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# An expedient synthesis of enantioenriched substituted (2-benzofuryl) arylcarbinols via tandem Rap–Stoermer and asymmetric transfer hydrogenation reactions

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ABSTRACT

An expedient synthesis of enantioenriched substituted (benzofuran-yl)-aryl and heteroaryl carbinols, is described. 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, heteroaryl ketones.

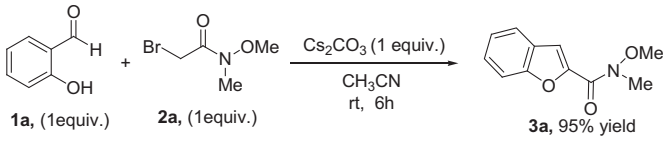


## 1. Introduction

Benzofuran structural moiety is present in numerous biologically active natural products.[1] These privileged pharmacophore containing molecules exhibit therapeutical properties over wide range of targets.[2] Owing to their prevalence in natural products as well as pharmaceuticals have 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.[3] Among them, Rap–Stoermer reaction appears to be a versatile straightforward approach for the synthesis of functionally varied benzofuran scaffolds.[3h,4] It was observed that the racemic substituted (benzofuran-yl)-phenyl carbinols and related compounds reduced blood lipids in both laboratory animals[5] and patients.[6] This prompted us to initiate a programme for the synthesis of enantioenriched substituted (benzofuran-yl)-aryl and heteroaryl carbinols in substantial amount.

## 2. Results and discussion

Initially, we have evaluated base mediated reaction of salicylaldehyde **1a** with 2-bromo-*N*-methoxy-*N*-methylacetamide **2a** employing solvent,[4a] solvent-free,[4a] and microwave-assisted conditions.[4b] The desired product *N*-methoxy-*N*-methybenzofuran-2-carboxamide **3a** was obtained in poor yield. Additionally, the reaction mixture TLC analysis showed multiple spots. In Rap–Stoermer reaction, the choice of base and solvent was found to be critical; hence we screened a number of bases (NaOAc, KOAc, $K_2CO_3$, $K_3PO_4$, $CsOH\cdot H_2O$, $Cs_2CO_3$) and solvents (toluene, $CH_2Cl_2$, $CHCl_3$, DMF, EtOAc, $CH_3CN$), but found that $Cs_2CO_3$ and acetonitrile gave the desired product **3a** in 95% yield (Scheme 1). The $Cs_2CO_3$ and EtOAc system also resulted in the desired product **3a** but slightly less yield (90%).




**1a**, (1equiv.) **2a**, (1equiv.) **3a**, 95% yield

**Scheme 1.**

The generality and scope of this protocol were evaluated using above optimized conditions and the results are summarized in Table 1. From the Table 1, it appears that the nature of acyl substitution has no effect on coupling reaction; hence the benzofuryl derivative products were obtained with excellent yields (entry 1, 3, and 4). Remarkably, 1-mercapto-benzaldehyde **1b** with *N*-methoxy-*N*-methyl α-bromoacetamide **2a** underwent coupling and the corresponding product **3d** furnished 92% indicating the efficiency of this protocol.

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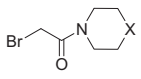
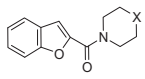
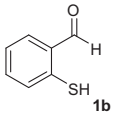
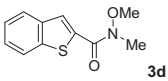
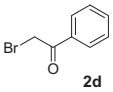
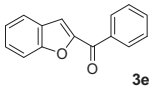
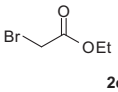
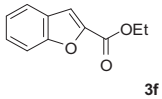
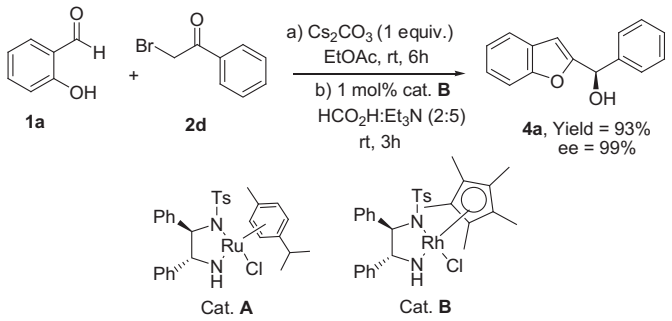
**Table 1**
Synthesis of various (benzofuran-yl)-*N*-substituted amide and keto derivatives as well as (benzothiophen-yl)-*N*-substituted amide[a,b,c]

| Entry | Substrate | α-haloketone | Product | Yield% |
|---|---|---|---|---|
| 1 | **1a** |  **2b**, X = O **2c**, X = NBoc |  **3b** , X = O **3c** , X = NBoc | 95 93 |
| 2 |  **1b** | **2a** |  **3d** | 92 |
| 3 | **1a** |  **2d** |  **3e** | 96 |
| 4 | **1a** |  **2e** |  **3f** | 95 |

[a] All reactions were carried out with substrate (1 mmol), α-haloketones (1 mmol) using base $Cs_2CO_3$ (1 equiv) in acetonitrile (5 mL) at ambient temperature stirring 6 h.
[b] All products were fully characterized.
[c] Unoptimized isolated yields.

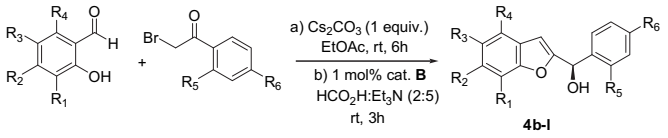
Having realized optimum conditions for synthesis of benzofuryl derivative; further, we envisaged to generate optically active carbinols via a Rap–Stoermer reaction/catalytic asymmetric transfer hydrogenation (ATH).[7] At the outset, we have selected salicylaldehyde **1a** and **2d** as test substrates and carried out the reaction under standard protocol (vide infra). After 6 h, the reaction mixture was filtered and the filtrate was evaporated. To the resulting residue, 2-propanol was added followed by 2 mol % of *R*,*R*-diamine–Ru catalyst **A** and heated to 60 °C for 10 h (Scheme 2). The anticipated product **4a** was not observed. While, the same reaction with HCOOH/$Et_3N$ azeotropic mixture (2:5) as hydrogen source, in EtOAc at room temperature for 3 h resulted in the desired carbinol **4a** in 96% yield with 82% enantiomeric ratio. Further, enantioenrichment of **4a** was achieved under similar conditions using 1 mol % of *R*,*R*-diamine–Rh catalyst **B** in place of catalyst **A**. Fortunately, employing EtOAc as solvent in both reactions (i.e., Rap–Stoermer reaction and ATH reaction) under otherwise identical conditions furnished the required product **4a** in 93% yield with 99% ee (Scheme 2). The absolute configuration of new stereogenic center was assigned as *R* by comparison of sign of rotation {$[\alpha]_D^{23}$ −7.9° (*c* 1.0, $CHCl_3$); lit.[8] $[\alpha]_D^{23}$ +3.5° (*c* 0.041, $CHCl_3$)}, which is also in agreement with Noyori's protocol,[9] i.e., *R*,*R*-diamine–Rh induces *R*-configuration, while *S*,*S*-diamine–Rh generates *S*-configuration.




**Scheme 2.**

To test the generality and efficiency of this methodology, we subjected various substituted salicylaldehydes with α-bromoaryl ketones and our results are shown in Table 2.

**Table 2**
Synthesis of enantioenriched substituted (benzofuran-yl)-phenylcarbinols[a,b,c]

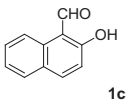
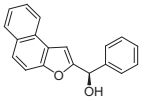
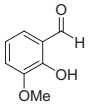
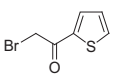
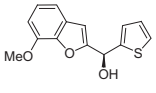
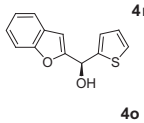
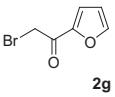
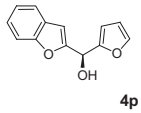



| Entry | Product | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ | Yield% | ee% |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **4b** | OMe | H | H | H | H | H | 96 | 99 |
| 2 | **4c** | OMe | H | H | H | H | OMe | 91 | 99 |
| 3 | **4d** | OMe | H | H | H | H | Cl | 87 | 95 |
| 4 | **4e** | OMe | H | H | H | H | F | 84 | 80 |
| 5 | **4f** | OMe | H | H | H | H | OBn | 92 | 82 |
| 6 | **4g** | H | H | H | H | OMe | OMe | 91 | 99 |
| 7 | **4h** | H | OBn | H | OBn | H | H | 89 | 85 |
| 8 | **4i** | H | H | *t*-Bu | H | H | H | 86 | 94 |
| 9 | **4j** | *t*-Bu | H | *t*-Bu | H | H | H | 78 | 90 |
| 10 | **4k** | H | H | H | H | H | OH | 83 | 92 |
| 11 | **4l** | H | H | Br | H | H | H | 84 | 88 |

[a] All reactions were carried out with substrate (1 mmol), α-haloketones (1.1 mmol) using base $Cs_2CO_3$ (1 equiv) in EtOAc (5 mL) at ambient temperature stirring 6 h using 1 mol % of *Cat. A* and HCOOH/$Et_3N$ (2:5) in EtOAc (5 mL) at rt stirring 3 h.
[b] All products were fully characterized.
[c] Enantiomeric excess was analyzed on chiral column OD-H (250×4.6 mm, 5 μm, $UV_{254\ nm}$, hexane/2-propanol (80:20)) using recemates for comparison.

A series of sterically and electronically differentiated salicylaldehydes and α-haloaryl ketones were subjected to this protocol. We were pleased to see that *o*-methoxy (**4g**, Table 2, entry 6) and *p*-methoxy (**4c**, Table 2, entry 2) aryl keto substrates underwent coupling/reduction efficiently and led to the products 91% yield with 99% ee, respectively. *p*-Chloro aryl keto substrate (Table 2, entry 3) also reduced with same efficacy and the anticipated product **4d** was obtained with 95%ee in an acceptable yield (87%), whereas, *p*-fluoro aryl keto substrate (Table 2, entry 4) gave **4e** in moderate ee (80%) and yield. 2-Hydroxy-1-naphthal **1c** and **2d** also reacted and the corresponding product **4m** was isolated in 90% yield with 99% ee (Table 3, entry 1). The reaction of 3-methoxy

**Table 3**
Synthesis of enantioenriched substituted (benzofuran-yl)-aryl and heteroaryl carbinols[a,b,c]

| Entry | Substrate | α-haloketone | Product[a] | Yield% | ee% |
|---|---|---|---|---|---|
| 1 |  **1c** | **2d** |  **4m** | 90 | 99 |
| 2 |  **1d** |  **2f** |  **4n** | 87 | 99 |
| 3 | **1a** | **2f** |  **4o** | 92 | 94 |
| 4 | **1a** |  **2g** |  **4p** | 85 | 87 |

[a] All reactions were carried out with substrate (1 mmol), α-haloketones (1 mmol) using base $Cs_2CO_3$ (1 equiv) in EtOAc (5 mL) at ambient temperature stirring 6 h using 1 mol % of *Cat. A* and HCOOH/$Et_3N$ (2:5) in EtOAc (5 mL) at rt stirring 3 h.
[b] All products were fully characterized.
[c] Enantiomeric excess was analyzed on chiral column OD-H (250×4.6 mm, 5 μm, $UV_{254\ nm}$, Hexane/2-propanol (80:20)) using recemates for comparison.