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Recent Advances in the Synthesis of Triarylmethanes by Transition Metal Catalysis

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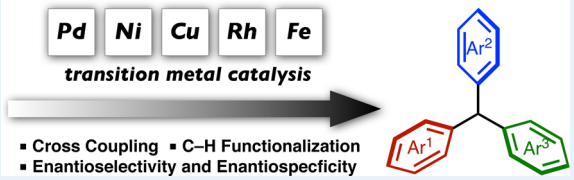
ABSTRACT: Triarylmethanes and related compounds are fascinating molecules because of their structural and physical properties, many potential applications in organic functional materials, and high biological activity. Recently, catalysis has provided new synthesis routes to triarylmethanes with high selectivity and diversity, including the possibility of preparing enantiomerically enriched derivatives, which is typically challenging using classical methods. This Perspective reviews recent advances in new synthesis approaches to triarylmethanes using well-defined transition metal catalysts. These methods will allow the development of new, unexplored triarylmethane structures.



KEYWORDS: *triarylmethane, transition metal catalysis, arylation, enantioselectivity, enantiospecificity*

1. INTRODUCTION

Triarylmethanes and related compounds have attracted much attention as a result of their unique structural and physical properties and applications to organic functional materials and biologically active compounds.[1] For example, since the discovery of organic dyes, including Crystal Violet, the triarylmethane motif has become one of the basic core structures for fluorescent molecules.[2] Recently, a variety of fluorescent compounds have been designed, synthesized, and applied in live cell imaging,[3] and several triarylmethanes bearing metal binding sites have been developed as selective sensors for metal ions.[4] Moreover, this substructure is also finding increased application in medicinal chemistry, including as antitubercular and anticancer agents[5] as well as potassium ion channel blockers.[6] Thus, it is becoming increasingly important to have efficient synthesis routes to triarylmethanes and their derivatives.

The Friedel–Crafts reaction is one of the most commonly employed methods for the synthesis of triarylmethanes, which involves the reaction of diarylmethanol or related derivatives with arenes in the presence of an acid catalyst;[7] however, only nucleophilic electron-rich arenes are reactive, and undesired regioisomers are often formed. The reduction of triarylmethanol derivatives with a reducing agent is also comparable to the Friedel–Crafts strategy, but a multistep process is required to access triarylmethanes.[8]

Recently, transition metal-catalyzed routes have emerged as an alternative method to address these issues and provide structurally diverse triarylmethanes. In addition, some of these systems have enabled the construction of enantioenriched triarylmethanes, which are exceptionally difficult to make by Friedel–Crafts chemistry.

In this Perspective, we focus on the most recent advances in versatile triarylmethane synthesis using transition metal catalysis. In particular, we review arylations catalyzed by transition metals, including Pd, Cu, Ni, and Fe, that are not catalysts for typical Friedel–Crafts reactions to afford symmetrical and unsymmetrical triarylmethanes. We also highlight novel examples of Ni-, Pd-, and Rh-catalyzed syntheses of enantioenriched triarylmethanes. This review will be restricted to the preparation of parent triarylmethanes; derivatives such as triarylmethanols or related compounds will not be discussed in this article.[9]

2. SYNTHESIS OF ACHIRAL TRIARYLMETHANES BY TRANSITION METAL CATALYSIS

2.1. Pd Catalysis. *2.1.1. Cross-Coupling of Multiply Arylated Electrophiles.* The Pd-catalyzed Suzuki-Miyaura cross-coupling reaction has become one of most fundamental methods for carbon–carbon bond formation in organic chemistry and materials chemistry.[10] The reaction is characterized by high selectivity and generality, with ready availability of building blocks enabling simple access to a variety of functional materials, drugs, and complex natural products. The first example of this type of reaction in the context of triarylmethane synthesis was reported by Molander, who described the Pd-catalyzed reaction of benzhydryl bromide with potassium 4-methoxyphenyltrifluoroborate to afford the desired triarylmethane product (Scheme 1a).[11] However, the benzhydryl bromide homocoupling byproduct was also observed in a 1:1.5 ratio, favoring the desired product. In 2009, Adrio and Carretero discovered that Grignard reagents were successful coupling partners for the same electrophile, such that the reaction of benzhydryl bromide with 4-fluorophenyl-magnesium bromide gave the corresponding

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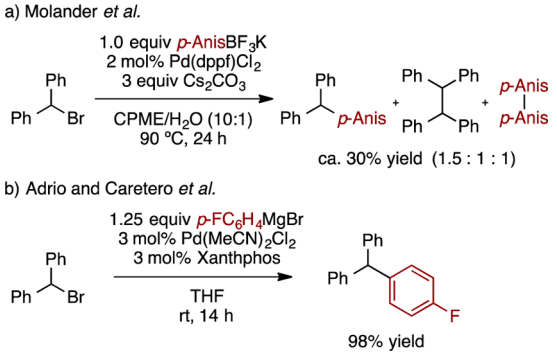
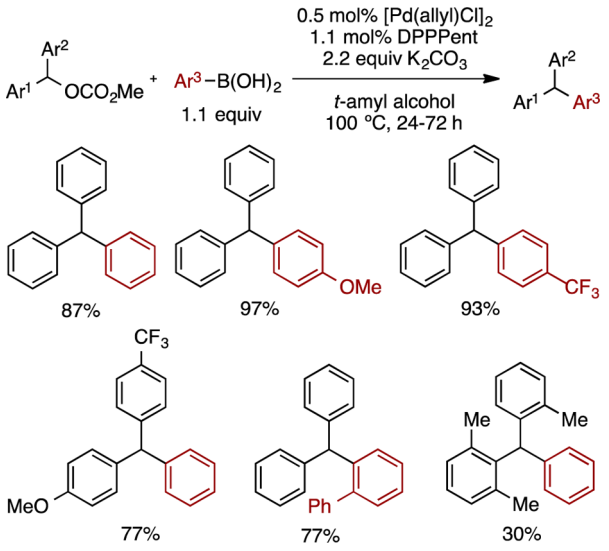
Scheme 1. Synthesis of Triarylmethanes via Pd-Catalyzed Arylation of Benzhydryl Bromide



triarylmethane in excellent yield employing a combination of $Pd(MeCN)_2Cl_2$ and Xantphos as the catalyst (Scheme 1b).[12]

In 2008, the Kuwano group reported that diarylmethyl methyl carbonate was a good alternative to diarylmethyl halides as the electrophile for the production of triarylmethanes (Scheme 2).[13] The carbonate derivatives were reacted with

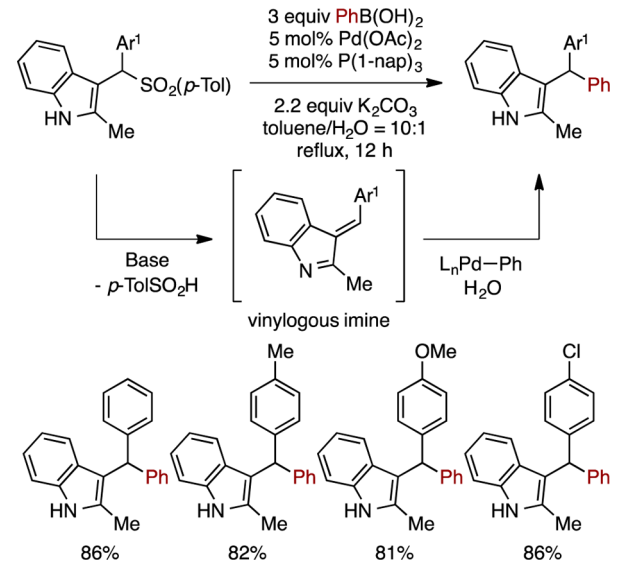
Scheme 2. Pd-Catalyzed Arylation of Diarylmethyl Carbonates with Arylboronic Acids



arylboronic acids in the presence of a catalytic amount of $[Pd(ally)Cl]_2$ with bidentate 1,5-bis(diphenylphosphino)-pentane (DPPPent) ligand and K_2CO_3 as the base. Arylboronic acids bearing electron-donating and -withdrawing groups were well tolerated, and even various triarylmethanes bearing bulky o-substituted aryl groups could be synthesized in moderate yields.

In 2012, Jiang described the Pd-catalyzed coupling reaction of phenylboronic acids with aryl(3-indolyl)methyl *p*-tolyl sulfones to give 3-indole-containing triarylmethanes (Scheme 3).[14] Although the use of sulfones as leaving groups in arylation reactions is rare,[15] it was found that *p*-tolyl sulfones bearing *p*-methyl, *p*-anisyl, and *p*-chloro groups reacted with phenylboronic acids to give products in good yields. The reaction is proposed to occur through the addition of a Pd−Ar group onto a vinylogous imine, which is generated in situ by base-promoted elimination of *p*-$TolSO_2H$.

Scheme 3. Pd-Catalyzed Arylation of Aryl(3-indolyl)methyl *p*-Tolyl Sulfones with Arylboronic Acids



Recently, our group developed the synthesis of completely unsymmetrical triarylmethanes employing methyl phenyl sulfone as a simple, inexpensive starting material.[16] Using two sequential Pd-catalyzed C−H arylations followed by a rare Pd−catalyzed arylative desulfonation, we were able to sequentially introduce three different aryl groups (Scheme 4). The key to preventing overarylation in the first step is the use of a bulky ligand and base. Remarkably, the use of LiO-*t*-Bu as the base for the first step was critical because no other base examined gave more than trace amounts of the desired monoarylated product.[17] The second arylation took place under conditions based on those developed by Yorimitsu/Oshima and Walsh.[17,18] For the final desulfonative arylation, the use of the N-heterocyclic carbene (NHC) SIPr as a ligand for Pd or the commercially available PEPPSI-IPr complex was necessary. The reaction gave high yields with electronically and structurally diverse arylboronic acids to afford a considerable variety of triarylmethanes. This transformation is distinct from the Pd-catalyzed C−SO_2 bond arylation described above, which required an electron-donating 3-indolyl substituent on the methyl group to assist the elimination of the sulfonyl group by an anionic rather than metal−catalyzed route (Scheme 3). To highlight the utility of the method, a concise five-step synthesis of an anti-breast cancer agent[19] was described.

2.1.2. C−H Arylation. Direct C−H bond functionalization has become one of the most fascinating topics in organic synthesis because it efficiently provides molecules from generally less reactive but simple and inexpensive substrates.[20] It can also minimize synthesis steps by eliminating the need to prepare reactive sites for bond formation, leading to robust synthesis methods for late-stage modification of target molecules.[21]

The Yorimitsu/Oshima group was the first to report triarylmethane synthesis through the Pd-catalyzed C−H arylation of aryl(azaaryl)methanes with arylhalides (Scheme 5).[22] The reaction was catalyzed by a $PdCl_2/PCy_3$ system to give triarylmethane products containing heteroarenes such as 2- and 4-pyridine, 2-quinoline, 2-benzoxazole, and 2-benzothiazole in good yields. The substrate reactivity seemed to be related to the acidity of the benzylic C−H bond: 2- and 4-benzylpyridine

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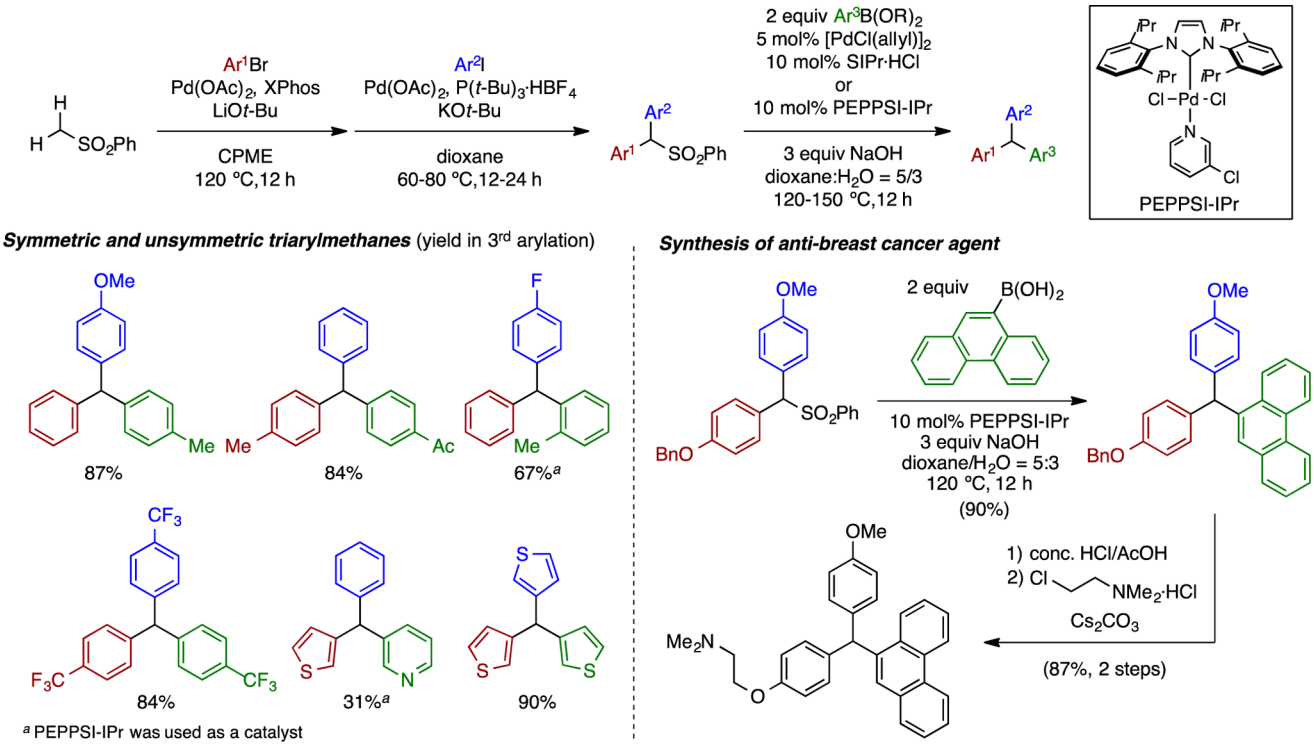
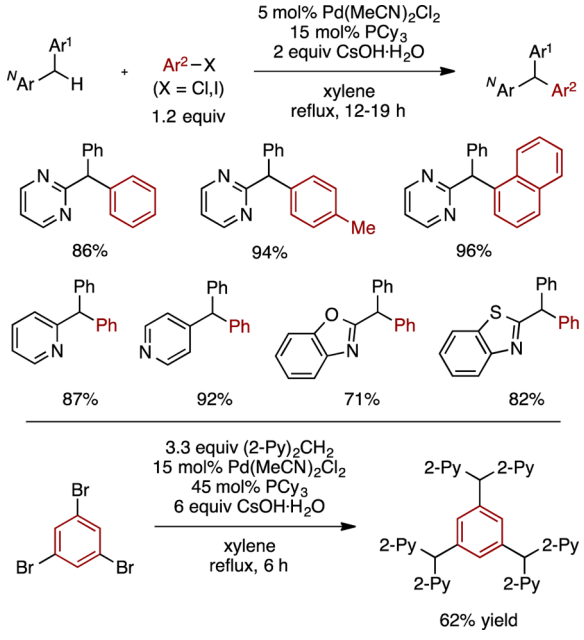
Scheme 4. Pd-Catalyzed Sequential Arylation of Methyl Phenyl Sulfone with Arylhalides and Arylboronic Acids[a]



[a]PEPPSI-IPr was used as a catalyst

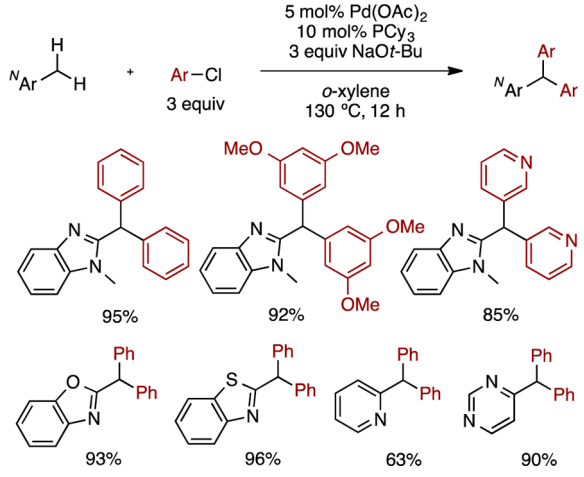
Scheme 5. Pd-Catalyzed C−H Arylation of Aryl(azaaryl)methanes with Arylhalides



having relatively more acidic C−H bonds (pK_a = 28.2, 26.7 in DMSO, respectively) reacted smoothly whereas 3-benzylpyridine and diphenylmethane (pK_a = 30.15, 32.2 in DMSO, respectively) resulted in no conversion.[23] The reaction with tribromobenzene as a coupling partner gave a highly azaarylated structure, which has interesting properties for coordination or supramolecular chemistry.

In 2011, Li reported the Pd-catalyzed sp^3 C−H diarylation of (2-azaaryl)methanes with chloroarenes (Scheme 6).[24] The

Scheme 6. Pd-Catalyzed C−H Diarylation of (2-Azaaryl)methanes with Chloroarenes



reaction proceeded smoothly with $Pd(OAc)_2/PCy_3$ as a catalyst and NaO-*t*-Bu as a base. Various types of (2-azaaryl)methanes, such as 1,2-dimethylbenzimizadole, 2-methylbenzoxazole, 2-methylbenzothiazole, 2-picoline, and 4-methylpyrimidine, were used, and the corresponding triarylmethanes were obtained in good to excellent yields. From theoretical studies, they proposed that this reaction may proceed via a palladium η^3-azaallylic intermediate formed through a metalation-assisted intramolecular deprotonation process. A downside of the method is that it is viable only for the introduction of two

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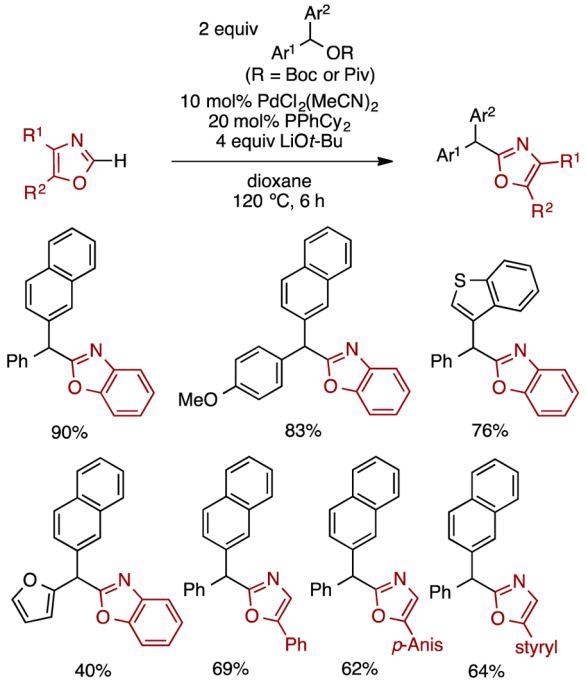
identical aryl groups because of the increased reactivity of the monoarylated intermediate.

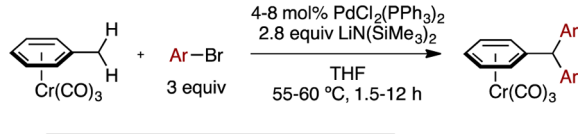
Recently, Hirano and Miura reported the C−H/C−O coupling of oxazoles and diarylmethyl carbonates or pivalates catalyzed by $PdCl_2(MeCN)_2/PPhCy_2$, resulting in the synthesis of azole-containing triarylmethanes (Scheme 7).[25] The reaction with benzoxazole or 5-substituted oxazoles gave a variety of unsymmetric triarylmethanes in good to excellent yields.

Scheme 7. Pd-Catalyzed C−H/C−O Coupling of Oxazoles and Diarylmethyl Carbonates or Pivalates



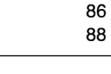
In 2010, Walsh reported the Pd-catalyzed direct C−H arylation of an $[(\eta^6\text{-toluene})Cr(CO)_3]$ complex with a variety of aryl bromides (Scheme 8).[26] $LiN(SiMe_3)_2$ was found to be

Scheme 8. Pd-Catalyzed Direct C−H Arylation of $[(\eta^6$-Toluene$)Cr(CO)_3]$ Complex with Aryl Bromides



Ar	yield (%)
C_6H_5	90
p-FC_6H_4	83
p-ClC_6H_4	78
p-t-BuC_6H_4	82
m-anisyl	86
o-MeC_6H_4	88

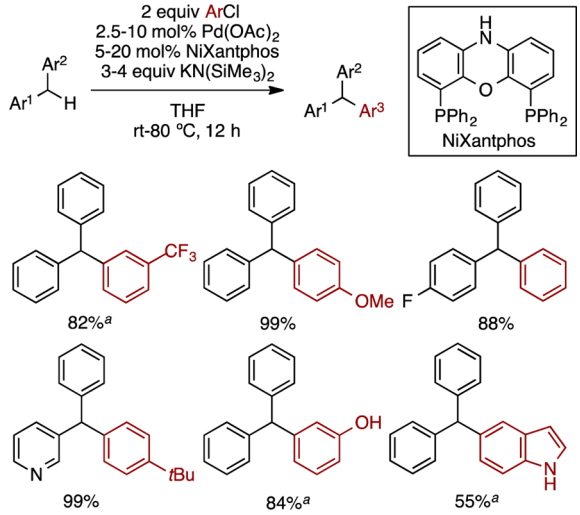
(Ar = *m*-anisyl)
hν
ether, 12 h
93% (*One-pot*)



an effective base because it can generate benzyllithium intermediates by deprotonation of benzylic protons activated by η^6-coordination of the arene to $Cr(CO)_3$. After Pd-catalyzed coupling of this deprotonated species, the resulting triarylmethane−$Cr(CO)_3$ complex was decomposed by exposure to air and light to give the triarylmethane in excellent yield. This is an effective strategy for the direct sp^3 C−H arylation of toluene activated by complexation of a catalytically inert transition metal.

After this initial report, Walsh and co-workers then established an efficient Pd-catalyzed system for direct sp^3 C−H arylation of diarylmethanes with bromo- and chloroarenes through a deprotonative cross-coupling process (Scheme 9).[27]

Scheme 9. Pd-Catalyzed Direct sp^3 C−H Arylation of Diarylmethanes with Chloroarenes[a]



[a] 1 equiv ofArCl and 1.2−3 equiv of diphenylmethane was used.

It is interesting to note that NiXantphos, which is a basic bidentate phosphine ligand, was critical for this arylation to occur. In addition, they demonstrated that the deprotonation followed by arylation of less acidic diarylmethanes could be affected with the use of $KN(SiMe_3)_2$. Under these conditions, a variety of symmetric and unsymmetric triarylmethanes could be prepared in good to excellent yields. Importantly, some sensitive functional groups bearing acidic O−H and N−H bonds could be introduced without protecting groups.

2.1.3. Reductive Coupling. In 2013, Wang reported a new synthesis approach to triarylmethanes involving a Pd-catalyzed reductive coupling process (Scheme 10).[28] The starting *N*-tosylhydrazones were prepared from the corresponding diarylketones and then reacted with aryl bromide in the presence of HCO_2NH_4 as a hydrogen source. The proposed reaction mechanism involves the formation of a Pd aryl carbene intermediate, which then undergoes aryl migration, followed by reductive elimination of a hydride from the formate anion. A variety of aryl groups bearing functional groups and heteroaryl groups can be introduced using this method.

2.2. Cu, Ni and Fe Catalysis. Catalytic carbon−carbon bond formation using naturally abundant transition metals, such as copper, nickel, and iron, as catalysts is an area of intense research.[29] In terms of triarylmethane synthesis, the Wang group developed Cu-catalyzed diarylmethylation of simple 1,3-azoles with *N*-tosylhydrazones (Scheme 11).[30] Under these conditions, benzoxazole and benzothiazole were reacted with various *N*-tosylhydrazone derivatives, yielding triarylmethanes in moderate to good yields. They also found that LiO*t*-Bu as a base was an effective promoter of this reaction.

In 2014, the Fu group reported the Cu-catalyzed Suzuki−Miyaura cross-coupling of benzhydryl halides with arylboronates to afford the corresponding triarylmethanes (Scheme

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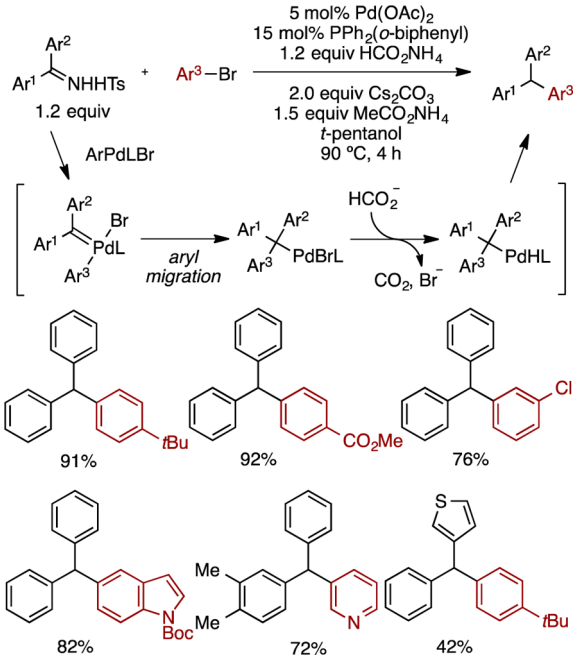
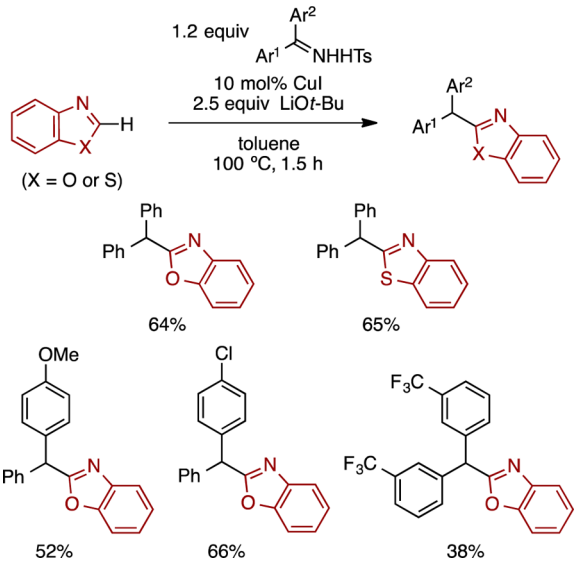
Scheme 10. Pd-Catalyzed Reductive Coupling of *N*-Tosylhydrazone with Arylbromides

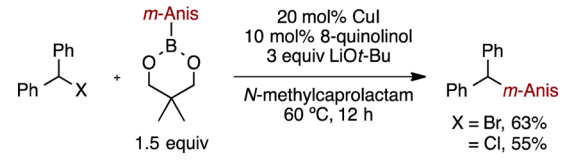


Scheme 11. Cu-Catalyzed Diarylmethylation of 1,3-Azoles with *N*-Tosylhydrazones



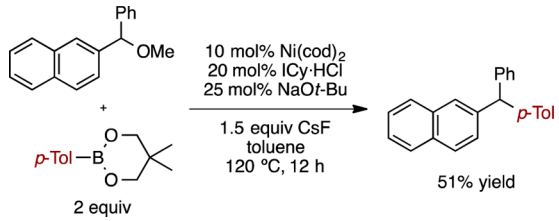
12).[31] The reaction of diphenylmethyl chloride or bromide with 3-methoxyphenylboronate took place in *N*-methylcaprolactam as solvent at 60 °C with the use of CuI and 8-quinolinol as catalyst and LiO*t*-Bu as the base.

Scheme 12. Cu-Catalyzed Suzuki−Miyaura Cross-Coupling of Benzhydryl Halides with Arylboronate



Tobisu and Chatani have developed cross-coupling reactions of methyl ethers with arylboron reagents that occur through cleavage of strong C(sp^2)−OMe bonds, followed by arylation with Ni catalysts.[32] The ready availability of the methoxy group and its high stability make this transformation truly remarkable. In a follow-up report, the use of 1,3-dicyclohexylimidazol-2-ylidene (ICy) as a ligand was described, promoting the arylation of benzylic C(sp^3)−OMe bonds with arylboronates (Scheme 13).[33] This method also boasts broadened substrate

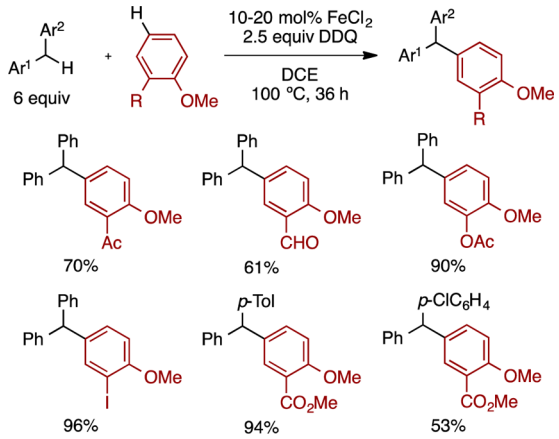
Scheme 13. Ni-Catalyzed Cross-Coupling of Diarylmethyl Methyl Ether with *p*-Tolylboronic Ester



scope compared with previous C(sp^2)−OMe bond arylation reactions. The Ni-catalyzed reaction of (2-naphthyl)-phenylmethyl methyl ether with 2-(*p*-tolyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane gave the triarylmethane in 51% yield.

In 2009, Shi discovered that $FeCl_2$ could catalyze the dehydrogenative cross-coupling of diarylmethanes with anisole derivatives under oxidative conditions (Scheme 14).[34] The use

Scheme 14. $FeCl_2$-Catalyzed Dehydrogenative Cross-Coupling of Diarylmethanes with Anisole Derivatives



of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) as an oxidant was critical for this transformation. Interestingly, other transition metal salts, such as Pd, Ni, and Cu salts, were less effective. Anisole substrates having *o*-ester, ketone, acetoxy, aldehyde, and halides were all smoothly reacted at the para position to give a single regioisomeric product.

3. SYNTHESIS OF ENANTIOMERICALLY ENRICHED TRIARYLMETHANES BY TRANSITION METAL CATALYSIS

As described above, various cross-coupling approaches to achiral triarylmethanes have been developed within the past decade; however, there are still relatively few examples of the synthesis of chiral, enantiomerically enriched triarylmethanes.

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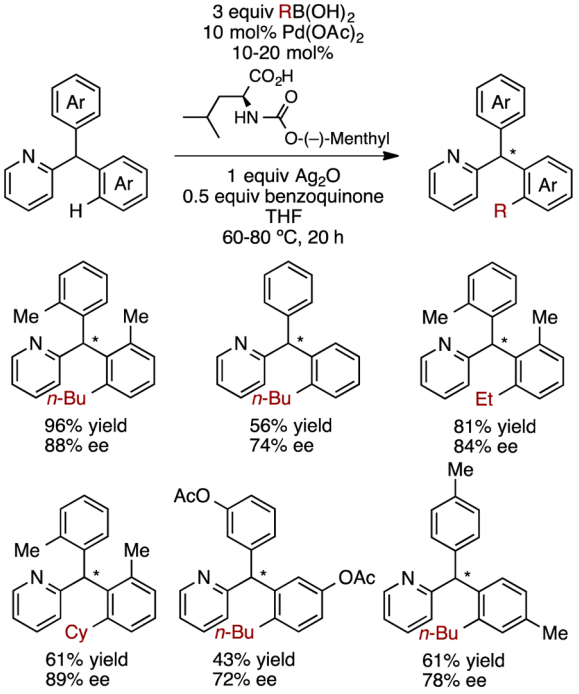
Yu reported the first transition metal-catalyzed enantioselective synthesis of triarylmethanes in 2008.[35] Specifically, diaryl(2-pyridyl)methanes were alkylated selectively at one of the two aryl substituents using $Pd(OAc)_2$ and a chiral amino acid derivative as a ligand (Scheme 15). The interesting

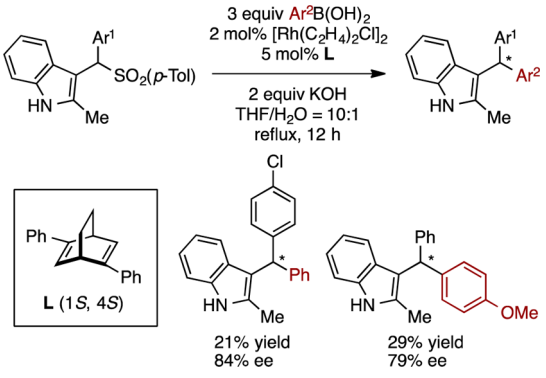
Scheme 15. Pd-Catalyzed Enantioselective Alkylation of Diaryl(2-pyridyl)methanes with Alkylboronic Acids



enantio-group-selective C−H activation followed by C−C coupling enables the installation of alkyl groups such as ethyl, *n*-butyl, and cyclohexyl groups in place of C−H bonds at the o-position of one of the aryl groups with good yield and enantioselectivity. Although ground-breaking, this reaction does require a pyridyl group to direct the C−H activation, and the need for the other two aryl groups to be identical for the group-selective C−H activation to take place, which limits the number of structures that can be prepared by this route.

Jiang and Zhou reported a Rh-catalyzed addition of arylboronic acids to vinylogous imines generated in situ from aryl(3-indolyl)methyl *p*-tolyl sulfones (Scheme 16).[36] In this

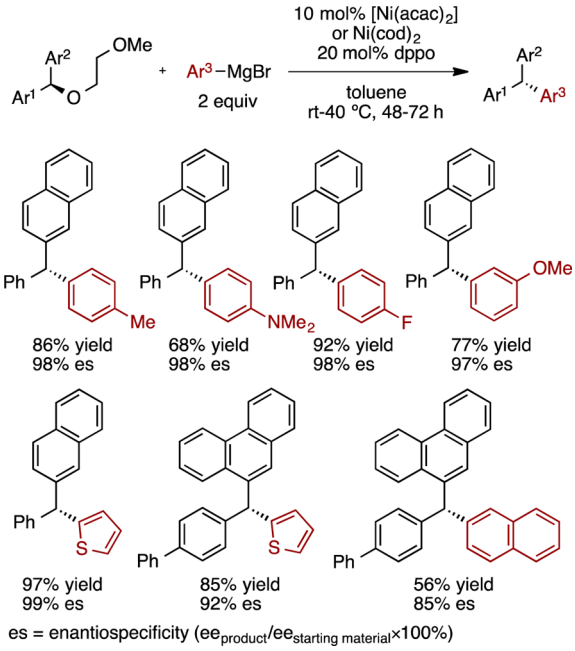
Scheme 16. Rh-Catalyzed Enantioselective Arylation of Aryl(3-indolyl)methyl *p*-Tolyl Sulfones with Arylboronic Acids



report, they demonstrated that the use of a catalytic amount of $[Rh(CH_2CH_2)Cl]_2$ with Hayashi's chiral diene ligand **L** afforded chiral 3-indole-containing triarylmethanes in low yield with moderate enantiomeric excess. For mechanistic reasons described above (Scheme 3),[14] the indole substituent is an essential part of this transformation.

In 2012, Jarvo developed an enantiospecific approach to chiral triarylmethanes through Ni-catalyzed cross-coupling reaction of chiral diarylmethanol derivatives with aryl Grignard reagents that has much improved substrate scope (Scheme 17).[37] To facilitate the cleavage of relatively inert C−O bonds

Scheme 17. Ni-Catalyzed Enantiospecific Cross-Coupling Reaction of Chiral Diarylmethanol Derivatives with Aryl Grignard Reagents



by the Ni catalyst, a chelating methoxyethyl group was employed. Using this method, various aryl and heteroarylmagnesium bromides could be reacted using 1,8-bis-(diphenylphosphino)octane (dppo) as the ligand to give enantioenriched triarylmethanes with excellent yields and enantiospecificities. The presence of a π-extended aromatic substituent (naphthyl or phenanthyl) as part of the electrophile structure is essential and likely points to the intermediacy of π-naphthyl or π-phenanthryl Ni species.

Diarylmethyl carbamates were also shown to be effective partners for the Ni-catalyzed coupling with arylboronic esters (Scheme 18).[38] Remarkably, the stereochemical course in this enantiospecific reaction was switched by simply changing the achiral ligand on Ni; PCy_3–ligated catalysts proceeded with retention, whereas SIMes as a ligand resulted in inversion of configuration. A broad range of functionalized arylboronic acids were used under these reaction conditions, providing either enantiomer of the corresponding product in good to excellent yields and enantiospecificities. As above, the electrophile features at least one π-extended aromatic.

At almost exactly the same time as Jarvo's report, the Ni-catalyzed stereospecific cross-coupling of (2-naphthyl)-phenylmethyl pivalates with arylboroxines was reported by the Watson group (Scheme 19).[39a] In this reaction,

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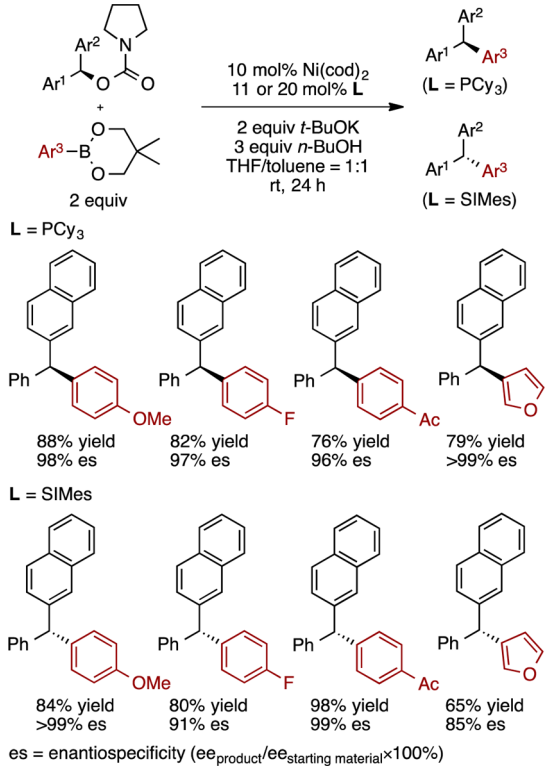
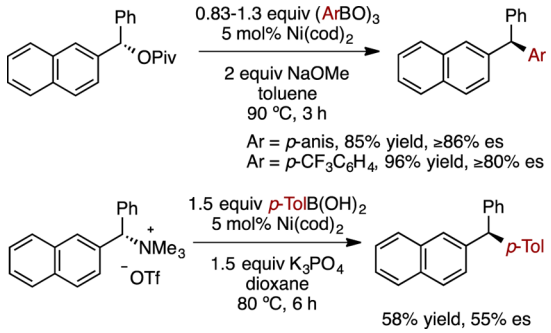
Scheme 18. Ni-Catalyzed Enantiospecific Cross-Coupling of Diarylmethyl Carbamates with Arylboronic Esters



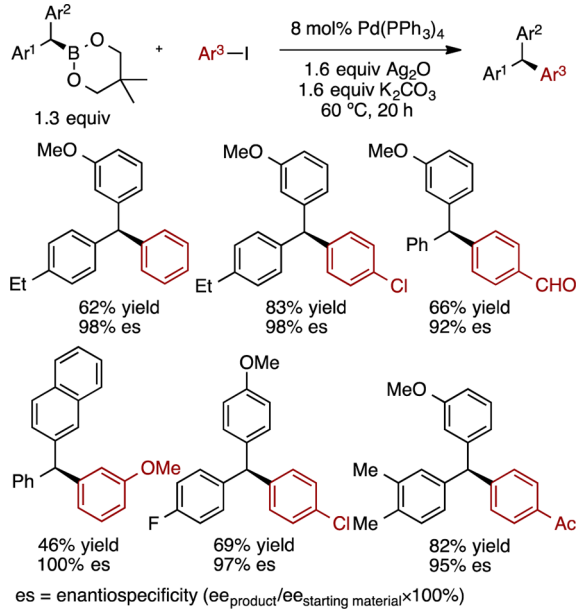
Scheme 19. Ni-Catalyzed Stereospecific Cross-Coupling of (2-Naphthyl)phenylmethyl Pivalate and Ammonium Triflate with Arylboronic Acids



arylboroxines bearing electron-donating and -withdrawing substituents were well-tolerated, giving good yields and enantiospecificities. In 2014, they also reported a similar Ni-catalyzed cross-coupling of diarylmethylammonium triflate to afford triarylmethanes with moderate enantiospecificity.[39b]

Our group has developed an enantiospecific Pd-catalyzed Suzuki–Miyaura cross-coupling reaction of chiral secondary organoboronates with aryl iodides to afford chiral diarylmethanes.[40] Recently, we successfully applied this enantiospecific Pd-catalyzed reaction strategy to the synthesis of enantiomerically enriched triarylmethanes with typically high and up to 100% enantiospecificity (Scheme 20).[41] The starting organoboronic esters were prepared using enantioselective lithiation of the corresponding benzylic carbamates and trapping with boronic esters.[42] For this reaction, to proceed with high enantioselectivity, the use of neopentyl boronic esters was shown to be essential. In the coupling of these substrates,

Scheme 20. Pd-Catalyzed Stereospecific Cross-Coupling of Diarylmethyl Boronic Esters with Aryliodides



functional groups such as chloro, acetyl, and formyl groups on aryl rings were tolerated, which could facilitate further derivatization of chiral triarylmethanes for the discovery of new bioactive molecules.

4. SUMMARY

Over just a few years, there has been remarkable progress in the development of transition metal-catalyzed routes for the synthesis of triarylmethanes. These new cross-coupling reactions provide highly functionalized triarymethanes in good yields. Some reactions involve new methods for the activation of inert bonds, including C–O, C–SO_2, and C–H bonds, significantly contributing to simplifying synthesis routes as well as minimizing synthesis steps. Thus, these methods will facilitate the preparation of new triarylmethane-based materials and pharmaceuticals from readily available substrates. In addition, new routes to enantioenriched triarylmethanes have been developed via enantioselective or enantiospecific reactions. Considering the importance of chirality in medicinal chemistry, molecules bearing unique chiral sp^3 carbon centers will reveal interesting opportunities to develop new drug candidates and biomolecules.

Despite these advances, further efforts toward the development of new methods for chiral triarylmethanes are needed. The appearance of new catalysts and chemical transformations is expected to provide avenues for the synthesis of unexplored triarylmethanes, leading to the discovery of new chemical and physical properties and biological activities.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

Xantphos, 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene; *p*-Tol, *p*-tolyl; DMSO, dimethyl sulfoxide; SIMes, 1,3-bis-(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene

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