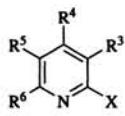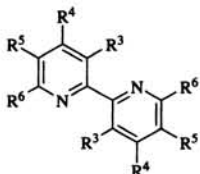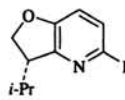
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C$_{5-12}$

R^3	R^4	R^5	R^6	X			
NO$_2$	H	H	Cl	Cl	Cu, DMF, 100°	(54)	842
NO$_2$	H	NO$_2$	H	Cl	Cu, DMF, 100°	(<10)	842
NO$_2$	H	Me	H	Cl	Cu, DMF, 100-105°	(63)	396
NO$_2$	H	OMe	Br	Br	Cu, DMF, 80°	(75)	842
NO$_2$	H	OMe	Br	Br	excess Cu, DMF, 100°	(0)	842
OMe	H	H	NO$_2$	I	Cu, DMF, 100°	(42)	841
H	H	OMe	Br	Br	Cu, DMF, 100°	(0)	842
F	OMe	H	H	Br	NiCl$_2$, Zn, PPh$_3$, DMF, 50°	(42)	876
Me	H	H	OH	Br	NiCl$_2$, Zn, PPh$_3$, DMF, 50°	(42)	140
Me	H	H	OH	I	Cu(I) thiophenecarboxylate, NMP, rt	(60)	71
CF$_3$	H	CF$_3$	H	Cl	Ni(PPh$_3$)$_2$Cl$_2$, Zn, Et$_4$NI, THF, 60°	(33)	848
CF$_3$	OMe	CF$_3$	H	Cl	Pd/C, PhCH$_2$NEt$_3$Cl, HCO$_2$Na, H$_2$O, reflux	(7)	848
OMe	OMe	H	H	Br	Cu, DMF, 150°	(<10)	144
OMe	OMe	H	H	Br	NiCl$_2$, Zn, PPh$_3$, DMF, 50°	(25-87)	144, 876-878
OMe	OMe	H	H	Br	Pd/C, HCO$_2$NH$_4$, CTAB, NaOH(aq), reflux	(15-20)	144
OMe	OMe	H	H	I	NiCl$_2$, Zn, PPh$_3$, DMF, 50°	(80)	879, 880
H	OMe	OMe	H	I	NiCl$_2$, Zn, PPh$_3$, DMF, 50°	(79)	881

| Me | H | H | | Br | Cu, 150° | (70) | 882 |

C$_{10}$

NiCl$_2$, PPh$_3$, Zn, DMF, 50°		(63)	883

TABLE 40. POLYSUBSTITUTED-2,2'-BIPYRIDYLS (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C$_{12}$

NiCl$_2$, PPh$_3$, Zn, DMF, 50°

(46)   884

NiCl$_2$, PPh$_3$, Zn, DMF, 60°

(50)   885

NiCl$_2$, PPh$_3$, Zn, DMF, 50°

(65)   884

C$_{13}$

NiCl$_2$, PPh$_3$, Zn, DMF, 50°

(66)   884

C$_{15}$

NiCl$_2$, PPh$_3$, Zn, DMF, 50°

(50)   884

C$_{17}$

NiCl$_2$, Zn, PPh$_3$, DMF, 50°

(91)   886, 887

C$_{20}$

Ni(PPh$_3$)$_2$Cl$_2$, Zn, Et$_4$NI, THF, 60°

(89)   85

TABLE 41. 3,3'-BIPYRIDYLS
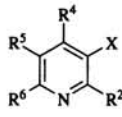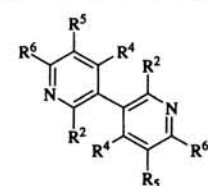
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C_{5-19}

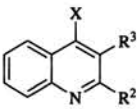| R^2	R^4	R^5	R^6	X	Conditions	Product(s) and Yield(s) (%)	Refs.
F	F	Cl	F	Cl	Cu, DMF, reflux	(15)	888
Cl	Cl	Cl	Cl	I	Cu, DMF, reflux	(71)	888
H	H	H	H	Cl	Ni(OAc)$_2$, NaH, t-BuOH, Ph$_3$P, DME, 65°	(90)	398, 834
H	H	H	H	Br	Cu, biphenyl, reflux	(34)	889
H	H	H	H	Br	Ni(OAc)$_2$, NaH, t-BuOH, Ph$_3$P, DME, 45°	(78)	398, 834
H	H	H	H	Br	NiCl$_2$, Zn, PPh$_3$, DMF, 50°	(80)	142, 839
H	H	H	H	Br	NiBr$_2$, Zn, PPh$_3$, Et$_4$NI, DMF, 50°	(90)	890
H	H	H	H	I	Cu, biphenyl, reflux	(7-8)	889
H	H	H	H	I	Cu, n-C$_4$H$_9$Ph, reflux	(2)	891
H	H	H	H	I	NiCl$_2$, Zn, PPh$_3$, DMF, 50°	(39)	892
H	H	H	H	I	NiCl$_2$(PEt$_3$)$_2$, Zn, KI, HMPA, 40°	(0)	401
NH$_2$	H	H	H	Cl	Ni(OAc)$_2$, NaH, t-BuOH, Ph$_3$P, DME, 65°	(40)	398
H	H	H	NH$_2$	Cl	CuSO$_4$, Na$_2$SO$_3$, benzene, 300°	(2)	893
H	H	H	NH$_2$	Cl	CuSO$_4$, EtONa, 300°	(2)	893
OMe	H	H	NO$_2$	I	Cu, DMF, reflux	(42)	841
OMe	H	H	H	Cl	NiCl$_2$, Zn, PPh$_3$, DMF, 50°	(51)	142, 839
OMe	H	H	H	Br	NiCl$_2$•6 H$_2$O, Ph$_3$P, Zn, DMF, 50°	(16)	852
H	OMe	H	H	Br	NiCl$_2$•6 H$_2$O, Ph$_3$P, Zn, DMF, 50°	(12)	852
H	H	OMe	H	Cl	NiCl$_2$•6 H$_2$O, Ph$_3$P, Zn, DMF, 50°	(42)	852
H	H	OMe	H	Cl	NiCl$_2$, Zn, PPh$_3$, DMF, 50°	(88-89)	142, 839
H	H	H	OMe	Br	NiCl$_2$, Zn, PPh$_3$, DMF, 50°	(56)	142, 839
H	H	CO$_2$Me	H	Br	NiBr$_2$(PPh$_3$)$_2$, Zn, Et$_4$NI, THF, 50°	(69)	139
H	H	t-BuS	H	Br	NiCl$_2$•6 H$_2$O, Zn, PPh$_3$, DMF, 50°	(40)	865
H	H	t-BuS	H	Br	NiCl$_2$•6 H$_2$O, Zn, PPh$_3$, KI, DMF, 50°	(74)	865
H	H	H	t-BuS	Br	NiCl$_2$•6 H$_2$O, Zn, PPh$_3$, DMF, 50°	(30)	865
H	H	H	t-BuS	Br	NiCl$_2$•6 H$_2$O, Zn, PPh$_3$, KI, DMF, 50°	(50)	865
OMe	POPh$_2$	H	OMe	Br	Cu, DMF, reflux	(80)	894

TABLE 42. 4,4'-BIPYRIDYLS

Substrate					Conditions	Product(s) and Yield(s) (%)	Refs.

C_{5-15}

R^2	R^3	R^5	R^6	X			
F	F	F	F	Br	Cu, 230°	(50)	895
F	F	F	F	Br	Cu, DMF, reflux	(40)	895
F	F	F	F	I	Cu, 200°	(59)	896
F	Cl	F	F	I	Cu, 200°	(59)	897
F	Cl	Cl	F	I	Cu, 190°	(78)	897
Cl	Cl	Cl	Cl	Br	Cu, DMF, reflux	(8-18)	888
Cl	Cl	Cl	Cl	I	Cu, DMF, reflux	(52)	888
Cl	Cl	Cl	Cl	I	Cu, 200-210°	(40)	898
H	H	H	H	Cl	Ni(OAc)$_2$, NaH, t-BuOH, Ph$_3$P, DME, 45°	(86)	398, 834
H	H	H	H	Cl	NiCl$_2$, Zn, PPh$_3$, DMF, 50°	(82)	142, 839
H	H	H	H	Cl	HCO$_2$Na, Pd/C, TEBAC, NaOH aq.	(46)	179
H	H	H	H	Br	Ni(OAc)$_2$, NaH, t-BuOH, Ph$_3$P, DME, 45°	(78)	398, 834
H	H	H	H	Br	PdCl$_2$(PPh$_3$)$_2$, Et$_4$NOTs, DMF, 2e$^-$	(91)	190
Me	H	H	H	I	Cu, 210°	(52)	899
OMe	H	H	H	I	NiCl$_2$•6 H$_2$O, Zn, PPh$_3$, DMF, 50°	(23)	852
H	OMe	H	H	Br	NiCl$_2$•6 H$_2$O, Zn, PPh$_3$, DMF, 50°	(32)	852
Ph	H	H	H	Cl	Ni(PPh$_3$)$_2$Br$_2$, Zn, Et$_4$NI, THF, heat	(47)	900
	H	H		Cl	Ni(PPh$_3$)$_2$Cl$_2$, PPh$_3$, Zn, DMF, rt	(20-70)	901, 902

TABLE 43. 2,2'-BIPYRIMIDYLS
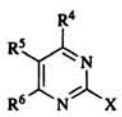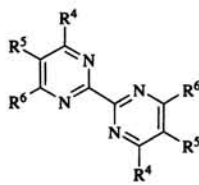
Substrate				Conditions	Product(s) and Yield(s) (%)	Refs.

C$_{4-16}$

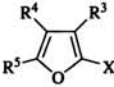| R^4	R^5	R^6	X			
H	H	H	Cl	NiCl$_2$, Zn, PPh$_3$, DMF, 50°	(60)	143
H	H	H	Cl	Ni(OAc)$_2$, NaH, t-BuOH, PPh$_3$, DME, 25°	(40)	398
H	H	H	Br	Cu, DMF, reflux	(10-50)	903, 904
H	H	H	Br	Cu, 110°	(10-20)	905
H	H	H	Br	Ni(OAc)$_2$, NaH, t-BuOH, PPh$_3$, DME, 25°	(30)	398
Me	H	H	Br	NiCl$_2$•6 H$_2$O, Zn, PPh$_3$, DMF, 50°	(12)	906
Me	H	Me	Cl	NiCl$_2$, Zn, PPh$_3$, DMF, 50°	(61)	143
Me	H	Me	Br	NiCl$_2$, Zn, PPh$_3$, DMF, 50°	(60)	143
Me	H	Me	Br	Cu, DMF, reflux	(26)	907
H	t-Bu	H	Cl	Cu, 190°	(25)	908
H	t-Bu	H	Cl	NiCl$_2$•6 H$_2$O Zn, PPh$_3$, DMF, 50°	(43)	908
Ph	H	H	Br	Cu, DMF, reflux	(20)	909
H	n-C$_6$H$_{13}$	H	Cl	NiCl$_2$•6 H$_2$O, Zn, PPh$_3$, DMF, 50°	(10-34)	908
Me	H	PhCH$_2$	Cl	Cu, cumene, heat	(0)	910
Ph	H	Ph	Cl	NiCl$_2$, Zn, PPh$_3$, DMF, 50°	(85)	143
Ph	H	Ph	Br	NiCl$_2$, Zn, PPh$_3$, DMF, 50°	(80)	143

TABLE 44. 4,4'-BIPYRIMIDYLS

Substrate				Conditions	Product(s) and Yield(s) (%)	Refs.

C₄₁₃

R²	R⁵	R⁶	X			
F	F	F	I	Cu, 180°	(58)	911
Me	H	Me	I	Pd/CaCO₃, N₂H₄, KOH, MeOH, reflux	(22)	912
Me	H	Me	I	Pd(OAc)₂, PPh₃, Et₃N, 160°	(50)	170
i-Pr	H	Me	I	Pd(OAc)₂, PPh₃, Et₃N, 160°	(97)	170
i-Pr	H	Me	I	Pd/C, acrylonitrile, Et₃N, 80°	(42)	840
n-Bu	H	Me	Cl	Cu, cumene, heat	(37)	910
Me	H	Ph	Cl	NiCl₂, Zn, PPh₃, DMF, 160°	(52)	913
Me	H	Ph	Cl	NiCl₂•6H₂O, Zn, PPh₃, DMF, 50°	(52)	914
Ph	H	Me	I	Cu, p-cymene, reflux	(28)	912
Et	H	Ph	Cl	NiCl₂, Zn, PPh₃, DMF, 160°	(30)	913
PhCH₂	H	Me	I	Cu, cumene, reflux	(63-64)	910, 915
i-Pr	H	Ph	Cl	NiCl₂, Zn, PPh₃, DMF, 160°	(67)	913

TABLE 45. 5,5'-BIPYRIMIDYLS
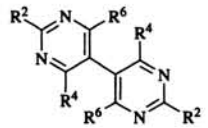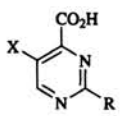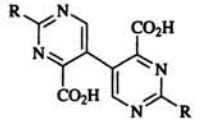
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C_{4-10}

R^2	R^4	R^6	X			
H	H	H	Br	Ni(OAc)$_2$, NaH, t-BuOH, PPh$_3$, DMF, 65°	(53)	398
Ph	H	H	Br	Pd/CaCO$_3$, N$_2$H$_4$, KOH, MeOH, reflux	(46)	912

C_{6-11}

R	X			
MeS	Br	Cu, DMF, reflux	(40), with accompanying decarboxylation	912
Ph	Br	Cu, DMF, reflux	(70), with accompanying decarboxylation	912

TABLE 46. 2,2'-BIQUINOLINES
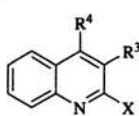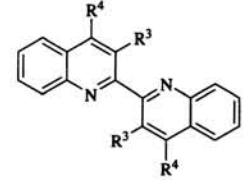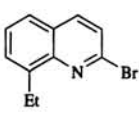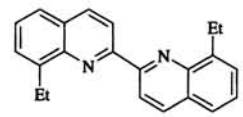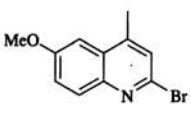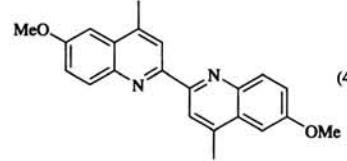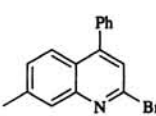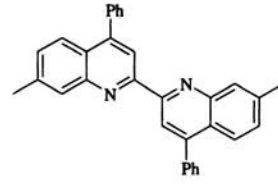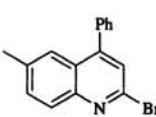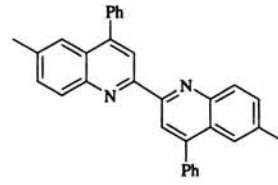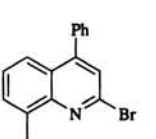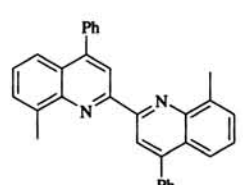
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C$_{9-15}$

R^3	R^4	X			
H	H	Cl	Ni(OAc)$_2$, NaH, t-BuOH, PPh$_3$, DME, 45-60°	(68-70)	398, 834
H	H	Cl	NiBr$_2$(PPh$_3$)$_2$, Zn, Et$_4$NI, THF, 50°	(84)	139
H	H	Cl	NiCl$_2$, PPh$_3$, Zn, DMF, 50°	(83)	142, 839
H	H	Cl	Pd(OAc)$_2$, K$_2$CO$_3$, i-PrOH, DMF, 115°	(62)	175
H	H	Br	NiBr$_2$(PPh$_3$)$_2$, Zn, Et$_4$NI, THF, 50°	(61)	139
OH	H	Br	NiCl$_2$•6 H$_2$O, PPh$_3$, Zn, DMF, 50°	(2)	140
H	Me	Cl	Cu, 218°	(<1)	916
OMe	H	Br	NiCl$_2$, PPh$_3$, Zn, DMF, 50°	(30)	140
H	Ph	Br	Cu, 260-280°	(3)	917
H	Ph	Br	Pd/CaCO$_3$, 5% KOH, MeOH, N$_2$H$_4$, heat	(11)	918

C$_{11}$

Cu, 210-220°

 (3)

919

Pd/CaCO$_3$, 5% KOH, MeOH, N$_2$H$_4$, heat

 (42)

918

C$_{16}$

Pd/CaCO$_3$, 5% KOH, MeOH, N$_2$H$_4$, heat

 (20)

918

Pd/CaCO$_3$, 5% KOH, MeOH, N$_2$H$_4$, heat

 (20)

918

Pd/CaCO$_3$, 5% KOH, MeOH, N$_2$H$_4$, heat

 (39)

918

TABLE 47. OTHER BIQUINOLINES
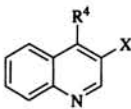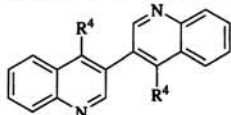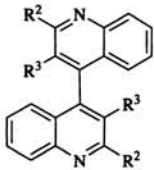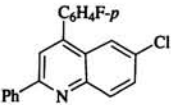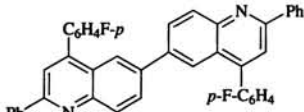
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C$_9$

R^4	X			
OH	Br	NiCl$_2$•6 H$_2$O, PPh$_3$, Zn, DMF, 50°	(27)	140
H	Br	NiBr$_2$(PPh$_3$)$_2$, Zn, Et$_4$NI, THF, 50°	(61)	139
H	Br	Ni(OAc)$_2$, NaH, t-BuOH, PPh$_3$, DME, 65°	(72)	398, 834
H	Br	Pd(OAc)$_2$, K$_2$CO$_3$, i-PrOH, DMF, 115°	(79)	175
H	Br	PdCO$_3$, N$_2$H$_4$, KOH, MeOH, heat	(53)	163
H	I	Pd(PPh$_3$)$_4$, BrZnCH$_2$CO$_2$Et, DME, THF, reflux	(47)	920

C$_{9-12}$

R^2	R^3	X			
H	H	Cl	NiBr$_2$(PPh$_3$)$_2$, Zn, Et$_4$NI, THF, 50°	(77)	139
H	H	Cl	NiCl$_2$, PPh$_3$, Zn, DMF, 50°	(70)	142, 839
H	H	Br	Ni(OAc)$_2$, NaH, t-BuOH, PPh$_3$, DME, 45°	(53)	398
H	H	Br	NiBr$_2$(PPh$_3$)$_2$, Zn, Et$_4$NI, THF, 50°	(60)	139
H	H	I	Pd(PPh$_3$)$_4$, BrZnCH$_2$CO$_2$Et, DME, THF, reflux	(10)	920
Me	H	Cl	Ni(OAc)$_2$, NaH, t-BuOH, PPh$_3$, DME, 45°	(71)	398, 834
Me	H	I	Pd(PPh$_3$)$_4$, BrZnCH$_2$CO$_2$Et, DME, THF, reflux	(32)	920
H	CO$_2$Et	Cl	NiBr$_2$(PPh$_3$)$_2$, Zn, Et$_4$NI, THF, reflux	(73)	921

C$_{21}$

NiCl$_2$, (o-tolyloxy)$_3$P, NaI, NMP, 60-80°	(73-75)	149, 922
NiCl$_2$(PPh$_3$)$_2$, NaI, PPh$_3$, Zn, NMP, 70°	(81)	922

TABLE 48. BI-ISOQUINOLINES
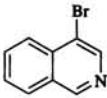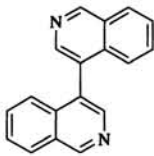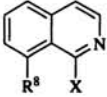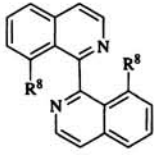
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C₉

| | Ni(PPh$_3$)$_2$Br$_2$, Zn, Et$_4$NI, THF, 50° | (60) | 139 |
| | Pd/CaCO$_3$, KOH, EtOH, N$_2$H$_4$•HCl | (33) | 923 |

C$_{9-10}$

R^8	X			
H	Cl	Ni(PPh$_3$)$_2$Br$_2$, PPh$_3$, Zn, Et$_4$NI, THF, 50°	(20)	924
H	Cl	Ni(PPh$_3$)$_2$Br$_2$, Zn, Et$_4$NI, THF, 50°	(37)	139
H	Br	Cu, 200°	(18)	925
H	Br	NiCl$_2$, PPh$_3$, Zn, DMF, 50°	(85)	926
Me	Cl	NiCl$_2$, PPh$_3$, Zn, DMF, 50°	(56-61)	927, 928
OMe	Cl	NiCl$_2$, PPh$_3$, Zn, DMF, 50°	(70)	927

501

TABLE 48. BI-ISOQUINOLINES *(Continued)*
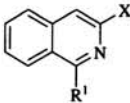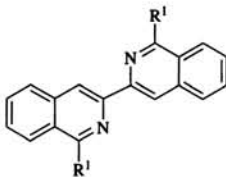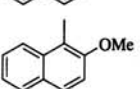
Substrate		Conditions	Product(s) and Yield(s) (%)	Refs.

C$_{9-20}$

R^1	X			
H	Br	Cu, 200°	(14)	925
Ph	Cl	NiCl$_2$, PPh$_3$, Zn, NaI, THF, reflux	(93)	929
o-Tolyl	Cl	NiCl$_2$, PPh$_3$, Zn, NaI, THF, reflux	(75)	929
p-Tolyl	Cl	NiCl$_2$, PPh$_3$, Zn, NaI, THF, reflux	(73)	929
	Cl	NiCl$_2$, PPh$_3$, Zn, NaI, THF, reflux	(81)	929
	Cl	NiCl$_2$, PPh$_3$, Zn, NaI, THF, reflux	(82)	929
	Cl	NiCl$_2$, PPh$_3$, Zn, NaI, THF, reflux	(64)	929
	Cl	NiCl$_2$, PPh$_3$, Zn, NaI, THF, reflux	(73)	929

TABLE 49.8,8'-BIQUINOLYL
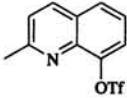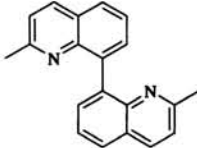
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{10}$			
	NiCl$_2$, PPh$_3$, Zn, NaI, DMF, reflux	(65)	930

TABLE 50. BIFURANS
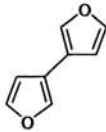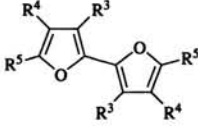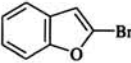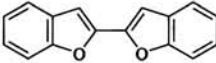
	Substrate				Conditions	Product(s) and Yield(s) (%)		Refs.

C₄

| | | | | | Ni(OAc)₂, NaH, t-BuOH, bpy, THF, 25° | (42) | | 398 |
| | | | | | NiCl₂(PEt₃)₂, Zn, KI, HMPA, 40° | (80) | | 401 |

C₄₋₁₁

R^3	R^4	R^5	X					
H	H	NO₂	Br		Cu, 190°	(9)		931
H	H	NO₂	Br		Cu, DMF, reflux	(76)		822
H	H	H	Br		Ni(OAc)₂, NaH, t-BuOH, bpy, THF, 25°	(10)		398
H	H	CHO	I		Cu, DMF, reflux	(44-50)		822, 932
H	H	CO₂Me	Br		Cu, DMF, reflux	(68)		822
H	H	CO₂Me	Br		NiCl₂(PEt₃)₂, Zn, KI, HMPA, 40°	(90)		401
H	Me	CO₂Me	Br		Cu, DMF, reflux	(62)		822
H	H	COPh	I		Cu, DMF, reflux	(40)		822

C₈

| | | | | | Ni(OAc)₂, NaH, t-BuOH, bpy, THF, 25° | (70) | | 398 |

TABLE 51. BIS-DIBENZOFURANS AND BIS-DIBENZODIOXANES
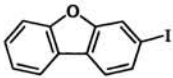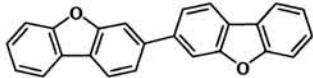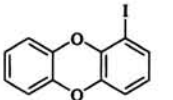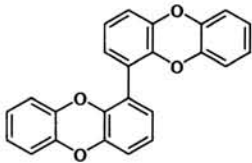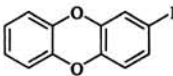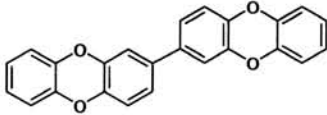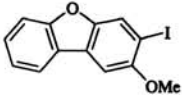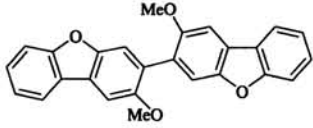
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{12}	Cu, 200-220°	(60)	933
	Cu, 250°	(22)	934
	Cu, 240-250°	(22)	934
C_{13}	Cu, 180-200°	(65)	933

TABLE 52. UNSUBSTITUTED 2,2'-BITHIENYL
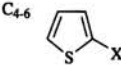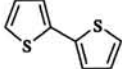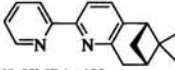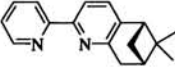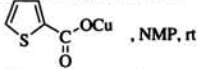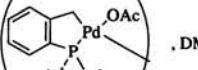
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{4-6}			
X			
Cl	Ni(OAc)$_2$, NaH, t-AmOH, bpy, THF, 25°	(60)	398
Cl	NiCl$_2$, PPh$_3$, Zn, DMAc, 50-80°	(98)	51
Br	Ni(OAc)$_2$, NaH, t-AmOH, bpy, THF, 25°	(70)	398
Br	NiI$_2$, Li, naphthalene, glyme, 85°	(45)	112
Br	Ni(cod)$_2$, DMF, 42°	(30)	49, 50
Br	Ni(PPh$_3$)$_2$Cl$_2$, Ph$_3$P, Zn, DMF, 50°	(41)	123
Br	NiCl$_2$, CrCl$_2$, Mn, THF, 25°	(22)	406
Br	NiCl$_2$(PEt$_3$)$_2$, Zn, KI, HMPA, 40°	(7)	401
Br	PdCl$_2$, HgCl$_2$, PhNHNH$_2$, NaOH, MeOH, reflux	(42)	165
I	Cu, 200-210°	(22)	935
I	Cu, DMF, reflux	(67)	936
I	NiCl$_2$(PEt$_3$)$_2$, Zn, KI, HMPA, 40°	(87)	401
I	NiCl$_2$, CrCl$_2$, Mn, THF, 25°	(87)	406
I	Pd/C, Zn, H$_2$O, acetone, rt	(64)	185
I	$\overset{OCu}{\underset{O}{C}}$, NMP, rt	(77)	71
I	Pd(OAc), o-tol, tol-o /2 , DMF, 150°	(87)	194
SiMe$_2$Cl	CuI, TBAF, MeCN, rt	(71)	72
SiMe$_2$Br	CuI, TBAF, MeCN, rt	(75)	72

TABLE 53. SUBSTITUTED 2,2'-BITHIENYLS
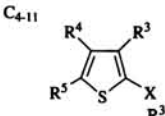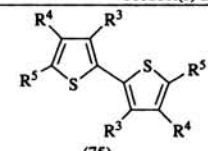
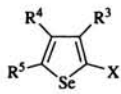| Substrate				Conditions	Product(s) and Yield(s) (%)	Refs.
R^3	R^4	R^5	X			
Cl	Cl	Cl	I	Cu, DMF, reflux	(75)	888
NO$_2$	H	NO$_2$	Cl	Cu, 200-215°	(43)	937
H	H	NO$_2$	Br	Cu, 220-225°	(86)	938
H	H	NO$_2$	Br	Pd(OAc)$_2$, i-Pr$_2$NEt, toluene, 105°	(58)	939
H	H	Cl	Br	Pd(OAc)$_2$, i-Pr$_2$NEt, n-Bu$_4$NBr, toluene, 105°	(68)	939
CHO	H	H	I	Cu, DMF, 130°	(79)	940
H	H	CHO	Br	NiCl$_2$, PPh$_3$, Zn, DMF, reflux	(85)	941
H	H	CHO	Br	Pd(OAc)$_2$, i-Pr$_2$NEt, n-Bu$_4$NBr, toluene, 105°	(71)	939
Me	H	H	I	Cu, 200-210°	(26)	942
H	H	H	I	Pd(OAc)$_2$, i-Pr$_2$NEt, toluene, 105°	(92)	939
H	H	Me	Br	Ni(OAc)$_2$, NaH, t-AmOH, bipy, THF, 25°	(73)	398
H	H	Me	I	Cu, 170-220°	(75-81)	943
NO$_2$	H	COMe	Cl	Cu, 200-215°	(39)	937
NO$_2$	H	CO$_2$Me	Cl	Cu, 205-225°	(53)	937
CO$_2$Me	H	H	Br	Cu, 210-225°	(24)	944, 945
H	H	COMe	Cl	Pd(OAc)$_2$, i-Pr$_2$NEt, n-Bu$_4$NBr, toluene, 105°	(73)	939
H	H	COMe	Br	Pd(OAc)$_2$, i-Pr$_2$NEt, n-Bu$_4$NBr, toluene, 105°	(80)	939
Me	Me	H	I	Cu, 200-210°	(23)	942
H	Et	Me	I	Cu, 210-245°	(22)	946
H	H	t-Bu	I	Cu, 190-200°	(80)	947
Et	Et	H	I	Cu, 200°	(37)	391
H	H	4-pyridyl	I	Pd(Hg), N$_2$H$_4$•H$_2$O, NaOH, MeOH	(46)	164
H	Ph	H	I	NiCl$_2$, PPh$_3$, Zn, DMF, 50°	(65)	164
H	Ph	H	Br	NiCl$_2$, PPh$_3$, Zn, DMF, 50°	(63)	399
H	H	Ph	Br	Cu, 200-210°	(38)	942
H	H	PhCH$_2$	I	Cu, 185-210°	(14)	948

TABLE 53. SUBSTITUTED 2,2'-BITHIENYLS (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C$_8$

NiCl$_2$, PPh$_3$, Zn, DMF, 50° — (66) — 949

Ni(PPh$_3$)$_2$Cl$_2$, Zn, Bu$_4$NI, THF, 50° — (87) — 950

C$_{7-8}$

R — thiophene — X

R	X			
1,3-dioxolane (H)	Br	Ni(OAc)$_2$, NaH, t-AmOH, bpy, THF, rt	OHC–thiophene–thiophene–CHO (53)	398
2-methyl-1,3-dioxolane	Br	Ni(OAc)$_2$, NaH, t-AmOH, bpy, THF, rt	Ac–thiophene–thiophene–Ac (67)	398

C$_9$

OHC–thiophene–thiophene–Br — NiCl$_2$, PPh$_3$, Zn, DMF, reflux — OHC–thiophene–(thiophene)$_2$–thiophene–CHO (78) — 941

H$_3$C–thiophene–thiophene–Br — Cu, 200° — H$_3$C–thiophene–(thiophene)$_2$–thiophene–CH$_3$ (9) — 951

C$_{11-12}$

R^1, R^2 substituted aryl–thiophene–I

R^1	R^2			
Me	H	NiCl$_2$, PPh$_3$, Zn, DMF, 50°	(75)	399
MeO	H	NiCl$_2$, PPh$_3$, Zn, DMF, 50°	(65)	399
Et	H	NiCl$_2$, PPh$_3$, Zn, DMF, 50°	(65)	399
Me	Me	NiCl$_2$, PPh$_3$, Zn, DMF, 50°	(59)	399

C$_{12}$

thiophene–thiophene–thiophene–Br — NiCl$_2$, PPh$_3$, Zn, DMF, 70° — thiophene–(thiophene)$_4$–thiophene (58) — 949

C$_{13}$

OHC–thiophene–thiophene–thiophene–Br — NiCl$_2$, PPh$_3$, Zn, DMF, reflux — OHC–thiophene–(thiophene)$_4$–thiophene–CHO (70) — 941

C$_{14}$

naphthyl–thiophene–Cl — NiCl$_2$, PPh$_3$, Zn, DMF, 50° — (82) — 399

tetrahydronaphthyl–thiophene–Cl — NiCl$_2$, PPh$_3$, Zn, DMF, 50° — (85) — 399

TABLE 53. SUBSTITUTED 2,2'-BITHIENYLS *(Continued)*

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{16}$	NiCl$_2$, PPh$_3$, Zn, DMF, 70°	(18)	949
C$_{18}$	Ni(PPh$_3$)$_3$, DMF	(53)	952
C$_{23}$	Cu, 250°	(90)	953
C$_{24}$	NiCl$_2$, Zn, PPh$_3$, DMF, 70°	(33)	954
C$_{26}$	Ni(PPh$_3$)$_3$, DMF	(29)	952

C$_{29-30}$

R			
n-C$_{17}$H$_{35}$	Ni(PPh$_3$)Cl$_2$, Zn, PPh$_3$, KI, DMF, 60°	(56)	955
n-C$_{16}$H$_{33}$OCH$_2$	Ni(PPh$_3$)Cl$_2$, Zn, PPh$_3$, KI, DMF, 60°	(81)	955
n-C$_{15}$H$_{31}$	Ni(PPh$_3$)Cl$_2$, Zn, PPh$_3$, KI, DMF, 60°	(82)	955

TABLE 54. 3,3'-BITHIENYLS
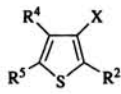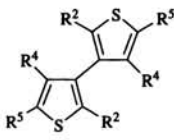
Substrate				Conditions	Product(s) and Yield(s) (%)	Refs.

C$_{4-8}$

R^2	R^4	R^5	X			
H	NO$_2$	H	I	Cu, CuSO$_4$, NH$_3$, MeCN, acetone, 25°	(86)	956
H	H	H	Cl	Ni(OAc)$_2$, NaH, t-AmOH, bpy, THF, 25°	(52)	398
H	H	H	Br	Ni(OAc)$_2$, NaH, t-AmOH, bpy, THF, 25°	(60)	398
H	H	H	Br	Pd/C, NaOH, H$_2$O, HCONHNH$_2$, 95°	(67)	55
H	H	H	I	NiCl$_2$(PEt$_3$)$_2$, Zn, KI, HMPA	(83)	401
NO$_2$	NO$_2$	Me	I	Cu, 148-155°	(29)	937
CO$_2$Me	NO$_2$	H	Br	Cu, DMF, reflux	(73)	957
CO$_2$Me	Br	H	Br	Cu, DMF, reflux	(12)	958
Me	H	Me	I	Cu, 220-240°	(47)	959
Me	CO$_2$Me	Me	I	Cu, 230-235°	(8)	937

TABLE 55. BIBENZOTHIOPHENES
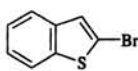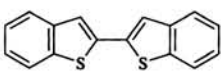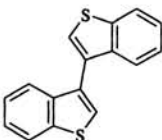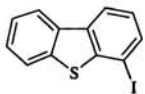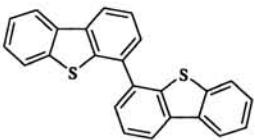
	Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₈		Ni(OAc)₂, NaH, t-AmOH, bpy, THF, 25°	(82)	398

<table>
<tr><td></td><td>X</td><td></td><td></td><td></td></tr>
<tr><td></td><td>Br</td><td>Ni(OAc)₂, NaH, t-AmOH, bpy, THF, 25°</td><td>(70)</td><td>398</td></tr>
<tr><td></td><td>I</td><td>Cu, 270-280°</td><td>(17)</td><td>960</td></tr>
</table>

C₁₂				
		Cu, 260°	(31)	961

TABLE 56. BISELENYLS
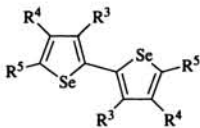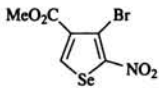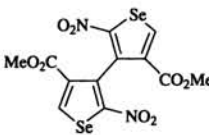
	Substrate				Conditions	Product(s) and Yield(s) (%)	Refs.

C₄₋₆

R³	R⁴	R⁵	X			
H	H	H	Br	Ni(PPh$_3$)$_2$Cl$_2$, Zn, Bu$_4$NI, THF, 50°	(19)	962
H	H	H	I	Cu, xylene, reflux	(76)	963
NO$_2$	H	H	Br	Cu, xylene, reflux	(70)	963
H	H	NO$_2$	I	Cu, xylene, reflux	(35)	963
NO$_2$	H	NO$_2$	I	Cu, xylene, reflux	(75)	963
H	H	OAc	I	Cu, xylene, reflux	(55)	963

C₆

Cu, xylene, reflux   (40)   964

TABLE 57. BIMETALLOCENES AND POLYMETALLOCENYLENES
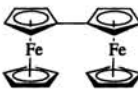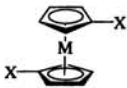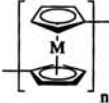
Substrate		Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{10}$				

	X			
	Cl	Cu, 140°	(65)	35
	Br	Cu, 140°	(97)	35
	I	Cu, 150°	(79)	965
	I	Cu, 140-150°	(100)	35
	I	Cu, biphenyl, 130-160°	(76)	35
	I	Zn, 145-150°	(17)	35

M	X			
Fe	Br	Ni(cod)$_2$, DMF	(20-28)	966
Fe	Br	Ni(PPh$_3$)$_4$, DMF	(50-60)	966
Fe	I	Ni(PPh$_3$)$_4$, DMF	(35-42)	966
Ru	I	Cu, 130-150°	(68)	966

TABLE 58. MISCELLANEOUS BI(HETEROCYCLE)
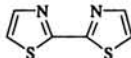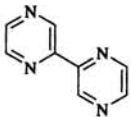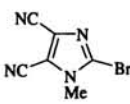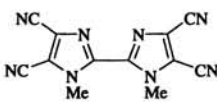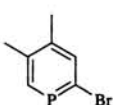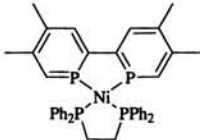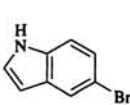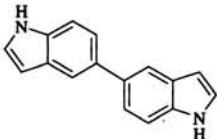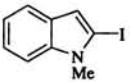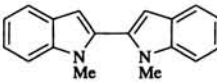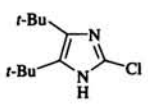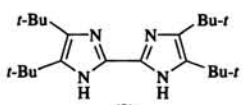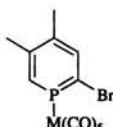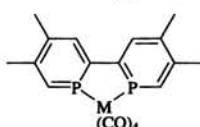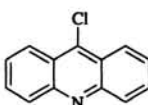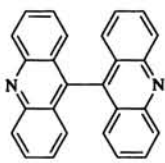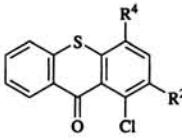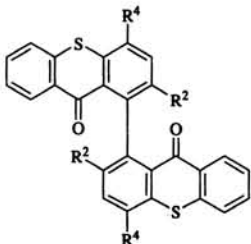
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_3 (2-bromothiazole)		(2,2'-bithiazole)	
	Ni(OAc)$_2$, NaH, t-BuOH, PPh$_3$, C$_6$H$_6$, 45°	(62)	398
	Pd(OAc)$_2$, i-Pr$_2$NEt, Bu$_4$NBr, toluene, 105°	(86)	
C_4 (2-chloropyrazine)	Ni(OAc)$_2$, NaH, t-BuOH, PPh$_3$, DME, 45°	(bipyrazine) (43)	398
C_6 (imidazole structure)	Cu, DMF, 85°	(product structure) (48)	967
C_7 (phosphinine structure)	Ni(dppe)Cl$_2$, Zn, THF, 50°	(Ni complex structure) (30)	968
C_8 (5-bromoindole)	Ni(bpy)Br$_2$, NaBr, MeOH, EtOH, 2e$^-$	(5,5'-biindole) (86)	53
C_9 (2-iodo-1-methylindole)	Cu, 205°	(2,2'-bi(1-methylindole)) (66)	969
C_{11} (imidazole structure)	Cu, heat	(0)	908
	NiCl$_2$, Zn, PPh$_3$, DMF, heat	(0)	908
C_{12} (phosphinine M(CO)$_5$)		(M(CO)$_4$ complex structure)	
Cr	Ni(dppe)Cl$_2$, Zn, THF, 50°	(55)	968
Mo	Ni(dppe)Cl$_2$, Zn, THF, 50°	(55)	968
W	Ni(dppe)Cl$_2$, Zn, THF, 50°	(35)	968
C_{13} (9-chloroacridine)	Cu, 140°	(9,9'-biacridine) (72)	970
C_{14-15} (thioxanthone structure)		(bithioxanthone structure)	

R^2	R^4			
H	Me	Cu, 180-250°	(44)	971
H	Me	Cu, naphthalene, reflux	(46)	971
Me	OMe	Cu, naphthalene, reflux	(57)	971

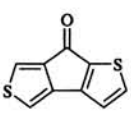TABLE 59. INTRAMOLECULAR COUPLINGS FORMING SYMMETRIC HETEROCYCLIC BIARYLS

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C9
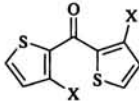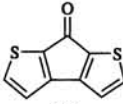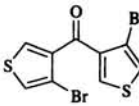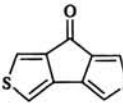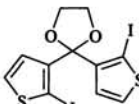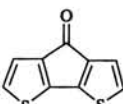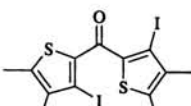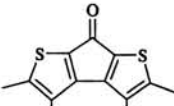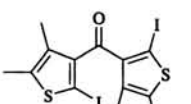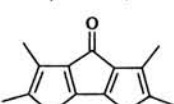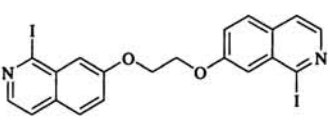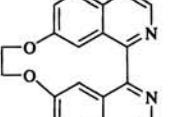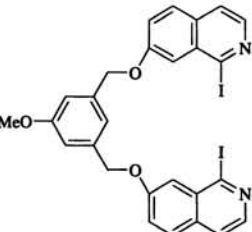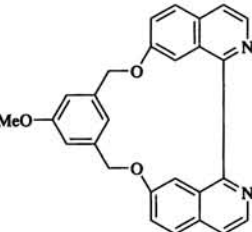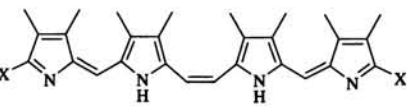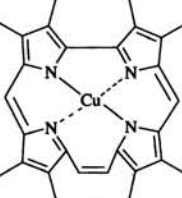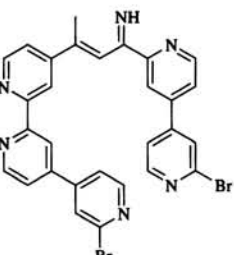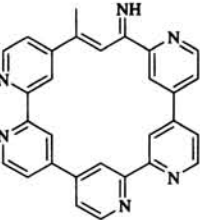
X			
Br	Cu, DMF, reflux	(49)	972
I	Cu, DMF, reflux	(100)	972

| | Cu, DMF, reflux | (37) | 972 |

C11

| | Cu, DMF, reflux | (99-100) | 972, 973 |

C13

| | Cu, DMF, reflux | (75) | 974 |

| | Cu, DMF, reflux | (89) | 974 |

C20

| | Cu, DMF, reflux | (28) | 975 |

C29

| | Cu, DMF, reflux | (18) | 975 |

C28

X			
Br	Cu, DMF, reflux	(50)	976
I	Cu, DMF, reflux	(50)	976

C29

	Cu, DMF, reflux	(0)	977
	Cu, biphenyl, reflux	(0)	977
	Ni(cod)2, bpy, DMF, heat	(0)	977
	Ni(PPh3)2Br2, Zn, Et4NI, THF, heat	(0)	977
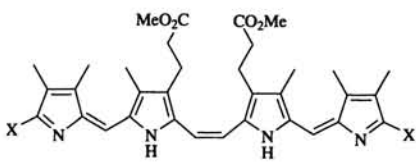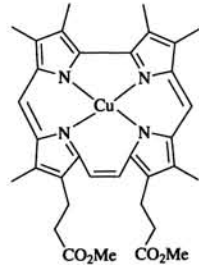
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C$_{34}$

X			
Br	Cu, DMF, reflux	(50)	976
I	Cu, DMF, reflux	(50)	976

TABLE 60. INTRAMOLECULAR COUPLINGS FORMING UNSYMMETRIC HETEROCYCLIC BIARYLS
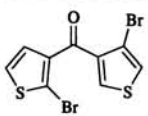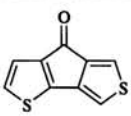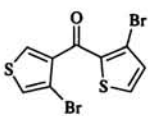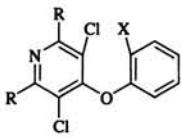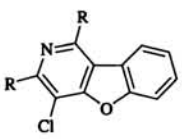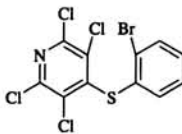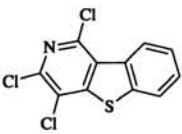
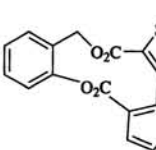| Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_9	Cu, DMF, reflux	(39)	972
	Cu, DMF, reflux	(57)	972
C_11			

R	X			
F	Cl	Cu, DMF, reflux	(27)	888
F	Br	Cu, DMF, reflux	(1)	888
Cl	Cl	Cu, DMF, reflux	(4)	888
Cl	Br	Cu, DMF, reflux	(41)	888

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Cu, DMF, reflux	(25)	888
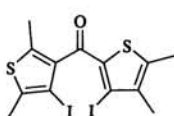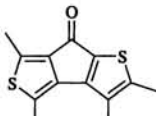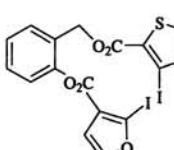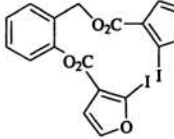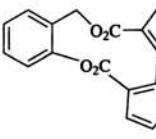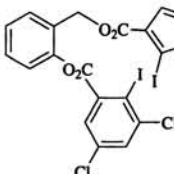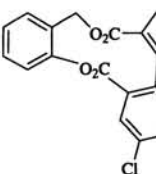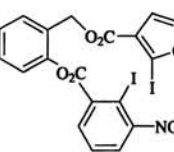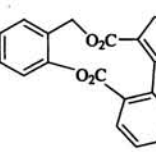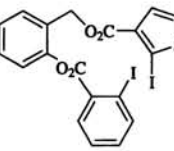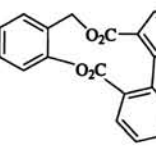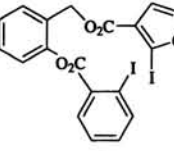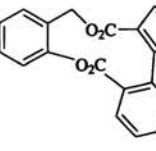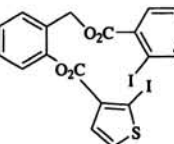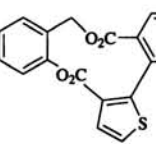
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{13}	Cu, DMF, reflux	(92)	974
C_{17}	Cu, DMF, reflux	(64)	978
	Cu, DMF, reflux	(81)	978, 979
C_{19}	Cu, DMF, reflux	(78)	978, 979
C_{19}	Cu, DMF, reflux	(83)	978, 979
	Cu, DMF, reflux	(87)	978
	Cu, DMF, reflux	(80)	978
C_{20}	Cu, DMF, reflux	(84)	978, 979

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Cu, DMF, reflux	(78)	978

$\dfrac{X}{}$			
Br	Cu, DMF, reflux	(28)	978
I	Cu, DMF, reflux	(67)	978, 979

C$_{21}$

	Cu, DMF, reflux	(63-67)	978, 979
	Cu, DMF, reflux	(87)	978
	Cu, DMF, reflux	(83)	978

TABLE 61. POLY(PARAPHENYLENES)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C_{6-7} X—⟨C6H4⟩—X
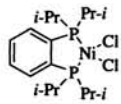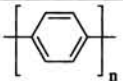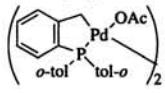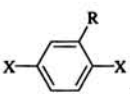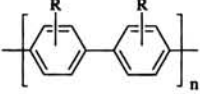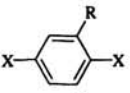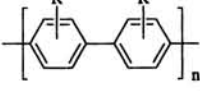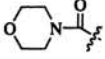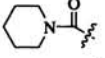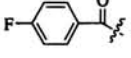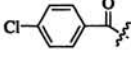
X	Conditions	Product(s) and Yield(s) (%)	Refs.
Cl	(i-Pr)₂P–Ni(Cl)₂–P(Pr-i)₂ chelate, DMSO, 65°, –2.2 V	(quantitative)	154
Br	Ni(cod)₂, bpy, DMF, 60°	(92)	246
Br	Ni(cod)₂, Ph₃P, DMF, 60°	(26)	246
Br	Ni(cod)₂, bpy, DMF, 30–60°	(95–99)	246
Br	Ni(diphos)Cl₂, LiClO₄, HMPA, THF, –2.5 V	(75)	251
I	Ni(cod)₂, bpy, DMF, 60°	(91)	246
I	(o-tol)₂P–Pd(OAc) complex, i-Pr₂NEt, DMF, 100°	(70)	194
OMs	Ni(PPh₃)₂Cl₂, Ph₃P, Zn, Et₄NI, THF, reflux	(49–50)	262, 263

C_8

Product: poly(phenylene) with R substituents

R	X	Conditions	Product(s) and Yield(s) (%)	Refs.
CO₂Me	Cl	Ni(PPh₃)₂Cl₂, Zn, Et₄NI, THF, 67°	(88)	261
CO₂Me	Cl	NiCl₂, Ph₃P, Zn, bpy, DMF, 90°	(72)	261
CO₂Me	Cl	NiCl₂, Ph₃P, Zn, DMF, 30–80°	(22–85)	233
CO₂Me	Br	Ni(PPh₃)₂Cl₂, Zn, Et₄NI, THF, 67°	(50)	261
CO₂Me	Br	NiCl₂, Ph₃P, Zn, bpy, DMF, 90°	(21)	261
CN	OMs	Ni(PPh₃)₂Cl₂, Ph₃P, Zn, Et₄NI, THF, reflux	(68)	263
CO₂Me	OTf	Ni(PPh₃)₂Cl₂, Zn, Et₄NI, THF, 67°	(16–65)	261
CO₂Me	OTf	NiCl₂, Ph₃P, Zn, bpy, DMF, 90°	(76)	261, 262
CO₂Me	OMs	Ni(PPh₃)₂Cl₂, Ph₃P, Zn, Et₄NI, THF, reflux	(85)	263
Me	OMs	Ni(PPh₃)₂Cl₂, Ph₃P, Zn, Et₄NI, THF, reflux	(87)	263

C_{8-18}

Product: poly(phenylene) with R substituents

R	X	Conditions	Product(s) and Yield(s) (%)	Refs.
Ph	Cl	NiCl₂, Ph₃P, Zn, bpy, DMF, 90°	(57)	261
Ph	Cl	Ni(PPh₃)₂Cl₂, Zn, Et₄NI, THF, 67°	(38–59)	261
Ph	Br	NiCl₂, Ph₃P, Zn, bpy, DMF, 90°	(15)	261
Ph	Br	Ni(PPh₃)₂Cl₂, Zn, Et₄NI, THF, 67°	(8–79)	261
CO₂Pr-i	OMs	Ni(PPh₃)₂Cl₂, Ph₃P, Zn, Et₄NI, THF, reflux	(88)	263
Ph	OTf	NiCl₂, Ph₃P, Zn, bpy, DMF, 90°	(8)	261
Ph	OTf	Ni(PPh₃)₂Cl₂, Zn, Et₄NI, THF, 67°	(6–49)	261, 262
Ph	OMs	Ni(PPh₃)₂Cl₂, Ph₃P, Zn, Et₄NI, THF, 67°	(82)	263
t-Bu	OTf	Ni(PPh₃)₂Cl₂, Zn, Et₄NI, THF, 67°	(5–17)	262, 263
t-Bu	OTf	NiCl₂, Ph₃P, Zn, bpy, DMF, 90°	(0)	261
t-Bu	OMs	Ni(PPh₃)₂Cl₂, Ph₃P, Zn, Et₄NI, THF, 67°	(85)	263
morpholino-C(=O)–	Cl	NiCl₂, Ph₃P, Zn, bpy, NaI, NMP, 50°	(100)	258
piperidino-C(=O)–	Cl	NiCl₂, Ph₃P, Zn, NaI, NMP, 50°	(100)	258
4-F-C₆H₄-C(=O)–	OMs	Ni(PPh₃)₂Cl₂, Ph₃P, Zn, Et₄NI, THF, reflux	(68)	263
4-Cl-C₆H₄-C(=O)–	OMs	Ni(PPh₃)₂Cl₂, Ph₃P, Zn, Et₄NI, THF, reflux	(98)	263
PhC(=O)–	Cl	NiCl₂, (o-tolyl-O)₃P, Zn, bpy, NaI, NMP, 90°	(92)	149
PhC(=O)–	OMs	Ni(PPh₃)₂Cl₂, Ph₃P, Zn, Et₄NI, THF, reflux	(95)	263
t-Bu-C₆H₄-C(=O)–	OMs	Ni(PPh₃)₂Cl₂, Ph₃P, Zn, Et₄NI, THF, reflux	(82)	263

TABLE 61. POLY(PARAPHENYLENES) *(Continued)*
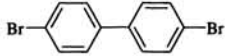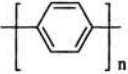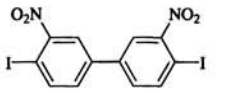
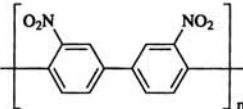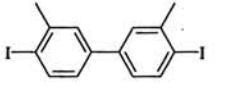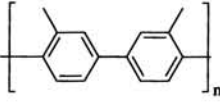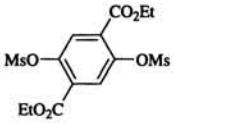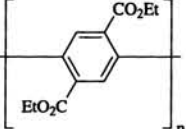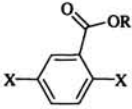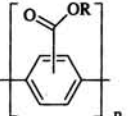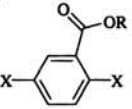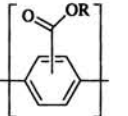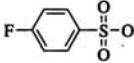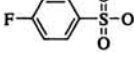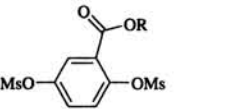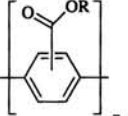| Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{12}$	Ni(cod)$_2$, bpy, DMF, 60°	(95)	246
	Cu, DMF, 140°	(95-97)	238
C$_{14}$	Cu, 240°	(85)	237
	Ni(PPh$_3$)$_2$Cl$_2$, Ph$_3$P, Zn, Et$_4$NI, THF, 67°	(81)	263

C$_{15}$

 R = 2-ethylhexyl

Ni(PPh$_3$)$_2$Cl$_2$, Zn, Et$_4$NI, solvent, reflux

X	solvent		
Cl	THF	(87)	263
Cl	dioxane	(82)	263
Br	THF	(81)	263
Br	dioxane	(84)	263

C$_{17-27}$

 R = 2-ethylhexyl

Ni(PPh$_3$)$_2$Cl$_2$, Zn, Et$_4$NI, solvent, reflux

X	solvent		
OMs	THF	(16-66)	263
OMs	dioxane	(48)	263
OTf	THF	(81)	263
OTf	dioxane	(83)	263
F—C$_6$H$_4$—SO$_2$—O	THF	(80)	263
F—C$_6$H$_4$—SO$_2$—O	dioxane	(94)	263

C$_{17}$

 R = 2-ethylhexyl

Ni(PPh$_3$)$_2$Cl$_2$, Ph$_3$P, Zn, Et$_4$NI, THF, reflux

 (89-97)

263

TABLE 62. POLY(METAPHENYLENES) AND POLY(BIPHENYLYLENES)
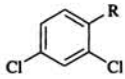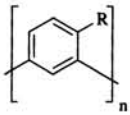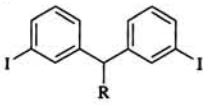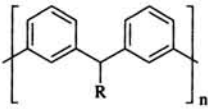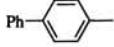
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₆₋₁₃			

R			
H	NiCl$_2$, Ph$_3$P, Zn, bpy, DMAc, 90°	(94)	257
CHO	NiCl$_2$, Ph$_3$P, Zn, bpy, DMAc, 90°	(77)	257
Me	NiCl$_2$, Ph$_3$P, Zn, bpy, DMAc, 90°	(91)	257
COMe	NiCl$_2$, Ph$_3$P, Zn, bpy, DMAc, 90°	(100)	257
COPh	NiCl$_2$, Ph$_3$P, Zn, bpy, DMAc, 90°	(100)	257

C$_{19-25}$

Cu, Hg, biphenyl, 225°   240

R	
Ph	(52)

(65)

(70)

TABLE 63. POLY(THIOPHENES)
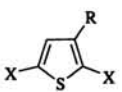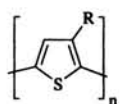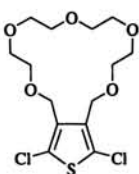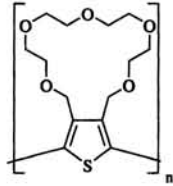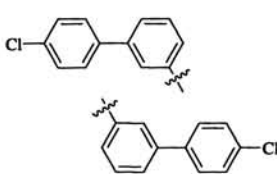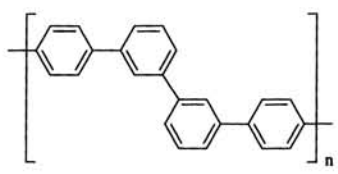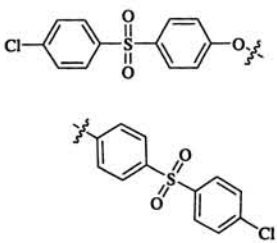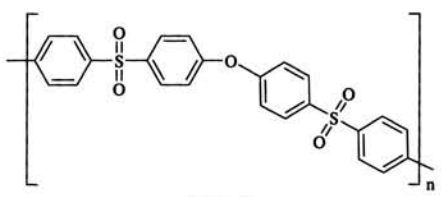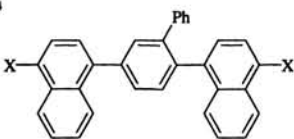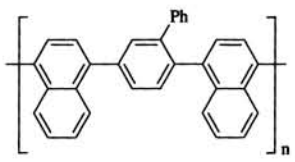
Substrate		Conditions	Product(s) and Yield(s) (%)	Refs.

C$_{4-14}$

R	X			
H	Cl	Ni(cod)$_2$, Ph$_3$P, DMF, 60°	(55)	246
H	Br	Ni(cod)$_2$, Ph$_3$P, DMF, 25-100°	(74-100)	246
H	Br	Ni(cod)$_2$, bpy, DMF, 25-60°	(91-93)	246
H	Br	Ni(PPh$_3$)$_4$, DMF, 60°	(63)	246
CN	Br	Ni(cod)$_2$, Ph$_3$P, DMF, 60°	(91)	246
CN	Br	Ni(cod)$_2$, bpy, DMF, 25°	(80)	246
CN	Br	Ni(dppp)Cl$_2$, Zn, HMPT, 140°	(24)	250
CHO	Br	Ni(dppp)Cl$_2$, Zn, HMPT, 140°	(81)	250
CH=NOH	Br	Ni(dppp)Cl$_2$, Zn, HMPT, 140°	(18)	250
Me	Br	Ni(cod)$_2$, Ph$_3$P, DMF, 25-100°	(76)	246
n-C$_6$H$_{13}$	I	Ni(cod)$_2$, Ph$_3$P, DMF, 25-100°	(60)	246
n-C$_6$H$_{13}$	I	Ni(cod)$_2$, bpy, DMF, 60°	(70-94)	246
n-C$_6$H$_{13}$	I	Ni(cod)$_2$, bpy, toluene, 60°	(60)	246
CO$_2$C$_6$H$_{13}$-n	Br	Cu, DMF, 145-150°	(40)	242
n-C$_8$H$_{17}$	I	Ni(cod)$_2$, bpy, DMF, 30-60°	(80)	246
CO$_2$C$_8$H$_{17}$-n	Br	Cu, DMF, 145-150°	(56)	242
n-C$_{10}$H$_{21}$	I	Ni(cod)$_2$, bpy, DMF, 60°	(87)	246

C$_{14}$

| | | Ni(cod)$_2$, bpy, DMF, 60° | (86) | 249 |

TABLE 64. MISCELLANEOUS POLY(ARENES)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₄	Ni(cod)₂, bpy, cod, 60°	(63)	980
C₅			
	Ni(cod)₂, PPh₃, bpy, DMF, rt	(64)	981
	Ni(cod)₂, PPh₃, bpy, DMF, 60°	(95)	981
	Ni(cod)₂, PPh₃, bpy, HMPA, 60°	(95)	981
	NiCl₂, Ph₃P, Zn, DMF, 60°	(59–66)	981
C₈₋₁₆			

R	X			
Bu	Br	Cu, DME, 200°	(56)	243, 982
Bu	I	Cu, DME, 200°	(67)	982
Me-O-CH₂-O-CH₂-O-CH₂	Br	Cu, DME, 200°	(58)	982
n-C₁₂H₂₅	Br	Cu, DME, 200°	(62)	982

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₁₀	Ni(cod)₂, bpy, DMF, 70°	(97)	983
C₁₄	Ni(cod)₂, Ph₃P DMF, 60°	(0)	246
	Ni(cod)₂, bpy, DMF, 60°	(90)	246
C₁₉	Cu, Hg, biphenyl	(36)	239
C₂₃	Cu, Hg, biphenyl	(62)	239
C₂₄			
	NiCl₂, Ph₃P, Zn, bpy, DMF, 70°	(6)	260
	Ni(PPh₃)₂Cl₂, Zn, Et₄NI, THF, 67°	(43)	260

TABLE 64. MISCELLANEOUS POLY(ARENES) *(Continued)*

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	NiCl$_2$, Ph$_3$P, Zn, bpy, DMF, 70°	(45)	260
	Ni(PPh$_3$)$_2$Cl$_2$, Zn, Et$_4$NI, THF, 67°	(41)	260
	NiCl$_2$, Ph$_3$P, Zn, bpy, DMAc, 90-100°	(99-100)	465

C$_{32-34}$

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
$\dfrac{X}{Cl}$	NiCl$_2$, Ph$_3$P, Zn, bpy, DMF, 70°	(89-91)	259
OMs	Ni(PPh$_3$)$_2$Cl$_2$, Zn, Et$_4$NI, THF, 67°	(2)	259