

University of Warsaw  
Faculty of Chemistry

Kacper Szczepański  
Student number: 407675

# Synthesis of triaryl phosphines and phosphine oxides by metal-free *P*-arylation with diaryliodonium salts

Master thesis  
in the field of studies Chemistry

Thesis done under the supervision of  
Marcin Kałek, PhD, D.Sc.  
and under the guidance of  
Robert S. Yafele, M.Sc.  
Laboratory of Chemical Synthesis Methodology  
Centre of New Technologies  
University of Warsaw

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## Abstract

Triarylphosphines and phosphine oxides are one of the most important classes of organophosphorus compounds. They are widely used in homogenous catalysis in various transformations as organocatalysts and ligands for transition metal-catalysts. Unfortunately, the majority of methods for their synthesis suffer from low functional group tolerance, harsh conditions, or high price and toxicity of employed reagents. The most general existing entry to triarylphosphines is the transition metal-catalyzed cross-coupling, however, it creates the issue of purification of the products from trace metal residues, which may pose problem in downstream applications. Thus, the development of novel methods for the preparation of triarylphosphines under mild and metal-free conditions remains an important research objective.

In this thesis, a promising alternative to the transition metal-catalyzed cross-coupling for the P–Ar bond-formation, namely the use of hypervalent iodine reagents, is explored. Iodine is orders of magnitude cheaper than platinum and palladium, less toxic and purification does not pose such problems as in the TM-catalyzed processes. In particular, diaryliodonium salts, known group-transfer reagents whose reactivity pattern resembles that of TM-complexes, are used for the synthesis of tertiary phosphine oxides by a direct P-arylation of secondary phosphines, followed by an *in situ* oxidation. The optimization of the reaction conditions was performed and subsequently the scope and limitations of the method were examined. The developed methodology was successfully used in the synthesis of 14 triarylphosphine oxides.

### **Keywords**

synthetic methodology, phosphines, phosphine oxides, diaryliodonium salts, hypervalent iodine, arylation, metal-free cross-coupling

### **Field of Science**

13.3 chemistry

### **Thesis title in polish**

Synteza triarylofosfin i tlenków fosfin poprzez *P*-arylowanie z użyciem soli diaryliodonowych bez użycia związków metali

## Streszczenie

Triarylofosfiny i tlenki fosfiny są jednymi z najważniejszych klas związków fosforoorganicznych. Są one szeroko stosowane w katalizie homogenicznej w różnorodnych transformacjach jako organokatalizatory i ligandy dla katalizatorów opartych o metale przejściowe. Niestety, większość metod ich syntezy obarczona jest niską tolerancją grup funkcyjnych, trudnymi warunkami lub wysokimi kosztami i toksycznością stosowanych reagentów. Najbardziej ogólnym istniejącym podejściem do syntezy triarylofosfin jest sprzęganie krzyżowe katalizowane metalami przejściowymi, jednak stwarza to problem oczyszczania produktów ze śladowych pozostałości metalu, co może stanowić problem w dalszych zastosowaniach. Stąd opracowanie nowych metod otrzymywania triarylofosfin w łagodnych i wolnych od metali warunkach pozostaje ważnym celem badawczym.

W niniejszej pracy badana jest obiecująca alternatywa dla katalizowanych przez metale przejściowe reakcji sprzęgania tworzących wiązanie P–Ar, mianowicie zastosowanie związków hiperwalencyjnego jodu. Jod jest o rzędy wielkości tańszy niż platyna i pallad, mniej toksyczny, a oczyszczanie produktów nie stwarza takich problemów jak w procesach katalizowanych przez metale przejściowe. W szczególności wykorzystano sole diarylodoniowe, znane odczynniki aryłujące wykazujące reaktywność podobną do tej cechującej kompleksy metali przejściowych, do syntezy trzeciorzędowych tlenków fosfiny poprzez bezpośrednią P-arylację drugorzędowych fosfin, a następnie utlenianie *in situ*. Przeprowadzono optymalizację warunków prowadzenia reakcji, a następnie zbadano jej zakres stosowalności i ograniczenia. Opracowana metodologia została z powodzeniem wykorzystana do syntezy 14 tlenków trzeciorzędowych fosfin.

### **Słowa kluczowe**

metodologia syntetyczna, fosfiny, tlenki fosfin, sole diarylojodoniowe, jod hiperwalencyjny, arylowanie, sprzęgania krzyżowe bez użycia metali

### **Dziedzina pracy**

13.3 chemia

### **Tytuł pracy w języku angielskim**

Synthesis of triaryl phosphines and phosphine oxides by metal-free P-arylation with diaryliodonium salts

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## Abbreviations

<b>2c-1e</b>	Two-center one-electron
<b>2c-2e</b>	Two-center two-electron
<b>3c-2e</b>	Three-center two-electron
<b>3c-4e</b>	Three-center four-electron
<b>AIBN</b>	Azobisisobutyronitrile
<b>BINAP</b>	([1,1'-Binaphthalene]-2,2'-diyl)bis(diphenylphosphane)
<b>DABCO</b>	1,4-Diazabicyclo[2.2.2]octane (triethylenediamine)
<b>DBN</b>	1,5-Diazabicyclo[4.3.0]non-5-ene (diazabicyclononene)
<b>DBU</b>	1,8-Diazabicyclo[5.4.0]undec-7-ene (diazabicycloundecene)
<b>DCE</b>	1,2-Dichloroethane
<b>DCM</b>	Dichloromethane
<b>DIBAL-H</b>	Diisobutylaluminium hydride
<b>DIPAMP</b>	(Ethane-1,2-diyl)bis[(2-methoxyphenyl)(phenyl)phosphane]
<b>DIPEA</b>	<i>N,N</i> -Diisopropylethylamine
<b>DMF</b>	<i>N,N</i> -Dimethylformamide
<b>DMP</b>	Dess-Martin periodinane
<b>DMSO</b>	Dimethyl sulfoxide
<b>DPPO</b>	Diphenylphosphine oxide
<b>HBpin</b>	Pinacolborane
<b>HFIP</b>	1,1,1,3,3,3-Hexafluoroisopropanol
<b>IBX</b>	2-Iodoxybenzoic acid
<b>MBH</b>	Morita–Baylis–Hillman (reaction)
<b><i>m</i>CPBA</b>	<i>meta</i> -Chloroperoxybenzoic acid
<b>MTBE</b>	Methyl <i>tert</i> -Butyl ether
<b>Ns</b>	<i>p</i> -Nitrobenzenesulfonyl group
<b>SET</b>	Single electron transfer
<b>SPO</b>	Secondary phosphine oxide
<b>TEA</b>	Triethylamine

<b>TEMPO</b>	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
<b>TFA</b>	Trifluoroacetic acid
<b>TfOH</b>	Trifluoromethanesulfonic acid
<b>THF</b>	Tetrahydrofuran
<b>TMEDA</b>	Tetramethylethylenediamine
<b>TMG</b>	<i>N,N,N,N</i> -Tetramethylguanidine
<b>TMS</b>	Trimethylsilyl group
<b>TPO</b>	Tertiary phosphine oxide
<b>TPPO</b>	Triphenylphosphine oxide
<b>TS</b>	Transition state
<b>TsOH</b>	<i>p</i> -Toluenesulfonic acid



# Chapter 1. Survey of literature

## 1.1. Phosphines and phosphine oxides

Organophosphorus compounds (Fig. 1) are widespread in nature and commonly used in chemistry, industry, and medicine. Phosphorus is the sixth most common element in human body and it is essential for life. In particular, phosphate esters are present in numerous types of biomolecules, such as nucleic acids, phosphoproteins, glycosides, phospholipids. Not surprisingly, many organophosphorus compounds are bioactive but because of their use as pesticides and nerve agents, they are somewhat infamous. However, a huge number of these compounds have medicinal properties and serve in the treatment of osteoporosis (bisphosphonates), as antibiotics, antiviral and anticancer agents, as well as enzyme inhibitors<sup>[1]</sup>. In industry, organophosphorus compounds are used as stabilizers, antioxidants, flame retardants, plasticizers, and plastic additives. In synthetic chemistry, they are valuable ligands and organocatalysts<sup>[2]</sup>.

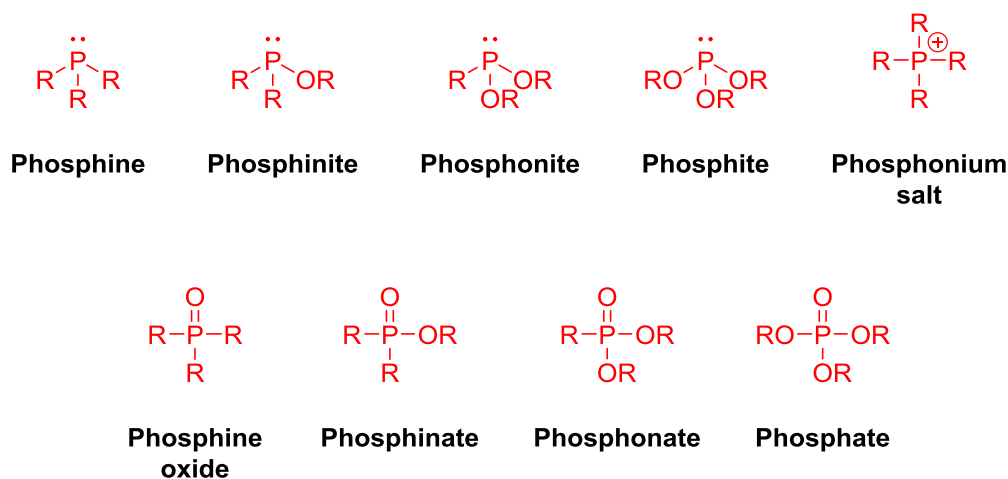


Fig. 1. Selected classes of organophosphorus compounds.

Phosphines are a class of organophosphorus(III) compounds. The term refers to parent hydride PH<sub>3</sub> (phosphine) and compounds derived from it by substituting hydrogen atoms by hydrocarbyl groups represented by RPH<sub>2</sub>, R<sub>2</sub>PH and R<sub>3</sub>P formulas that refer to primary, secondary, and tertiary phosphines, respectively. Most of phosphines are susceptible to air and spontaneously oxidize to phosphine oxides which are class of organophosphorus(V) compounds, having the generic formula R<sub>3</sub>P=O ↔ R<sub>3</sub>P<sup>+</sup>-O<sup>-</sup> [3, 4].

Primary and secondary phosphines are often pyrophoric compounds. Tertiary phosphines with aliphatic substitution are lipophilic, malodorous, generally toxic, colourless liquids, whereas triarylphosphines are generally solid. Triarylphosphines display greater

resistance towards aerial oxidation, but as most of phosphines are air-sensitive. Similarly to amines, phosphines have trigonal pyramidal structure, but due to the larger energy barrier of inversion, phosphines have fixed geometry. Thus, phosphines with three different substituents are optically active<sup>[5, 6]</sup>.

Primary phosphine oxides are unstable and disproportionate unless a substituent stabilizes molecule by steric bulk. Secondary and tertiary phosphine oxides are generally crystalline, colourless, and odorless substances, stable at room temperature and of low toxicity. Secondary oxides disproportionate to phosphinic acid and phosphine at high temperatures. Phosphine oxides are highly polar, which helps with separation of phosphines and their oxides after reduction or oxidation. Some display high solubility in water<sup>[2, 5]</sup>. Due to a relatively easy deprotonation of the P–H bond, secondary phosphine oxides can undergo addition to carbonyl compounds, isocyanates, C–C multiple bonds, and serve as nucleophiles in cross-coupling reactions<sup>[7]</sup>.

The range of phosphine applications is wide, both on the laboratory and industrial scale. There are numerous phosphine-promoted processes such as the Wittig, Mitsunobu, Staudinger, and Appel reactions and phosphine-catalyzed ones, such as the MBH, Michael, Rauhut-Currier, and Henry reactions. Catalytic variants of these also exist, as well as numerous types of annulation reactions<sup>[8, 9]</sup>. Phosphines are used in homogenous catalysis in their own right (as organocatalysts) and phosphine complexes with transition metals have been applied in organometallic catalysis for a wide range of transformations. Some of such complexes also exhibit therapeutical properties<sup>[5, 10, 11]</sup>. Main fields of applications of phosphine oxides are also organocatalysis and transition metal-catalysis (as ligands).

### **1.1.1. Applications**

#### **1.1.1.1. Transition metal-catalysis**

The importance of transition metal homogeneous catalysis is best illustrated by the award of as many as three Nobel Prizes in chemistry: “for [...] work on chirally catalysed hydrogenation reactions” (2001)<sup>[12]</sup>, “for the development of the metathesis method in organic synthesis” (2005)<sup>[13]</sup> and “for palladium-catalyzed cross couplings in organic synthesis” (2010)<sup>[14]</sup>. In all the above cases, phosphines were employed as ligands in the complexes used for the catalysis.

Reppe and Schweckendiek were the first to apply metal-phosphine complexes in homogenous catalysis in 1948. They discovered promising catalytic properties of metal-phosphine complexes during the development of catalysts for acrylic ester synthesis from acetylene, carbon oxide, and alcohols. The application of triphenylphosphine nickel carbonyl

complexes in catalytic cyclization of acetylene to benzene, its monosubstituted derivatives to benzene derivatives, and propargyl alcohol to mesitylene and pseudocumene allowed these processes to be carried out under much milder conditions in terms of temperature and pressure<sup>[15, 16]</sup>.

Wilkinson (1973 Nobel laureate in Chemistry) and coworkers developed in late 1960s rhodium-based catalyst for alkene hydrogenation under mild conditions<sup>[16, 17]</sup>. This type of reactions, mediated by chlorotris(triphenylphosphine)rhodium(I) [RhCl(PPh<sub>3</sub>)<sub>3</sub>] (Wilkinson's catalyst), proceed stereospecifically under mild conditions and do not reduce aromatic compounds, ketones, carboxylic acids, amides, esters, nitriles, or nitro compounds. This have been successfully exploited to effect chemo-, regio-, and stereoselective alkene reductions in many organic syntheses. Wilkinson's catalyst also promotes many other transformations including hydro-silylations, -stannylations, -acylations, -formylations, hydroborations, decarbonylations, coupling reactions, and other<sup>[18]</sup>.

Just two years later, Knowles started to modify rhodium-based catalysts with chiral phosphines. In his first paper on this subject, he reported the hydrogenation of 2-phenylacrylic acid in the presence of trichlorotris(methylpropylphenylphosphine)rhodium(III) [RhCl<sub>3</sub>(\*PPhMePr)<sub>3</sub>] catalysts with modest 15% ee<sup>[19]</sup>. During his further work on transition metal catalyzed asymmetric hydrogenation, he obtained several amino acids with improved enantioselectivity, up to 96% ee and switched to diphosphine ligands, such as (*R,R*)-DIPAMP (Fig. 2) applied in *L*-DOPA synthesis<sup>[19-21]</sup>, which is used in treatment of Parkinson's disease. Also, Ryoji Noyori has made significant contribution to the area of chiral phosphine ligands, by developing BINAP (Fig. 2)<sup>[22-25]</sup> and using it for the asymmetric hydrogenation of ketones with Ru complexes<sup>[26, 27]</sup>, currently known as Noyori asymmetric hydrogenation. This methodology has applied in industrial synthesis of several pharmaceuticals<sup>[28]</sup>. Knowles and Noyori shared the Nobel Prize in Chemistry in 2001 for their work on catalytic asymmetric hydrogenation reactions<sup>[12]</sup> (Barry Sharpless being the third awardee for the development of asymmetric metal-catalyzed oxidations).

When discussing homogeneous transition metal catalysis, one cannot fail to mention the cross-coupling reactions. In the late 1950s and 1960s numerous researchers obtained products of oxidative addition of halocarbons to complexes of transition metals such as platinum<sup>[29-31]</sup>, palladium<sup>[32, 33]</sup> and nickel<sup>[34]</sup>. This works allowed improvement to Heck's methodology from 1968, when he reported, in several articles, a reaction of organomercury compounds with alkenes in the presence of catalytic amounts of Li<sub>2</sub>[PdCl<sub>4</sub>]. In the early 1970s Mizoroki<sup>[35, 36]</sup> and Heck<sup>[37-39]</sup> independently reported a reaction of halides (mainly aryl halides) with alkenes catalyzed by palladium compounds now known as Mizoroki-Heck

reaction. Mizoroki used palladium(II) chloride as the catalyst and Heck initially applied palladium(II) acetate, but later switched to palladium-phosphine complexes, mainly  $[\text{PdX}_2(\text{PPh}_3)_2]$ .

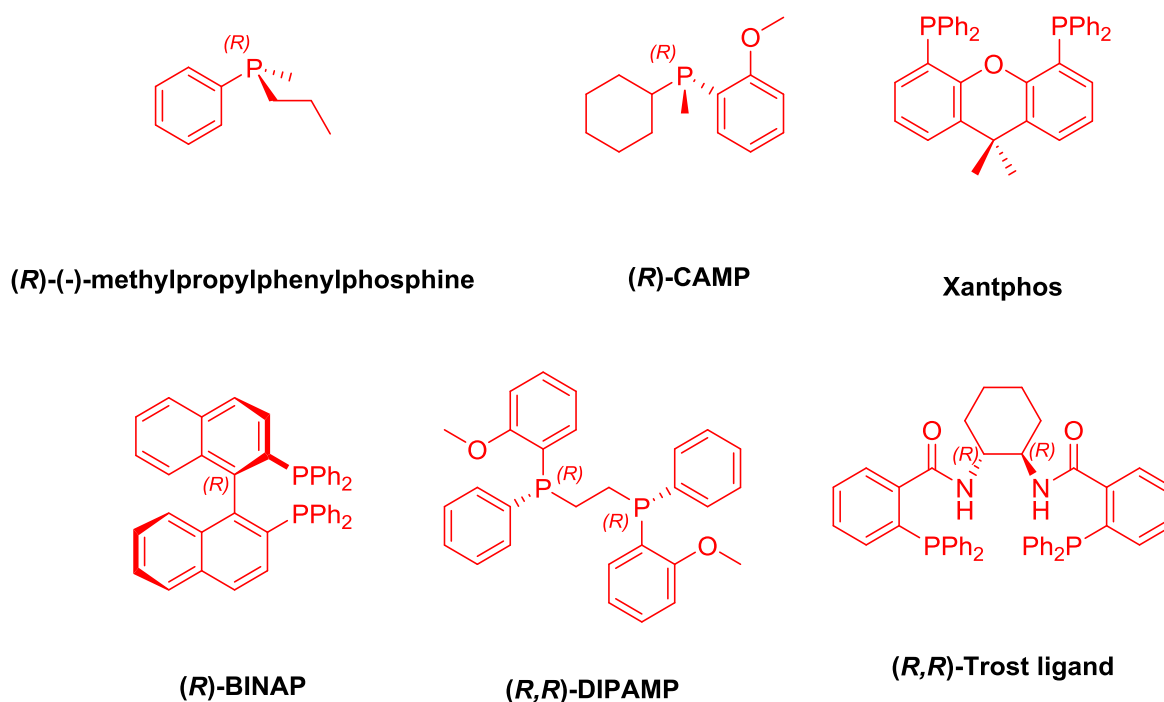
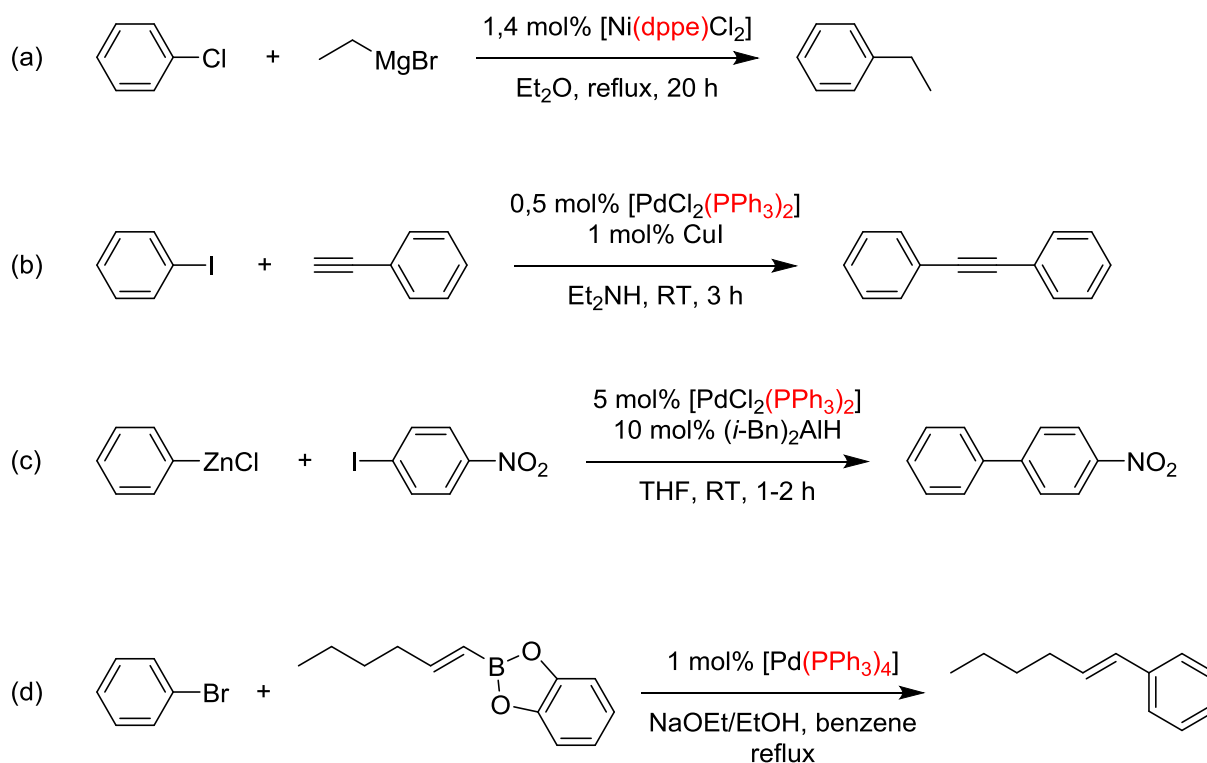


Fig. 2. Selected phosphine-based ligands.

Negishi in the late 1970s reported that organoaluminum<sup>[40]</sup> and organozinc<sup>[41, 42]</sup> reagents are suitable coupling partners and that the reaction proceeds in presence of palladium or nickel complexes, however latter exhibit stereospecificity deterioration in conjugated dienes synthesis. Reaction of organozinc compounds was the first that allowed the synthesis of unsymmetrical biaryls in good yields and it is now known as the Negishi coupling (Fig. 3 c). By this discovery, Negishi and coworkers proved that magnesium and lithium can be replaced with other metals and they carried out a screening of organometallic reagents. In result they achieved successful coupling of alkenes with zinc-, boron- and tin-based reagents<sup>[43, 44]</sup>.

Later Suzuki and Miyaura developed cross-coupling based on boranes and catalytic amounts of tetrakis(triphenylphosphine)palladium(0)  $[\text{Pd}(\text{PPh}_3)_4]$  (Fig. 3 d)<sup>[45]</sup>. The advantages of their reaction include air and moisture stable boranes as starting materials, mild reaction conditions, and facile removal of less-toxic inorganic byproducts, which made it especially useful for industrial applications<sup>[43]</sup>. Heck, Negishi, and Suzuki shared the Nobel Prize in Chemistry in 2010 for developing the palladium-catalyzed cross-couplings in organic synthesis<sup>[14]</sup>.



**Fig. 3.** Selected cross-coupling reactions: (a) Kumada (1972), (b) Sonogashira (1975), (c) Negishi (1977), Suzuki and Miyaura (1979)

Phosphine ligands were also involved in olefin metathesis. In the 1990s Grubbs (2005 Nobel Prize laureate) and coworkers presented ruthenium alkylidene  $[\text{Ru}(=\text{CHR})\text{L}_2\text{X}_2]$  complexes with  $\text{PPh}_3$  and  $\text{PCy}_3$  as ligands, which catalyze olefin metathesis. Triphenylphosphine was used initially, later replaced with tricyclohexylphosphine, which increased the catalytic activity of  $[\text{Ru}(=\text{CHPh})\text{Cl}_2(\text{PCy}_3)_2]$  complex, now known as the first-generation Grubbs catalyst. These complexes are less active than Schrock molybdenum catalysts, but their main advantages are robustness and wider functional group tolerance<sup>[46]</sup>. Soon the research groups of Nolan<sup>[47]</sup>, Grubbs<sup>[48]</sup>, Herrmann, and Fürstner<sup>[49]</sup> independently reported ruthenium-based catalysts with *N*-heterocyclic carbene (NHC) ligands. Substitution of one of the phosphine ligands with a bulky NHC ligand IMes led to a complex (second-generation Grubbs catalyst), which displays improved catalytic activity, maintaining the high functional group tolerance and thermal stability of original catalyst. Latter can be further improved if the second phosphine ligand is replaced with bidentate alkylidene, in accordance to Hoveyda modifications (second-generation Grubbs-Hoveyda catalyst)<sup>[50]</sup>. This further development in metathesis catalysis left phosphines as obsolete ligands in that field and the current main application of first-generation Grubbs catalyst is as the precursor to new generations of catalysts.

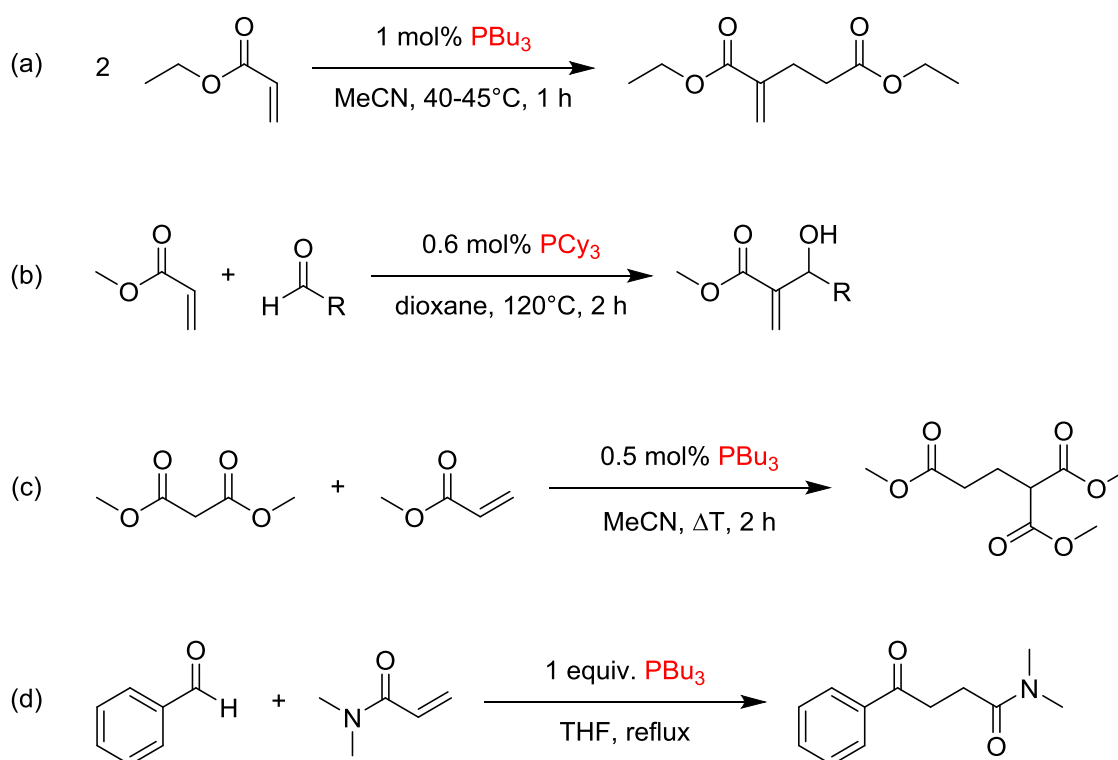
### 1.1.1.2. Organocatalysis and related topics

Late 1950s and early 1960s are marked by the thalidomide disaster – the sedative drug that turned out to be teratogenic<sup>[51, 52]</sup>. Concerns about safety, further regulation of pharmaceutical industry, and greater emphasis on clinical trials and the demonstration of drug effectiveness have increased the demand for asymmetric synthesis methods. In the following decades, transition metal catalysts dominated the area and, apart from enzymes, were basically only the tools for asymmetric catalysis till the eve of the 21st century, when asymmetric organocatalysis has emerged and caught the attention of researchers with List's report on proline-catalyzed aldol reaction<sup>[53]</sup> and MacMillan's amine-catalyzed enantioselective Diels-Alder cycloaddition<sup>[54]</sup>. They received Nobel prize in 2021 for the development of asymmetric organocatalysis<sup>[55]</sup>.

In addition to well recognized chiral amines, phosphoric acids, and thiourea catalysts, phosphines also play important role in (asymmetric) organocatalysis. One of the first examples of phosphine organocatalysis was Rauhut-Currier reaction reported in 1963 (Fig. 4 a)<sup>[56]</sup>. Tributylphosphine catalyzed the dimerization of ethyl acrylate to diethyl 2-methyleneglutarate. Five years later, Morita reported a similar reaction of acrylonitrile and methyl acrylate with various aldehydes, catalyzed by tricyclohexylphosphine (Morita-Baylis-Hillman reaction, Fig. 4 b)<sup>[57]</sup>. Phosphines were reported to catalyze Michael addition by White and Baizer in 1973 (Fig. 4 c)<sup>[58]</sup>, and Stetter reaction in 2002 (Fig. 4 d)<sup>[59]</sup>. They also promote Staudinger<sup>[60]</sup>, Wittig<sup>[61]</sup>, Mitsunobu<sup>[62]</sup>, and Appel<sup>[63]</sup> reactions yielding corresponding phosphine oxide as the byproduct. The catalytic variants of these reactions have also been developed. Phosphines also catalyze numerous annulations, ring openings, and other reactions of different alkene, allene, alkyne electrophiles, and MBH alcohol derivatives (MBHADs)<sup>[9]</sup>.

First reports on chiral phosphine-catalyzed enantioselective reactions appeared at the beginning of intensive research of asymmetric organocatalysis in 1990s. Vedejs and coworkers reported the asymmetric acylation of alcohols (Fig. 5 a)<sup>[64]</sup>, Kenso Soai and coworkers – enantioselective Morita-Baylis-Hillman reaction (Fig. 5 b)<sup>[65]</sup> and a chiral phosphine-catalyzed  $\gamma$ -Umpolung was presented by Xumu Zhang and coworkers (Fig. 5 c)<sup>[66]</sup>. In 2011, Xin-Yan Wu and coworkers presented their results on enantioselective Rauhut-Currier reaction catalyzed by chiral phosphinothiourea (Fig. 5 d)<sup>[67]</sup>. Phosphine-catalyzed enantioselective Michael addition was reported in 2012 by San N. Khong and Ohyun Kwon. They synthesized indoline derivatives in double-Michael reaction catalyzed by chiral amino-phosphines, however, with poor enantioselectivity (<10% ee)<sup>[68]</sup>. Shortly later Yixin Lu and coworkers presented their work on asymmetric Michael addition of 3-substituted

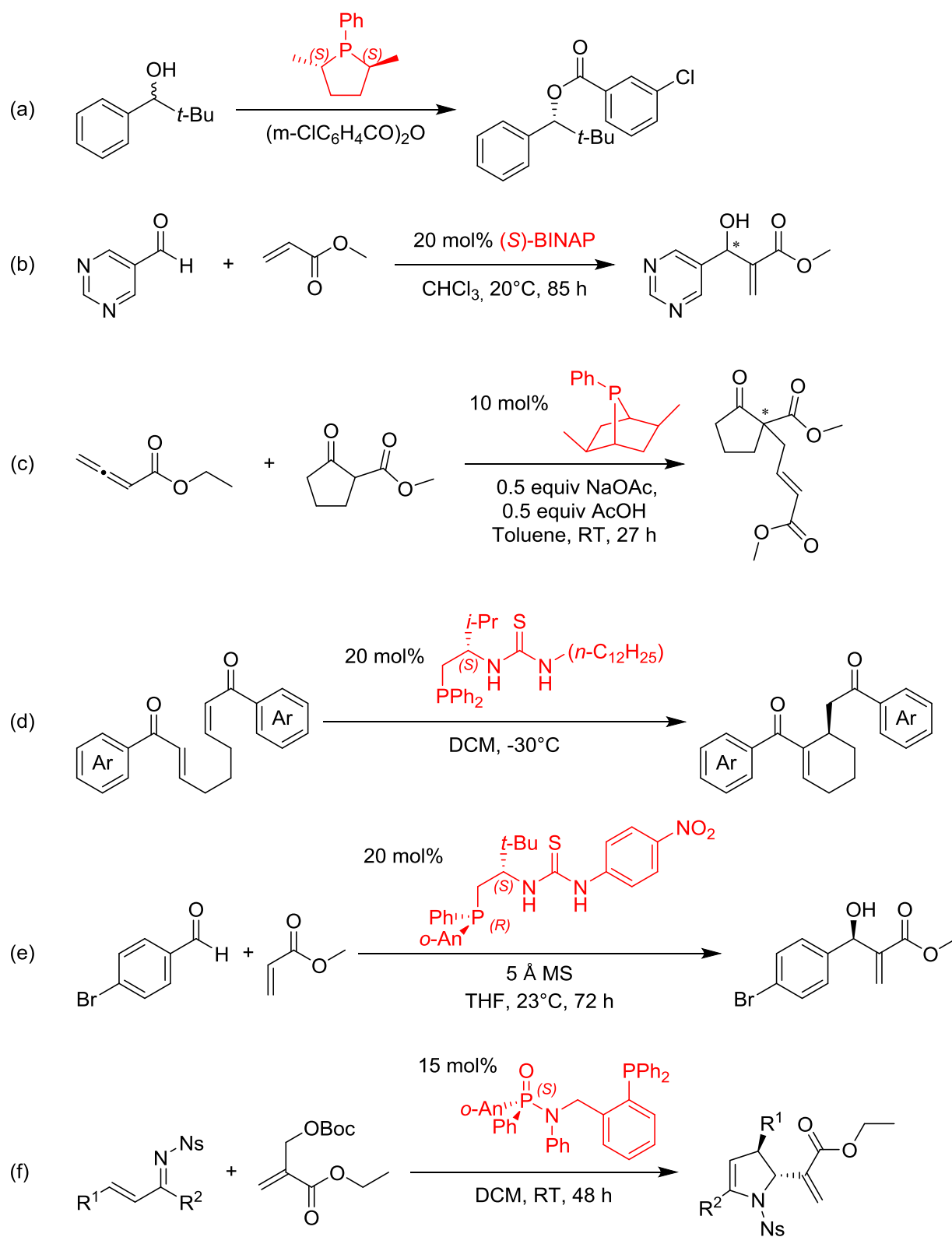
oxindoles to activated alkenes. Reaction catalyzed by chiral amino-phosphine gave products with 86-96% ee<sup>[69]</sup>. Usually in the catalysts there are simple phosphino groups present, however there are some examples of more interesting and P-stereogenic phosphine and phosphine oxide organocatalysts. Su and Taylor applied complex P-chiral phosphinothiourea catalyst in MBH reaction (Fig. 5 e)<sup>[70]</sup> and Zhengjie He and coworkers reported [4+1]-annulation catalyzed by *P(O)*-chiral phosphine oxide-phosphine (Fig. 5 f)<sup>[71]</sup>. For more details, I refer you to the extensive literature reviews on the topic<sup>[9, 72]</sup>.



**Fig. 4.** (a) Rauhut-Currier reaction (1963), (b) Morita reaction (1968), phosphine catalyzed: (c) Michael addition (1973), (d) Stetter reaction (2002)

### 1.1.1.3. Other applications

Besides organocatalysis and metal-catalysis (as ligands), phosphines and phosphine oxides are applied in other areas. Phosphine and phosphine oxides are introduced as an additive to polymers, often for the immobilization of transition metals catalysts<sup>[73, 74]</sup>, but also for other applications<sup>[75-77]</sup> or as flame retardants<sup>[78]</sup>. Phosphine oxides-containing materials are used in OLED diodes<sup>[79, 80]</sup>. In contrast to other classes of organophosphorus compounds, phosphines and phosphine oxides are rarely used as biocides except from phosphine gas (PH<sub>3</sub>)<sup>[81, 82]</sup>.



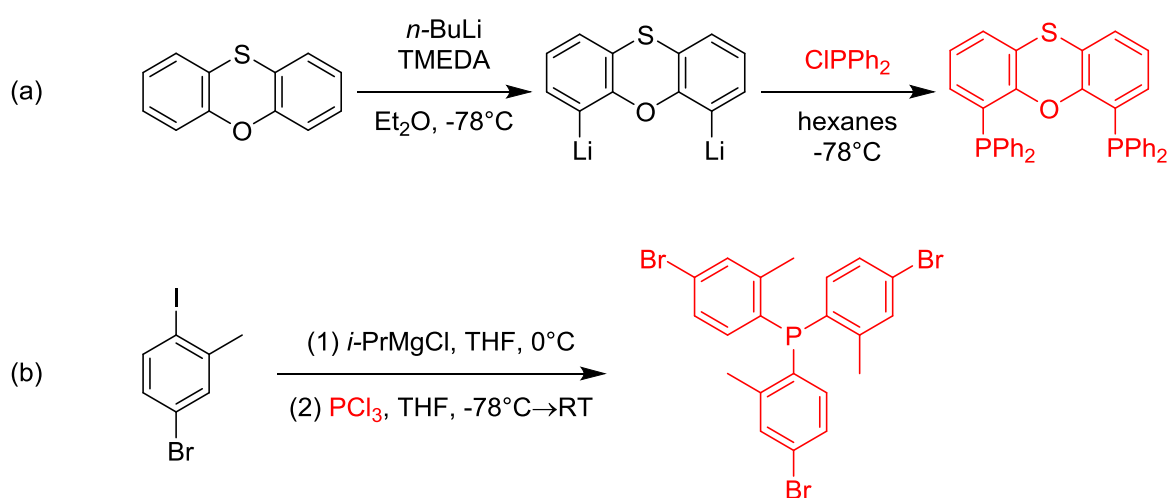
**Fig. 5.** (a) Vedejs and coworkers (1996), 25% conv., 81% ee; (b) Kenso Soai and coworkers (1998), 24% yield, 44% ee; (c) Xumu Zhang and coworkers (1998), 76% yield, 74% ee; (d) Xin-Yan Wu and coworkers (2011), 16 examples, 64-99% yield, 81-99% ee; (e) Su and Taylor (2017), 80% yield, 81% ee; (f) Zhengjie He and coworkers (2017), 69-95% yields, 64-99% ee, all *dr* ratios >20:1



### 1.1.2. Preparation

Phosphines can be obtained by several synthetic routes: (1) by a nucleophilic substitution of halophosphines with organometallic compounds, mainly organolithium and Grignard reagents, (2) the reaction of metal phosphides with organic halides, (3) by a reduction of phosphine oxides and related P(V) compounds, (4) by the addition of P–H nucleophiles to unsaturated compounds, or in substitution, including cross-couplings.

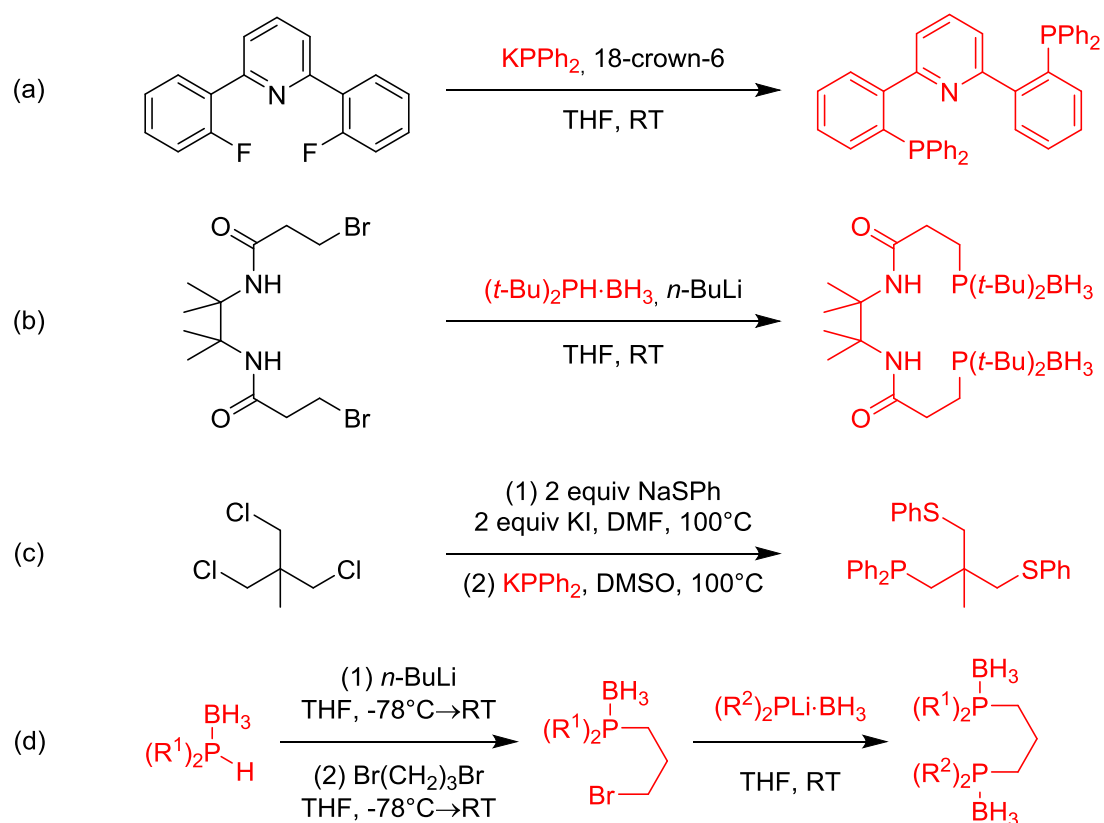
Reaction of halophosphines with organometallic compounds is mainly used in the synthesis of tertiary phosphines, especially ones with three identical substituents from  $\text{PCl}_3$  or  $\text{PBr}_3$  (Fig. 6)<sup>[5, 83, 84]</sup>.



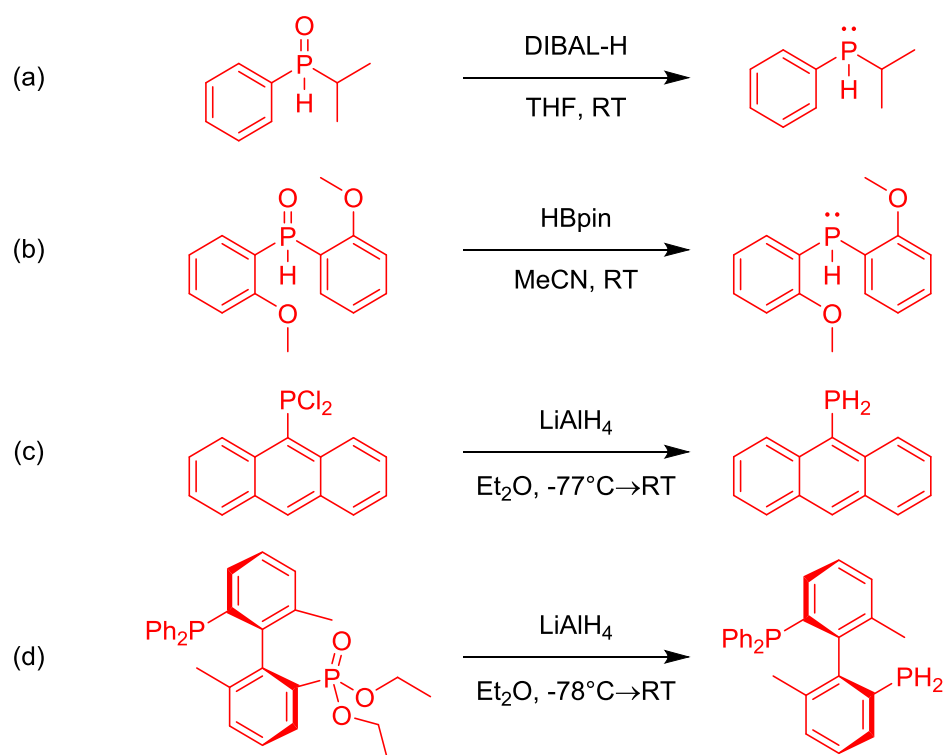
**Fig. 6.** Examples of phosphines preparation by the reaction of halophosphines with organometallic compounds: (a) organolithium in the synthesis of Xantphos-type ligands<sup>[85]</sup> and (b) Grignard reagents in the synthesis of triarylphosphine polymers<sup>[86]</sup>.

All phosphines, from primary to tertiary, can be obtained from metal phosphides (Fig. 7) and by the reduction of corresponding P(V) compounds (Fig. 8), such as secondary and tertiary phosphine oxides, phosphonic halides  $\text{R}_2\text{P}(\text{O})\text{X}$  and dihalides  $\text{RP}(\text{O})\text{X}_2$ , and their thiophosphonic derivatives  $\text{R}_2\text{P}(\text{S})\text{X}$ ,  $\text{RP}(\text{S})\text{X}_2$ , phosphinates  $\text{R}_2\text{P}(\text{O})\text{OR}$ , and phosphonates  $\text{RP}(\text{O})(\text{OR})_2$ . Organophosphorus compounds(III), such as halophosphines  $\text{R}_2\text{PX}$ , dihalophosphines  $\text{RPX}_2$ , and phosphonites  $\text{RP}(\text{OR})_2$  also react with LAH to give primary and secondary phosphines<sup>[5, 83, 84]</sup>. Electrochemical methods have also been developed<sup>[87]</sup>.

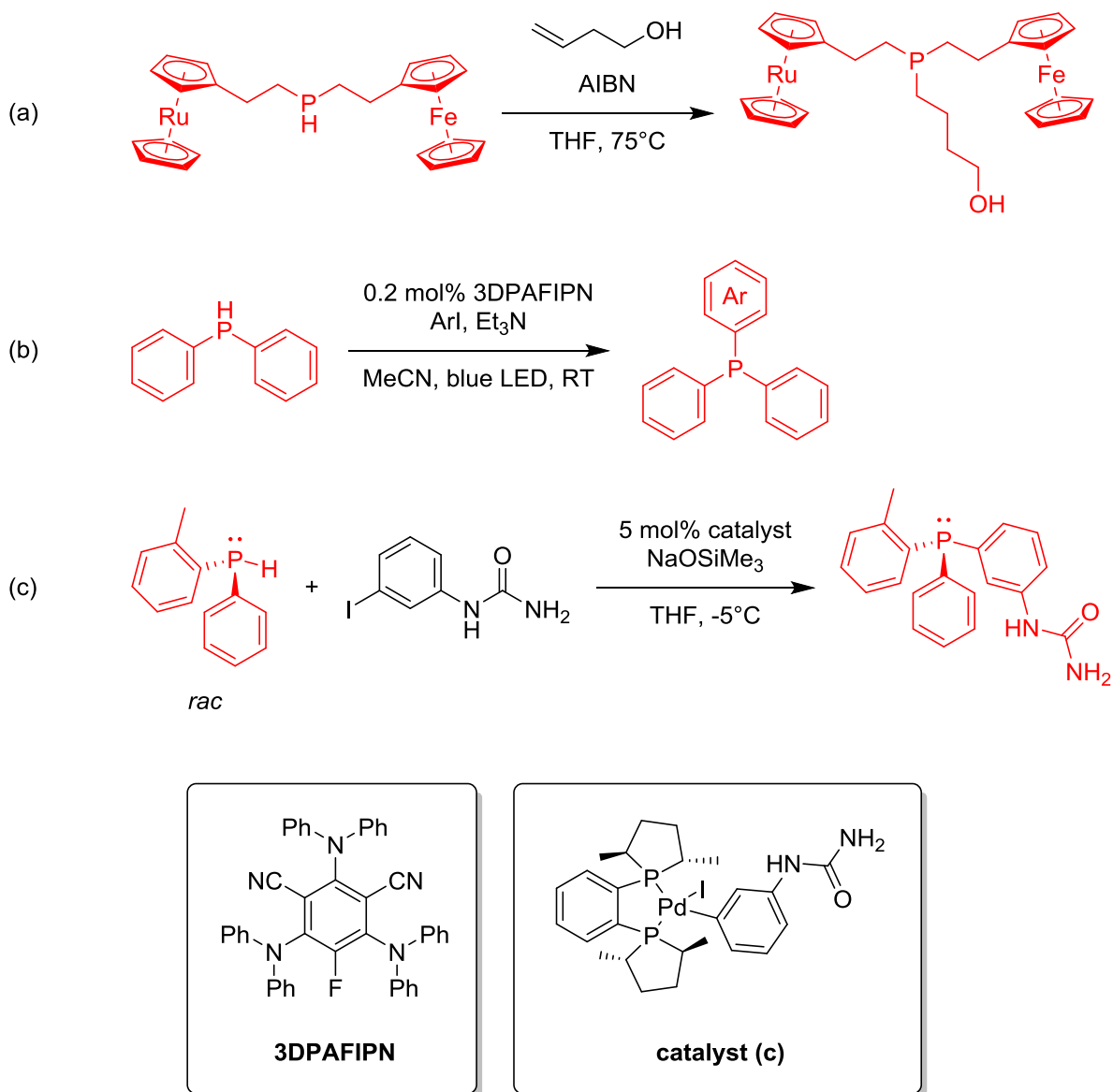
Secondary and unsymmetrical tertiary phosphines can be obtained also by the cleavage of C–P bond in tertiaryphosphine with alkali metals and subsequent hydrolysis or reaction with organohalide<sup>[5, 83, 84, 88]</sup>.



**Fig. 7.** Examples of phosphines preparation by the reaction of metal phosphides with organic halides in the synthesis of (a) chelate ligands<sup>[89]</sup>, (b) (P-B-P)-pincer ligand<sup>[90]</sup>, (c) sulfur containing Triphos homologs<sup>[91]</sup>, (d) 1,3-diphosphinopropanes<sup>[92]</sup>.



**Fig. 8.** Examples of phosphines preparation by reduction of (a, b) phosphine oxides<sup>[93, 94]</sup>, (c) halophosphine<sup>[95]</sup>, (d) phosphonate<sup>[96]</sup>.

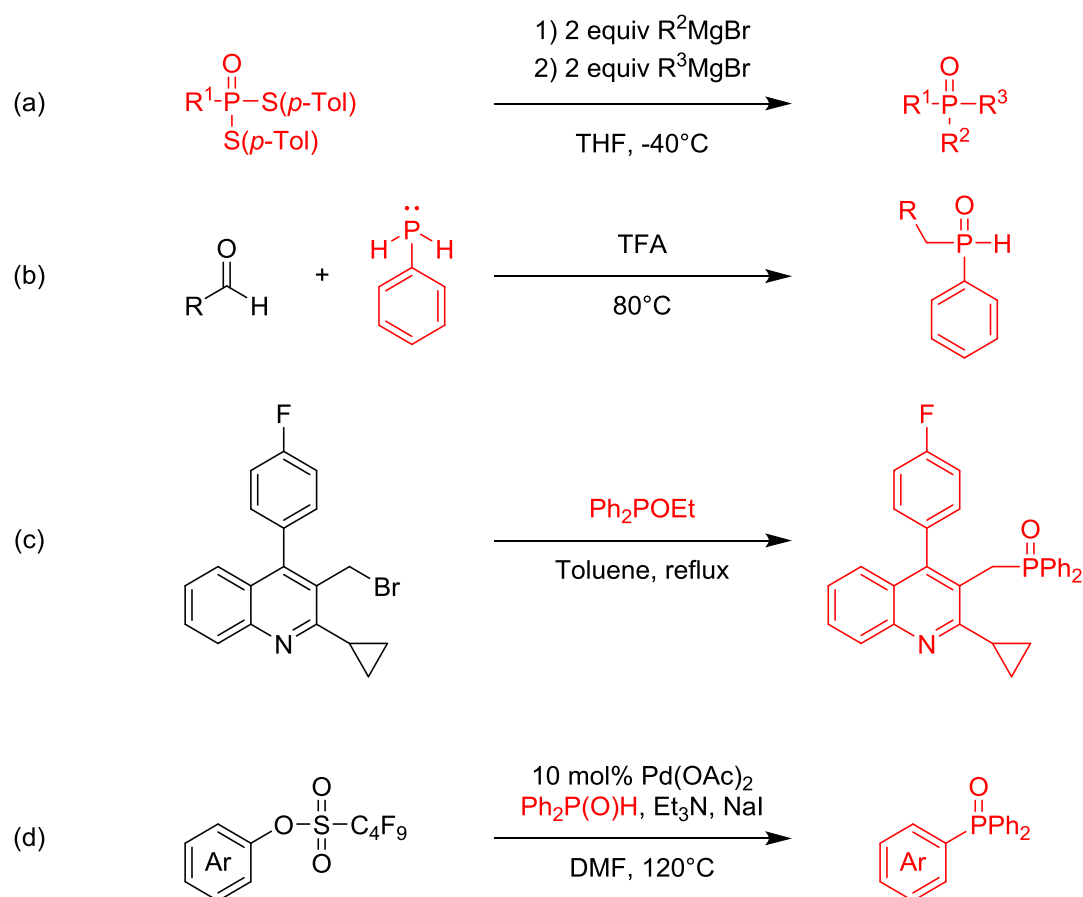


**Fig. 9.** Phosphine synthesis. Examples of (a) radical<sup>[97]</sup> and (b) photocatalyzed<sup>[98]</sup> addition to P-H, (c) transition metal-catalyzed cross-coupling<sup>[99]</sup>.

However, the first three classical methods suffer from the use of hazardous or air- and moisture-sensitive reagents, harsh reaction conditions, and difficult procedures with problematic reproducibility<sup>[98]</sup>. Another way towards phosphines is to utilize the reactivity of P-H group. Primary, secondary phosphines, and  $\text{PH}_3$  undergo addition to unsaturated bonds, so-called hydrophosphination reaction, which is the most straightforward and atom-economical strategy for the preparation of various phosphines. This C-P bond formation proceeds under base- or acid-catalyzed conditions, upon radical activation (UV light, AIBN, peroxides, etc.), using metal complex catalysts, or photocatalysis. Phosphine  $\text{PH}_3$  requires a base catalyst for its addition even to strongly electrophilic alkenes, while primary and

secondary phosphines are capable of adding to some electron-deficient olefins without a catalyst.

Primary and secondary phosphines as well as phosphine halides, silyl- and stannylphosphines, and secondary phosphine oxides are also coupling partners for C–P cross-coupling reactions catalyzed by transition metal complexes, typically of palladium and nickel<sup>[100–102]</sup>. Despite its generality and mild reaction conditions, this method suffers from high price of transition metals and toxicity of these catalysts. Thus, the demand for metal-free methodologies have been increasing recently. Example of those may be Zeitler and Wolf visible-light-driven arylation of primary and secondary phosphines with an organic photocatalyst (Fig. 9 b)<sup>[98]</sup>.



**Fig. 10.** Examples of phosphine oxides preparation (a) from organometallic compounds<sup>[103]</sup>, (b) by reaction of phosphines with aldehydes<sup>[104]</sup>, (c) Michaelis-Arbusov reaction<sup>[105]</sup> and (d) transition metal-catalyzed cross-coupling<sup>[106]</sup>.

Similar methods are used in synthesis of phosphine oxides. Organometallic compounds are often employed in reactions with a much more diverse group of organophosphorus(III) and (V) compounds with halide, -OH, -OR, or -SR substituents on the

phosphorus atom, for instance phosphonates  $RP(O)(OR)_2$ , phosphonothioates  $RP(O)(SR)(OR)$ , or phosphonodithioates  $RP(O)(SR)_2$  to obtain phosphine oxides (Fig. 10 a)<sup>[7, 103, 107]</sup>. A popular method for obtaining phosphine oxides is to oxidize the corresponding phosphines. Exposure to air is not a practical method since side products with P-O-C bonds might be formed, therefore oxidizing agents, such as  $H_2O_2$ , organic peroxides/hydroperoxides, sodium periodate under phase-transfer conditions, and other are applied<sup>[5]</sup>. Reaction of phosphines with ketones and aldehydes often yields phosphine oxides (Fig. 10 b)<sup>[7]</sup>. Tertiary phosphine oxides are also formed in Michaelis-Arbuzov reaction of phosphinite with organohalide<sup>[5]</sup>. Also, the cross-coupling reactions are a popular method for the synthesis of tertiary phosphine oxides, especially in an enantioselective manner<sup>[106, 108-111]</sup>.



## 1.2. Diaryliodonium salts

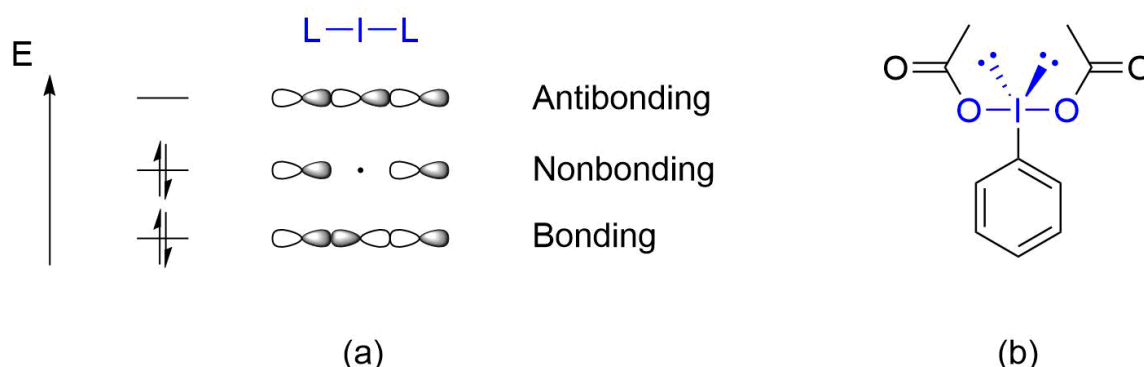
Diaryliodonium salts are a class of hypervalent iodine compounds with the general formula  $Ar_2IX$ . They consist of two aryl and one heteroatom ligands (e.g., halogen, OTs, OTf,  $BF_4$ , OCOR) attached to the iodine atom. They have found use in organic synthesis as arylating reagents, and because their reactivity patterns resemble those of organometallic compounds, diaryliodonium salts provide a cheaper, less toxic and more environmentally friendly alternative to transition metal-catalysts.

Most molecules of main-group elements follow the octet rule and atoms are bonded in such a way that each atom attain eight electrons in a valence shell (the closed shell configuration as in noble gases). However, there are known exceptions from this rule that have either unfilled valence shell known as hypovalent compounds and these with expanded octet or hypervalent. Dihydrogen ( $H_2^+$ ) and dihelium ( $He_2^+$ ) cations, nitric oxide (NO) and diborane ( $B_2H_6$ ) are examples of the first group. Electronic structures of these can be explained invoking 2c-1e (two-center one-electron) bond to describe dihydrogen cation, 2c-3e bond to dihelium cation and nitric oxide, and 3c-2e to diborane (two BHB bridges).

The term hypervalent refers to molecules or ions of main group elements bearing more than eight electrons within a valence shell, such as triiodide ( $I_3^-$ ). The term was introduced by Musher in 1969<sup>[112]</sup>. The first hypervalent iodine compounds were prepared by Willgerodt in 1885<sup>[113]</sup> - and the first diaryliodonium salt by Hartmann and Meyer in 1894<sup>[114]</sup>. In the 1920s, Lewis and Langmuir debated over how to rationalize the bonding in hypervalent species. Pauling in 1931<sup>[115]</sup>, as well as Lewis, opted for the dominance of 2c-2e bonds and octet expansion, while Langmuir for the dominance of octet rule, which involves the formation of a new type of highly ionic orbital without the involvement of *d* orbitals. On the basis of the MO theory, Pimentel and Rundle proposed the 3c-4e bond in 1950s, the concept that is used to rationalize bonding in hypervalent compounds to this day<sup>[116, 117]</sup>.

In triiodide, formation of 3c-4e bond can be explained by combination of  $\sigma$  and  $\sigma^*$  molecular orbitals of diiodine  $I_2$  with one of  $I^-$  orbitals, resulting in the formation of three new molecular orbitals of triiodide: bonding, nonbonding and antibonding, with the first two occupied by four electrons (Fig. 11 a)<sup>[118]</sup>. In organoiodine(III) compounds of type  $RIL_2$ , the description is similar, but the bond is formed from combination of one filled 5*p* orbital of iodine and two half-filled orbitals from each of the ligands. The highest occupied molecular orbital (HOMO), which is nonbonding in this case, contains a node at the iodine, making the hypervalent bond highly polarized. Due to such electron distribution in 3c-4e bond, iodine atom is electrophilic and more electronegative atoms usually occupy axial position, while carbon ligand R is bound by normal covalent 2c-2e bond in  $RIL_2$  molecules and resides

similar to lone pairs of electrons in the equatorial positions of distorted trigonal bipyramid (Fig. 11 b)<sup>[119]</sup>. In iodonium salts instead of one axial ligand there is another carbon substituent R.



**Fig. 11.** Examples of hypervalent compounds (a) PIDA, (diacetoxyiodo)benzene ( $RIL_2$  type hypervalent iodane(III)), (b) diagram illustrating the molecular orbitals of 3c-4e bond.

Among hypervalent organoiodates, we distinguish iodanes(III) and iodanes(V), depending on the oxidation state of the iodine atom. Additionally, inorganic iodanes(VII) are known. Common classes of iodanes(V) include noncyclic iodoxyarenes, five-membered heterocyclic benziodoxole derivatives, such as IBX and DMP, pseudocyclic iodylarenes, or pseudocyclic derivatives of 2-iodylbenzenesulfonic acid. Iodanes(III) include iodosoarenes, [bis(acyloxy)iodo]arenes (e.g. PIDA, PIFA), and aryl iodine(III) organosulfonates. These classes similarly as iodanes(V) are oxidizing agents and serve for oxidative functionalizations of organic substrates. (Dihaloiodo)arenes are halogenating agents. Five-membered iodine heterocycles (benziodoxoles and benziodazoles), iodonium salts, ylides, and imides are common electrophilic group-transfer reagents. Benziodoxoles and benziodazoles transfer hetroatom ligands. Iodonium imides are reagents for aziridination and amidation. Iodonium salts and ylides are usefull for C–C bond-forming reactions (Fig. 12). Among diaryliodonium salts, another three subclasses can be distinguished - alkenyl(aryl)iodonium salts (alkenylation reagents), alkynyl(aryl)iodonium salts (alkynylation reagents), and diaryliodonium salts (aryllating reagents). Alkyl(aryl)iodonium salts are generally unstable which limits their applicability, however, they can be generated *in situ*<sup>[117]</sup>.



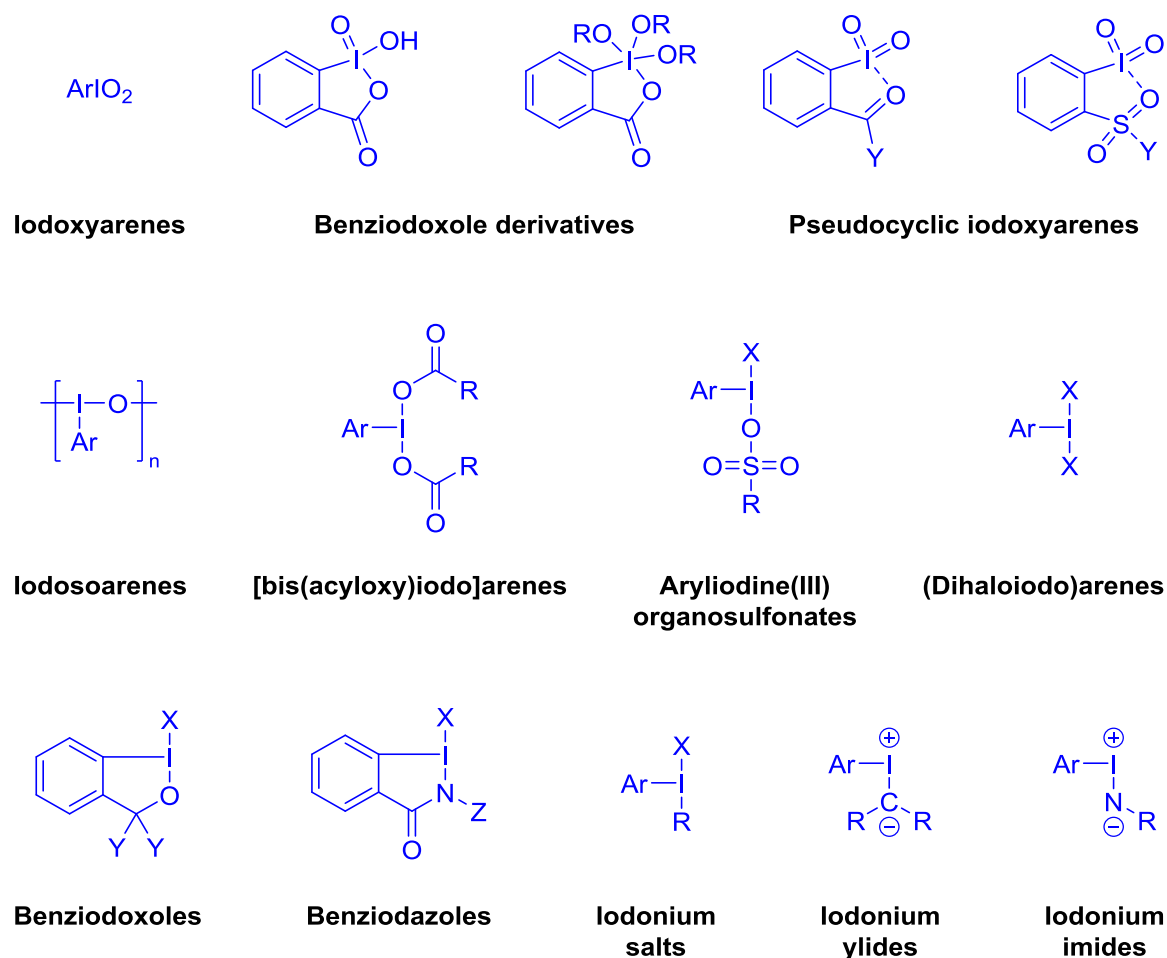
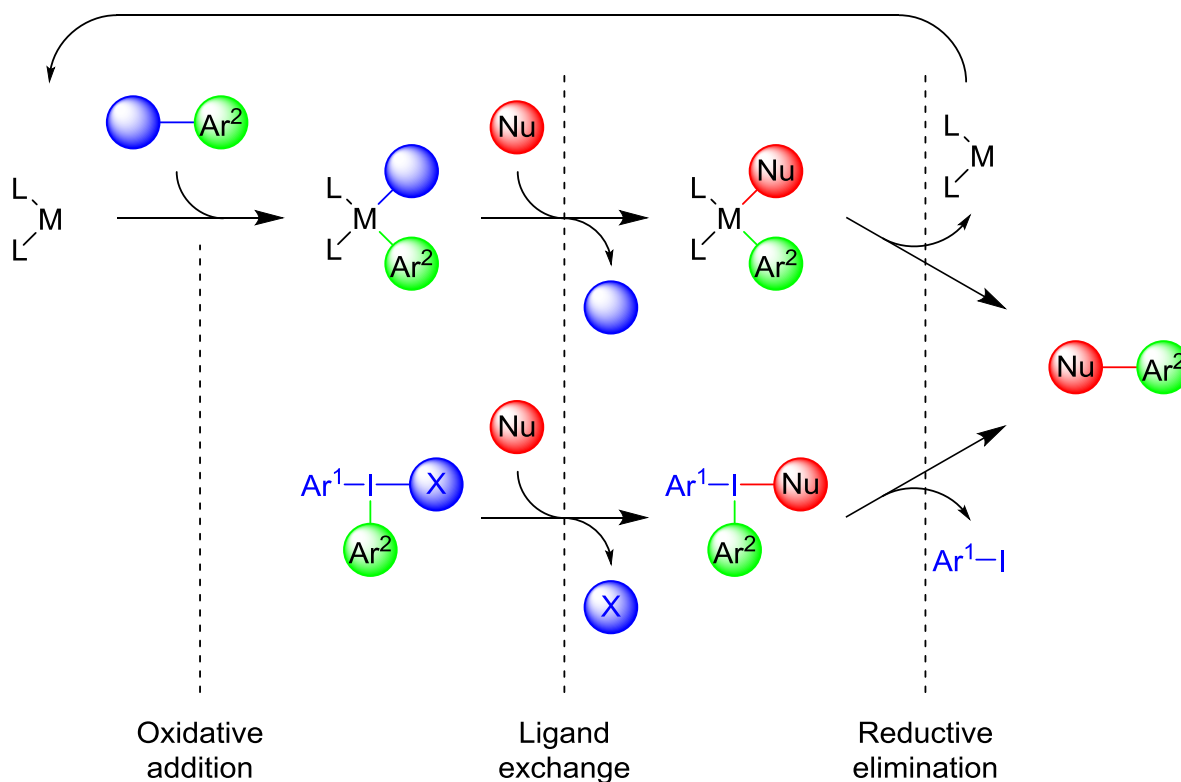


Fig. 12. Selected classes of organoiodates.

### 1.2.1. Reactivity of diaryliodonium salts

Diaryliodonium salts reactivity can be explained with elementary steps that these species can undergo. These are specifically: ligand exchange, reductive elimination, nucleophilic attack on ligand, reductive  $\beta$ -elimination, homolytic cleavage, and single electron transfer (SET), which are very similar to those that organometallic transition metal complexes can undergo (Fig. 13). At the same time, having similar reactivity patterns, diaryliodonium salts are much cheaper and less toxic than transition metal complexes.



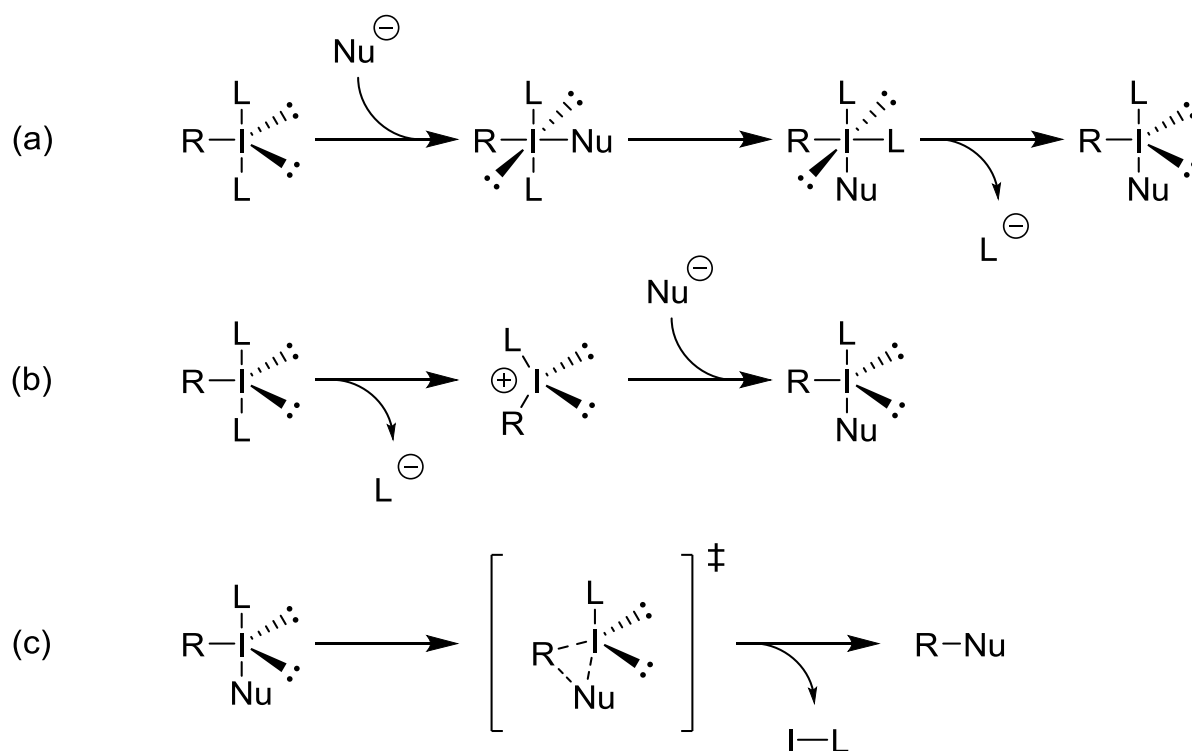
**Fig. 13.** Comparison of the mechanism of metal complex-catalyzed cross-coupling and the arylation with diaryliodonium salt (inner sphere mechanism).

There are two major general mechanisms of the aryl transfer from diaryliodonium salts to a nucleophile. The first one is the inner sphere pathway. It is initiated by the ligand exchange that can be either associative or dissociative. In the former, a nucleophile attacks iodine atom to form tetracoordinated square-planar intermediate, which undergoes isomerization from *trans* to *cis* iodate, and subsequently the elimination of L ligand (Fig. 14 a). The dissociative pathway proceeds via the initial ligand cleavage to form dicoordinate iodonium ion, which then binds with nucleophile (Fig. 14 b). Resulting T-shaped intermediate undergoes then the reductive elimination of the nucleophile and the R group via a three-membered transition state (Fig. 14 c) and iodoarene is formed as a byproduct<sup>[117, 119, 120]</sup>.

In the outer-sphere mechanism, a nucleophile directly attacks the ligand, substituting the iodine as a leaving group. This pathway yields similar products as inner sphere pathway and the two can be typically distinguished only by computations.

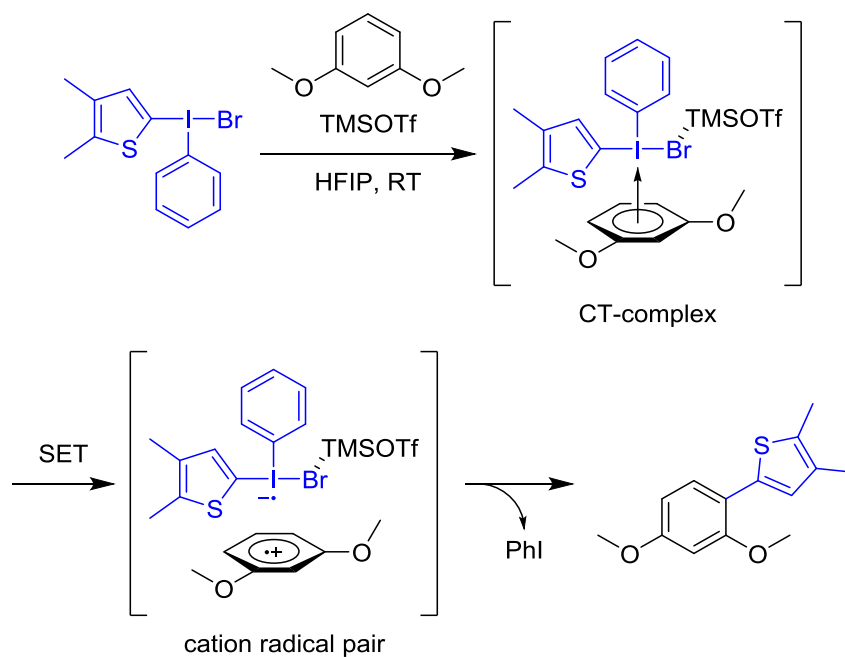
Alternative more rare mechanism for the aryl transfer from diaryliodonium salts involves the  $\beta$ -elimination of iodine that results in the formation of benzyne, which undergoes further transformations<sup>[119]</sup>. Reaction with diaryliodonium salts can also proceed via a single

electron transfer (SET). An electron-rich arene forms CT-complex with diaryliodonium salts to subsequently form cation radical, to which heteroaryl group is transferred. The reaction proceeds in polar, non-nucleophilic solvents such as HFIP (Fig. 15)<sup>[117, 120–122]</sup>.

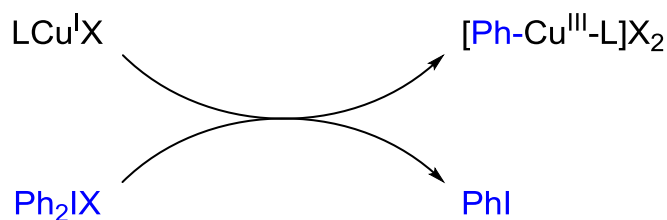


**Fig. 14.** Inner sphere pathway: ligand exchange step (a) associative and (b) dissociative pathways, (c) reductive elimination.

Finally, metal-catalysts can be applied to effect the aryl transfer from diaryliodonium salts. In this case, the diaryliodonium salt does not directly interact with the substrate, but instead the aryl is first transferred to the complex via an oxidative addition (of the metal center; Fig. 16), which then undergoes a reaction with the substrate through the regular cross-coupling mechanism (Fig. 13). In the metal-catalyzed reactions, selectivity is usually controlled by steric factors, but in metal-free reactions, the most electron-deficient aryl group transfer is favored. Often, especially for heteroatom nucleophiles, *ortho*-substituted aryl groups are transferred despite being more electron-donating<sup>[120]</sup>.



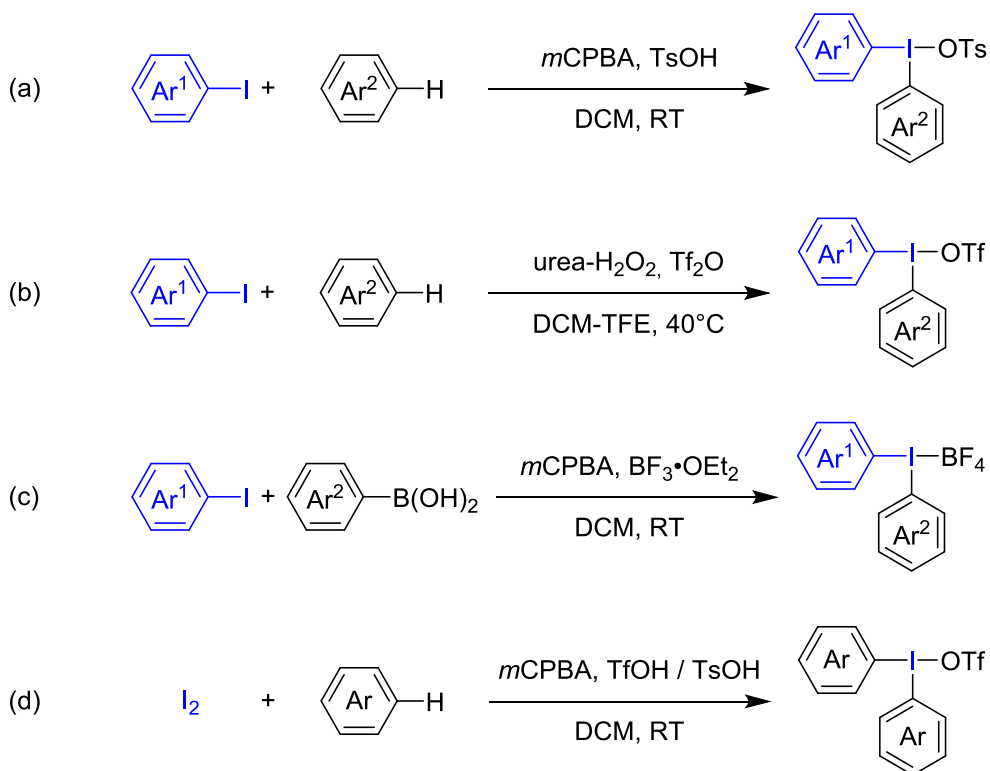
**Fig. 15.** Arylation with diaryliodonium salts via SET mechanism, *Kita and coworkers (2010), 10 examples, 50-81% yield*<sup>[121]</sup>.



**Fig. 16.** Simplified formation of complex in metal-catalyzed diaryliodonium salt arylation<sup>[110, 123]</sup>.

### 1.2.2. Preparation of diaryliodonium salts

Most methods for the preparation of diaryliodonium salts are two- or three-step sequences that can be carried out in a stepwise or one-pot manner. Step-by-step synthesis is convenient with commercially available organic and inorganic iodine(III) reagents, such as iodine trichloride, (diacetoxyiodo)benzene (PIDA), [bis(trifluoroacetoxy)iodo]benzene (PIFA) and [hydroxy(tosyloxy)iodo]benzene, known as the Koser's reagent. The latter is the most reactive and, unlike the others, does not require acid activation.



**Fig. 17.** Olofsson's methods for diaryliodonium salts preparation: (a) 37 examples, 52-94% yield (with TfOH)<sup>[124, 125]</sup>; 9 examples, 34-100% yield (with TsOH)<sup>[126]</sup>; (b) 20 examples, ≤ 86% yield<sup>[127]</sup>; (c) 24 examples, 31-88% yield<sup>[128]</sup>; (d) 4 examples, 24-81% yield (with TfOH)<sup>[125]</sup>; 9 examples, ≤ 89% yield (with TsOH)<sup>[126]</sup>.

One-pot reactions were for a long time limited in scope and required harsh conditions<sup>[129, 130]</sup>, but with the beginning of the 21st century, efficient methods have been developed. Typical preparation of both symmetrical and unsymmetrical salts starts with the oxidation of iodoarene, usually under acidic conditions. The research groups of Olofsson and Kitamura have contributed greatly to the development of one-pot preparation methods in recent years. Both teams obtain diaryliodonium salts with these methods from iodoarenes or directly from iodine in combination with arylating reagents, such as arylboronic acids. Hossain and Kitamura used potassium persulfate with TFA or AcOH<sup>[131-133]</sup>, while Olofsson's methods typically employ *m*CPBA as the oxidant in combination with triflic acid (TfOH), tosylic acid (TsOH), or BF<sub>3</sub>·OEt<sub>2</sub>, depending on the target salt<sup>[124-128]</sup> (Fig. 17). *m*CPBA have previously been used in the synthesis of (diacetoxyiodo)arenes and other iodines(III) and proved efficient, since both the oxidant and its reduced form are soluble in Et<sub>2</sub>O, thus enabling facile purification by the precipitation of diaryliodonium salt. The triflic acid method is the most versatile, while tosylic acid is more suitable for electron-rich salts. BF<sub>3</sub>·OEt<sub>2</sub> is applied with arylboronic acids in a regioselective synthesis of otherwise inaccessible diaryliodonium salts<sup>[120]</sup>.

The number of salts that can be selectively obtained by reaction with simple arene is limited because it depends on the aryl substituents and their directing effect. In these reactions, the usefulness of aryl is limited to those with electron-donating groups that favor substitution at the *para*-position. Electron-withdrawing groups on aryl often lead to poor yields and selectivity, and *ortho*-substitution is unfavourable because of steric hinderance. To avoid by-product formation, when synthesizing unsymmetrical salts, more electron-deficient aryl should come from iodoarene and the more electron-donating from arene<sup>[120, 134]</sup>.

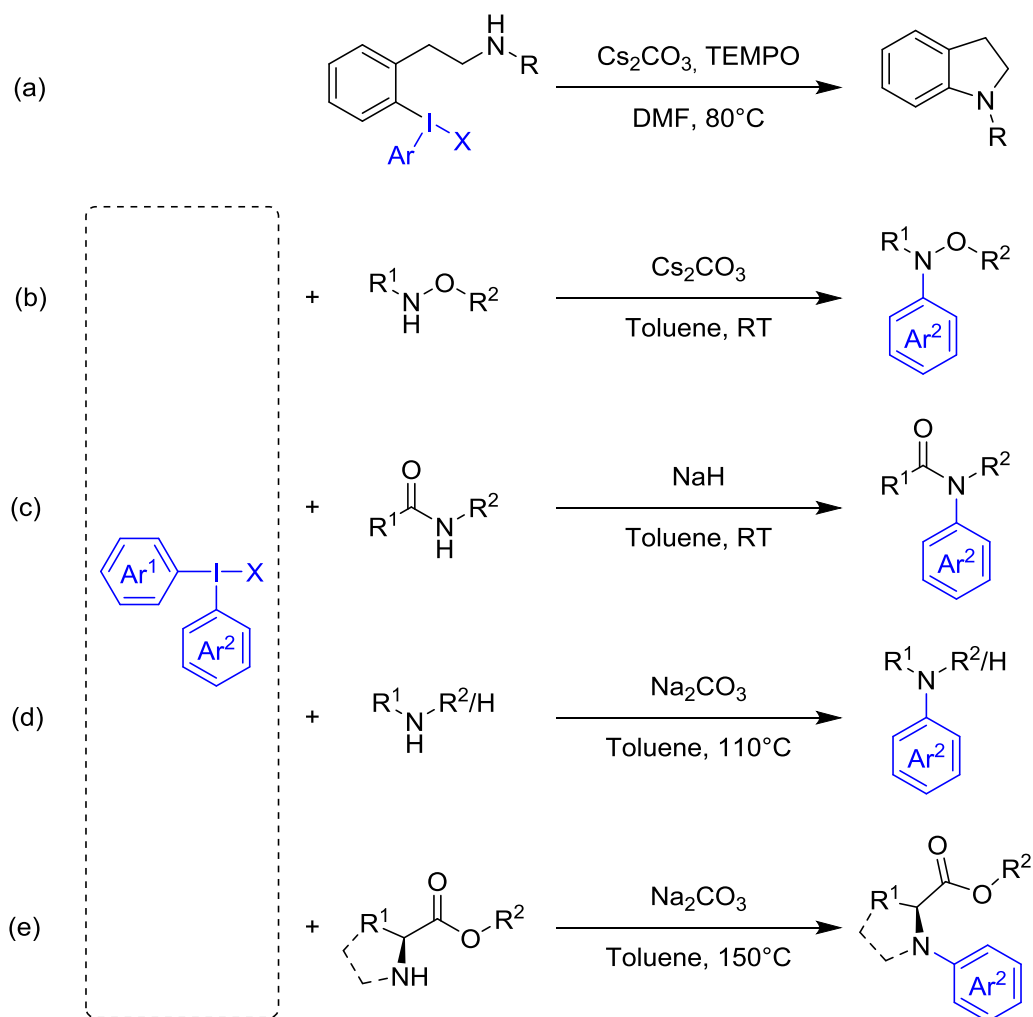
### 1.2.3. Arylation of nucleophiles with diaryliodonium salts

During the last two decades, considerable progress has been made in the application of diaryliodonium salts in organic chemistry. Methods for the arylation of various heteroatom and carbon nucleophiles under mild and metal-free conditions have been developed and applied in the synthesis of biologically active compounds, pharmaceutical agents, and their synthetic intermediates. Metal-free conditions of this type of reactions with diaryliodonium salts are of a great advantage, especially in the drug preparation, where contamination of the product with trace metal residues is a major drawback of transition metal-catalysts based methods, in addition to their price.

#### 1.2.3.1. Nitrogen nucleophiles

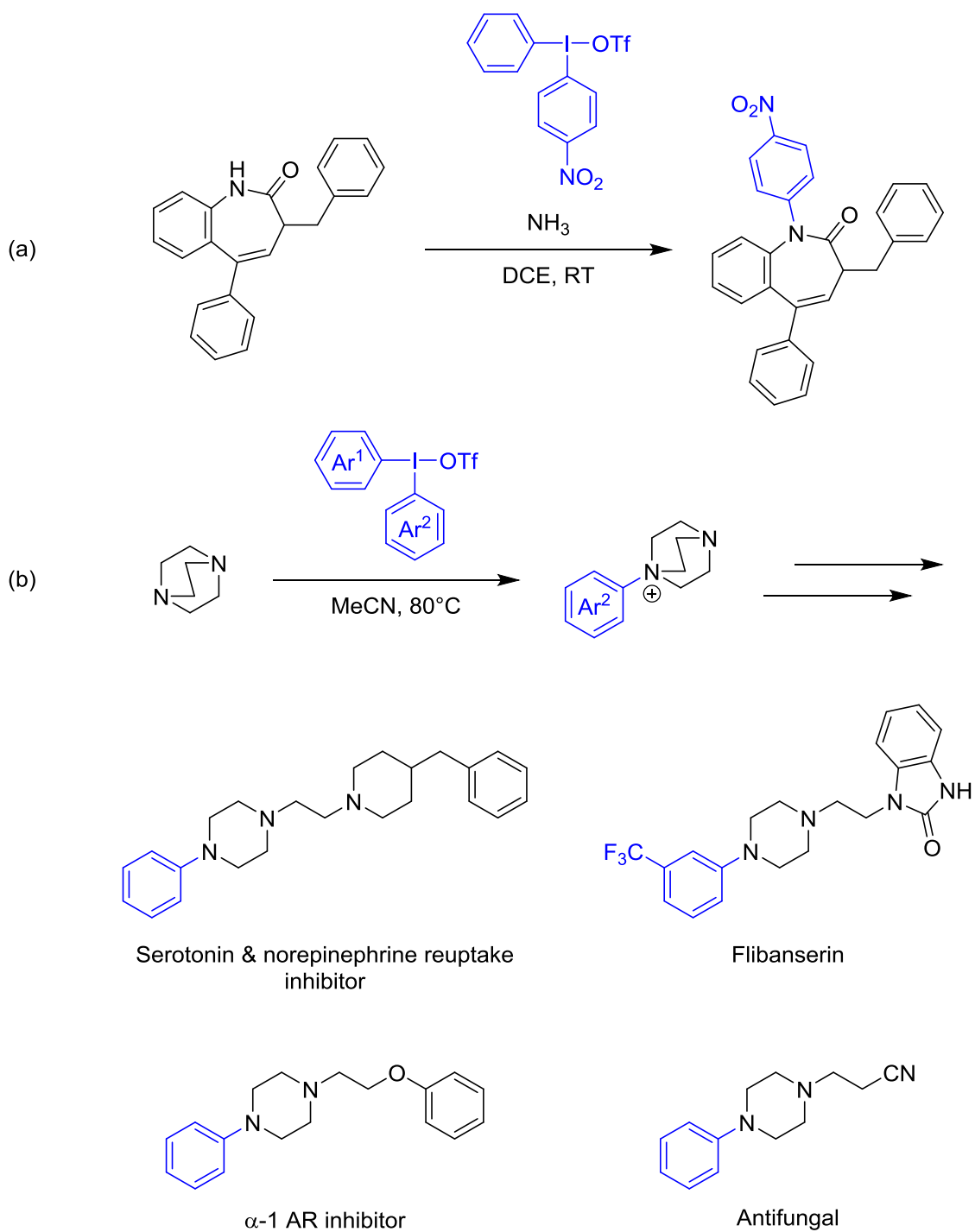
In recent years metal-free *N*-arylations of several classes of nitrogen compounds have been developed including aliphatic amines<sup>[135, 136]</sup>, hydroxylamines<sup>[137]</sup>, anilines<sup>[138]</sup>, amides<sup>[139, 140]</sup> and heterocycles<sup>[141]</sup> (Fig. 18).

In 2018 Spencer and coworkers used diaryliodonium salts for the synthesis of several 1,4-benzodiazepines, such as a bradykinin receptor antagonist (Fig. 19 a)<sup>[142]</sup>. In the same year, Karchava and coworkers reported their promising results in *N*-arylation of DABCO to *N*-aryl-DABCO salts, which are the precursors for 1,4-disubstituted piperazines including desatinib (leukemia treatment), aripiprazole (antipsychotic), trazodone (antidepressant), and niaprazine (sedative-hypnotic drug). They have shown the applicability of their method in the synthesis of flibanserin and other compounds known for their bioactivity, including serotonin and norepinephrine reuptake inhibitor (serotonin reuptake inhibitors are known antidepressants),  $\alpha$ -1 AR inhibitor, and an antifungal compound (Fig. 19b)<sup>[141]</sup>.



**Fig. 18.** Arylations of nitrogen nucleophiles: (a) Chi and coworkers synthesis of indoline<sup>[136]</sup>; (b) Wang and coworkers arylation of hydroxylamines<sup>[137]</sup>, 19 examples, 45-98% yield; Olofsson and coworkers: (c) arylation of secondary amides<sup>[139]</sup>, 21 examples, 40-99% yield; (d) arylation of primary and secondary aliphatic amines<sup>[135]</sup>, 63 examples, 41-99% yield; (e) arylation of amino esters<sup>[143]</sup>, 30 examples, 41-91% yield, 76-98% ee.

In 2021, Olofsson's group developed a methodology for transition metal-free *N*-arylation of amino acid esters with unsymmetrical diaryliodonium triflates in toluene at 150°C<sup>[143]</sup>. The anisyl ligand was used as a "dummy" group to provide both high chemoselectivity and yields, since raising the reaction temperature to overcome the initial moderate reactivity of the substrates resulted in a drop of chemoselectivity. They have developed an array of *N*-arylated products, by transferring electron deficient, electron rich, and sterically hindered aryl groups with a variety of substituents.



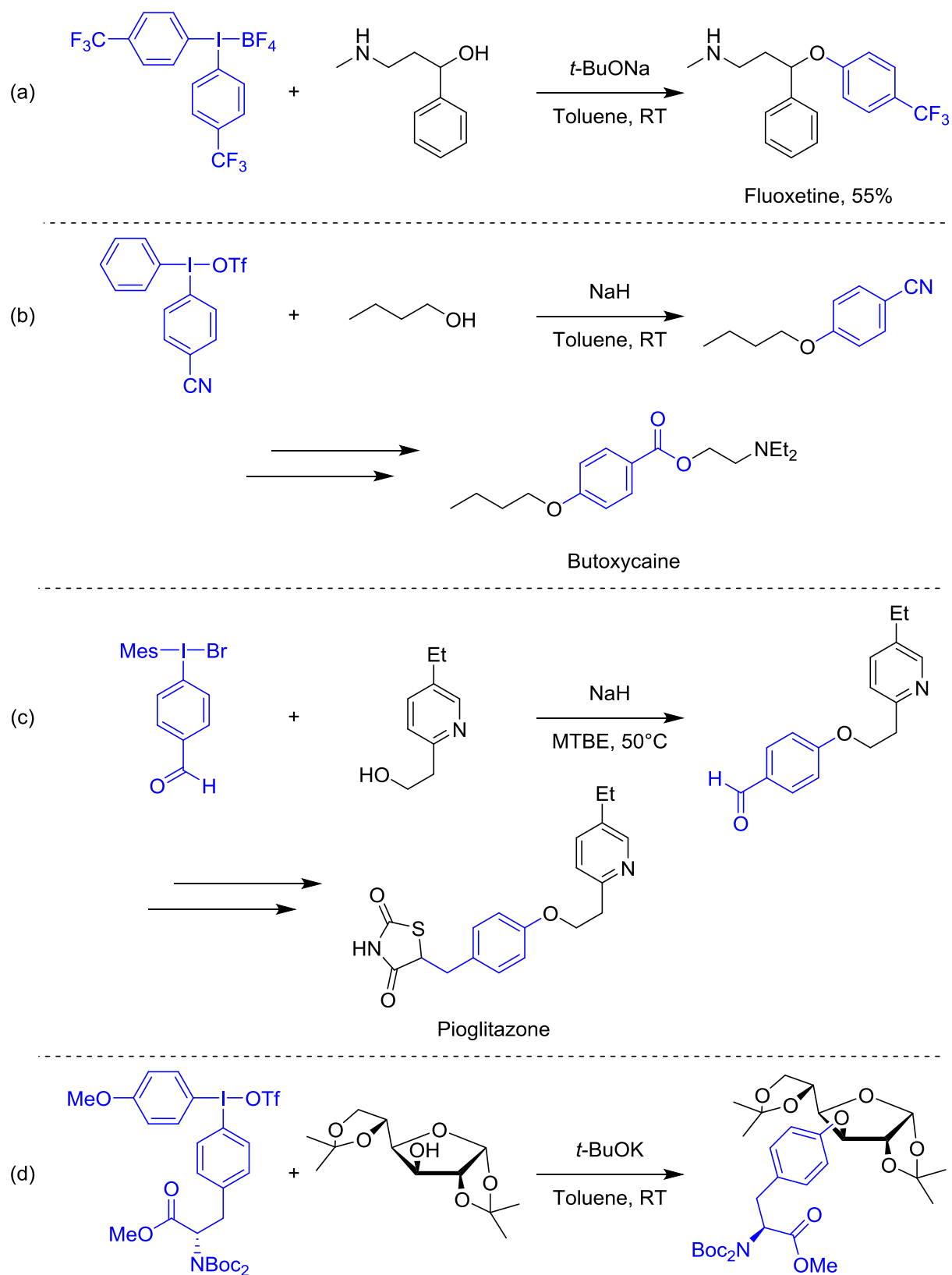
**Fig. 19.** (a) Synthesis of 1,4-benzodiazepines by *N*-arylation with diaryliodonium salts<sup>[142]</sup>, 8 examples, 70-99% yield; (b) *N*-arylation of DABCO<sup>[141]</sup>, 20 examples, 42-96% yield.



### 1.2.3.2. Oxygen nucleophiles

In the field of metal-free *O*-arylations with diaryliodonium salts, ether synthesis from various types of alcohols has received most attention. Since classical etherification methods, such as Williamson or Ullmann reactions often require harsh conditions or transition metal-catalyzed cross-couplings, metal-free mild condition methods for *O*-arylations with diaryliodonium salts seem to be a huge step forward in ether synthesis. A smaller number of papers have addressed arylation of other oxygen nucleophiles – carboxylic acids<sup>[144]</sup>, N-O nucleophiles - oximes<sup>[137]</sup>, *N*-hydroxysuccinimide and *N*-hydroxyphthalimide<sup>[145]</sup>, and P-O nucleophiles such as phosphinates, phosphonates and phosphates<sup>[146]</sup>. Progress in *N*- and *O*-arylations with diaryliodonium salts up to 2015 has been reviewed in detail by Olofsson<sup>[120]</sup>. Their group is known for their diaryliodonium salt preparation methods, heteroatom arylation reactions, mechanistic, and chemoselectivity studies<sup>[147, 148]</sup>.

The applicability of *O*-arylations with diaryliodonium salts has been demonstrated in synthesis of pharmaceuticals, bioactive compounds, and their synthetic intermediates. Olofsson's team presented the synthesis of fluoxetine (SSRI-type antidepressant, Fig. 20 a) and a formal synthesis of butoxycaine (anesthetic drug, Fig. 20 b) via *O*-arylation of aliphatic alcohols<sup>[149]</sup>. Sundalam and Stuart proposed a formal synthesis of pioglitazone (antidiabetic, Fig. 20 c)<sup>[150]</sup>. They extended the scope and improved the functional group tolerance by using sodium hydride in MTBE at 50°C. Olofsson and coworkers reported *O*-functionalization of carbohydrates with diaryliodonium salts and the synthesis of cyclodextrin derivative and glucose-tyrosine glycopeptide-type system with this method (Fig. 20 d)<sup>[151]</sup>. They showed the formal synthesis of phenoxazine, which is the core structure of numerous compounds with interesting biological or photophysical properties<sup>[152]</sup>.



**Fig. 20.** Olofsson's synthesis of (a) fluoxetine and (b) formal synthesis of butoxycaine<sup>[149]</sup>, (c) Sundalam and Stuart formal synthesis of pioglitazone<sup>[150]</sup>, (d) Olofsson's glucose tyrosine glycopeptide-type system synthesis<sup>[151]</sup>.

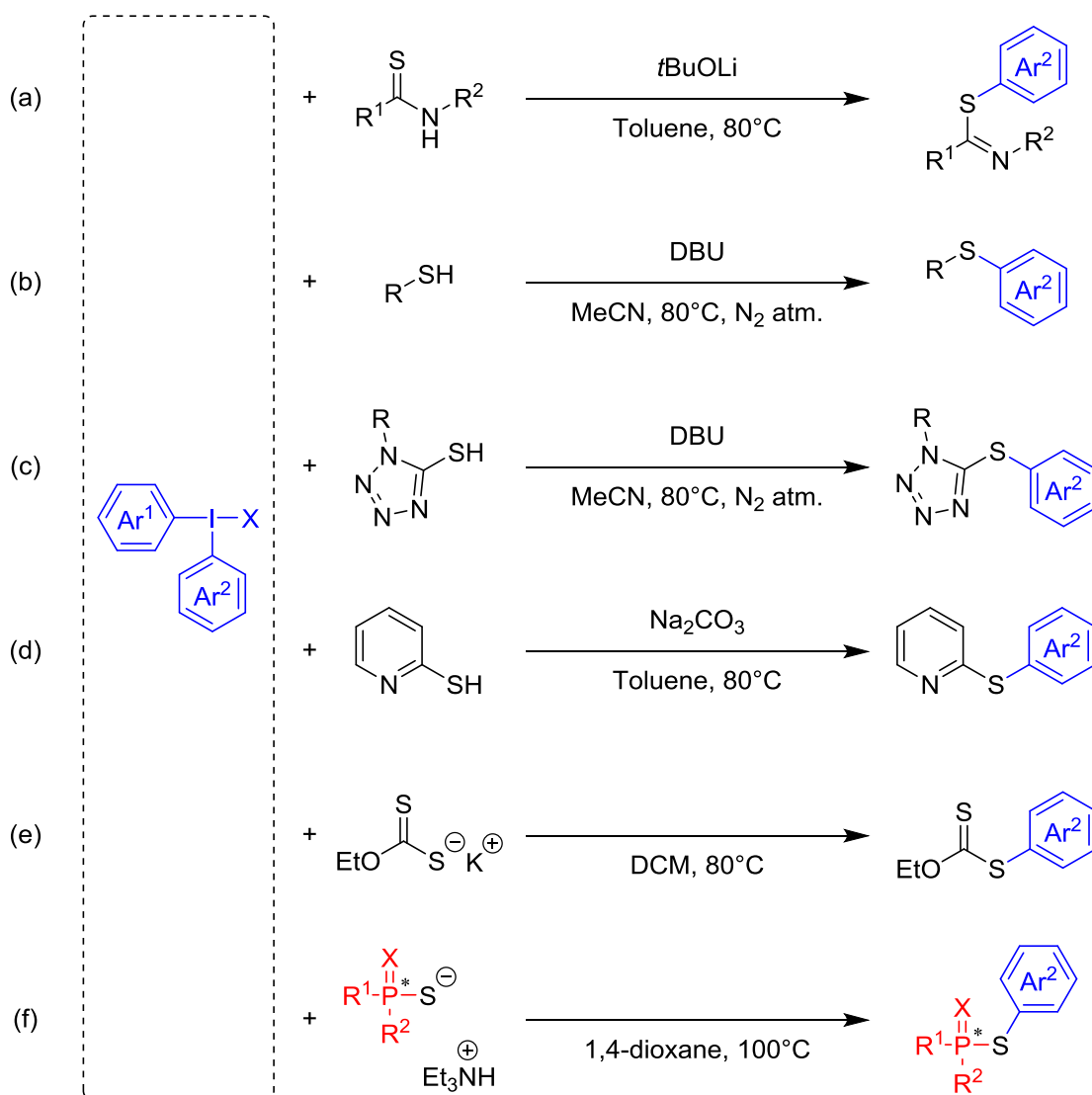
### 1.2.3.3. Sulfur nucleophiles

Similar to *N*- and *O*-arylation, studies on the arylation of sulfur nucleophiles with diaryliodonium salts can be traced back to the early 1940s and the progress on this topic until the last decade was summarized by Olofsson in 2015<sup>[120]</sup>. Since then, several articles have been published on the topic of metal-free protocols. In 2018, Olofsson and coworkers presented the *S*-arylation of secondary thioamides with diaryliodonium salts under basic conditions<sup>[153]</sup>. The reaction was fully selective towards *S*-arylated products for acyclic and aromatic thioamides yielding thioimidates, but thiolactams preferentially undergo *N*-arylation (Fig. 21 a).

*S*-arylations with diaryliodonium salts have also recently been a topic of interest in our research group. In the late 2021, a paper by our group members was published covering the synthesis of aryl sulfides by direct metal-free arylation of thiols with diaryliodonium salts (Fig. 21 b)<sup>[154]</sup>. Aryl sulfide moiety is ubiquitous in natural products and bioactive molecules including several drug candidates and pharmaceuticals. The scope included various five-membered (benzazoles, thiazole, 2-thiazoline, 1,3,4-oxadiazole, 2-mercaptoimidazole) and six-membered heterocycles (pyridine and pyrimidine), and thiophenols. The reaction tolerates starting materials ranging from simple alkyl, through benzyl, to functional group-containing thiols. Additionally, a 1-thio- $\beta$ -D-gucose derivative was successfully *S*-arylated, demonstrating the usefulness of the method. This was quickly followed by an Indian group publication similar in topic, which focused more on specific examples of 5-mercaptotetrazoles and 2-mercaptopyridine arylations (Fig. 21 c and Fig. 21 d)<sup>[155]</sup>.

Early this year, Karchava and coworkers described *S*-arylation of potassium alkyl xanthates with diaryliodonium salts (Fig. 21 e)<sup>[156]</sup>. These can be further converted to aryl sulfides *via* Leuckart thiophenol reaction or to *S*-heterocyclic compounds.

Another paper from our research group was published on the *S*-arylation of phosphorothioate diesters and related compounds (Fig. 21 f)<sup>[157]</sup>. The reaction is operationally simple and proceeds without any additional reagents. The method was tested on broad scope of phosphorothioates, -dithioates, -selenoates, phosphonothioates, and phosphinothioates, and of diaryliodonium salts. Applicability of the procedure was demonstrated by the arylation of dinucleoside phosphorothioate and phosphonate(-)-menthol derivative, with a full retention of the stereochemical configuration at the phosphorus atom.



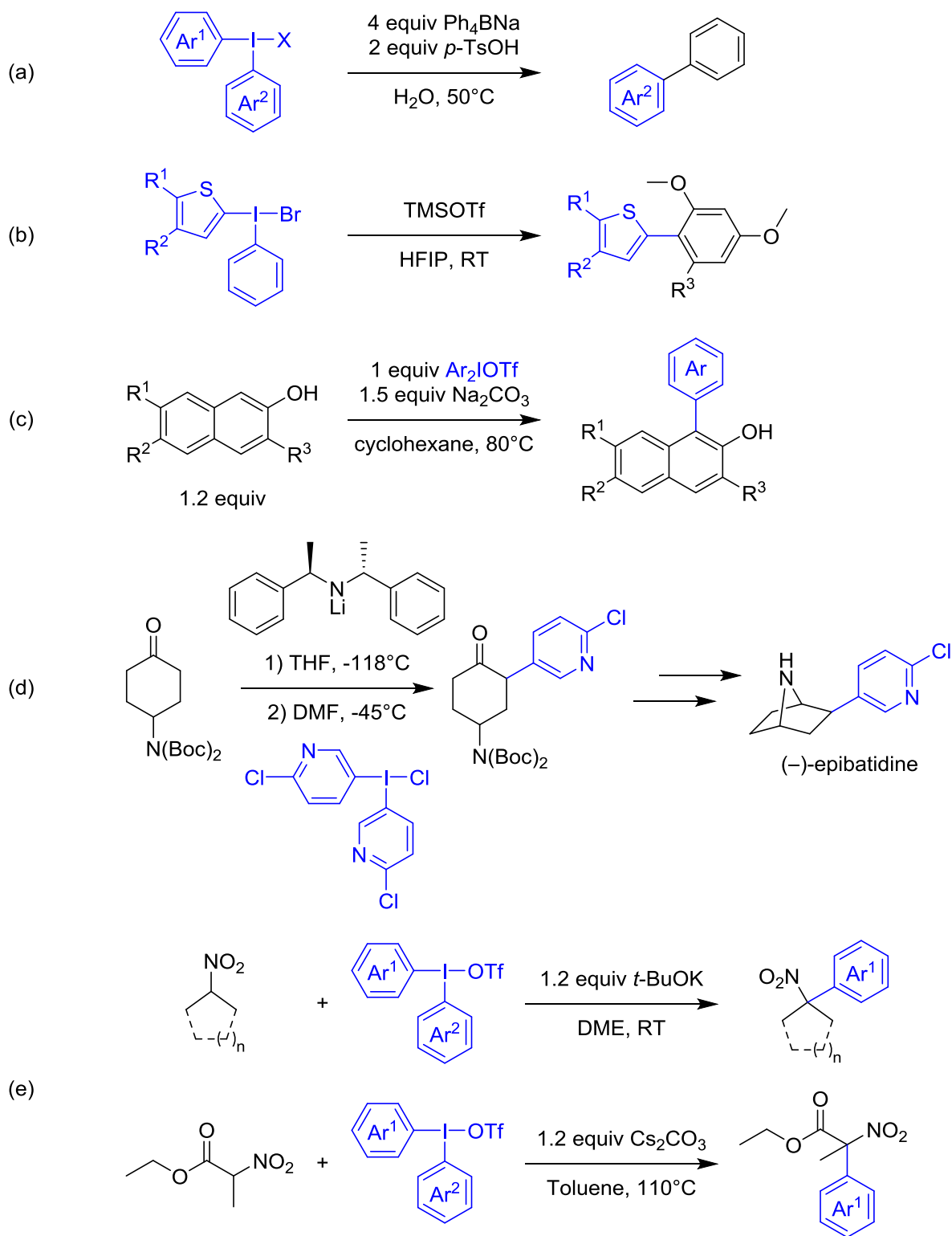
**Fig. 21.** Arylation of sulfur nucleophiles: (a) Oloffson and coworkers (2018)<sup>[153]</sup>, 25 examples, 32-93% yield; (b) Kalek and coworkers (2022)<sup>[154]</sup>, 28 examples, yields up to 100% (c) Thakur and coworkers (2022)<sup>[155]</sup> 5-mercaptotetrazoles, 23 examples, 62-91% yield and (d) 2-mercaptopyridine, 10 examples, 62-88% yield; (e) Karchava and coworkers (2023)<sup>[156]</sup>, >30 examples, 65-91% yield; (f) Sarkar and Kalek (2023)<sup>[157]</sup>, 30 examples, yields up to 100%.

#### 1.2.3.4. Carbon nucleophiles

Diaryliodonium salts were successfully used in metal-free arylations of several carbon nucleophiles, such as electron rich arenes or carbonyl compounds. Jie Yan and coworkers were first to report the synthesis of biaryls in 2006 (Fig. 22 a)<sup>[120, 158]</sup>. They treated diaryliodonium salts with excess sodium tetraphenylborate and *p*-TsOH in water at 50°C. In 2010, Kita's group reported *ipso* substitution of thiophene ring of unsymmetrical iodonium salt by 5-substituted 1,3-dimethoxybenzenes proceeding *via* SET mechanism in HFIP with the activation of the salt with TMSOTf (Fig. 22 b)<sup>[121]</sup>. Kalek group developed C-arylation of 2-naphthols using diaryliodonium salts (Fig. 22 c)<sup>[159]</sup>. The method provides complete C1

regioselectivity and enables the introduction of electron-poor aryl rings, affording biaryl scaffold with potential for the synthesis of pharmaceutically relevant compounds.

Beringer performed initial studies of employing diaryliodonium salts for the  $\alpha$ -arylations of carbonyl compounds, such as esters, ketones,  $\beta$ -diketones,  $\beta$ -ketoesters, and malonates in the 1960s. Yields of the reactions were moderate, sometimes mixtures of mono- and diarylated products were obtained, and the C/O-selectivity was not always complete. In the 1990s research was continued and Koser discovered that diphenyliodonium fluoride could be utilized in  $\alpha$ -phenylation of silyl enol ethers. Oh and coworkers reported in 1999 the arylation of  $\alpha$ -substituted malonates with NaH in DMF at room temperature<sup>[120]</sup>. Aggarwal and Olofsson in 2005, used  $\alpha$ -arylation of *N,N*-di(tert-butyloxycarbonyl)aminocyclohexanone with a diaryliodonium salt in the total synthesis of (-)-epibatidine (Fig. 22 d) and the formal synthesis of (+)-epibatidine<sup>[160]</sup>. Also in 2015, Olofsson's group extended the scope of  $\alpha$ -arylation of nitroalkanes and  $\alpha$ -nitroesters with excellent functional group tolerance (Fig. 22 e)<sup>[161]</sup>. Fu-Min Zhang and coworkers reported metal-free C-arylation of  $\alpha$ -nitroketones with diaryliodonium salts towards tertiary  $\alpha$ -amino- $\alpha$ -aryl ketones and alcohols, which are widespread motifs in numerous natural alkaloids and clinical medicines<sup>[162]</sup>. Mohanan's group reported the arylation of  $\alpha$ -fluoro- $\alpha$ -nitroacetamides<sup>[163]</sup>.



**Fig. 22.** Arylation of carbon nucleophiles: (a) Jie Yan and coworkers (2006)<sup>[158]</sup>, 9 examples, 61-95% yield; (b) Kita and coworkers (2010)<sup>[121]</sup>, 10 examples, 50-81% yield; (c) Kalek and coworkers (2019)<sup>[159]</sup>, 34 examples, 20-91% yield; (d) Aggarwal and Olofsson total synthesis of (-)-epibatidine (2005)<sup>[160]</sup>; (e) Olofsson and coworkers (2015)<sup>[161]</sup>, 36 examples, 24-93% yields.

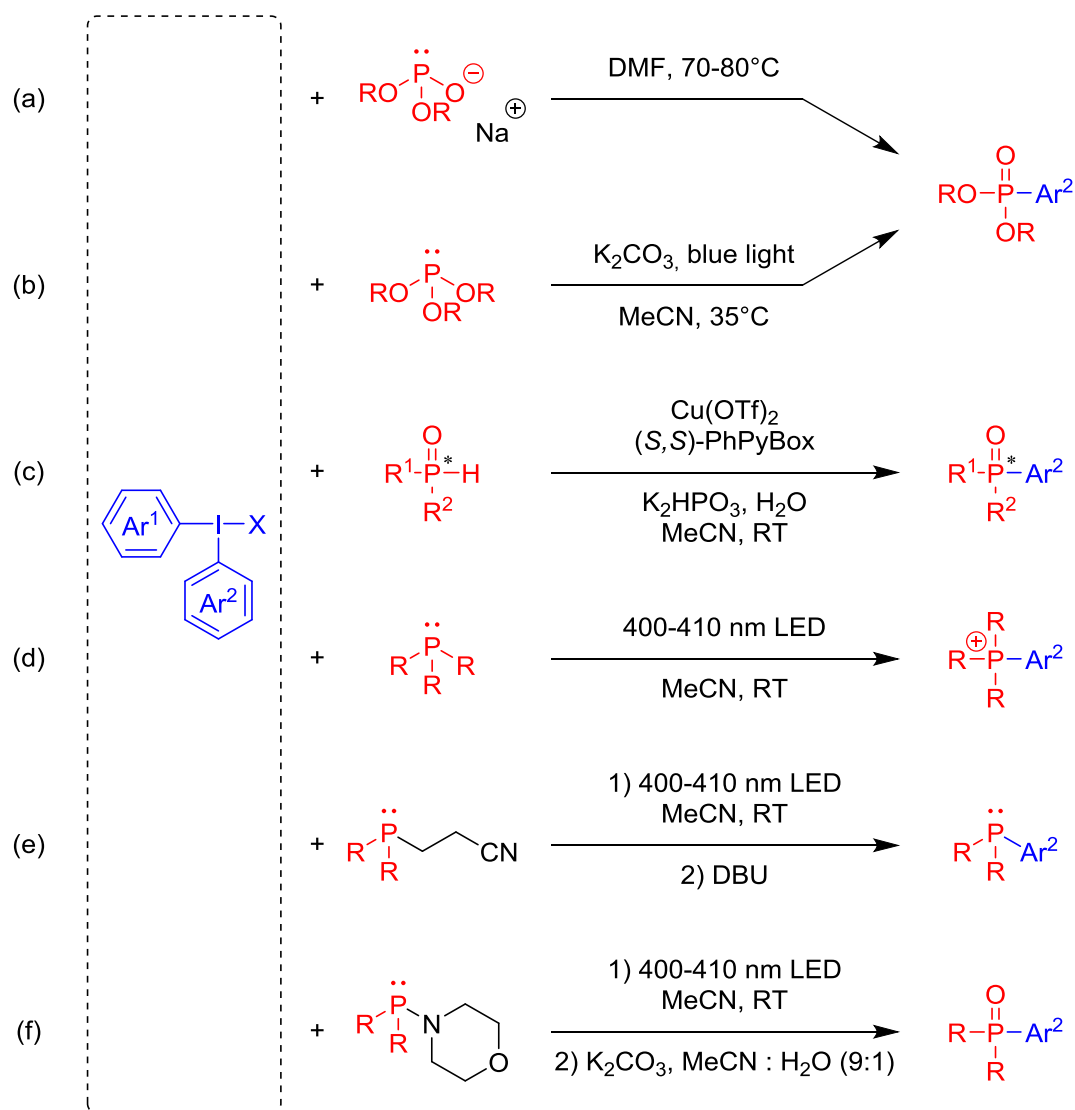
### 1.3. *P*-arylation of phosphorus nucleophiles with diaryliodonium salts

Chen and Liu in 1993 achieved the first *P*-arylation of *H*-phosphonates with diaryliodonium salts in DMF, at 70-80°C, under nitrogen, providing arylphosphonates with 79-93% yield (Fig. 23 a)<sup>[164]</sup>. Lakhdar and coworkers achieved the Arbuzov-type arylation of phosphites with diaryliodonium salts under mild, metal-free conditions and they synthesized two bioactive compounds with their methodology (a steroid derivative and a calcium antagonist, Fig. 23 b)<sup>[165]</sup>. Two other papers on *H*-phosphonate arylation have also been published by Chen and Zhou in 2001<sup>[166]</sup>, and Zhao and coworkers in 2013<sup>[167]</sup>, but they used transition metal catalysts [tetrakis(triphenylphosphine)-palladium(0)] and copper (I) chloride respectively.

Zhao and coworkers reported *P*-arylation of secondary phosphine oxides to the corresponding tertiary derivatives. These can be used directly as ligands in transition metal complexes or can be easily reduced to tertiary phosphines, which also serve as organocatalysts and ligands. In 2016, Gaunt's group reported a method for the enantioselective arylation of secondary phosphine oxides with diaryliodonium salts by the *in situ* generated copper-(S,S)-diphenylpybox complex in acetonitrile. They obtained 35 chiral tertiary phosphine oxides (TPOs) with yields ranging from 79% to 99% and enantiomeric excesses above 90% in most cases, up to 98% ee (Fig. 23 c)<sup>[110]</sup>.

Quarternization of phosphines was carried out by the *P*-arylation with diaryliodonium salts. Hanamoto and coworkers synthesized  $\alpha$ -fluorovinyltriphenyl-phosphonium triflate in 82% yield by the arylation of  $\alpha$ -fluorovinyl-diphenylphosphine with diphenyliodonium triflate in the presence of copper(I) chloride in 1,1,2,2-tetrachloroethane at 140°C<sup>[168, 169]</sup>. In 2016, Denton and coworkers presented a photoredox-mediated arylation using Ru(bipy)<sub>3</sub>Cl<sub>2</sub> complex in acetonitrile at room temperature<sup>[170]</sup>. Dalla reported the arylation of phosphiranes in the presence of copper metal and copper(I) chloride in DCE at 50°C or higher for one hour, but only three different phosphiranium salts were synthesized<sup>[171]</sup>.

Karchava and coworkers proposed the first mild and metal-free conditions for the *P*-arylation of tertiary phosphines with diaryliodonium salts in 2019 by simple irradiation of salt and phosphine mixture with 400-410 nm light in acetonitrile at RT for 2 h. Based on control experiments, they proposed reaction mechanism involving initial formation of electron donor-acceptor (EDA) complex followed by single electron transfer (SET) from phosphorus to iodine. This leads to the decomposition of the complex and the formation of aryl radical, phosphorus cation radical, and 2-iodomesitylene as by-product. The final step is the recombination of radicals leading to phosphonium salt product (Fig. 23 d)<sup>[172]</sup>.



**Fig. 23.** (a) Chen and Liu aryl phosphonates preparation from *H*-phosphites after deprotonation with NaH<sup>[164]</sup>, 7 examples, 81-93% yield; (b) Lakhdar and coworkers aryl phosphonates preparation from phosphites<sup>[165]</sup>, 25 examples, 28-94% yield; (c) Beaud, Phipps and Gaunt enantioselective arylation of SPOs<sup>[110]</sup>, 35 examples, 79-99% yield, 58-98% ee; (d) Karchava and coworkers tertiary phosphine quaternarization<sup>[172]</sup>, 28 examples, 44-94% yield; (e) Bugaenko and Karchava preparation of tertiary phosphines from pre-made 2-cyano-ethylphosphines<sup>[173]</sup>, 30 examples, 35-86% yield; (f) Bugaenko and Karchava preparation of TPOs from pre-made 4-(diphenylphosphanyl)morpholine<sup>[174]</sup>, 26 examples, 12-85% yield.

Bugaenko and Karchava recently proposed the synthesis of tertiary phosphines, but their method requires first conversion of secondary phosphine to 2-cyanoethylphosphines, which “surrogates” secondary phosphine in a subsequent arylation with diaryliodonium salt in acetonitrile at RT for 4 h, resulting in the formation of quaternary phosphonium salt. This intermediate is then, without isolation, decomposed to the target tertiary phosphine with DBU (Fig. 23 e)<sup>[173]</sup>. Since the *P*-arylation with diaryliodonium salt step converts tertiary phosphine to quaternary phosphonium salt, it only mimics the tertiarization of secondary phosphines and thus does not correspond to the reaction described in this thesis.



In May of this year another paper by Bugaenko and Karchava was published. They presented the preparation of tertiary phosphine oxides, but again – they started from 4-(diphenyl-phosphanyl)morpholine which was quaternarized with diaryliodonium salt under the previously developed photochemical conditions. Subsequently in the proposed mechanism, the quaternary phosphonium salt reacts with hydroxyl or carbonate anion yielding tertiary phosphine oxide as the final product (Fig. 23 f)<sup>[174]</sup>. The Karchava's works are a considerable advancement, since they are the only developed methods of quaternarization of tertiary phosphines in mild and metal-free conditions with subsequent transformations providing different classes of organophosphorus compounds.

## Chapter 2. Results

### 2.1. Reaction design and initial experiments

The number of practical methods for the preparation of phosphines remains limited and suffers from drawbacks, such as harsh conditions, limited functional group tolerance, or the use of transition metal catalysts (see 1.1.2. Preparation). Main disadvantages of the latter are high price and toxicity. For example, palladium costs ~1,200 \$/oz. and platinum ~900 \$/oz (August 2<sup>nd</sup>, 2023) and the most of their mine production is localized in unstable (either politically or economically) or hostile countries, such as Russia, South Africa, and Zimbabwe (85% of palladium and 92% of platinum mine production is located in these three countries<sup>[175]</sup>), which can rapidly impact their price and availability. Therefore, finding novel mild and metal-free methods for phosphine synthesis is a justified research goal.

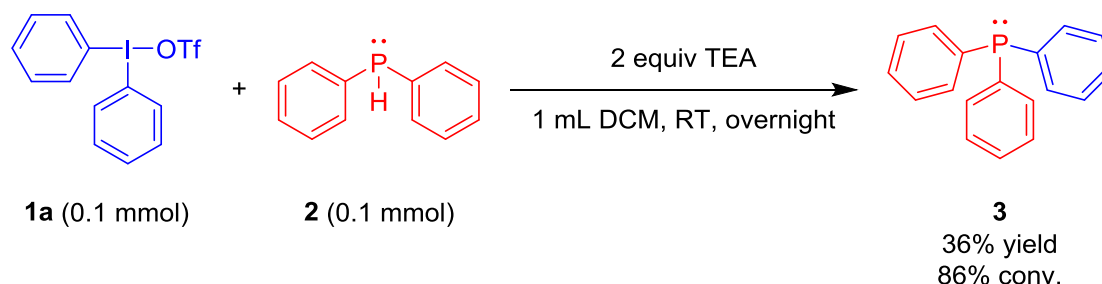
Transition metal catalysts can be replaced in some transformations by hypervalent iodine species, such as diaryliodonium salts in arylation reactions. The latter exhibit similar reactivity patterns, while being cheap and nontoxic. Main byproducts are iodoarenes that do not require special purification techniques unlike transition metal complexes<sup>[176]</sup> and can be reused in iodonium salt synthesis. Literature review showed that iodonium salts have been applied in arylation (see 1.3. *P*-arylation of phosphorus nucleophiles), alkenylation<sup>[177, 178]</sup>, and alkynylation<sup>[177, 179]</sup> of tertiary phosphines to quaternary phosphonium salts and that reactions can proceed under mild conditions. It also showed that the reactions of iodonium salts with secondary phosphines remains an unexplored area.

From that we conceived an idea to develop a method for the synthesis of unsymmetrical tertiary phosphines by the direct arylation of secondary phosphines with diaryliodonium salts.

#### 2.1.1. Experimental setup

The initial experimental setup was simple and consisted of mixing secondary phosphine, diaryliodonium salt, and a base in a solvent. Diphenylphosphine (**2**) and diphenyliodonium triflate (**1a**) were selected as the model substrates. Triethylamine, simple organic base to neutralize acid formed in the reaction and to prevent phosphine protonation ( $pK_a$  of TEA's conjugated acid is around 11, while  $pK_a$  of phosphines' conjugated acids close to 0<sup>[180–182]</sup>). Diphenylphosphine is liquid and, as a typical secondary phosphine, highly susceptible to air oxidation. Therefore, the setting up of the reaction was conducted in an inert atmosphere glovebox. The initial reaction conditions were: 1 equiv. of phosphine and iodonium salt, 1.5 equiv. of TEA, stirring for 24 h at RT in DCM (at 0.1 M conc. of the limiting substrate). The reaction outcome was analyzed with <sup>31</sup>P NMR spectroscopy using internal

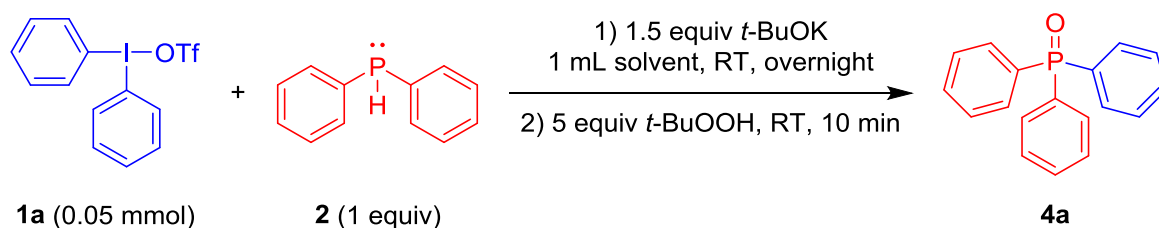
standard to quantify the yield (trimethyl phosphate, added after the reaction). The NMR spectra was measured directly on the reaction mixture (in non-deuterated DCM), by employing a coaxial insert tube with H<sub>3</sub>PO<sub>4</sub> solution in D<sub>2</sub>O, which allows for locking and referencing the chemical shift. A number of identical reaction were set up and they indeed resulted in the formation of expected triphenylphosphine product (**3**) in 28-36%, accompanied by a mixture of byproducts and unreacted Ph<sub>2</sub>PH (Fig. 23).



**Fig. 24.** Results of initial experiments.

With these promising results, I moved to the optimization of the reaction conditions, however, I encountered several technical problems that required some changes in the experimental procedure. First, in many of the solvents, the reaction mixtures were non-homogenous, possibly falsifying the measured yields. To overcome this issue, the solvent was removed on rotavapor and the residue was redissolved in DCM (that solubilizes all the material) prior to the NMR measurement. However, the evaporation led to partial erratic oxidation of the product and of the unreacted substrate to triphenyl- and diphenylphosphine oxides, respectively (TPPO and DPPO). In this situation, I decided that it will be beneficial to deliberately oxidize samples after the reaction, which should ease handling, thus streamline the analysis and the optimization procedure. Therefore, from now on, 5 equiv. of *tert*-butyl hydroperoxide were always added after the reaction, followed by concentration, redissolving in DCM, and NMR analysis.

The second issue concerning the reaction setup was the order of addition. Diaryliodonium salts are solid, so they were weighted directly in the vial, in which reaction was conducted, followed by the addition of the solvent, phosphine, and liquid base. For solid bases, they were added to the vial before the solvent and phosphine. However, after conducting a series of experiments, I found that the order, in which the substrates were added significantly impacts the yield of reaction. In particular, I discovered that adding the base before the phosphine has a detrimental effect on the yield (Table 1). Although the reason for such outcome is unclear, in all the subsequent reactions, the base was added last (even for solid ones).

**Table 1.** Results of experiments with different substrate addition order.

Solvent	Base added before phosphine		Phosphine added before base	
	Entry	Yield [%] <sup>a</sup>	Entry	Yield [%] <sup>a</sup>
AcOEt	1	20	9	46
DME	2	28	10	64
1,2-DCE	3	17	11	44
DMF	4	20	12	70
MeCN	5	31	13	88
MeNO <sub>2</sub>	6	19	14	36
DMSO	7	41	15	91
EtOH	8	31	16	56

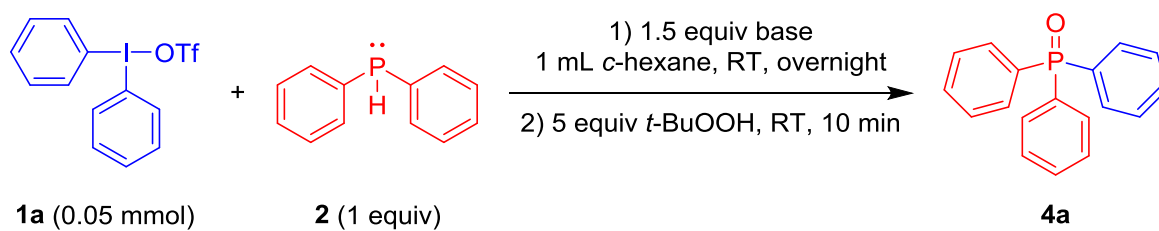
<sup>a</sup> Yields were determined by <sup>31</sup>P NMR spectroscopy using internal standard.

## 2.2. Optimization of reaction conditions

Base screening was conducted using cyclohexane as the solvent (Table 2). Potassium *tert*-butoxide (77%) was found to be the best base among ones tested, followed by potassium hydroxide (54%) and caesium carbonate (45%).

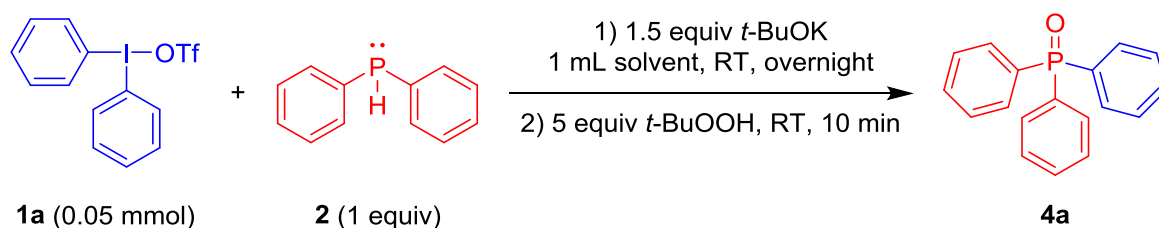
In the next step, I conducted the solvent screening, with potassium *tert*-butoxide as the base (Table 3). The best results were obtained in DMSO (91%) and acetonitrile (88%), the difference being in the order of the experimental error. Due to the high boiling point of DMSO, possibly complicating the work-up procedure, I decided to use acetonitrile during the further optimization.

**Table 2.** Results of base screening.



Entry	Base	Yield [%] <sup>a</sup>
1	TEA	37
2	DBU	38
3	DBN	33
4	DIPEA	10
5	DABCO	32
6	TMG	38
7	2,6-lutidine	1
8	Pyridine	2
9	Imidazole	21
10	<i>t</i> -BuOK	77
11	Cs <sub>2</sub> CO <sub>3</sub>	45
12	AcOK	36
13	NaHCO <sub>3</sub>	-
14	KOH	54
15	Li <sub>2</sub> CO <sub>3</sub>	4
16	Na <sub>2</sub> CO <sub>3</sub>	2

<sup>a</sup> Yields were determined by <sup>31</sup>P NMR spectroscopy using internal standard.

**Table 3.** Results of solvent screening.

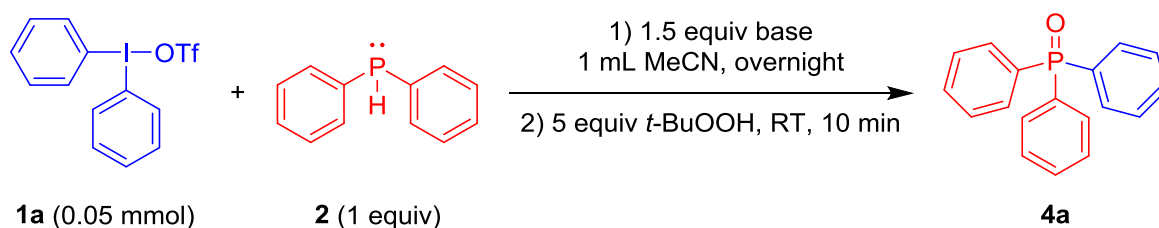
Entry	Solvent	Yield [%] <sup>a</sup>	Entry	Solvent	Yield [%] <sup>a</sup>
1	<i>c</i> -hexane	61	11	1,2-DCE	44
2	<i>n</i> -hexane	63	12	DMF	70
3	Toluene	63	13	MeCN	88
4	Benzene	81	14	MeNO <sub>2</sub>	36
5	Diethyl ether	73	15	DMSO	91
6	CPME	63	16	EtOH	56
7	1,4-dioxane	59	17	DCM	35
8	Acetone	56	18	THF	58
9	AcOEt	46	19	PhCF <sub>3</sub>	83
10	DME	64			

<sup>a</sup> Yields were determined by <sup>31</sup>P NMR spectroscopy using internal standard.

Next, I conducted the optimization of the reaction temperature, using both potassium *tert*-butoxide and KOH. This showed that the yield of reaction increases as the temperature decreases (Table 4). However, I decided to keep the existing reaction conditions, i.e. RT, which secures a satisfactory yield. Namley, to run the reaction at 0 °C, the reaction vessel needs to be moved to a cooled workstation outside the glovebox. Adding solid bases, while keeping the protective atmosphere is possible, but adds to a considerable difficulty.

Because potassium hydroxide provided better yield in the experiments presented in Table 4, I conducted an additional small solvent screening with KOH instead of *t*-BuOK. However, the yields were lower with potassium hydroxide in acetonitrile and dimethyl sulfoxide. Specifically, the reactions with KOH gave triphenylphosphine oxide in 70% and 76% yield, respectively, while these with *t*-BuOK in 88% and 91% yield, respectively. For diethyl ether and ethanol yields were similar (but low) for both the bases, and for ethyl acetate – 54% yield with KOH and 46% with *t*-BuOK.

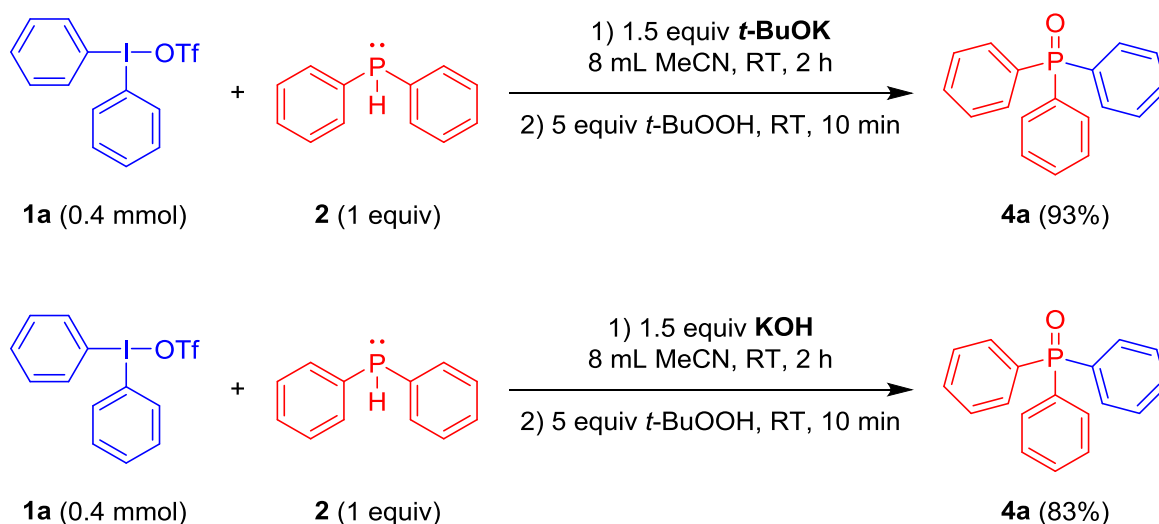
**Table 4.** Results of temperature optimization.



Entry	Conditions	Yield [%] <sup>a</sup>
1	50°C, KOH	82
2	RT, KOH	91
3	0°C, KOH	100
4	50°C, <i>t</i> -BuOK	70
5	RT, <i>t</i> -BuOK	78
6	0°C, <i>t</i> -BuOK	100

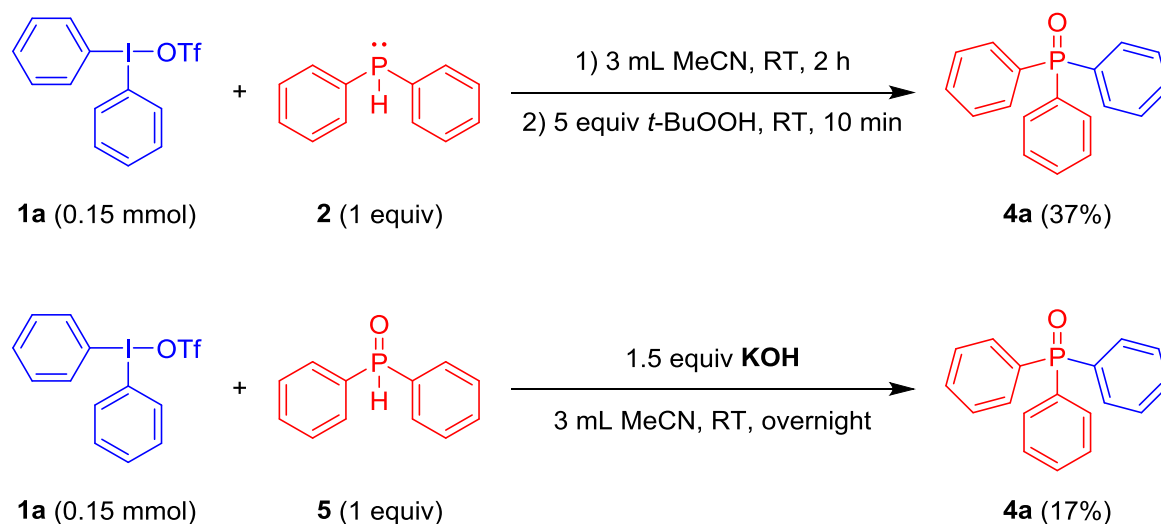
<sup>a</sup> Yields were determined by <sup>31</sup>P NMR spectroscopy using internal standard.

Finally, I examined the progress of the reaction with time. Quite surprisingly, it was discovered that the reaction proceeded very quickly. Namely, already within 5 minutes >50% of diphenylphosphine was consumed, and high yields of product were formed. After half an hour at room temperature the yield was 99% with potassium *tert*-butoxide and 73% after an hour with potassium hydroxide. To make sure that reaction is finished for other, perhaps slower reacting, substrate combinations, I decided to use a 2-hour reaction time in the future.



**Fig. 25.** Testing final conditions on 0.4 mmol scale. Values in brackets are isolated yields.

To verify that the optimized reaction conditions are scalable, I conducted two experiments on 0.4 mmol scale (Fig. 25). The obtained isolated yields match very well those observed during the small-scale experiments.



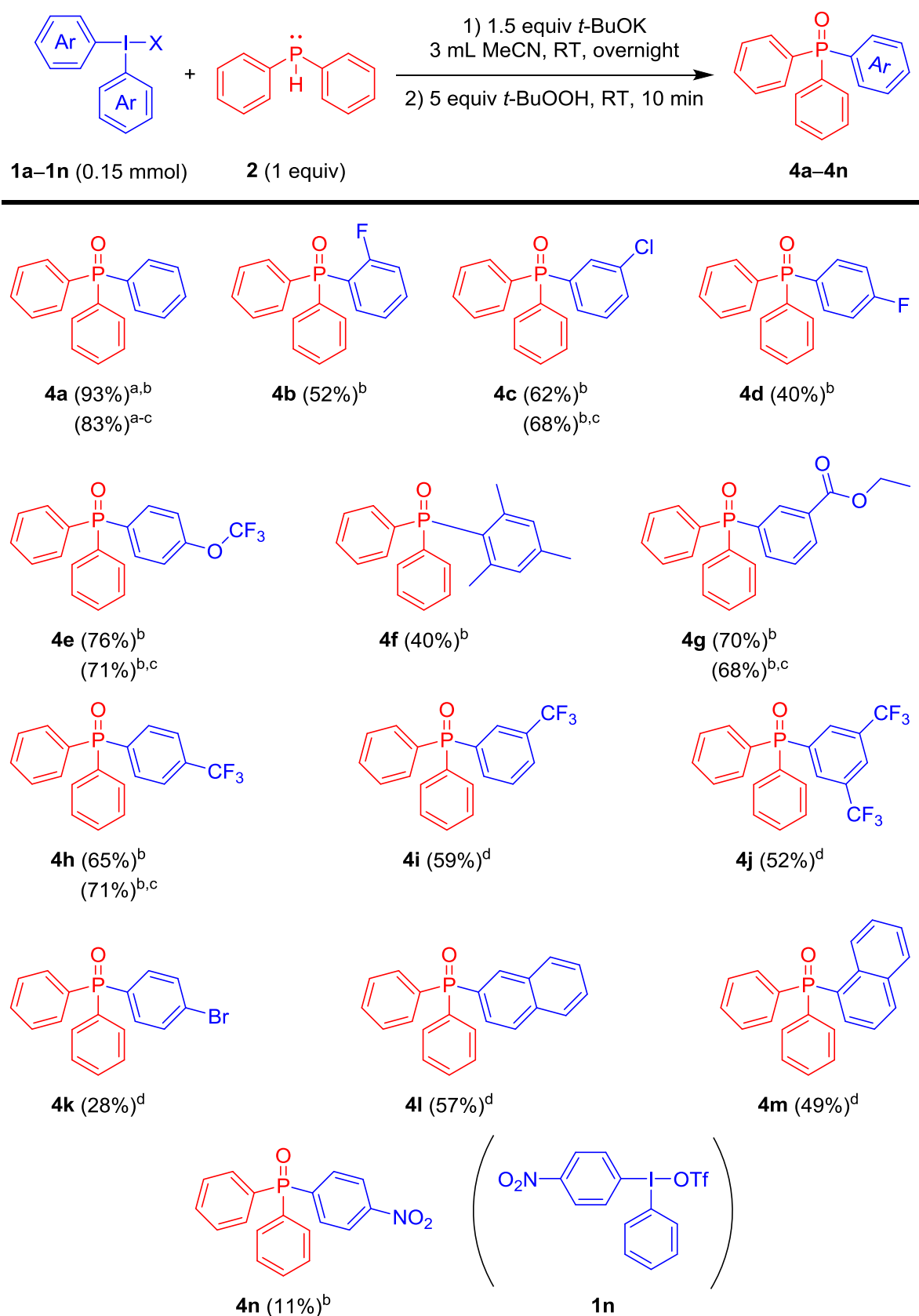
**Fig. 26.** The control experiments. Lack of base reduces yield (above) and diphenylphosphine oxide **5** reacts poorly with diaryliodonium salt in reaction conditions.

I have also conducted two control experiments (Fig. 26). They showed that yield is significantly reduced if reaction is carried out without the base, probably due to protonation of substrate phosphine during the reaction. Also, diphenylphosphine oxide reacts very poorly with diaryliodonium salt. This second result is important because it shows that possible further arylation of diphenylphosphine oxide after substrate oxidation at step 2 should have a minimal effect on final yield of reaction.

### 2.3. Scope and limitations

With the optimized conditions in hand, I moved to explore the scope and limitations of the method with respect to the diaryliodonium salt. The reactions were performed on a small-scale and the yields are determined by  $^{31}\text{P}$  NMR spectroscopy using internal standard. Reaction gives triphenylphosphine oxide **4a** in excellent yield and it works for aryl rings carrying different types of substituents. Halide-substituted rings (**4b–4d**) and aryls containing electron-donating (**4e**, **4f**) and diverse electron-withdrawing substituents (**4g–4j**) furnish the desired products in fair to good yields. Extended aryl systems, 1- and 2-naphthyl, were also successfully transferred (**4l**, **4m**). Only *para*-bromo- and *para*-nitrophenyl were transferred in lower yields (**4k**, **4n**).





**Fig. 27.** Results of scope with respect to the diaryliodonium salt. Yields were determined by <sup>31</sup>P NMR spectroscopy using internal standard, <sup>a</sup> reaction at 0.4 mmol scale, isolated yield, <sup>b</sup> X = –OTf, <sup>c</sup> KOH instead of *t*-BuOK, <sup>d</sup> X = –BF<sub>4</sub>.

## 2.4. Conclusions

The work described in this thesis demonstrates that the diaryliodonium salts can be applied to effect a metal-free arylation of secondary phosphines to tertiary phosphines. The reaction conditions have been optimized, including the establishment of the best solvent, base, temperature, and reaction time. Subsequently, the scope of the reaction was explored with respect to diaryliodonium salt, successfully synthesizing 14 phosphine oxides in yields ranging from 11 to 93%.

To fully develop a synthetic method, the future work will require to evaluate the scope with regard to the phosphine nucleophile substrate, as well as to obtain all the products in isolated yields. Additionally, a possibility to isolate free phosphines (without oxidation) needs to be tested.

## Acknowledgments

I would like to express my gratitude and thank everyone who contributed to this work. First of all, I wanted to thank my supervisor **Marcin Kalek** for his support and time during my studies. I learned a lot from you, and working in your team was a great experience.

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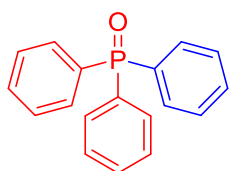
## Experimental section

Unless otherwise noted, all materials were purchased from commercial suppliers and used without purification. Anhydrous toluene, dichloromethane and diethyl ether were purified prior to use by passage through a column of neutral alumina under nitrogen (Solvent Purification System, SPS).

$^1\text{H}$ ,  $^{19}\text{F}$ , and  $^{31}\text{P}$  NMR spectroscopic data were collected on Varian 400 MHz spectrometer at ambient temperature. The chemical shifts are reported in ppm relative to solvent peaks.

## Experimental procedures and characterization of compounds

### Triphenylphosphine oxide (4a)



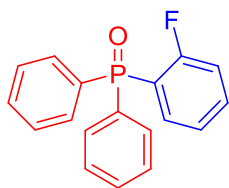
A 20 ml vial was charged with diphenyliodonium triflate **1a** (172 mg, 0.4 mmol), acetonitrile (anhydrous, 8 mL), diphenylphosphine **2** (78.4 mg, 0.4 mmol, 95% purity) followed by the addition of potassium *tert*-butoxide (67.3 mg, 0.6 mmol). The mixture was stirred for 2 hours at room temperature. Then, *tert*-butyl hydroperoxide (257 mg, 2 mmol, 70% solution in water) was added and reaction mixture was stirred for additional 10 minutes, followed by the removal of the solvent under reduced pressure. After purification by flash chromatography (silica, *n*-hexane/ethyl acetate) the product **4a** was obtained as white solid (103 mg, 93%).  $^1\text{H}$  and  $^{31}\text{P}$  NMR spectra of compound is consistent with that reported in the literature<sup>[106, 167]</sup>.

$^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  7.69 – 7.60 (m, 6H), 7.55 – 7.47 (m, 3H), 7.46 – 7.34 (m, 6H).  $^{31}\text{P}$  NMR (162 MHz, Deuterium Oxide)  $\delta$  29.06.

### General procedure A

A 4 ml vial was charged with diaryliodonium salt **1a-n**, acetonitrile (anhydrous, 3 mL), diphenylphosphine **2** (29.4 mg, 0.15 mmol, 95% purity) followed by the addition of potassium *tert*-butoxide (25.2 mg, 0.225 mmol). The mixture was stirred for 2 hours at room temperature. Then *tert*-butyl hydroperoxide 70% solution in water (96.6 mg, 0.75 mmol) was added and reaction mixture was stirred for additional 10 minutes. Then trimethyl phosphate (21 mg, 0.15 mmol) was added. Yields were assessed by  $^{31}\text{P}$  NMR relative to internal standard (trimethyl phosphate). Products were purified by preparative TLC (silica, *n*-hexane/ethyl acetate).

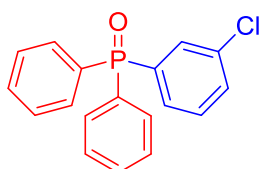
### (2-fluorophenyl)diphenylphosphine oxide (**4b**)



The compound **4b** was prepared according to General procedure A from bis(2-fluorophenyl)-iodonium triflate **1b** (69.9 mg, 0.15 mmol).  $^1\text{H}$  NMR spectra of compound is consistent with that reported in the literature<sup>[106]</sup>.

$^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  7.94 – 7.83 (m, 1H), 7.79 – 7.68 (m, 4H), 7.62 – 7.52 (m, 3H), 7.52 – 7.43 (m, 4H), 7.35 – 7.28 (m, 1H), 7.14 – 7.05 (m, 1H).  $^{19}\text{F}$  NMR (376 MHz, Chloroform-*d*)  $\delta$  -99.41 (dt,  $J$  = 10.7, 5.9 Hz).  $^{31}\text{P}$  NMR (162 MHz, Deuterium Oxide)  $\delta$  24.37.

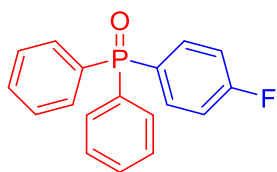
### (3-chlorophenyl)diphenylphosphine oxide (**4c**)



The compound **4c** was prepared according to General procedure A from bis(3-chlorophenyl)-iodonium triflate **1c** (74.9 mg, 0.15 mmol).  $^1\text{H}$  NMR spectra of compound is consistent with that reported in the literature<sup>[106]</sup>.

$^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  7.70 – 7.62 (m, 5H), 7.61 – 7.54 (m, 3H), 7.54 – 7.52 (m, 1H), 7.52 – 7.46 (m, 5H), 7.43 – 7.38 (m, 1H).  $^{31}\text{P}$  NMR (162 MHz, Deuterium Oxide)  $\delta$  27.97.

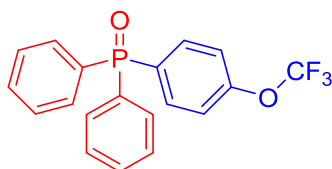
#### (4-fluorophenyl)diphenylphosphine oxide (**4d**)



The compound **4d** was prepared according to General procedure A from bis(4-fluorophenyl)iodonium triflate **1d** (69.9 mg, 0.15 mmol).  $^1\text{H}$  and  $^{31}\text{P}$  NMR spectra of compound is consistent with that reported in the literature<sup>[167]</sup>.

$^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  7.72 – 7.60 (m, 6H), 7.59 – 7.52 (m, 2H), 7.51 – 7.42 (m, 4H), 7.20 – 7.10 (m, 2H).  $^{31}\text{P}$  NMR (162 MHz, Deuterium Oxide)  $\delta$  28.39.

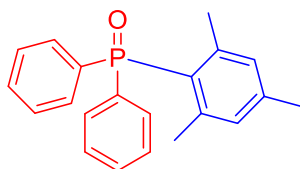
#### Diphenyl(4-(trifluoromethoxy)phenyl)phosphine oxide (**4e**)



The compound **4e** was prepared according to General procedure A from bis(4-(trifluoromethoxy)phenyl)iodonium triflate **1f** (89.7 mg, 0.15 mmol).  $^1\text{H}$ ,  $^{19}\text{F}$  and  $^{31}\text{P}$  NMR spectra of compound is consistent with that reported in the literature<sup>[167, 183]</sup>.

$^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  7.76 – 7.62 (m, 6H), 7.61 – 7.53 (m, 2H), 7.52 – 7.45 (m, 4H), 7.33 – 7.27 (m, 2H).  $^{19}\text{F}$  NMR (376 MHz, Chloroform-*d*)  $\delta$  -57.62.  $^{31}\text{P}$  NMR (162 MHz, Deuterium Oxide)  $\delta$  28.02.

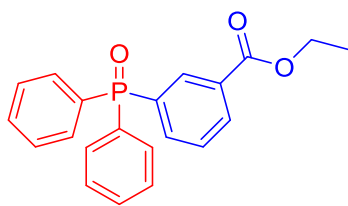
#### Mesityldiphenylphosphine oxide (**4f**)



The compound **4h** was prepared according to General procedure A from dimesityliodonium triflate **1h** (77.2 mg, 0.15 mmol).  $^1\text{H}$  and  $^{31}\text{P}$  NMR spectra of compound is consistent with that reported in the literature<sup>[167]</sup>.

$^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  7.69 – 7.62 (m, 5H), 7.54 – 7.47 (m, 2H), 7.47 – 7.40 (m, 5H), 6.90 – 6.86 (m, 2H), 2.30 (s, 3H), 2.12 (s, 6H).  $^{31}\text{P}$  NMR (162 MHz, Deuterium Oxide)  $\delta$  30.50.

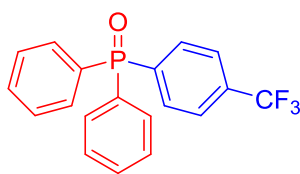
### Ethyl 3-(diphenylphosphoryl)benzoate (4g)



The compound **4g** was prepared according to General procedure A from bis(3-(ethoxycarbonyl)phenyl)iodonium triflate **1g** (86.1 mg, 0.15 mmol).  $^1\text{H}$  and  $^{31}\text{P}$  NMR spectra of compound is consistent with that reported in the literature<sup>[184]</sup>.

$^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.42 – 8.32 (m, 1H), 8.26 – 8.18 (m, 1H), 7.92 – 7.74 (m, 1H), 7.72 – 7.62 (m, 4H), 7.61 – 7.41 (m, 7H), 4.35 (q,  $J = 7.1$  Hz, 2H), 1.35 (t,  $J = 7.1$  Hz, 3H).  $^{31}\text{P}$  NMR (162 MHz, Deuterium Oxide)  $\delta$  28.47.

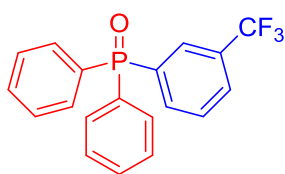
### Diphenyl(4-(trifluoromethyl)phenyl)phosphine oxide (4h)



The compound **4e** was prepared according to General procedure A from bis(4-(trifluoromethyl)phenyl)iodonium triflate **1e** (84.9 mg, 0.15 mmol).  $^1\text{H}$  and  $^{31}\text{P}$  NMR spectra of compound is consistent with that reported in the literature<sup>[106, 108]</sup>.

$^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  7.86 – 7.78 (m, 2H), 7.75 – 7.62 (m, 6H), 7.61 – 7.55 (m, 2H), 7.53 – 7.45 (m, 4H).  $^{31}\text{P}$  NMR (162 MHz, Deuterium Oxide)  $\delta$  28.10.

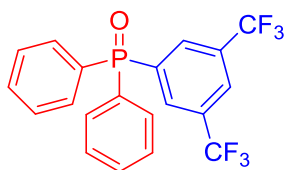
### Diphenyl(3-(trifluoromethyl)phenyl)phosphine oxide (4i)



The compound **4i** was prepared according to General procedure A from bis(4-(trifluoromethyl)phenyl)iodonium tetrafluoroborate **1i** (75.6 mg, 0.15 mmol).  $^1\text{H}$  and  $^{31}\text{P}$  NMR spectra of compound is consistent with that reported in the literature<sup>[167]</sup>.

$^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.03 – 7.95 (m, 1H), 7.89 – 7.76 (m, 2H), 7.71 – 7.55 (m, 7H), 7.54 – 7.46 (m, 4H).  $^{31}\text{P}$  NMR (162 MHz, Deuterium Oxide)  $\delta$  27.99.

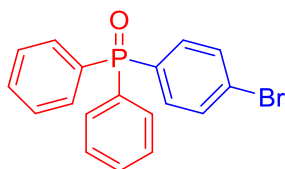
### (3,5-bis(trifluoromethyl)phenyl)diphenylphosphine oxide (4j)



The compound **4j** was prepared according to General procedure A from bis(3,5-di(trifluoromethyl)phenyl)iodonium tetrafluoroborate **1j** (96 mg, 0.15 mmol).  $^1\text{H}$  and  $^{31}\text{P}$  NMR spectra of compound is consistent with that reported in the literature<sup>[111]</sup>.

$^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.19 – 8.09 (m, 2H), 8.06 – 8.02 (m, 1H), 7.72 – 7.58 (m, 6H), 7.57 – 7.48 (m, 4H).  $^{31}\text{P}$  NMR (162 MHz, Deuterium Oxide)  $\delta$  26.80.

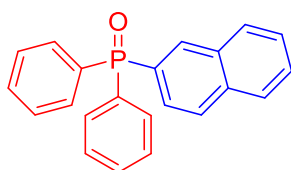
### (4-bromophenyl)diphenylphosphine oxide (4k)



The compound **4k** was prepared according to General procedure A from bis(4-fluorophenyl)iodonium tetrafluoroborate **1k** (78.9 mg, 0.15 mmol).  $^1\text{H}$  and  $^{31}\text{P}$  NMR spectra of compound is consistent with that reported in the literature<sup>[167]</sup>.

$^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  7.69 – 7.44 (m, 14H).  $^{31}\text{P}$  NMR (162 MHz, Deuterium Oxide)  $\delta$  28.40.

### Naphthalen-2-ylidiphenylphosphine oxide (4l)

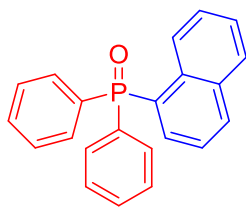


The compound **4l** was prepared according to General procedure A from bis(2-naphthyl)iodonium tetrafluoroborate **1l** (70.2 mg, 0.15 mmol).  $^1\text{H}$  and  $^{31}\text{P}$  NMR spectra of compound is consistent with that reported in the literature<sup>[106, 111]</sup>.

$^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.33 – 8.26 (m, 1H), 7.94 – 7.85 (m, 3H), 7.76 – 7.68 (m, 4H), 7.68 – 7.52 (m, 5H), 7.51 – 7.44 (m, 4H).  $^{31}\text{P}$  NMR (162 MHz, Deuterium Oxide)  $\delta$  29.06.



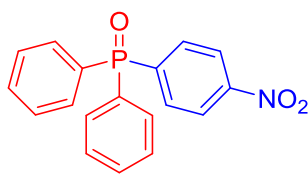
### Naphthalen-1-yl-diphenylphosphine oxide (**4m**)



The compound **4m** was prepared according to General procedure A from bis(1-naphthyl)-iodonium tetrafluoroborate **1m** (70.2 mg, 0.15 mmol).  $^1\text{H}$  and  $^{31}\text{P}$  NMR spectra of compound is consistent with that reported in the literature<sup>[167]</sup>.

$^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.62 – 8.55 (m, 1H), 8.06 – 7.98 (m, 1H), 7.93 – 7.86 (m, 1H), 7.74 – 7.63 (m, 4H), 7.59 – 7.51 (m, 2H), 7.51 – 7.43 (m, 6H), 7.43 – 7.35 (m, 1H), 7.34 – 7.26 (m, 1H).  $^{31}\text{P}$  NMR (162 MHz, Deuterium Oxide)  $\delta$  32.23.

### (4-nitrophenyl)diphenylphosphine oxide (**4n**)



The compound **4n** was prepared according to General procedure A from bis(4-nitrophenyl)-iodonium triflate **1n** (71.3 mg, 0.15 mmol).  $^1\text{H}$  and  $^{31}\text{P}$  NMR spectra of compound is consistent with that reported in the literature<sup>[185]</sup>.

$^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.34 – 8.26 (m, 2H), 7.95 – 7.84 (m, 2H), 7.72 – 7.58 (m, 6H), 7.57 – 7.42 (m, 4H).  $^{31}\text{P}$  NMR (162 MHz, Deuterium Oxide)  $\delta$  27.59.

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