SYNOPSIS

Thesis Title: *"Sulfenylation of H-Phosphonates, H-Phosphonites, Phosphine Oxides, Indoles and Synthesis of substituted (benzofuran-yl)- aryl chiral carbinols"*

The contents of thesis are put together in four chapters. **Chapter I**, deals with important reported prior art sulfenylation methods. **Chapter II**, describe the synthesis of a library of phosphorothioate derivatives. **Chapter III**, provides metal and base free synthesis of a collection of 3-thio aryl / alkyl indole derivatives. **Chapter IV**, illustrates the synthesis of substituted (benzofuran-yl) aryl and heteroaryl chiral carbinols.

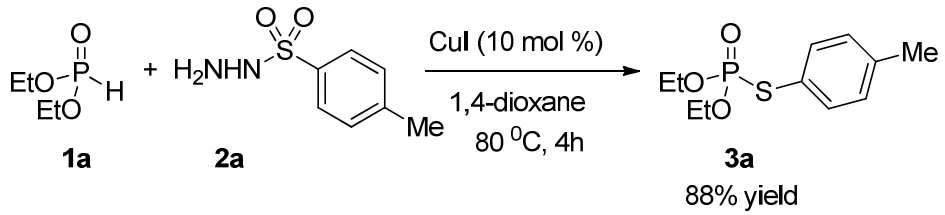
Chapter I:

This chapter consists of prominent synthetic routes for the insertion of sulfur into organic molecules, sulfenylation of Phosphonates and C (sp^2)–H bonds. The sulfenylating agents for the thiolation of phosphonates and C (sp^2)-H bonds include disulfdes, sodium sulfinates, sulfenyl halides, *N*-thioarylphthalimides, and sulfonyl hydrazides. Mostly, the reactions were induced by iodine or metal salts. This chapter provides an outlook of the topic designated that intended to carryout basic idea exploration.

Chapter II: Copper (I)-Induced Sulfenylation of H-Phosphonates, H-Phosphonites and Phosphine Oxides with Aryl/alkylsulfonylhydrazides as a Thiol Surrogate

Thiophosphates are important skeletons in biology and organic synthesis, as a result, the synthesis of thiophosphates has gained much attention. The derivatives of thiophosphates display diverse biological activities, e.g. antiproliferative agents, anticholinesterases, antibacterials, pesticides, curing accelerators, antistatic agents, insecticides, enzyme modifiers, and potential HIV-1 and ACHE inhibitors.

The well-known routes for the synthesis of thiophosphorus compounds include i) Michaelis-Arbuzov reaction of trisubstituted derivatives of phosphites with alkyl- or arylsulfonyl chlorides; ii) reaction of H-phosphonates with various sulfenyl chlorides, sulfenyl cyanides, and substituted disulfides; and iii) condensation of phosphorochloridates with thiols or their metal salts. However methods for the synthesis of the thiophosphate class of compounds are extremely limited due to oxidative self-dimerization catalysed by air/metal complexes in the presence of a base.



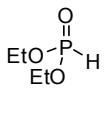
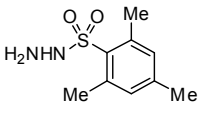
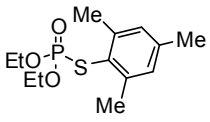
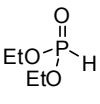
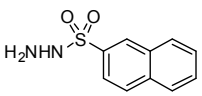
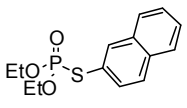
Scheme 1

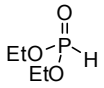
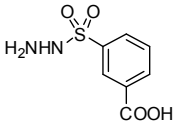
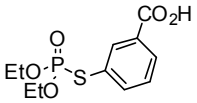
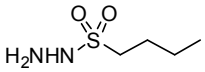
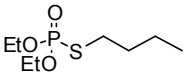
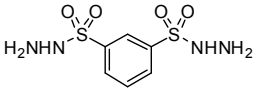
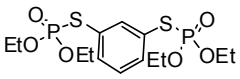
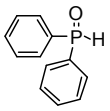
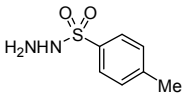
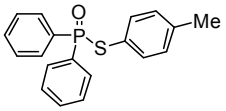
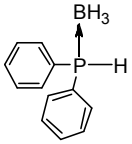
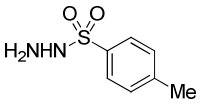
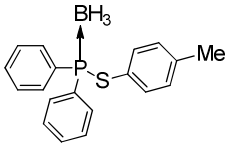
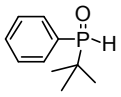
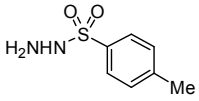
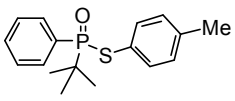
Hence, there is still a great need for the development of functional group compatible and convenient protocol to produce various thiophosphate derivatives. In this chapter our results regarding on reductive coupling of dehydrogenative cross-coupling of H-phosphonates with sulfonylhydrazides as aryl / alkyl thio surrogates are described (Scheme 1).

Also the chapter provides complete details of various copper salts, catalyst loading and solvent tested.

Further, we ensured the generality and scope of this protocol by extending to various sulfonyl hydrazide substrates and various aryl / alkyl phosphine oxides, under the typical conditions. The reaction is not only compatible with various substitutions on phosphorus, but also maintains the substitution pattern of the sulfonyl hydrazine aromatic nucleus.

Table 1: Scope of sulfenylation with the functional group substituted aryl- alkyl sulfonyl chlorides.[a]

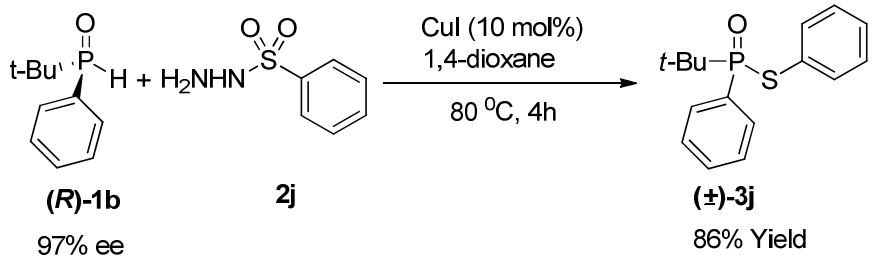
Entry	Phosphine oxide	Sulfonyl hydrazide	Product	Yield (%)[b]
1	 **1a**	 **2b**	 **3b**	85
2	 **1a**	 **2c**	 **3c**	76

3				75
	1a	**2d**	**3d**	
4				86
	1a	**2e**	**3e**	
5				56
	1a	**2f**	**3f**	
6				86
	1a	**2g**	**3g**	
7				85
	1a	**2h**	**3h**	
8				85
	1a	**2i**	**3i**	

a) All reactions were carried out on the 2 mmol scale using **1a** (2.0 equiv.), **2b-i** (1.0 equiv.), I_2 (10 mol%) in dioxane heated at 80 ℃ in open air.
b) Isolated yields.

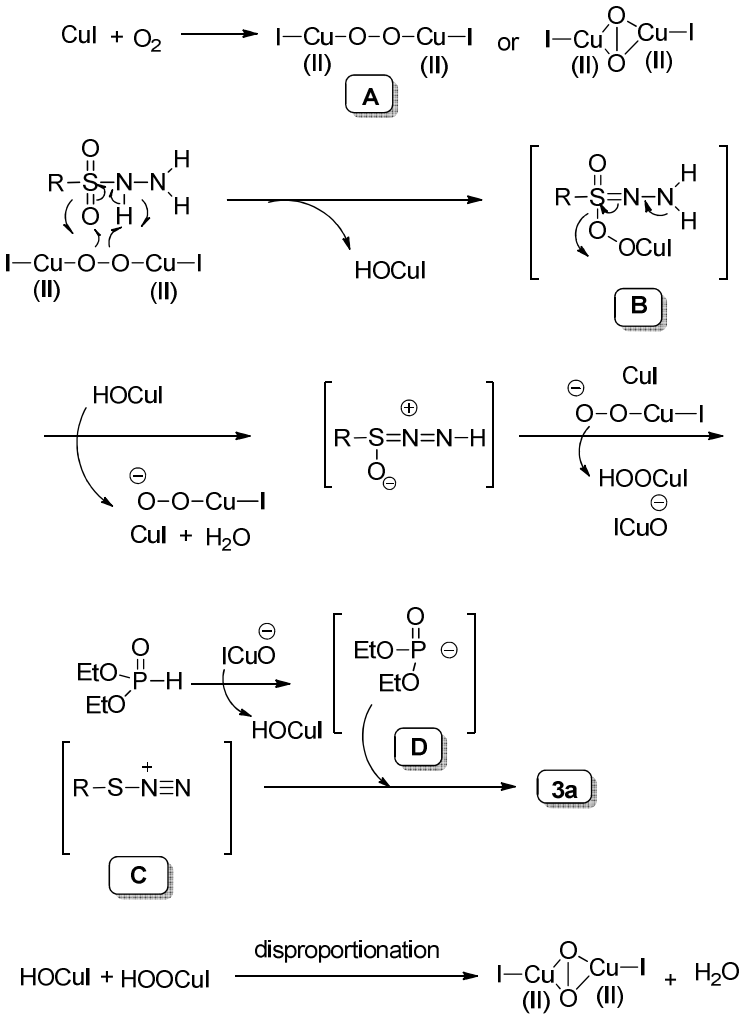
Sulfenylation of chiral phosphine oxide

Nucleophilic substitution reactions of chiral tetracoordinate secondary phosphorus compounds having a P-H bond can possibly result in racemisation. In light of these observations, we explored whether the copper-catalyzed dehydrogenative cross-coupling reaction proceeds with retention or inversion of the configuration of phosphorus. Consequently, enantioenriched **(*R*)-1b** prepared with 97%ee and allowed to react with **2j** under typical reaction conditions. The expected product **(±)-3j** was obtained at an 86% yield with racemization indicating the configuration of phosphorus is not preserved during the transformation (Scheme 2).



Scheme 2

A plausible mechanism is proposed by analogy with dehydrogenative cross-coupling reactions. Initially, the oxidation of Cu(I) by molecular oxygen generates the copper (II) peroxo species, [**A]** which then dissociates in the presence of sulfonyl hydrazide resulting in metallo-organic peroxide [**B]** and HO-Cu(II). Then, sequential removal of hydrogen and oxygen atoms from the putative intermediate [**B]** could lead to thiodiazonium, [**C]**. The nucleophilic substitution reaction of phosphite anion, [**D]** on thiodiazonium [**C]** eventually results in the desired thiophosphate, **3a** (Scheme 3).

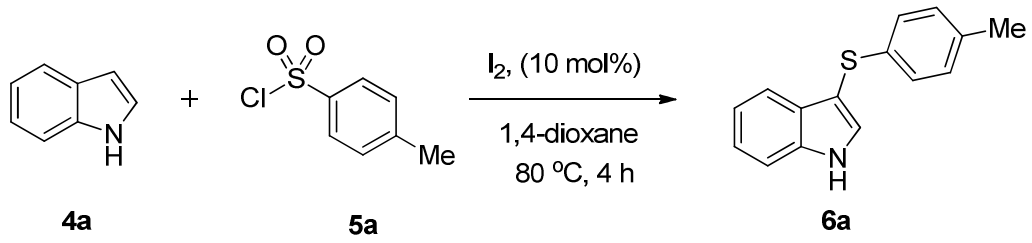


Scheme 3

In conclusion, we have provided the successful synthetic procedure for the synthesis of library of phosphorothioates and the particulars along their supporting analytical data as well as with relevant discussions.

Chapter III: Metal- and base-free syntheses of aryl/ alkylthioindoles by the iodine-induced reductive coupling of aryl/alkyl sulfonyl chlorides with indoles.

In this chapter we have depicted the results of efficient cross-coupling reaction of indole with low-cost, and readily available, stable aryl- / alkyl sulfonyl chlorides through C(sp^2)-H bond activation for the syntheses of various 3-alkyl-/ arylthioethers (Scheme 4).



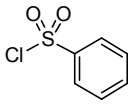
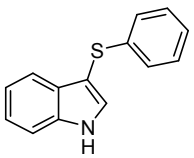
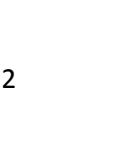
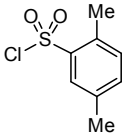
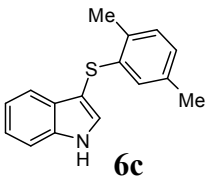
4a **5a** **6a**

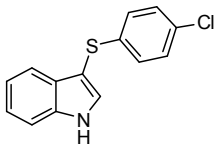
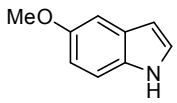
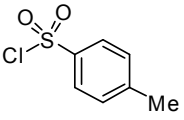
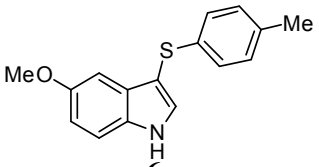
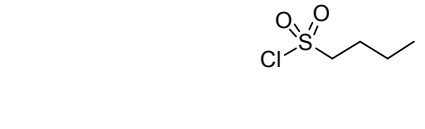
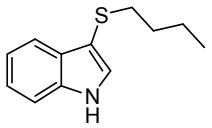
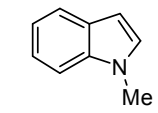
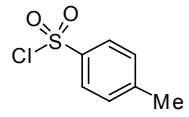
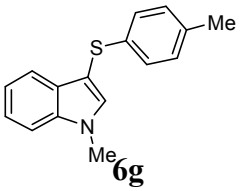
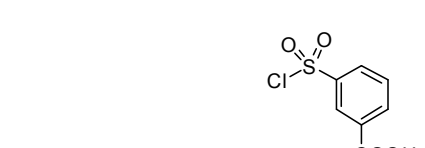
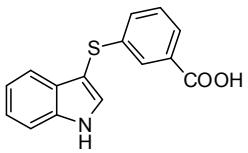
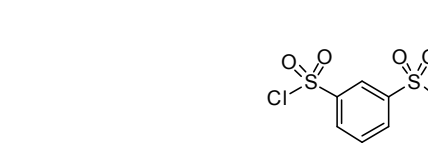
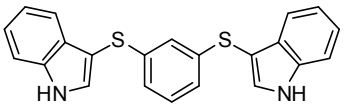
Scheme 4

Brief survey of an alternative source of iodine as a catalyst, solvent effects and optimum catalyst loading were also explored. Also, with the optimal conditions in hand, the scope of the substrate was surveyed. According to the results, the electron-donating and electron–withdrawing functional groups on the phenyl ring of sulfonyl chloride were compatible under the standard protocol and reacted with equal efficiency.

With the optimal conditions in hand, the scope of the substrate was surveyed. These results are shown in Table 2.

Table 2: Scope of sulfenylation with the functional group substituted aryl- alkyl sulfonyl chlorides.[a]

Entry	Substrate	Sulfonyl chloride	Product	Yield (%)[b]
1	**4a**	 **5b**	 **6b**	85
2	 **4a**	 **5c**	 **6c**	85

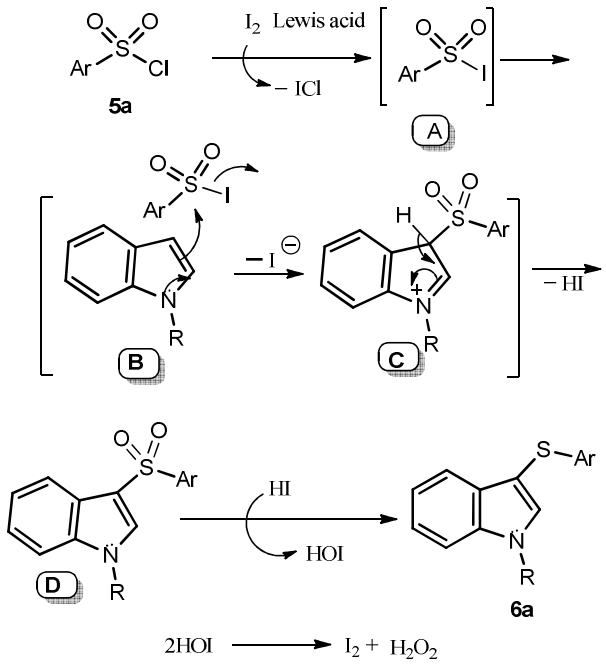
3	 **4a**	**5d**	 **6d**	81
4	 **4b**	 **5a**	 **6e**	78
5	 **4a**	**5e**	 **6f**	80
6	 **4c**	 **5a**	 **6g**	77
7	 **4a**	**5f**	 **6h**	77
8	 **4a**	**5g**	 **6i**	82

a) All reactions were carried out on the 2 mmol scale using **1a** (2.0 equiv.), **2b-i** (1.0 equiv.), I_2 (10 mol%) in dioxane heated at 80 ℃ in open air.
b) Isolated yields.

According to the above results, the electron-donating and electron–withdrawing functional groups on the phenyl ring of sulfonyl chloride were compatible under the standard protocol and reacted with equal efficiency.

Study of mechanistic pathway

Several control experiments were carried out to understand this transformation. Considering the results, a plausible reaction mechanism is delineated and is shown below (Scheme 5).



Scheme 5

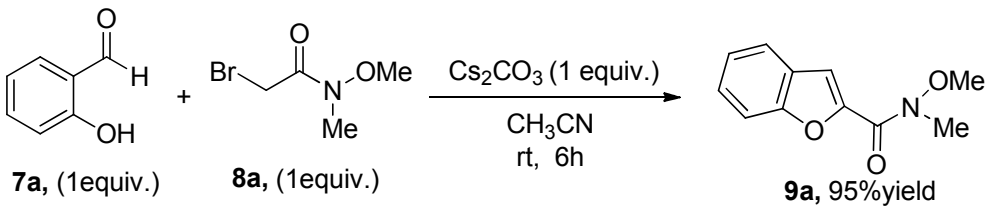
In conclusion, this process is remarkable in that stoichiometric reducing trivalent phosphorous compounds are avoided, this is the first method on sulfenylation wherein catalytic iodine acts as a reducing agent in combination with air and avoids the creation of oxides of phosphorous. The full details with discussion along with duly characterized compound data is given in this chapter.

Chapter IV: An expedient synthesis of substituted (2-benzofuryl) aryl chiral carbinols via tandem Rap-Stoermer and asymmetric transfer hydrogenation reactions

Benzofuran structural moiety is present in numerous biologically active natural products. These privileged pharmacophore containing molecules exhibit therapeutical properties over wide range of targets. Owing to their prevalence in natural products as well as pharmaceuticals has stimulated significant interest in the synthesis of benzofuran

containing heterocycles. A flurry of synthetic methods has been appeared in the literature for the synthesis of benzofurans and their derivatives. Among them, Rap-Stoermer reaction is appears to be a versatile straightforward approach for the synthesis of functionally varied benzofuran scaffolds. It was observed that the racemic substituted (benzofuran-yl)-phenylcarbinols and related compounds reduced blood lipids in both laboratory animals and patients. This prompted us to initiate a programme for the synthesis of substituted (benzofuran-yl)-phenyl chiral carbinols in substantial amount.

Initially, we have evaluated base mediated reaction of salicylaldehyde **7a** with α-haloacyl *N*-methoxy-*N*-methylketone **8a** employing solvent, solvent-free and microwave-assisted conditions. The desired product (benzofuran-yl)-*N*-methoxy-*N*-methyketone **9a** was obtained in poor yield. We have also evaluated a number of bases (NaOAc, KOAc, K_2CO_3, K_3PO_4, $CsOH.H_2O$, Cs_2CO_3) and solvents (toluene, CH_2Cl_2, $CHCl_3$, DMF, EtOAc, CH_3CN), and found that only Cs_2CO_3 and acetonitrile gave the desired product **9a** in 95% yield (Scheme 6).

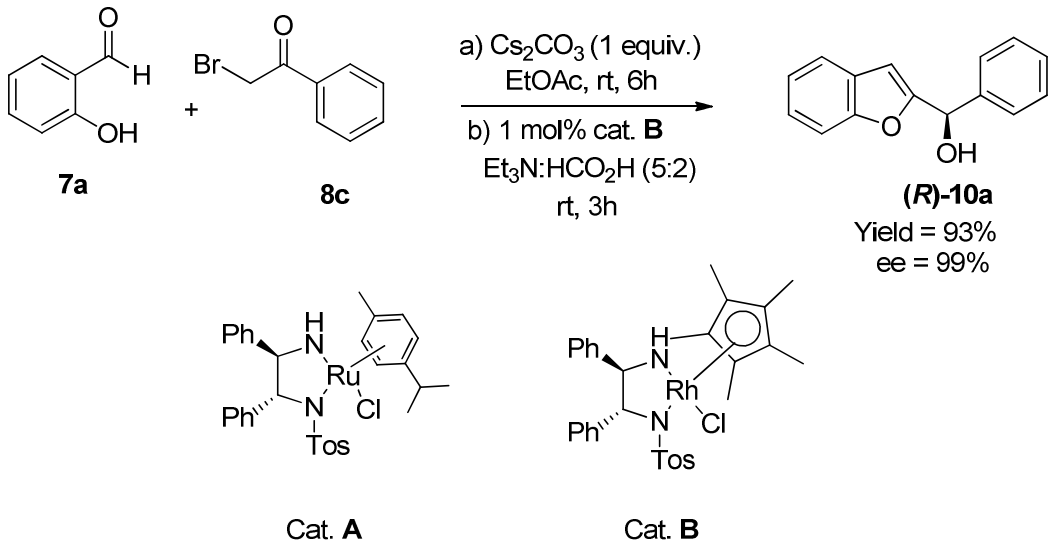


Scheme 6

In this chapter, the particulars of an expedient synthesis of substituted (benzofuran-yl)-aryl and heteroaryl chiral carbinols with high optical and chemical yields are found. A key feature of this protocol is synthesis of functionally varied benzofuran scaffolds via a Rap-Stoermer reaction / catalytic asymmetric transfer hydrogenation (ATH) using substituted salicylaldehyde and α-haloaryl ketones.

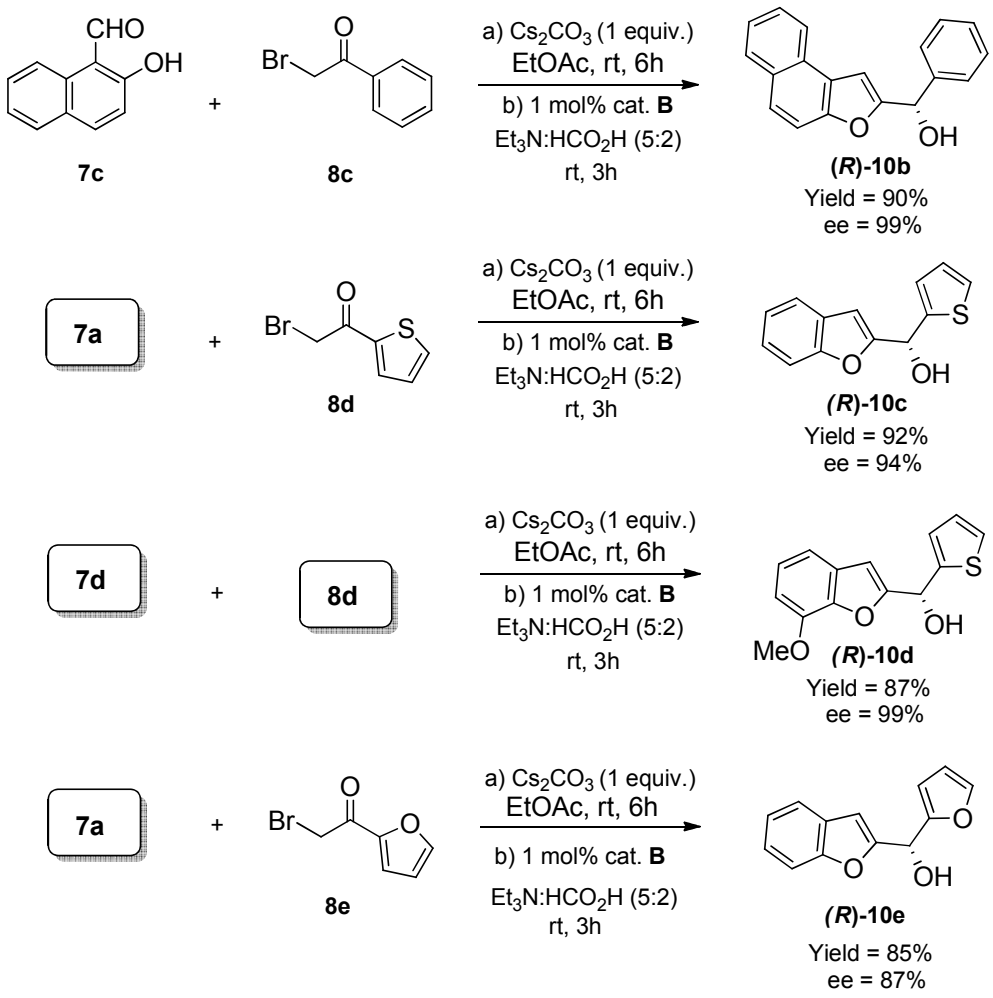
After considerable experimentation, using 1 mol% of *R*,*R*-diamine-Rh catalyst **B** employing EtOAc as solvent in both reactions (i.e. Rap-Stoermer reaction and ATH reaction) furnished the desired product **10a** in 93% yield with 99%ee (Scheme 6). The enantiomeric excess was analyzed by HPLC on chiral column OD-H and the absolute

configuration of new stereogenic center was assigned as *R* by comparison of sign of rotation {$[\alpha]^{23}_D$ = -7.9° (*c* = 3.0, $CHCl_3$); lit. $[\alpha]^{23}_D$ = + 3.5° (*c* = 0.041, $CHCl_3$ for the opposite isomer} (Scheme 7).



Scheme 7

Additionally, we tested the generality and efficiency of this methodology and subjected to various substituted salicylaldehydes with α-bromoaryl and heteroaryl ketones and our results are shown in Scheme 8.



Scheme 8

The inclusive details along with the supporting spectral data of each compound are placed in this chapter. In conclusion, we have developed an expedient synthesis of substituted (benzofuran-yl)-aryl and heteroaryl chiral carbinols with high optical and chemical yields. A key feature of this protocol is synthesis of functionally varied benzofuran scaffolds via a Rap-Stoermer reaction / catalytic asymmetric transfer hydrogenation (ATH) using substituted salicylaldehyde and α-haloaryl ketones.