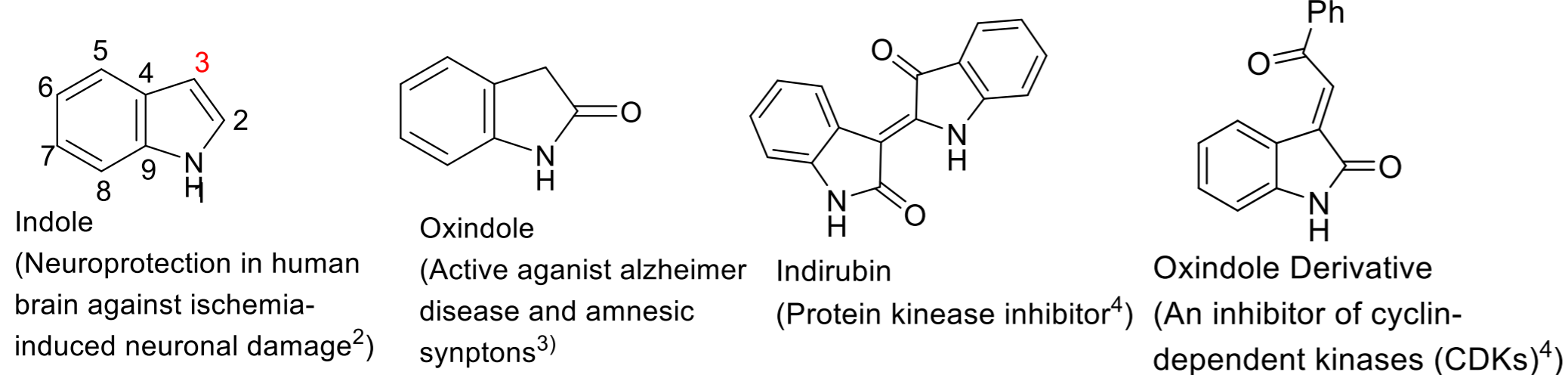




# Bronsted Acid Mediated Z-selective Synthesis of Phenylethylidene Indoles from 3-Diazooxindoles

## Introduction

Indoles and its derivatives are the core structure of many natural products, which show great potential in biological and pharmaceutical aspects<sup>1</sup>.

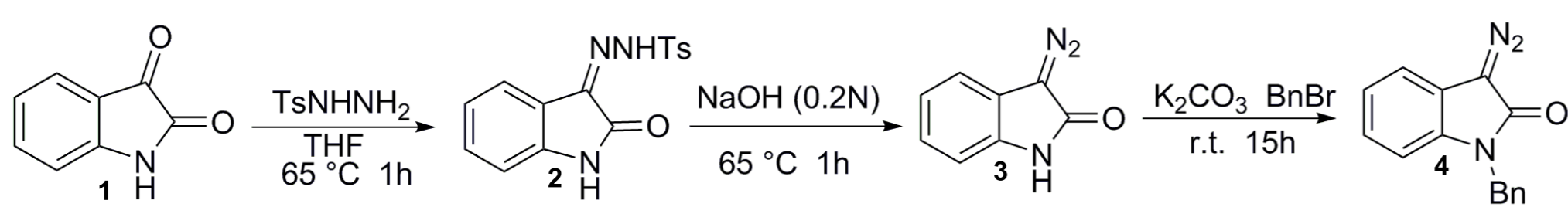


Oxindoles are electrophilic at carbon position 3. Taking advantage of this property, we synthesized a new oxindole derivative, (Z)-1-benzyl-3-(2-phenylethylidene)indolin-2-one, by reacting Isatin with styrene. (Z)-1-Benzyl-3-(2-phenylethylidene)indolin-2-one is expected to be a candidate in drug discovery.

## Reactions and Analysis

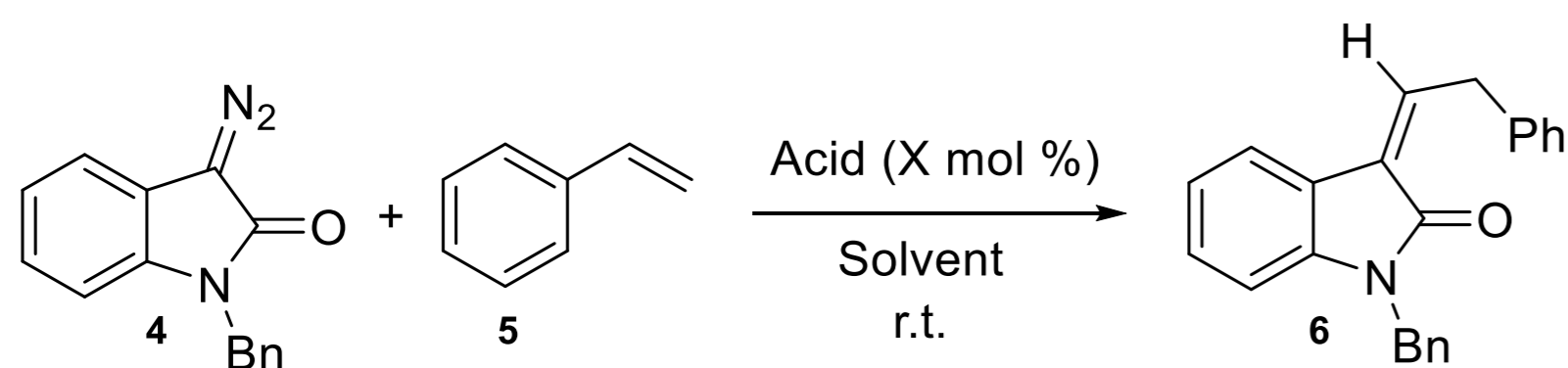
### 1. Preparation

We prepared the starting material, N-benzyl-3-diazooxindole, by a series of reactions.



### 2. Optimization of Reaction Condition

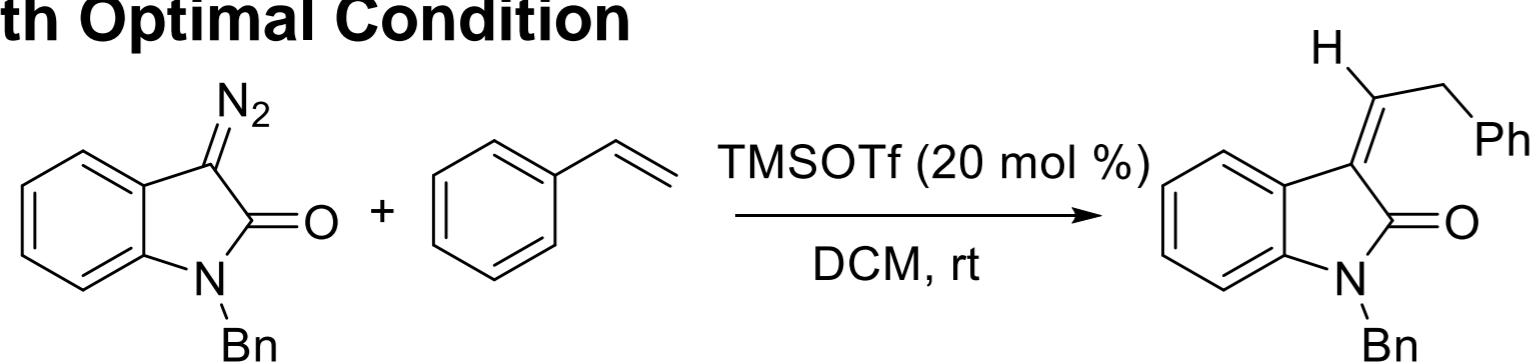
We chose different styrene to react with N-benzyl-3-diazooxindole using different catalysts and solvents to find out the optimal reaction condition.



Entry	Alkene/Alkyne	Acid	X (mol %)	Solvent	yield (%) <sup>a</sup>
1	Styrene	TMSOTf	20	DCM	70%
2	Styrene	TMSOTf	20	Toluene	60 % <sup>b</sup>
3	Styrene	BF <sub>3</sub> ·(OEt) <sub>2</sub>	20	Toluene	Reaction
4	Styrene	Cu(OTf) <sub>2</sub>	20	Toluene	NA
5	Phenyl acetylene	TMSOTf	20	Toluene	<5%
6	Phenyl acetylene	TMSOTf	20	DCM	NA
7	none	TMSOTf	20	Toluene	NA
8	Phenyl acetylene	Zn/BrCH <sub>2</sub> COOCH <sub>3</sub>	100	DCM	NA
9	Phenyl acetylene	Et <sub>2</sub> Zn	200	DCM	NA

<sup>a</sup>yield obtained after separation . <sup>b</sup>unidentified compound.

### 3. Synthesis of (Z)-1-benzyl-3-(2-phenylethylidene)indolin-2-one with Optimal Condition



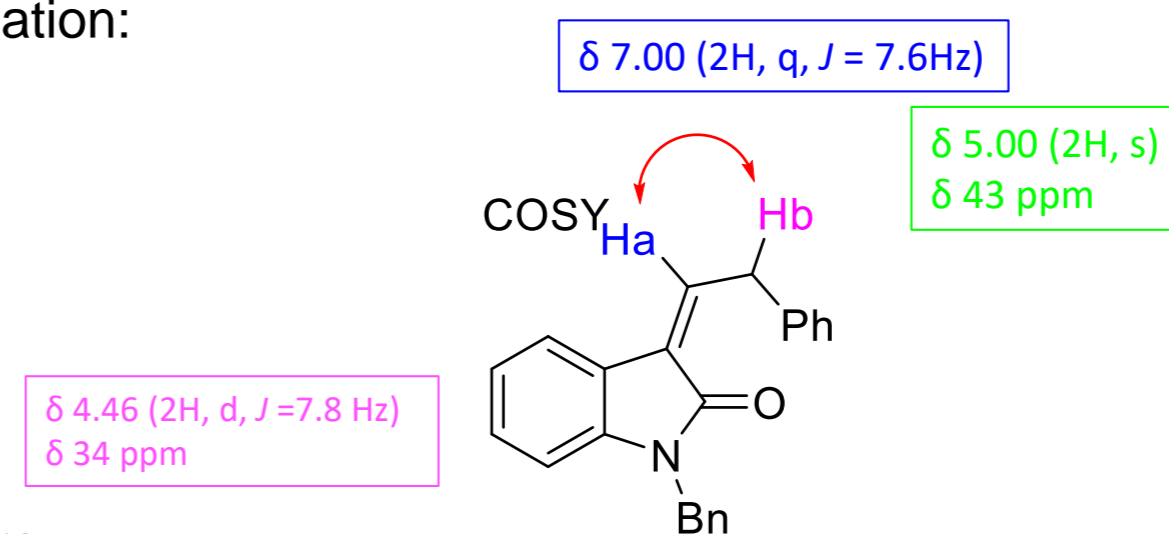
Under an air atmosphere, to the mixture of 3-diazooxindoles (80 mg, 0.32 mmol) and styrene (1.2 eq) in DCM was added TfOH (20 mol %) in 0.7 mL of DCM at room temperature. After completion of the addition, the mixture was stirred for another 10 min. Excess solid sodium bicarbonate was added to neutralize the acid. After filtration, the solvent was removed under reduced pressure and subjected to flash chromatography on silica gel to afford the corresponding products.

### 4. Characterization of the Product

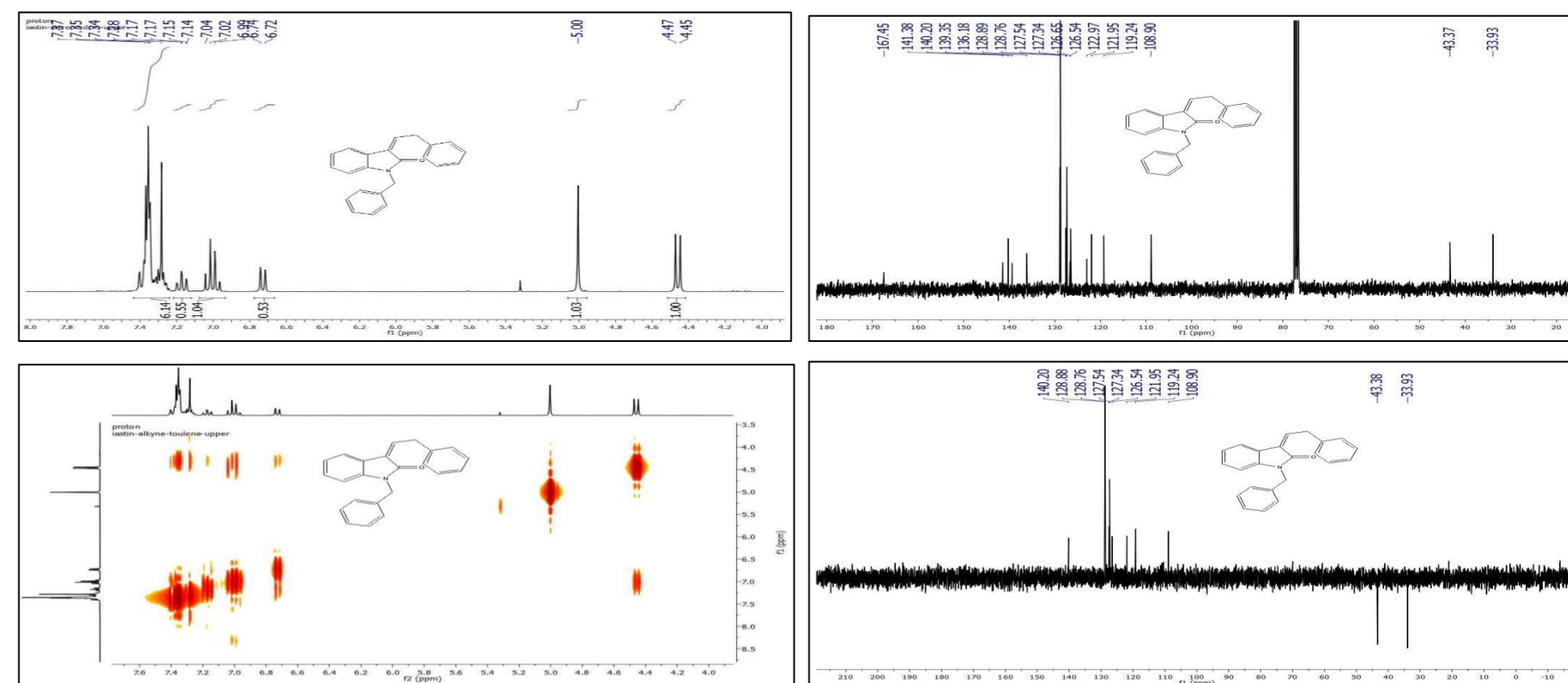
The structure of our product ((Z)-1-benzyl-3-(2-phenylethylidene)indolin-2-one) was confirmed by NMR Spectra (proton, carbon, and COSY) and Mass Spectroscopy.

- <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.45 – 7.28 (m, 10H), 7.17 (t, J = 7.7, 1H), 7.00 (q, J = 8.0 Hz, 2H), 6.73 (d, J = 7.8 Hz, 1H), 5.00 (s, 2H), 4.46 (d, J = 7.8 Hz, 2H).
- <sup>13</sup>C NMR (300 MHz, CDCl<sub>3</sub>) δ 167.4, 141.3, 140.2, 139.3, 136.1, 128.8, 128.7, 127.5, 127.3, 126.6, 126.5, 122.9, 121.9, 119.2, 108.9, 43.3, 33.9.
- HRMS: calcd for C<sub>10</sub>H<sub>7</sub>NNaO [M+Na]<sup>+</sup> = 257, found 257.

• COSY correlation:

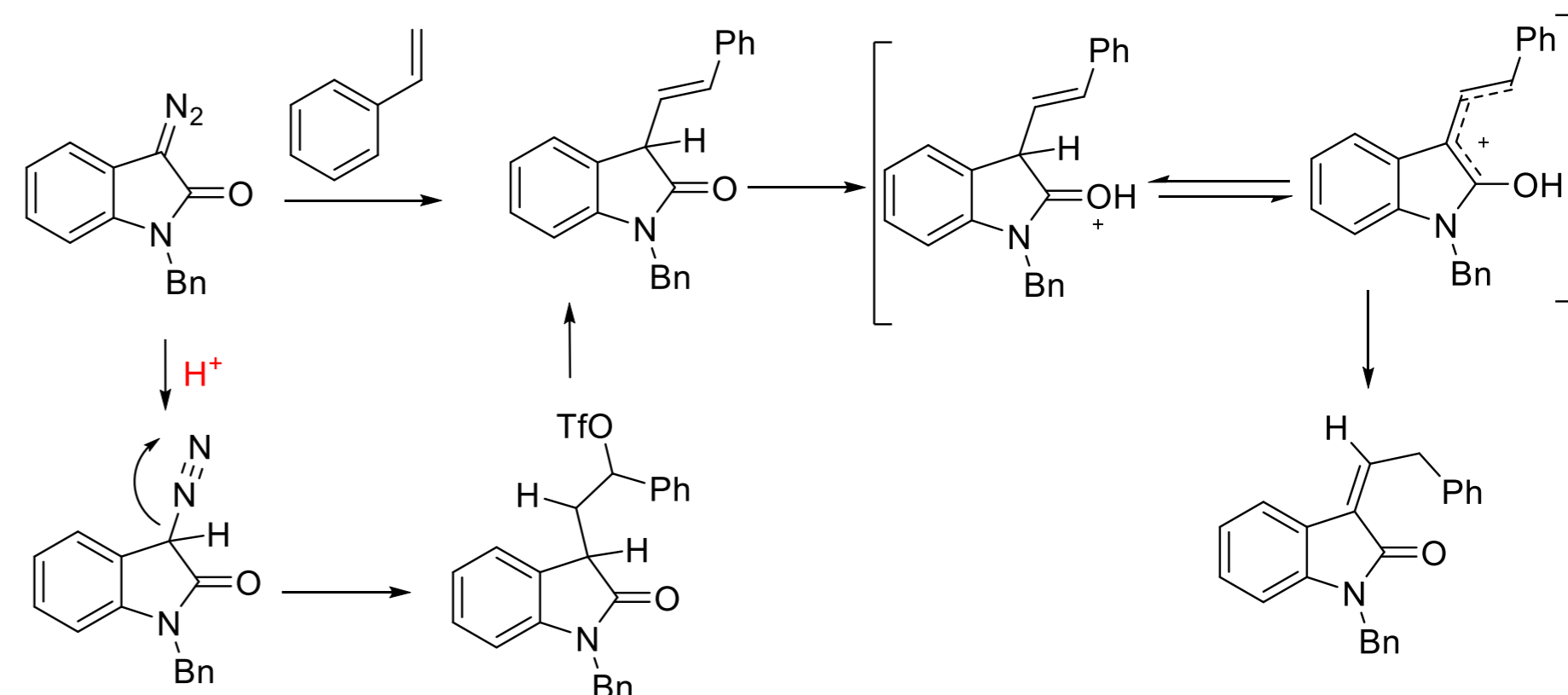


• NMR Spectra:



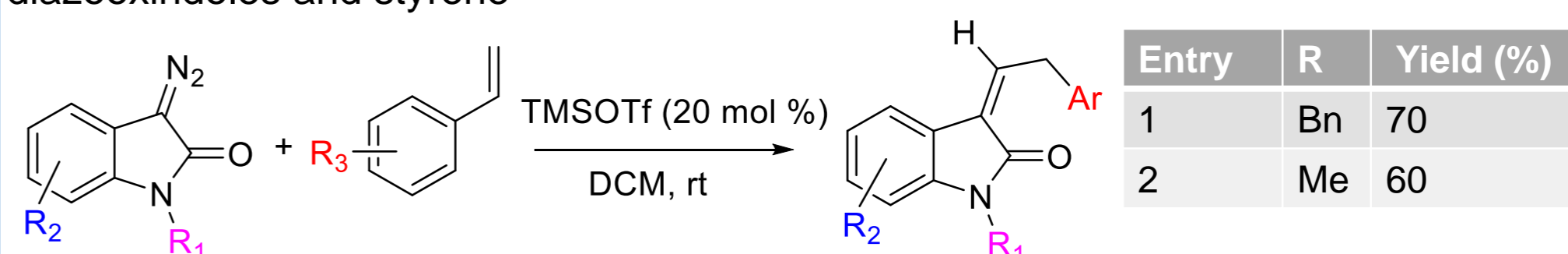
## 5. Mechanism

Overall mechanism for the reaction is shown below:



## Reaction Scope

Under the optimal condition, the scope of the reaction was tested with N-substituted 3-diazooxindoles and styrene

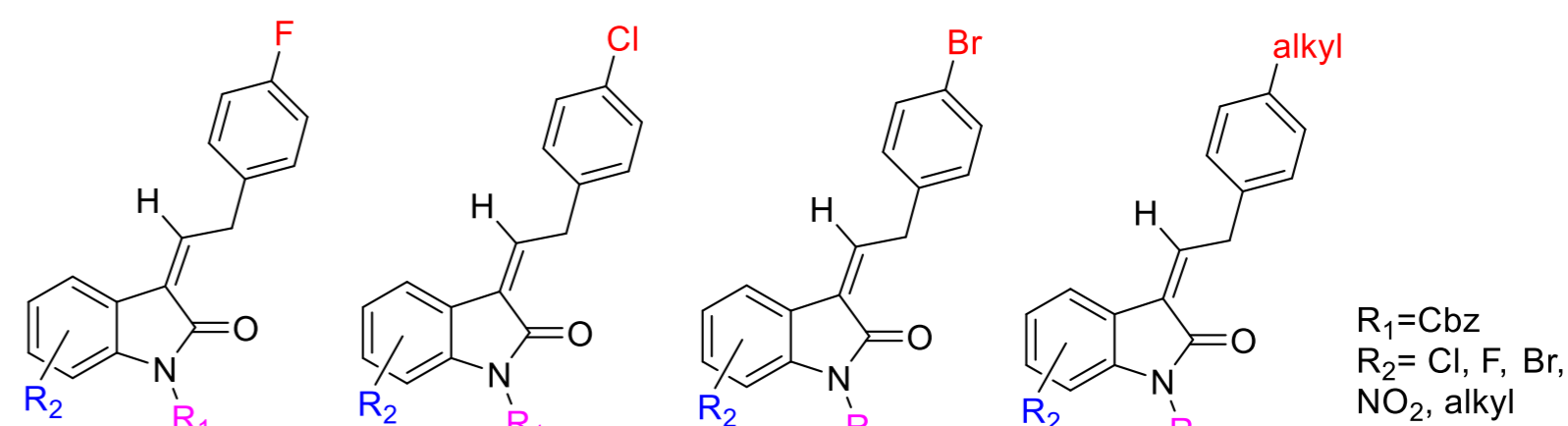


## Conclusion

- A metal free TfOH-catalyzed alkylation of styrenes with 3-diazooxindoles was described. A library of 3-aryloxindoles can be synthesized in good yields and with high stereoselectivity.
- The structure of product was confirmed by NMR Spectra and Mass Spectroscopy.

## Future Plan

1. We plan to synthesis the following products:



- We are going to change the substitutions on both the benzene rings of indole and styrene .
- We need to confirm the ratio of cis trans configuration of the product.

## References

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