SYNTHESIS OF DIMERIC ARYLS AND HETEROARYLS THROUGH DIMERIZATION

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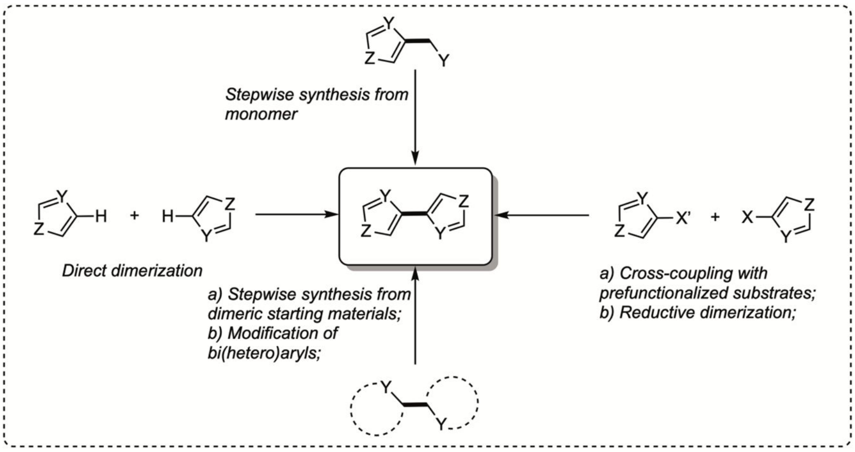
Abstract. *Dimeric aryls and heteroaryls are common units occurring frequently in natural products, pharmaceutically important compounds and other functional molecules. From the perspective of green and sustainable chemistry, the construction of aromatic and heteroaromatic dimers through direct homocoupling-based dimerization can be regarded as an attractive and easy choice. In this chapter, typical achievements in this research field covering from 2013 to 2023 are discussed.*

Contents

1. Introduction

Dimeric aryls and heteroaryls have a wide occurrence as key motifs in a huge number of natural products, pharmaceutically interesting compounds, ligands, catalysts, and other functional molecules.[1-4] Additionally, aromatic and heteroaromatic dimers are also valuable building blocks used for the construction of structurally complicated molecules.[5-9] Considering their great importance in various research fields, much efforts have been paid on their synthesis. There are several main strategies developed so far for the construction of dimeric aryls and heteroaryls, including direct dehydrogenative homocoupling of two (hetero)aryls, reductive dimerization or cross-coupling of functionalized (hetero)aryls, stepwise modification of one monomer, assembly of dimeric architectures and further transformation, late-stage modification of dimeric (hetero)aryls, *etc.* Among these reported routes, direct dimerization of two aromatic or heteroaromatic molecules through homo-coupling can be regarded as one of the most attractive and efficient approach for the synthesis of dimers (Scheme 1).[10-16]



Scheme 1. Strategies toward the synthesis of dimeric (hetero)aryls.

Compared to other methods, the homocoupling-based dimerization strategy features high efficiency, generation of less waste, the use of readily accessible starting materials, easy manipulation, good atom and step economy.

In the past decade, plenty of elegant dimerization methodologies have been established and consequently provided numerous highly functionalized dimeric aryls and heteroaryls. Breakthroughs always took place in the design of novel catalysts/catalytic systems, the introduction of new aromatic and/or heteroaromatic substrates, and modification of less reactive aryls with directing groups. Recently, several important reviews have selectively collected and discussed these achievements focusing on oxidative coupling reactions and homocoupling of (hetero)aryls. For example, Bolm[10] and Knölker[11] summarized iron-mediated and iron-catalyzed dimerization of arenes and heteroarenes in their reviews respectively; the You group systematically reviewed recent progress in the field of oxidative C−H/C−H coupling reactions between two arenes and/or heteroarenes;[12] Kozlowski offered a perspective on oxidative fragment coupling including the synthesis of dimeric phenols through C−C bond construction;[13] the Kita group disclosed a report on recent progress on hypervalent iodine(III) mediated construction of biaryls;[14] Butenschön and Gryko reviewed recent preparations of biaryls and polycyclic arenes through oxidative homocoupling reactions;[15] Miao and co-workers provided a deep discussion on the Scholl reaction based synthesis of polycyclic aromatics.[16]

However, there is no focused review on dimerization-based synthesis of aromatic and heteroaromatic dimers through homocoupling reactions. In order to summarize these attractive catalysts and reaction systems, to collect the novel dimeric architectures and to inspire future rational design and breakthroughs in related research fields, it is extremely desirable to review the synthesis of dimeric aryls and heteroaryls through homocoupling-involved dimerization. Achievements covering from 2013 to 2023 are summarized here. This chapter was divided into dimerization through the formation of aryl−aryl bond and the formation of heteroaryl−heteroaryl bond.

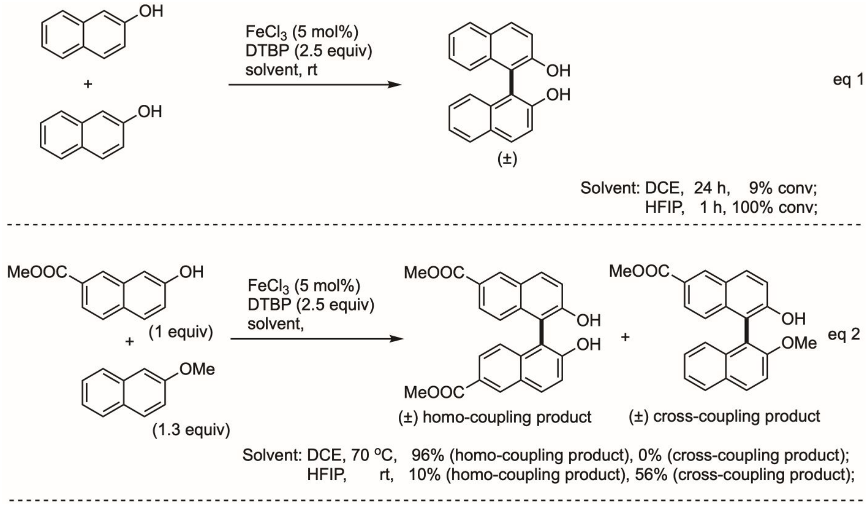
2. Formation of aryl–aryl bond

Dimerization of aryls through the formation of aryl–aryl bond can be realized by several reaction pathways: *in situ* formation of cation radical or radical of naphthols, phenols and phenolic ethers; transition metal catalyzed or mediated C–H activation of directing group (carboxylic acid, aminoquinoline, pyridine) incorporated arenes; reductive dimerization.

Both the efficiency and the chemoselectivity of iron-catalyzed oxidative coupling reactions of phenols can be significantly enhanced by the use of fluorinated solvents, especially the employment of HFIP as solvent. Pappo and co-workers found that the significant enhancement of reaction rate can be achieved by using fluoroalcohol such as HFIP (1,1,1,3,3,3-hexafluoro-2-propanol) as solvent instead of using common organic solvents.[17] For instance, only 9% conversion was observed in the oxidative dimerization of 2-naphthol in DCE after 24 h. In sharp contrast, complete conversion was reached when performing this reaction in HFIP in only 1 h (eq 1, Scheme 2).

Interestingly, cross-coupling reaction was preferred when the reaction was performed in HFIP (eq 2, Scheme 2). When the mixture of 6-methoxycarbonyl-2-naphthol (1 equiv) and 2-methoxynaphthalene (1.3 equiv) was treated with iron chloride (5 mol%) and DTBP (di-*tert*-butyl peroxide) in DCE, only 96% yield of homo-coupling product was obtained; cross-coupling product of 6-methoxycarbonyl-2-naphthol and 2-methoxynaphthalene was obtained as major product (56% yield) and homo-coupling product was afforded as minor product (10%) when running this reaction in HFIP at rt. The authors reasoned that the efficiency and the selectivity of reaction was affected by the solvent-dependent change of oxidation potentials of phenols. Therefore, the authors further developed cross-coupling reactions of various nucleophiles with phenols in fluoroalcohols. Note that these reactions were not able to proceed in common organic solvents.

Synthesis of chiral BINOL through direct catalytic asymmetric oxidative homocoupling of 2-naphthols seems to be an attractive route considering its simplicity and atom economy. However, this synthetic approach has proven to be difficult, partly due to the undesired secondary racemization. In 2016, Pappo and co-workers employed a novel chiral iron phosphate complex as catalyst for promoting an asymmetric oxidative homocoupling of 2-naphthol derivatives (Scheme 3).[18] A variety of C1- and C2-symmetric BINOLs have been prepared efficiently with a high degree of optical purity. It is the first synthesis of C1-symmetric BINOLs with 3- and 3'-positions available for further functionalization. On the basis of the results and previous reports, the authors proposed a radical-anion coupling mechanism. A high-valent iron complex may be formed by the coordination of the peroxide with iron and a following peroxide cleavage. Ligand exchange and a subsequent radical-anion coupling give an iron-BINOL complex. A final ligand exchange delivers the desired product.



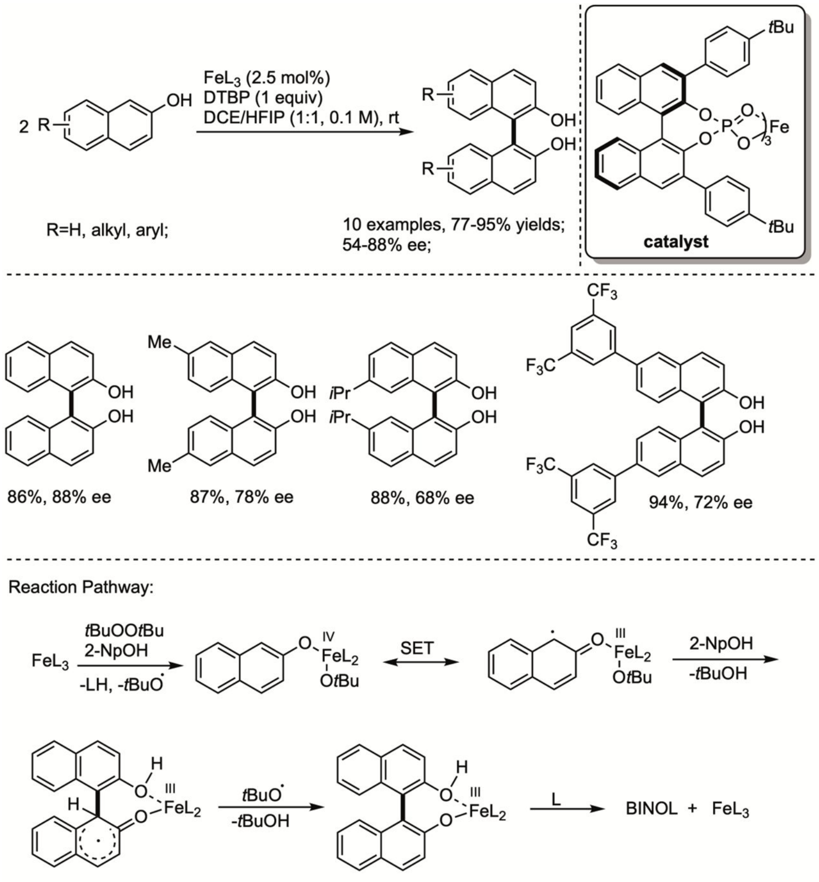
Scheme 2. Iron-catalyzed dimerization of 2-naphthol.[17]

Although the oxidative synthesis of BINOL-like axially chiral diols from 2-hydroxyanthracenes has already been achieved through dimerization, dearomatized 1,4-diketone intermediates have never been reported. Hiroto and Shinokubo found that the treatment of 2-hydroxy-9,10-bissilylethynylanthracenes with MnO_2 in DCM at room temperature gave metastable dimeric 1,4-diketone rather than stable aromatic diol in 50% yield (Scheme 4).[19] A base-mediated tautomerization afforded the enol-form in 59% yield. The observation of keto-form intermediate was intriguing, as no keto-enol tautomerism has been reported in BINOL derivatives, probably due to the instability of corresponding keto-forms.

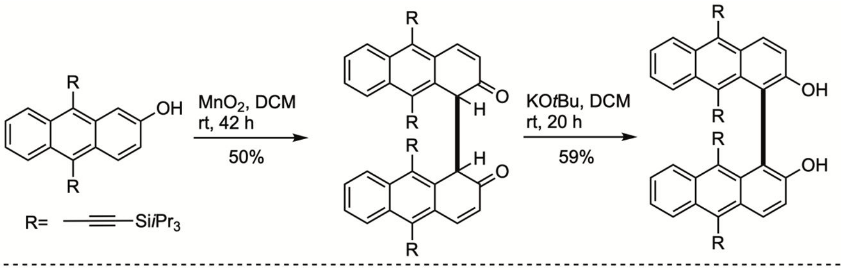
Considering the limited petrochemical resources, plant biomass can be regarded as a generally non-toxic and sustainable alternative for the production of monomers and polymers. Thermosetting epoxy resins as a versatile class of polymers have exhibited wide applications in coatings, composites and adhesives. The Waldvogel group disclosed an efficient synthesis of dimeric eugenol through electrochemical dehydrogenative dimerization.[20] The dimeric eugenol has been synthesized in 80% yield in an undivided cell with RVC (reticulated vitreous carbon) anode and GC (glassy carbon) cathode. Readily accessible MTBS (methyl tributylammonium methyl sulfate) was used as supporting electrolyte and environmentally benign methanol was employed as the solvent. Two biobased epoxy resins were then prepared in good to excellent yields through methylation/epoxidation or allylation/epoxidation consequences respectively (Scheme 5).

The hibarimicins as complex aromatic polyketide natural products are believed to be formed through a biosynthetic pathway with an oxidative dimerization of a tetracyclic monomer as the key step. In 2015, the Sulikowski group reported a biomimetic oxidative dimerization strategy for the construction of hibarimicins.[21] Bisphenol can be selectively homo-coupled through C6−C6' and C2−C2' coupling respectively (Scheme 6). Successive treatment of the phenol with $AlCl_3$ and $FeCl_3$ afforded bisphenol in 60% yield through C6−C6' connection. In contrast, the benzyl ether of phenol can be homocoupled through C2−C2' connection to give biaryl in 47% yield through a direct *ortho* lithiation at C2 position, cuprate formation and oxidation sequence.

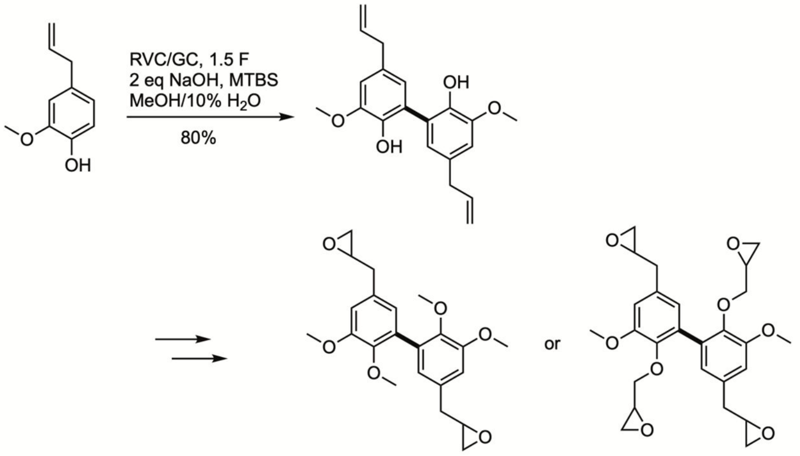
To facilitate the homocoupling of phenols, blocking groups can be introduced first as assistance. A vanadium(V)-mediated dimerization strategy has been employed by the Porco group in the total synthesis of natural product gonytolide A (Scheme 7).[22] An *ortho*-bromine blocking group was used by the authors to realize a *para-para* coupling and to achieve a kinetic resolution of (±)-gonytolide C. As a dimeric chromanone natural product, gonytolide A has been identified as a potent innate immune promoter. However, other dimeric chromanone derivatives connected with *ortho-para* biaryl bond linkage or the monomers gonytolide C were found to be non-active. The authors hypothesized that by blocking the *ortho*-position of the phenol of the monomer with a halogen substituent, a *para-para* oxidative coupling would result in the formation of dimeric chromanone.



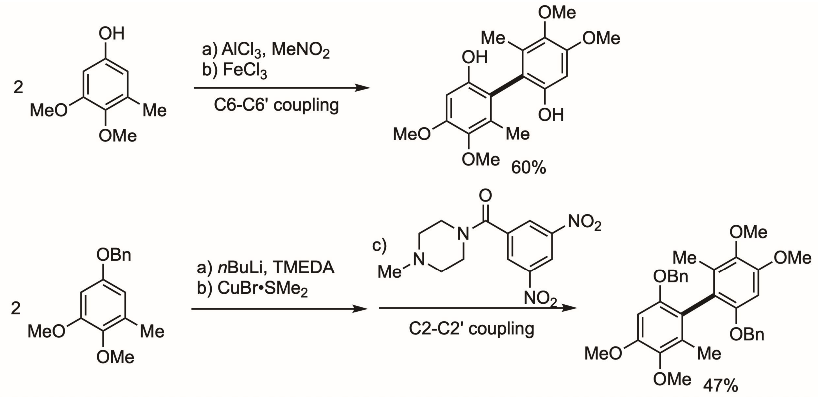
Scheme 3. Iron-catalyzed asymmetric dimerization of 2-naphthol.[18]



Scheme 4. Synthesis of axially diol with 1,4-diketone.[19]



Scheme 5. Synthesis of dimeric eugenol through electrochemical dimerization.[20]

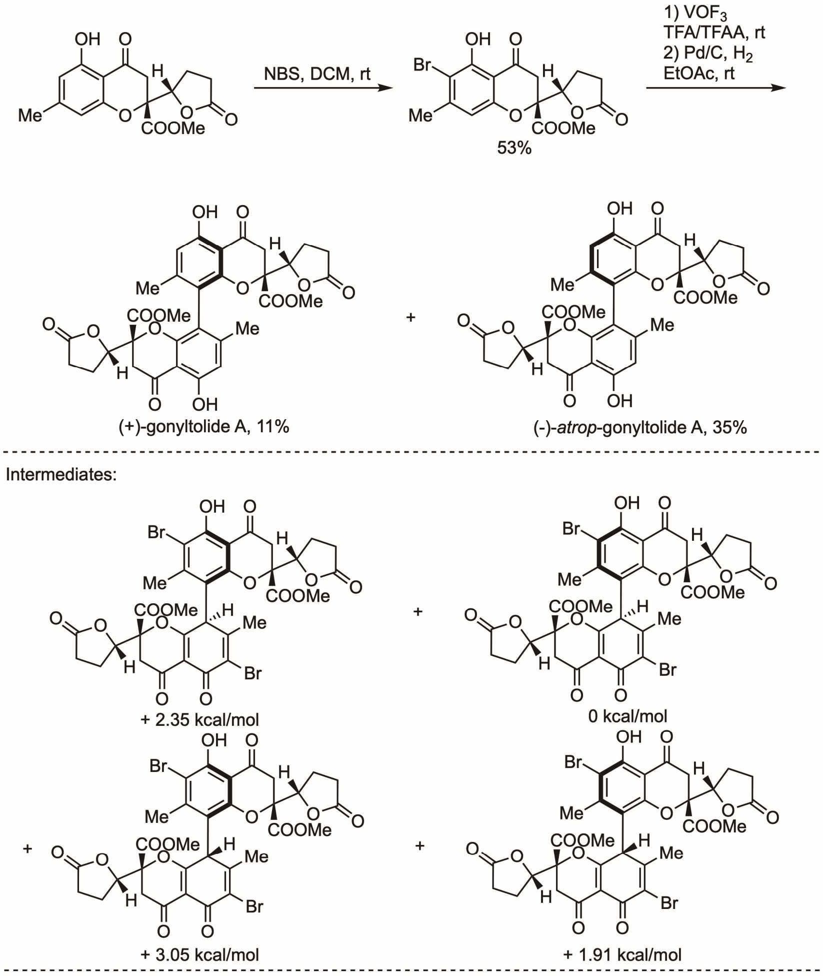


Scheme 6. Biomimetic oxidative dimerization of phenols.[21]

The *ortho*-fluorine blocking group inhibited the reactivity completely, indicating the crucial role of halogen blocking group in the dimerization. Atroposelectivity can be tuned by introducing different halogen blocking groups. Introduction of an *ortho*-iodo blocking group gave exclusively atrop-gonytolide A, while the utilization of a bromine blocking group afforded a 1:3 ratio of atropisomers in favor of atropo-gonytolide A. Switching to *ortho*-chlorine blocking group led to a nearly 1:1 ratio of atropisomers. The halogen blocking group was proposed to have several different roles in the dimerization: 1) to stabilize the cation radical intermediate *in situ* formed after oxidation; 2) to control the *para-para* coupling selectivity; 3) to tune the atropodiastereoselection, allowing access to both natural gonytolide A and its natural atropisomers.

Although 2,2'-diaryl acids serve as valuable building blocks for some high-performance polymers, metal-organic frameworks and biologically active compounds, the methodology development for constructing this kind of molecules is not satisfied. The Li group developed a straightforward and regiospecific dimerization of easily accessible aromatic acids for the construction of 2,2'-diaryl acids through rhodium-catalyzed activation of C–H bond in water (17 examples, 36-90% yields).[23]

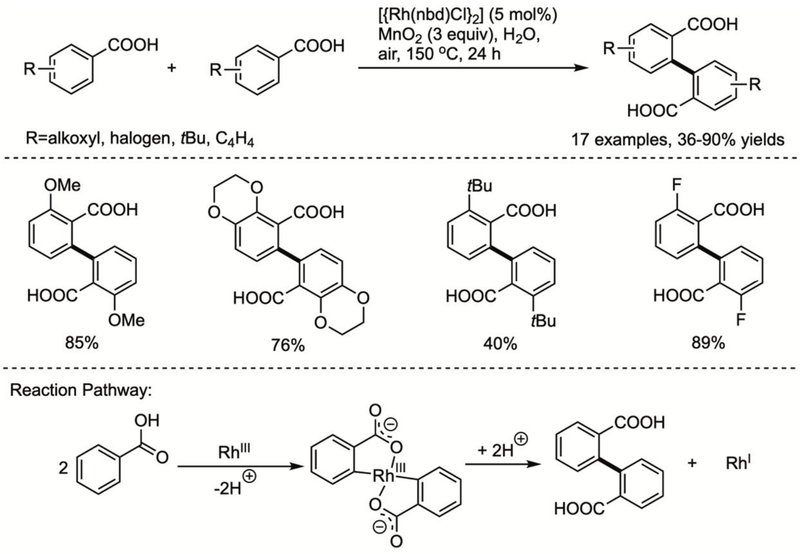
Generally, benzoic acids bearing electron-donating groups afforded better reaction yields except for the one with *meta*-substituent. The use of 3,4,5-trimethoxybenzoic acid gave 40% yield because of the *meta*-methoxy group resulted in steric hindrance. Notably, this process can be easily scaled up to gram level with 80% yield by the utilization of only 0.4 mol% of the catalyst. The authors proposed that this reaction proceeded through a Rh(III)-initiated dual cyclometallation and a following reductive elimination. The Rh(I) species was reoxidized to active Rh(III) catalyst by employing MnO_2 as the oxidant. As a proof of concept, the authors efficiently assembled the antitumor natural product ellagic acid on gram scale from 3,4,5-trimethoxybenzoic acid in only two steps (Scheme 8).



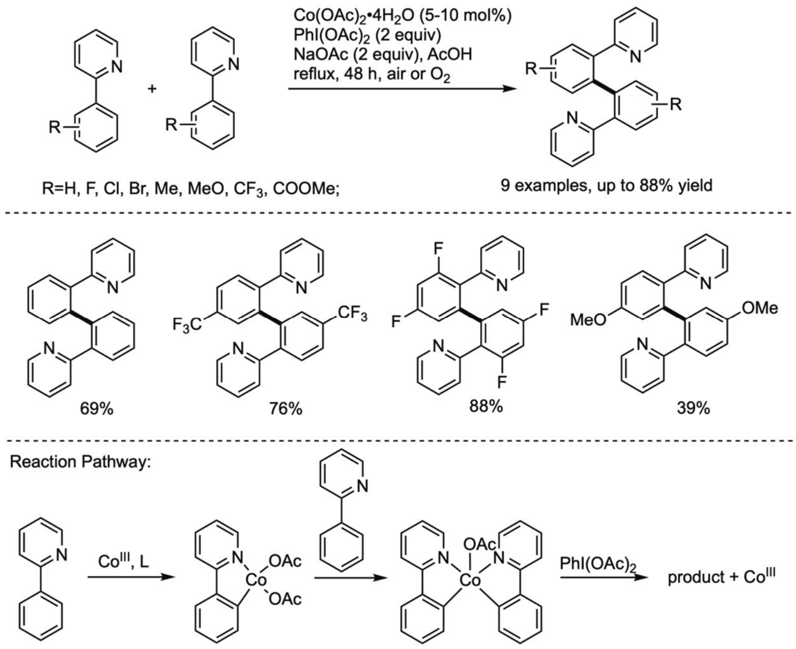
Scheme 7. Total synthesis of gonytolide A *via* bromine blocking strategy.[22]

In 2016, Wu, Zhou and Liu achieved an efficient oxidative dimerization of 2-phenylpyridine utilizing a abundant cobalt catalyst with $PhI(OAc)_2$ as the oxidant (9 examples, up to 88% yield).[24] In the cases with O_2 as the co-oxidant, the higher efficiency was observed. Bromo, chloro, fluoro, ether, and ester moieties were all compatible in this process (Scheme 9). Generally, better results in terms of yields were obtained with the substrates bearing electron-withdrawing groups than those with electron-donating groups. As hypothesized by the authors, the reaction underwent through successive metalation of cobalt catalyst with phenylpyridine and a subsequent demetallation. Cobalt catalyst was recycled by the oxidation with $PhI(OAc)_2$.

8-Aminoquinoline, picolinamide and 2-pyridinylmethylamine auxiliaries have been widely employed in transition metal-catalyzed C−H bond functionalization. The Daugulis group found that the aminoquinoline auxiliary could be able to direct cobalt-promoted C−H activation/arene migratory insertion sequences, affording biphenyldicarboxylic acid derivatives with dioxygen as the terminal oxidant (14 examples, 37-91% yields).[25]

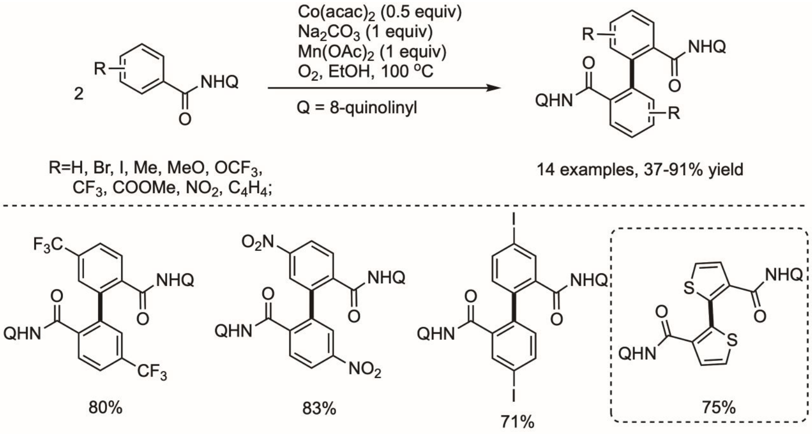


Scheme 8. Synthesis of 2,2'-diaryl acids.[23]



Scheme 9. Oxidative dimerization of 2-phenylpyridines.[24]

8-Thiophene carboxamide was also reactive under the current reaction system, giving the desired dimer in high yield. It is worth nothing that the directing group can be easily removed by KOH-promoted hydrolysis of the amides to give dicarboxylic acid. This process features good functional group compatibility with bromo, iodo, nitro, ether, and ester moieties tolerant with the reaction conditions. Excellent selectivity was achieved, as only one isomer of product was observed in all cases (Scheme 10).



Scheme 10. Cobalt-promoted synthesis of biphenyldicarboxylic acid derivatives.[25]

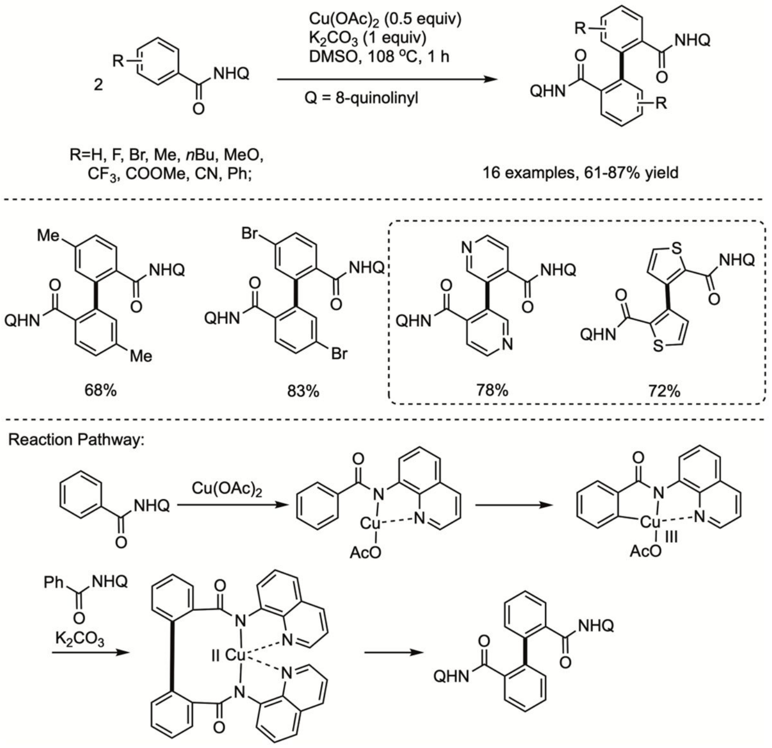
Hu and Sun devised a convenient copper-promoted oxidative dimerization of benzamides. In this process, both electron-donating and electron-withdrawing groups (including alkyl, methoxy, trifuoromethyl, fluoro, and bromo) are compatible with the current reaction system, providing the desired dimers in moderate to excellent yields (Scheme 11).[26] It is worth noting that heteroarenes, such as pyridines and thiophenes, were also suitable candidates for this procedure, demonstrating a good functional group compatibility of this robust approach. The authors proposed a copper promoted C–H cleavage pathway rather than an electrophilic aromatic substitution or a radical pathway. Two-ligand coordination on the copper and a following reductive elimination lead to the formation dimeric benzamide. Interestingly, this reaction system could be tuned to give hydroxylation products only by increasing the amount of mediater and switching the additive to TBAI (tetrabutylammonium iodide).

Compared to the oxidative synthesis of BINOL derivatives, the homocoupling of benzenes is a far more challenging task because of the generation of regioisomers and oxidation byproducts. In 2015, the Greaney group reached a one-pot, two-step construction of atropisomeric biaryls with chelating S, Se, or N substituents in the 2,2' positions (Scheme 12).[27] Benzyne intermediates would be generated under Knochel conditions with 2-iodophenylsulfonates and *i*PrMgCl. A following addition of this intermediate to thiol, selenol and amine nucleophiles afforded aryl Grignard intermediate and further treatment with a copper salt and an oxidant delivered symmetric biaryls in moderate to good yields (15 examples, 33-76% yields). Lower yields were obtained in the N-series compared with those of S-series, likely due to higher steric hindrance and lower nucleophilicity compared to thiols.

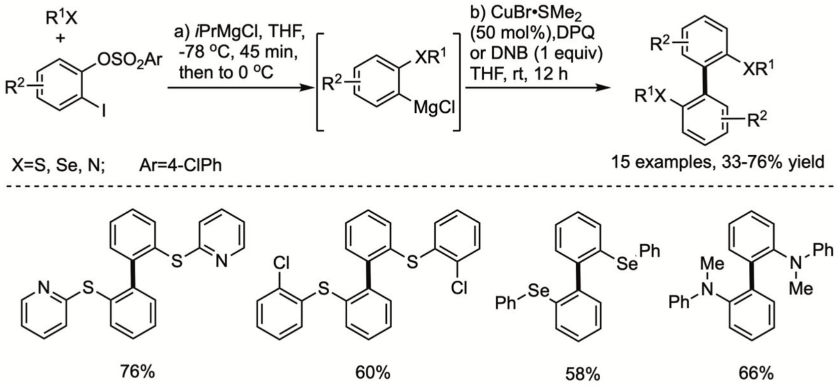
Wirtanen and Helaja extended their oxidized carbon nanotubes catalysis to the synthesis of dimeric electron-rich aryls (Scheme 13).[28] The authors found that the yield of the dimerization reaction correlated well with the substrate's oxidation potential. Substituted electron-rich biaryls can be accessed by this recyclable carbocatalytic method by the use of aryls with lower oxidation potentials (3 examples, 60-86% yield). Unfortunately, bromo-substituted phenylic ether with a higher oxidation potential cannot be compatible in this reaction system.

The first stereoselective total synthesis of (–)-crisamicin A has been achieved by Brückner and co-workers (13 steps, 5% yield totally).[29] A late-stage oxidative Hartwig borylation/oxidative homocoupling sequence for the construction of dimeric naphthoquinonopyrano-γ-lactone can be regarded as the key step for this work. The less hindered naphthyl–H bond of naphthoquinonopyrano-γ-lactone can be activated under an

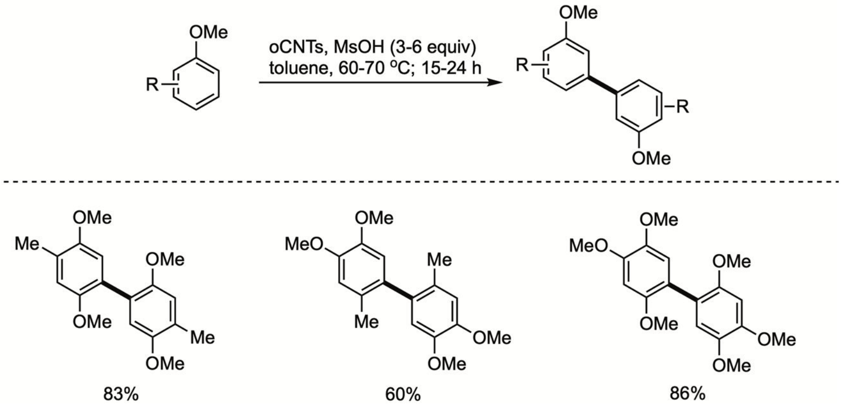
Ir catalysis delivering boronic ester. A Pd-catalyzed oxidative coupling gave the desired binaphthyl under operationally simple reaction conditions (Scheme 14).



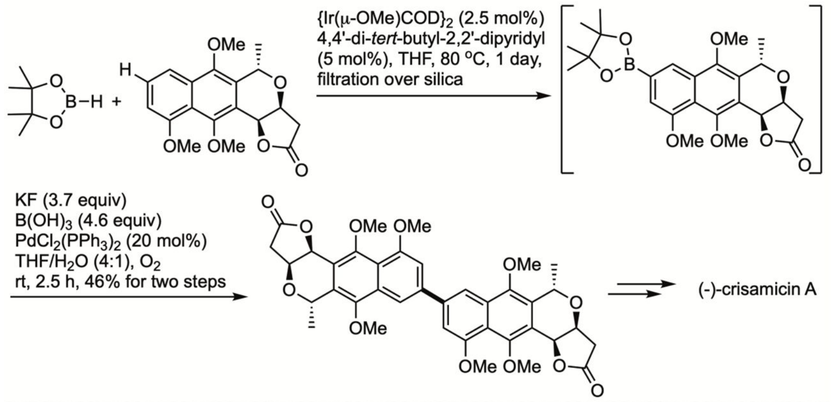
Scheme 11. Copper-promoted oxidative dimerization of benzamides.[26]



Scheme 12. One-pot dimerization of benzenes.[27]



Scheme 13. oCNTs catalyzed synthesis of biaryls.[28]



Scheme 14. Late-stage oxidative Hartwig borylation/oxidative homocoupling.[29]

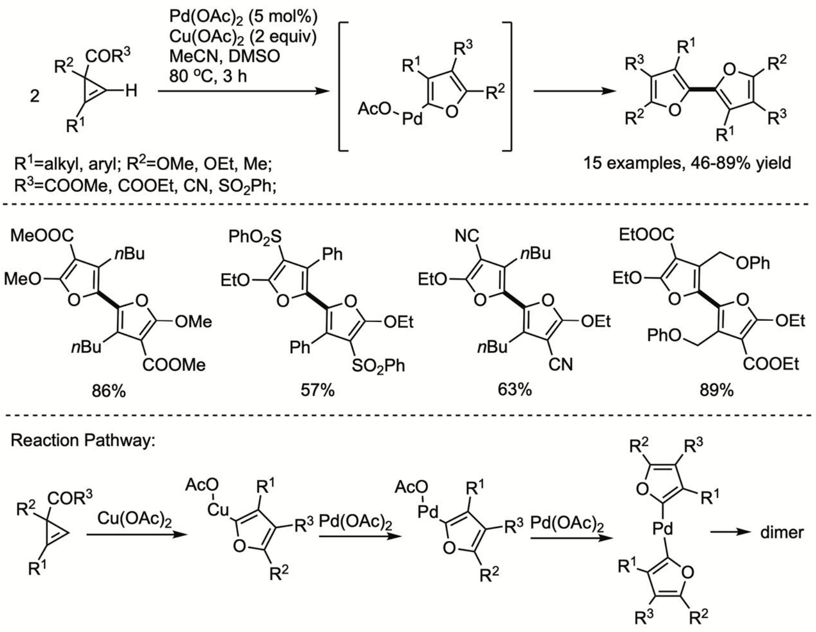
2. Formation of heteroaryl–heteroaryl bond

There are more choices for the synthesis of dimeric heteroaryls than the biaryl synthesis, depending on the mode of connection and oxidation potentials of heteroarene. Formation of heteroaryl–heteroaryl bond can be achieved by the *in situ* generation of heteroaryl–metal complex from nonaromatic starting matericals, transition metal catalyzed direct C–H functionalization of heteroarene, and formation of heterocyclic cation radical. In general, electron-rich heteroarenes such as indole, benzofuran and benzothiophene are prone to react with another molecule through the *in situ* oxidative generation of cation radical, while electron-deficient heteroarenes such as pyridine are always used for constructing dimers through C–H functionalization.

Inspired by recent studies which suggested that bifurans may have similar properties to longer oligofurans, Xu and co-workers hypothesized that the introduction of a bifuran unit into organic materials might be a rational design for conjugated organic electronic materials (Scheme 15).[30] To avoid the in advance preparation of heteroaryl organometallics and halides, the authors developed a cycloisomerization/dimerization approach for synthesizing bifurans through tandem metal relay catalysis.

A key furan palladium intermediate can be generated *in situ* by a copper-mediated ring-opening/cycloisomerization sequence and subsequent transmetallation to palladium. Disproportionation of this intermediate afforded a bifuranylpalladium intermediate, which would undergo reductive elimination to give the bifuran product. Palladium catalysis can be achieved by the reoxidation of Pd(0) with $Cu(OAc)_2$. Both alkyl and aryl can be incorporated at the R^1 position. The alkoxy group could be introduced at the R^3

position and various electro-withdrawing groups including CO_2Et, CO_2Me, CN and SO_2Ph can be compatible at R^2 position (15 examples, 46-89% yield). The dimeric furans may find promising applications as optoelectronic materials.



Scheme 15. Palladium-catalyzed synthesis of dimeric furans.[30]

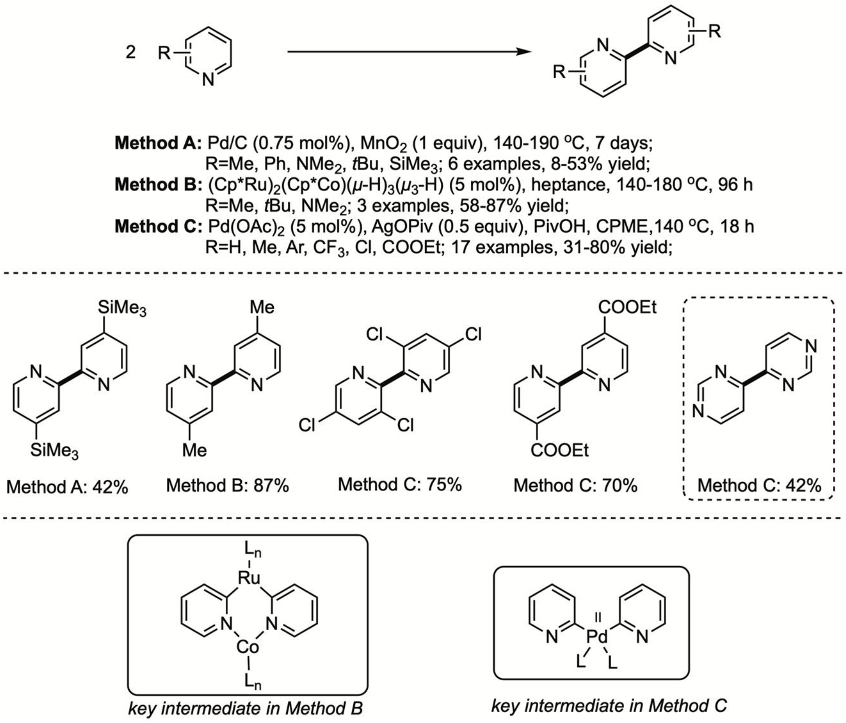
Bipyridine is not only a key substructure present in natural products, but also a key unit in numerous bidentate ligands in the research fields of coordination, nanomolecular, supramolecular, macromolecular, analytical chemistry and photochemistry. Compared to the traditional cross-coupling strategy and reductive dimerization strategy, the dehydrogenative dimerization route can be regarded as a more attractive way because of its high efficiency, atom economy, and step economy. The Weix group reported a Pd/C-catalyzed dehydrogenative coupling of substituted pyridines for the synthesis of bipyridines and terpyridines (Scheme 16). A series of substituted pyridines has been successfully dimerized in the presence of Pd/C as a catalyst and MnO_2 as the oxidant (R=Me, Ph, NMe_2, *t*Bu, $SiMe_3$; 6 examples, 8-53% yield).[31]

Later in 2016, Takao and co-workers developed a dimerization of 4-substituted pyridines using a trinuclear complex of ruthenium and cobalt as a catalyst. 4-Substituted pyridines possessing electron-donating groups can be compatible in this process providing corresponding bipyridines in good yields (R=Me, *t*Bu, NMe_2; 3 examples, 58-87% yield). However, this reaction is highly dependent on the basicity of the N atom in pyridine as no desired products can be isolated in the cases with pyridines bearing electron-withdrawing groups.[32]

Murakami and Itami also disclosed a palladium-catalyzed regioselective dehydrogenative dimerization of pyridines. A range of pyridines has been regioselectively coupled at the C2 position, allowing access to 2,2'-bipyridines successfully in moderate to good yield (R=H, Me, Ar, CF_3, Cl, COOEt; 17 examples, 31-80% yield). It is worth noting that steric hindered 3-substituted pyridines can also be compatible in this process, enabling the straightforward formation of axially twisted 2,2'-bipyridyl ligands.[33]

Although copper-promoted direct homocoupling has the advantages of using less expensive and abundant copper salts and complexes, the substrate scope is limited to the utilization of relatively acidic arenes, such as 1,3-azoles and polyfluoroarenes. In 2014, Miura and Hirano expanded the copper-mediated dimerization protocols to nonacidic thiophenes and indoles, through a functional group-direct dual C–H cleavage strategy (Scheme 17).[34] In the presence of copper acetate, a variety of thiophenecarboxamides could be homocoupled efficiently. Unfortunately, it was found that other arenecarboxamides including benzene, furan and pyrrole-involved substrates could not be compatible in this process, and the dimerization was unique to the thiophene ring.

The authors proposed that this reaction proceeded through the following pathway: 1) N,N-double chelation-assisted C–H cupration to give Cu(II)-containing metallacycle; 2) oxidation of Cu(II) to Cu(III) through disproportionation; 3) C–H metalation with a second molecule of thiophene at the Cu(II) center; 4) reductive elimination of two thiophene ligands from Cu(III) intermediate. The disproportionation or second C–H cleavage was proposed to be the rate-limiting step.

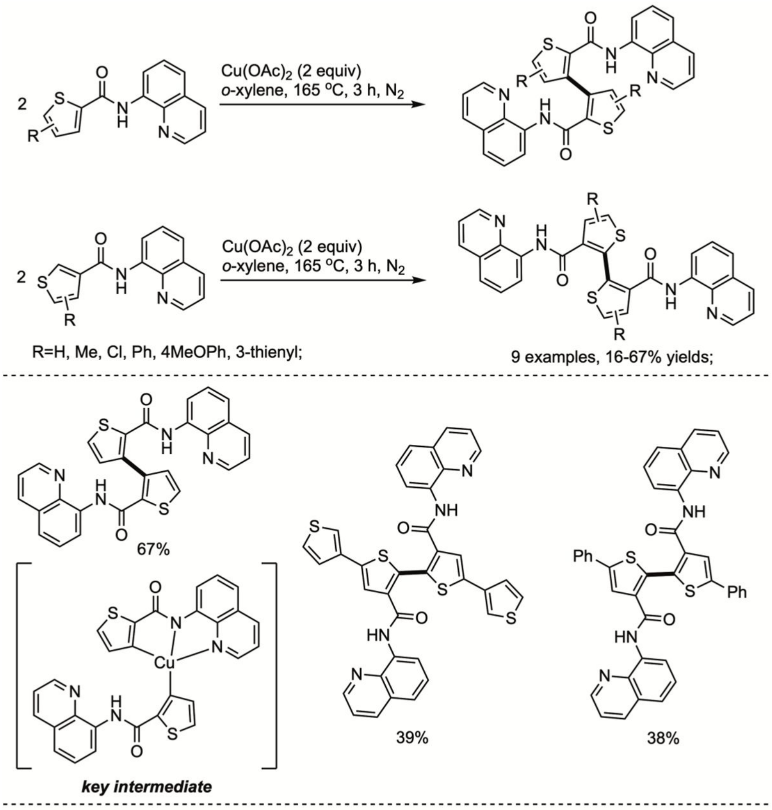


Scheme 16. Synthesis of bipyridines.[31-33]

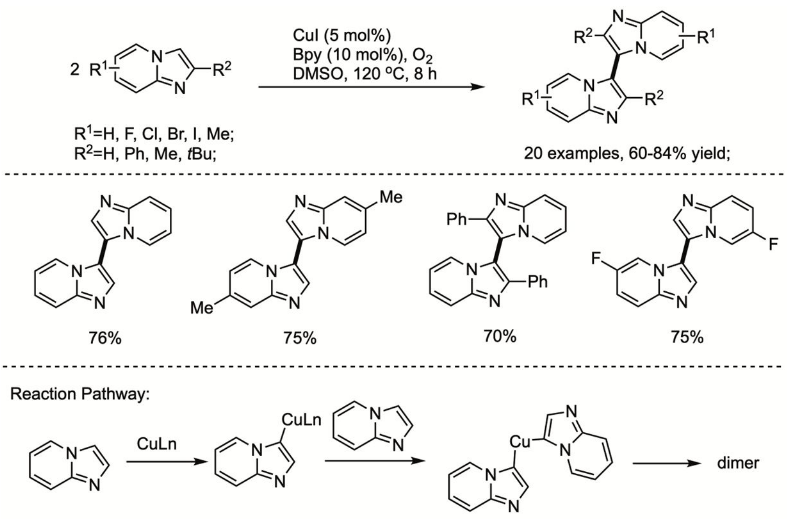
Imidazo[1,2-*a*]pyridine as a key structural unit appearing in a great number of natural products, pharmaceutically interesting compounds, and materials, has attracted continuing attention of organic chemists on its direct synthesis and modifications. In 2015, the Cao group has reported an efficient regioselective C-3 homocoupling of imidazo[1,2-*a*]pyridine derivatives under the catalysis of copper iodate (Scheme 18).[35] This strategy allows access to various biimidazo[1,2-*a*]pyridines in a straightforward manner (20 examples, 60-84% yield).

The authors proposed that the coordination of Cu(I) with imidazo[1,2-*a*]pyridine would yield a Cu(I) species, which then reacted with another molecule of imidazo[1,2-*a*]pyridine affording a copper bridged dimer. The copper bridged dimer underwent a subsequent reductive elimination in the presence of oxygen leading to the formation of the desired dimeric imidazo[1,2-*a*]pyridine.

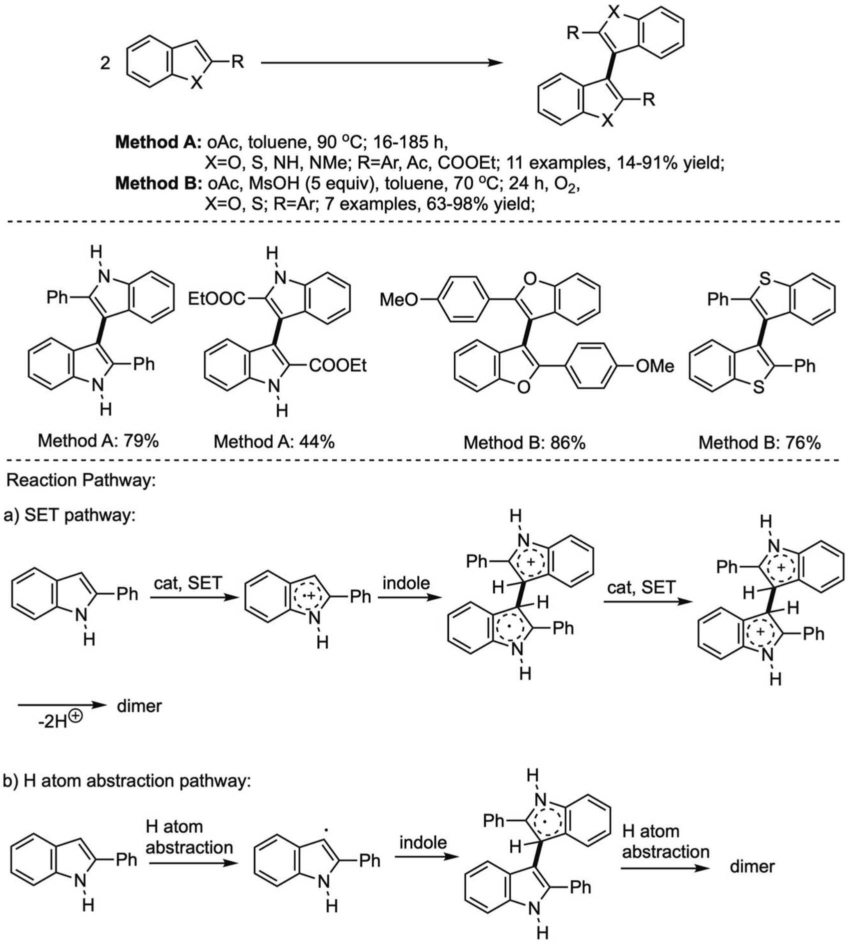
Heterogeneous carbon-based catalysts such as AC (active carbon) have been traditionally employed in oxidative dehydrogenation of hydrocarbons. In 2015, Helaja and co-workers have achieved an OAC (oxidized amorphous carbon)-catalyzed oxidative dimerization of benzofused heterocycles through Csp^2–Csp^2 homocoupling (Scheme 19).[36] In the presence of OAC, a range of biindoles can be obtained in good yields by heating indoles in toluene in 90 °C (Method A).



Scheme 17. Copper promoted dimerization of thiophenes.[34]



Scheme 18. Copper-catalyzed dimerization of imidazo[1,2-*a*]pyridines.[35]

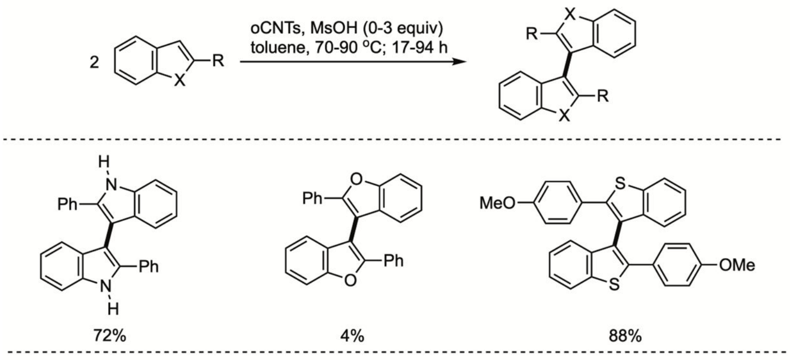


Scheme 19. OAC-catalyzed dimerization of heteroarenes.[36]

However, low yields were obtained when treating benzofuran and benzothiophene with this reaction system. Interestingly, based on the consideration that an acid additive may boost the oxidative processes by OAC, the authors successfully prepared a series of dimeric benzofurans and benzothiophenes in excellent yields by using the combination of OAC and MsOH (Method B).

Two plausible reaction pathways may be involved in this reaction process as proposed by the authors. In the SET pathway, cation radical may be formed in the presence of OAC, further coupling, oxidation of the distonic cation radical and deprotonation of the dication would provide the desired dimer. In the H atom abstraction pathway, the reaction of neutral radical formed through an H atom abstraction way with another molecule of indole would generate a radical dimer. Further oxidation of this radical dimer and a final deprotonation gave the desired dimeric indole.

Based on previous studies on oxidized active carbon-catalyzed homocoupling of indoles, Wirtanen and Helaja hypothesized that oxidized carbon nanotubes might be suitable catalysts for realizing a straightforward dehydrogenative C−C bond formation of electron-rich aryls and heteroaryls in the presence of dioxygen as a terminal oxidant (Scheme 20).[28] Dimeric benzofused heteroaryls except for benzofuran, have been readily prepared (3 examples, up to 88% yield). Since benzofuran has a high oxidation potential, the dimerization of benzofuran is disfavored. The authors suggested that carbonyls/quinones should be the catalytically active site of the carbocatalyst based on model compounds and titration experiments. Experimental and DFT calculation indicated a competing acid-catalyzed and radical cationic pathways.



Scheme 20. oCNTs-catalyzed dimerization of heteroarenes.[28]

The Antonchick group devised a metal-free dehydrogenative coupling of indoles, benzofurans and benzothiophenes using nitrosonium ion as catalyst in 2018 (Scheme 21). Ambient molecular oxygen was utilized as a terminal oxidant. This robust and versatile procedure provided a direct access to various bibenzofurans, allowing the introduction of a variety of aryls at the C2 position (R=H, Ph, Br, F; 18 examples, 31-92% yield).[37] Bibenzothiophenes can be obtained in good yields in a short reaction time with similar trends in functional group compatibility (4 examples, 50-71% yield). The authors next expanded this strategy to the synthesis of dimeric 3-arylindoles (R^1=H, F, Me; R^2=H, Ac, Me; 8 examples, 36-71% yield).

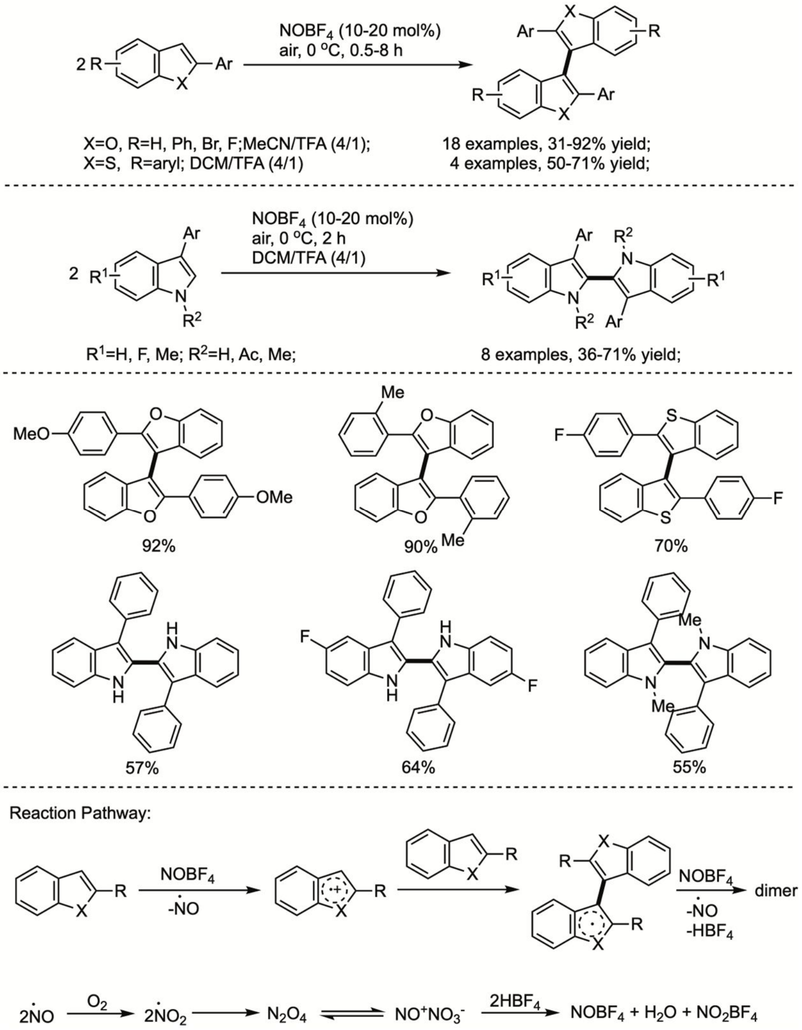
As proposed by the authors, cation radical may be generated through single electron transfer (SET) by oxidation of the heteroarene. Radical S_EAr and a second SET resulted in the rearomatization giving the desired dimer. *In situ* formed nitrogen monoxide was oxidized by molecular oxygen to give nitrogen dioxide. The subsequently generated dinitrogen tetroxide would release a nitrosonium and a nitronium ion upon protonation in the presence of acidic water. The dimeric scaffolds may represent a potential source for discovering biologically active molecules. Several bisindoles were identified as novel inhibitors of hedgehog signaling pathway. On the other hand, the monomeric materials were found to be inactive.

Miura and Hirano also successfully prepared 2,2'-bisindoles through this copper-promoted process with *N*-(2-pyrimidyl)-indole and *N*-(2-pyridyl)-indole (Scheme 22). By the aid of directing group incorporated at the N1 position, the dimerization occurred at the C2 position of the indole ring.[34]

The synthesis of arene-fused cyclooctatetraenes has attracted much attention owing to the saddle-shaped π-conjugated architectures may cause unique structural and electronic properties. However, limited effective methodologies have been achieved in the field of constructing heteroarene-fused cyclooctatetraenes. Miura and Nishii reached a palladium-catalyzed dehydrogenative cyclodimerization strategy in 2017 (Scheme 23).[38] Unsymmetrical biheteroaryls, 2-phenyl-4-(5-phenylthiophen-3-yl)furan and 2-phenyl-4-(5-phenylthiophen-3-yl)thiazole, can be dimerized under palladium catalysis to corresponding heteroarene-fused cyclooctatetraenes as a single regioisomer in 42% and 27% yields respectively.

The authors proposed that a high-valent palladium complex might be generated after the two-fold C−H activation and further oxidation with silver salts. Mechanistic study indicated that the formation of five-membered palladium complex through two-fold C−H activation should be the turnover-limiting step for this process.

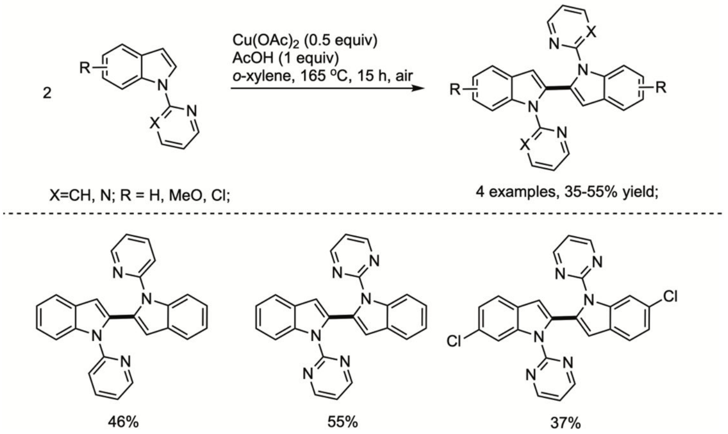
As a bisindole framework, 6,7,12,13-tetrahydro-5*H*-cyclohepta[2,1-*b*:3,4-*b'*]diindole has attracted little attention. Yang and Zhang established a hypervalent iodine(III) mediated synthesis of 6,7,12,13-tetrahydro-5*H*-cyclohepta[2,1-*b*:3,4-*b'*]diindole derivatives through intramolecular oxidative coupling. In this process, the seven-membered ring was constructed efficiently in the presence of PIFA, DDQ and TMSCl (Scheme 24).[39]



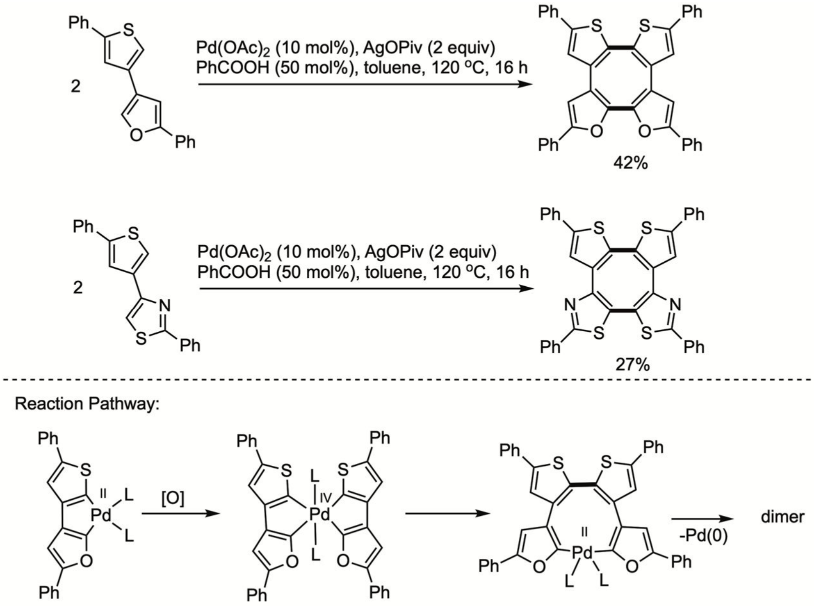
Scheme 21. NOBF$_4$-catalyzed dimerization of heteroarenes.[37]

This practical protocol features good functional group tolerance. Two possible reaction pathways may be involved in this reaction. The major one began with an oxidative formation of cation radical through SET in the presence of PIFA and DDQ. A following oxidation through SET resulted in the generation of a distonic intermediate. Further deprotonation, oxidation and a second deprotonation gave the desired product. In addition, a Friedel-Crafts type intermediate was detected by LC-MS, indicating a protonation/Friedel-Crafts type addition/oxidation cascade sequence, in the presence of TMSCl as a Lewis acid.

Traditionally, BODIPY (boron-dipyrromethenes) dimers have been prepared through *de novo* synthesis from 2,2'-bipyrrole derivatives, or by the use of stoichiometric strong oxidants including FeCl$_3$, PIFA and electrochemical way mediated direct dimerization of existing BODIPY monomers. However, limited BODIPY dimers have been produced to date due to the requirement of a multistep synthesis, relatively harsh reaction conditions, poor regioselectivity and polymerization side reactions. Jiao and Hao disclosed a photoinduced assembly of structurally unprecedented BODIPY dimers through α,α- and α,γ- couplings (Scheme 25).[40]

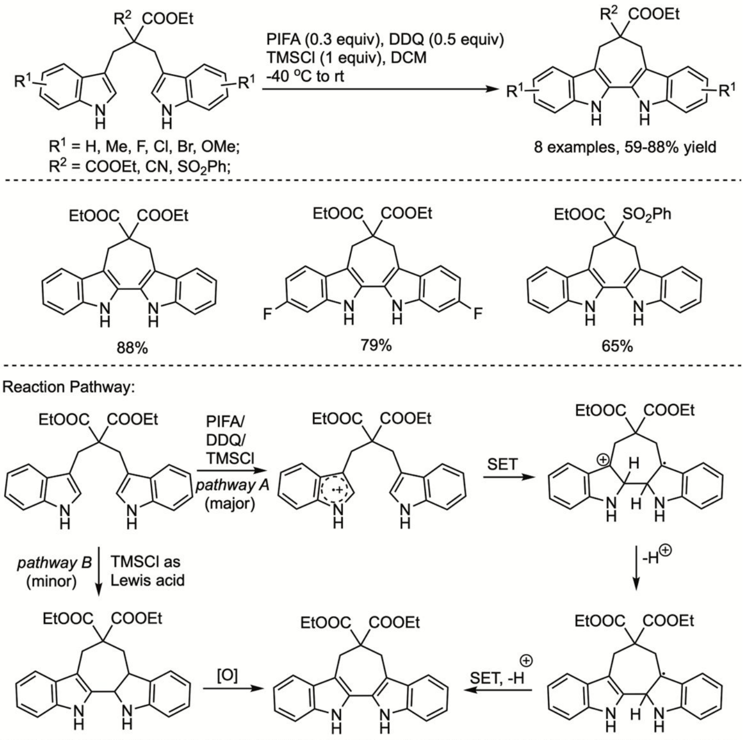


Scheme 22. Copper-promoted dimerization of indoles.[34]



Scheme 23. Palladium-catalyzed dehydrogenative cyclodimerization.[38]

This strategy takes advantages of the ability of BODIPY to absorb visible-light. A series of α,α- and α,γ-linked dimers can be readily prepared in 36-71% and 18-30% yields respectively using AgTFA as an oxidant. The presence of strong electron-withdrawing group, C_6F_5, resulted low reactivity leading to corresponding dimers in 15% and 13% yield respectively. In comparison to monomer, α,α-linked dimers have broaden absorption and emission spectra in the NIR region, likely due to extension of the conjugation of the BIDOPY units.

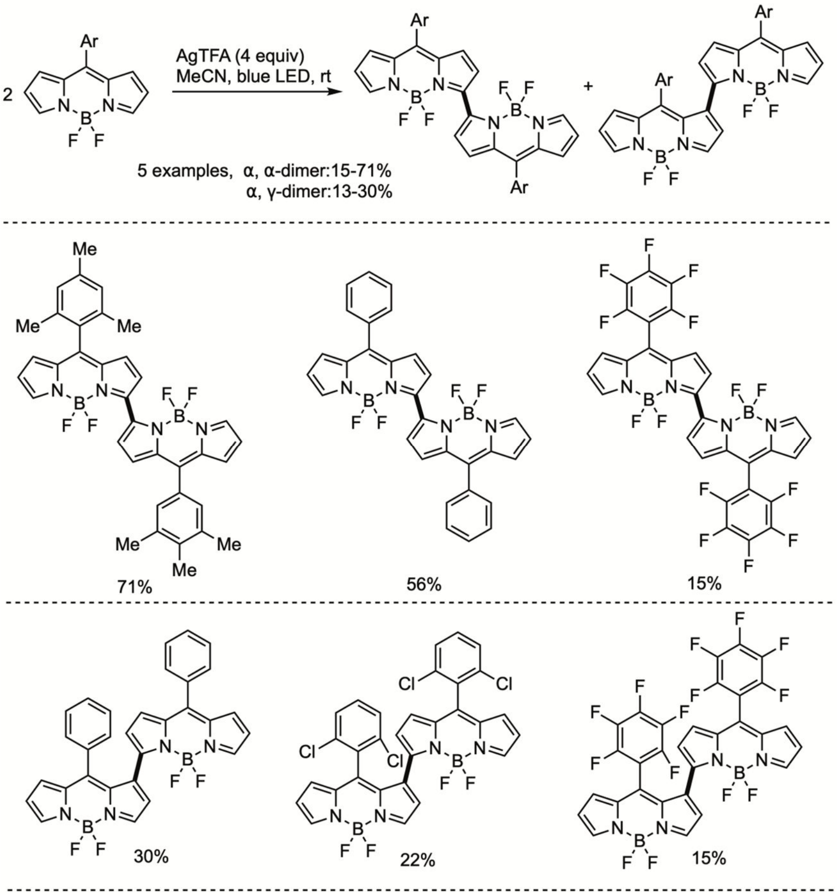


Scheme 24. Hypervalent iodine(III) mediated homocoupling of indoles.[39]

As a key unit present in natural products lamelllarin family and other bioactive synthetic molecules, pyrrolo[2,1-*a*]isoquinoline has attracted much attention on its direct synthesis and further modification. Since late-stage modification is an easy and rapid way for accessing structurally complicated molecules, modification of pyrrolo[2,1-*a*]isoquinoline can be considered as an attractive way for producing useful compounds. In addition, modification of pyrrolo[2,1-*a*]isoquinoline can provide better understanding of the chemistry of pyrrolo[2,1-*a*]isoquinoline framework, as the chemistry of pyrrolo[2,1-*a*]isoquinoline has not been fully studied as that of indole, pyrrole, isoquinoline and other related heterocycles. Cui and co-workers have developed an iron-mediated dimerization of pyrrolo[2,1-*a*]isoquinoline derivatives (16 examples, 35->99% yield).[41-44]

In most cases, the use of 2 equivalents of $FeCl_3$ afforded highly functionalized dimeric pyrrolo[2,1-*a*]isoquinolines in moderate to excellent yields (Scheme 26). A cation radical reaction pathway was proposed on the basis of the results and previous reports. A key cation radical intermediate can be yielded *in situ* in the presence of $FeCl_3$ as an oxidant and a following addition with another molecule of pyrrolo[2,1-*a*]isoquinoline resulted in the formation of a distonic cation radical. Further oxidation and deprotonation of the dication delivered the desired dimer.

From the point of view of green and sustainable chemistry, a catalytic version of dimerization would be more attractive. Therefore, an iron-catalyzed dimerization of pyrrolo[2,1-*a*]isoquinoline and pyrrolo[1,2-*a*]quinoline derivatives was developed using DTBP as the terminal oxidant and HFIP as the solvent (19 examples, 42-76% yields).[45] In this approach, both isoquinoline-derived fully aromatized pyrrolo[2,1-*a*]isoquinolines and quinoline-derived pyrrolo[1,2-*a*]quinolines were well compatible, providing the corresponding dimers in modest to good yields (Scheme 27).



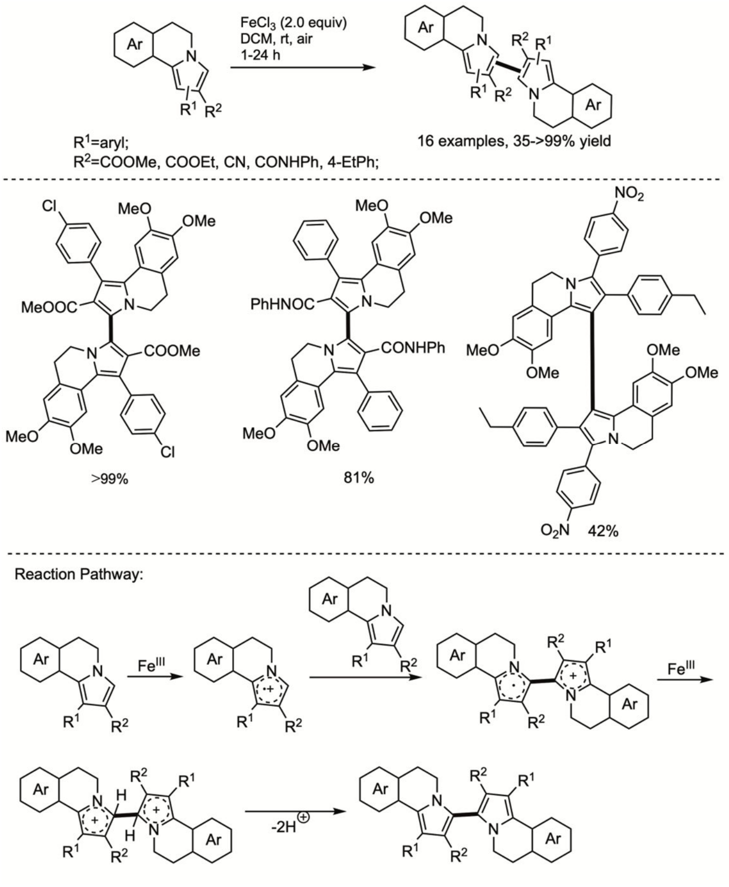
Scheme 25. AgTFA-mediated synthesis of BODIPY dimers.[40]

4. Conclusion

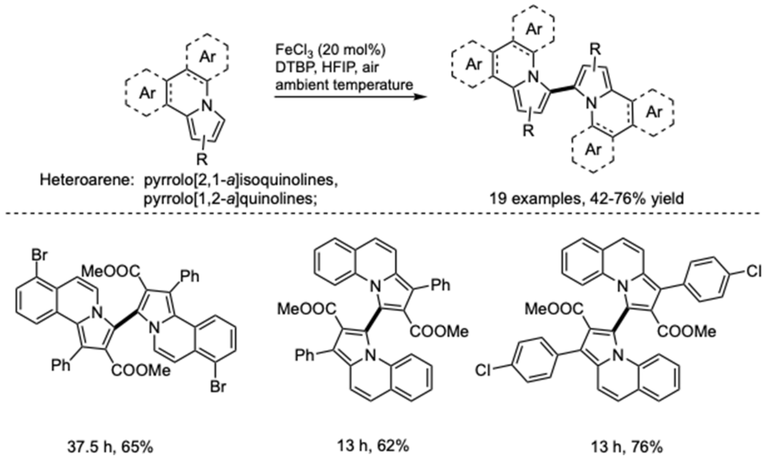
Given the great importance of dimeric aryls and heteroaryls in natural products, pharmaceutically interesting compounds, ligands, catalysts, and other functional molecules, a range of convenient constructions of aromatic and heteroaromatic dimers has been established in the past decades. Direct dimerization strategy through homocoupling reactions can be regarded as the most attractive one, owing to its high efficiency, easy manipulation, utilization of readily available materials, step and atom economy. Two main reaction pathways are involved in this strategy including cation radical based pathway and transition metal catalyzed or mediated C−H functionalization with or without the aid of directing groups.

Since important achievements have also been made in the field of cross-coupling-based synthesis of aryls and heteroaryls, rational designs may be encouraged by these advances. Similarly, homocoupling-based dimerizations can also be extended to the developments of cross-coupling reaction systems if properly addressing the issues of chemoselectivity and regioselectivity. Hopefully, same catalysts or reaction systems might be able to provide symmetric and unsymmetric biaryls and biheteroaryls selectively.

Future efforts should still be devoted to solve the problems such as: a) how to avoid the employment of directing groups; b) preparation of dimeric aryls and heteroaryls in a green and sustainable manner; c) extension of current reaction systems to more kinds of aryls and heteroaryls; d) introduction of new scientific concepts and technologies to this research fields.



Scheme 26. Iron-promoted dimerization of pyrrolo[2,1-*a*]isoquinolines.[41-44]



Scheme 27. Iron-catalyzed dimerization of pyrrolo[2,1-*a*]isoquinolines and pyrrolo[1,2-*a*]quinolines.[45]

Acknowledgements

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