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Deblina Roy, Gautam Panda

PII: S0040-4020(18)31064-0

DOI: 10.1016/j.tet.2018.09.009

Reference: TET 29781

To appear in: *Tetrahedron*

Received Date: 10 May 2018

Revised Date: 1 August 2018

Accepted Date: 4 September 2018

Please cite this article as: Roy D, Panda G, A dehydrative arylation and thiolation of tertiary alcohols catalyzed by *in situ* generated triflic acid - Viable protocol for C-C and C-S bond formation, *Tetrahedron* (2018), doi: 10.1016/j.tet.2018.09.009.

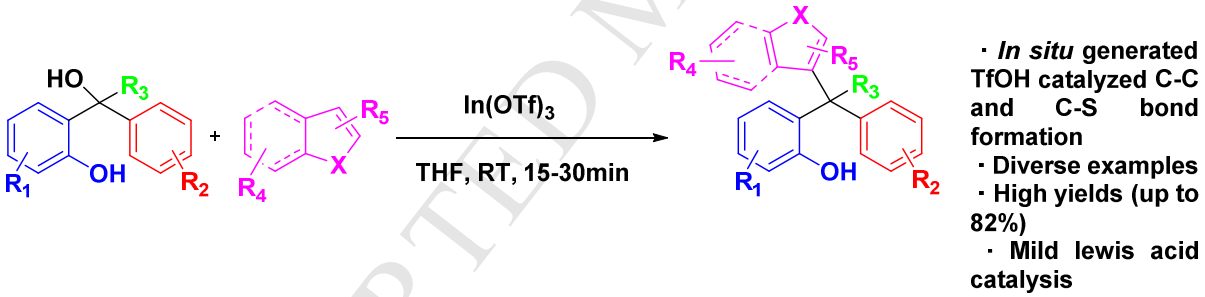
A dehydrative arylation and thiolation of tertiary alcohols catalyzed by *in situ* generated Triflic Acid - Viable protocol for C-C and C-S Bond Formation

Deblina Roy and Gautam Panda*

Medicinal and Process Chemistry Division, CSIR-Central Drug Research Institute, Sitapur Road, Jankipuram Extension, Lucknow-226031, UP, India

Abstract

The title paper discusses a mild strategy for an efficient C-C and C-S bond formation through *ortho*-quinone methide intermediate. A total of 29 examples (23 tetrasubstituted methanes with a quaternary carbon center and 6 triarylmethyl thioarenes) with diverse substitution patterns could be prepared in high yields (up to 82 %). Use of indium triflate allowed the transformation to be carried out in an open flask without taking special care leaving water as the only by product. Control experiments revealed that the triflic acid generated *in situ* from indium triflate, probably through the coordination with substrate, acted as the actual catalyst for the transformation. Further this protocol can be utilized for the synthesis of promising bioactives such as CDRI-830 analogues, dihydrochromeno[2,3-*b*]indoles and 9-(1H-indol-3-yl)-9-phenyl-9H-xanthen-1-ol.



Introduction

Compounds having unsymmetrical 1,1-diaryl motif have been found to be very important class of molecules from medicinal chemistry perspective.[1] These types of molecules have shown wide variety of bioactivities like analgesics,[1,2] **(1)** antiarrhythmics **(4)**,[3] anticancer **(3)**,[4] antitubercular **(6)**,[5] antifungal **(5)**,[6] etc **(Fig. 1)**. Moreover, the thioether compounds **(5)** and triarylmethane **(6)** having such unsymmetrical 1,1-diaryl motif developed by us, showed significant antimalarial and antitubercular activity respectively.[5,7] Also, tetraaryl methanes, another class of molecules having the unsymmetrical 1,1-diaryl motif have been found to be important molecules for drug delivery [8] and been used to detect protein translocation.[9] As the pharmaceutical industry ventures into new disease areas and new target classes, unexplored molecules having unique shape and

binding properties[10] like tetra substituted methanes and thioethers with such unsymmetrical 1,1-diaryl motif might be found useful.

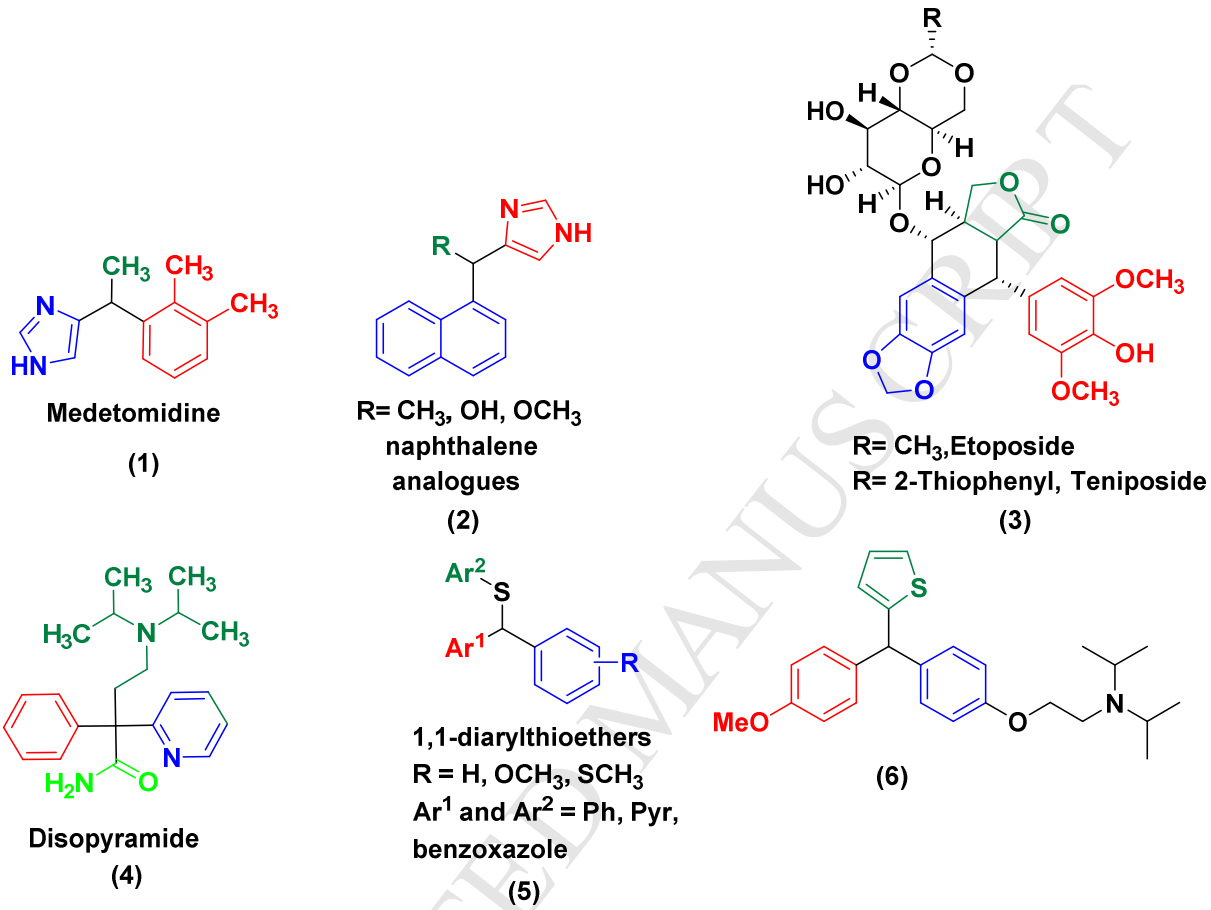
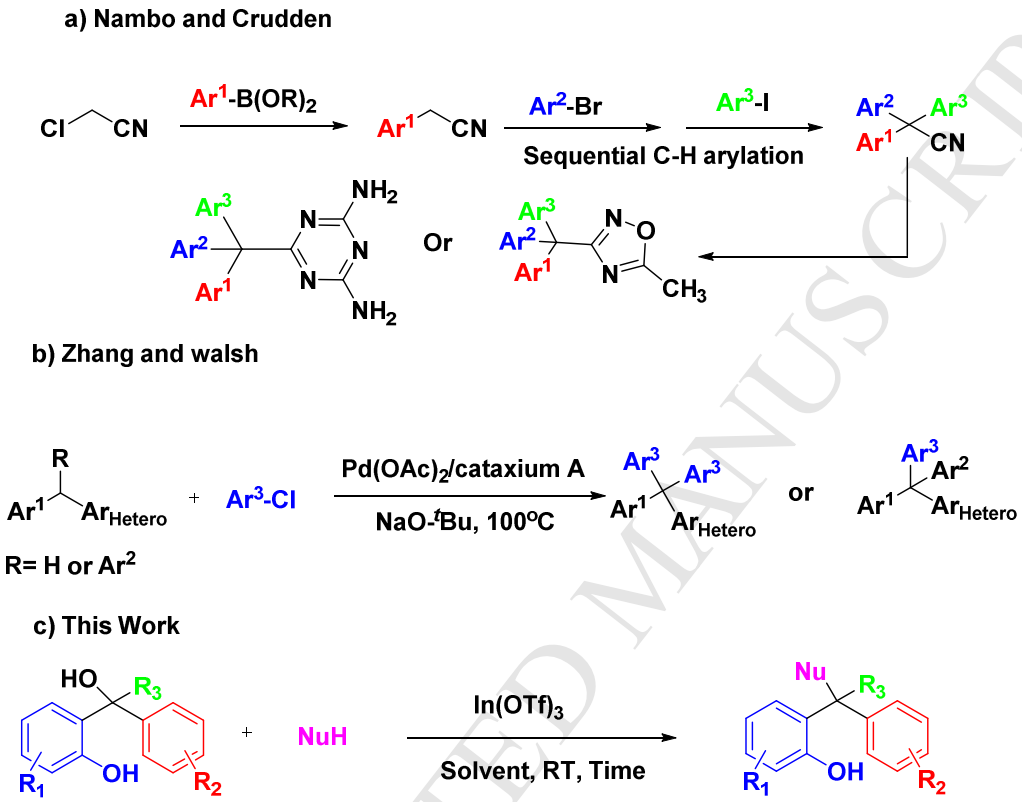


Figure-1 Some bioactive compounds with unsymmetrical 1,1-diarylmethyl groups.

The methods used to synthesize the tetraarylmethanes involve Friedel Crafts arylation,[11] nucleophilic addition of organometallic reagents to benzophenone derivatives,[12] transition metal catalyzed C-H arylation of 4-benzyl pyridines,[13] triarylmethanes and heteroarylmethanes, [14] cross dehydrogenative coupling between triarylmethanes and an arene[15]. However, the reported protocols suffer from various limitations like harsh reaction conditions, providing mixture of inseparable regioisomeric products as well as multistep organic synthesis etc.

From green chemistry perspective, alcohols are ideal electrophiles since most of them are nontoxic, cheap, readily available, air, light and moisture stable and on substitution leave water as the sole by product.[16] Recently we reported indium triflate as a mild Lewis acid catalyst for the Friedel Crafts alkylation of *bis*-benzylic alcohols with electron rich arenes for the synthesis

of unsymmetrical triarylmethanes with water as by product.[17] Continued research to develop biologically important scaffolds derived from tetrasubstituted methanes and triarylmethyl thioarenes, we report here an efficient C-C and C-S bond formation strategy with indium triflate as a mild Lewis acid catalyst through the intermediate formation of *ortho*-quinone methides **(Scheme 1)**.



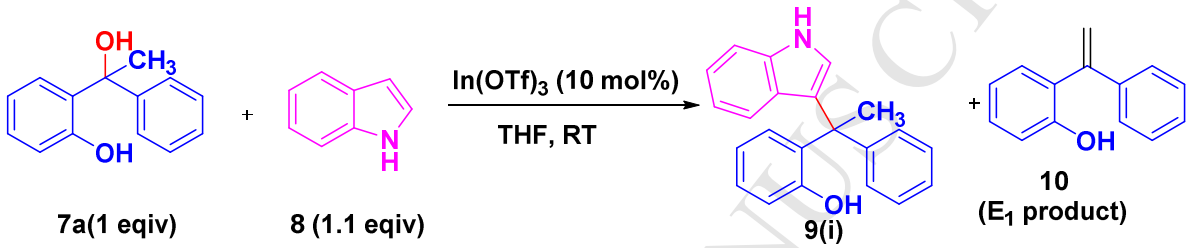
Scheme 1 Synthesis of Tetraarylmethanes. **(a)** sequential C-H arylation, (**b)** arylation of 4-benzyl pyridine and (heteroaryl)diphenylmethanes to yield tetraarylmethane derivatives, (**c**) Friedel-crafts arylation through "*O*"-quinone methide intermediate.

Results and Discussions

Initially, we investigated the C-C bond formation reaction between the tertiary alcohol **(7a)** with indole **(8)** using various reaction conditions[18] (Table-1). Interestingly, along with the desired triarylethane product **(9(i)),** the corresponding elimination product **(10)** was also obtained albeit in moderate amounts. We further screened various mild Lewis acid catalysts like copper (II) halides (chloride, bromide, iodide), copper (II) triflate, copper(II) acetate, indium(III) triflate, scandium triflate in different types of solvents like dichloromethane, toluene, water, ethanol, THF (Table-1) for this C-C and C-S bond formation reaction. However, most of the applied catalysts proved to be ineffective (Table-1 entries1-7). However, scandium (III) triflate and indium (III) triflate showed some catalytic activity with indium (III) triflate was found to be a

superior one. Next the catalyst loading was optimized and it was found 10 mol% of the Lewis acid to be optimal. Applying both lower and higher loadings of indium (III) triflate resulted in decreased yields. Further, various other reaction parameters like solvent, temperature etc. were optimized. Of all the solvents screened, THF was found to be the best. Interestingly, the reaction could be carried out at room temperature, in an open flask without taking any special care and when it was carried out in THF at room temperature, the desired tetraaryl methane with the quaternary center could be obtained in very good yield (82% yield). Reaction at higher temperature probably promotes the elimination reaction.

Table -1 Optimization Studies[a]



Entry	Lewis Acid used (mol %)	Solvent	Temp.	Time	% Yield (isolated through PTLC)
1	$CuBr_2$(10)	Dichloromethane	RT	2h	n.r.[b]
2	$CuCl_2$(10)	Dichloromethane	RT	2h	n.r.[b]
3	$CuBr_2$(10)	Toluene	RT	2h	n.r.[b]
4	$CuCl_2$(10)	Toluene	RT	2h	n.r.[b]
5	CuI_2(10)	Toluene	RT	2h	n.r.[b]
6	$Cu(OAc)_2$(10)	Toluene	RT	2h	n.r.[b]
7	$Cu(OTf)_2$(10)	Toluene	RT	2h	n.r.[b]
8	$In(OTf)_3$(10)	Toluene	RT	2h	60%
9	$Sc(OTf)_3$(10)	Toluene	RT	2h	Trace
10	$In(OTf)_3$(10)	Dichloromethane	RT	30min	65%
11	$In(OTf)_3$(10)	Water	RT	2h	n.r.[b]
12	$In(OTf)_3$(10)	EtOH	RT	2h	50%
13	**$In(OTf)_3$(10)**	**Tetrahydrofuran**	**RT**	**15min**	**82%**
14	$In(OTf)_3$(10)	Tetrahydrofuran	55°C	15min	70%

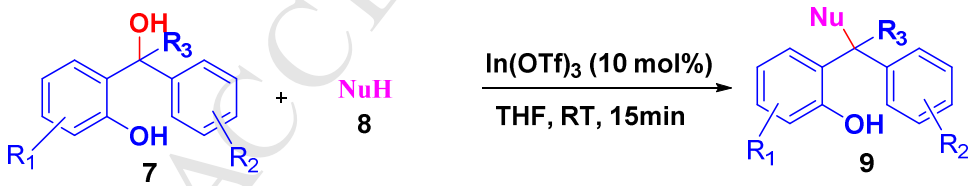
[a] *Reaction Conditions :* All reactions were performed with 0.089 mmol of **7a** in solvent and 0.098 mmol of **8**. RT = Room Temperature. THF = Tetrahydrofuran. n.r.[b] = No Reaction.

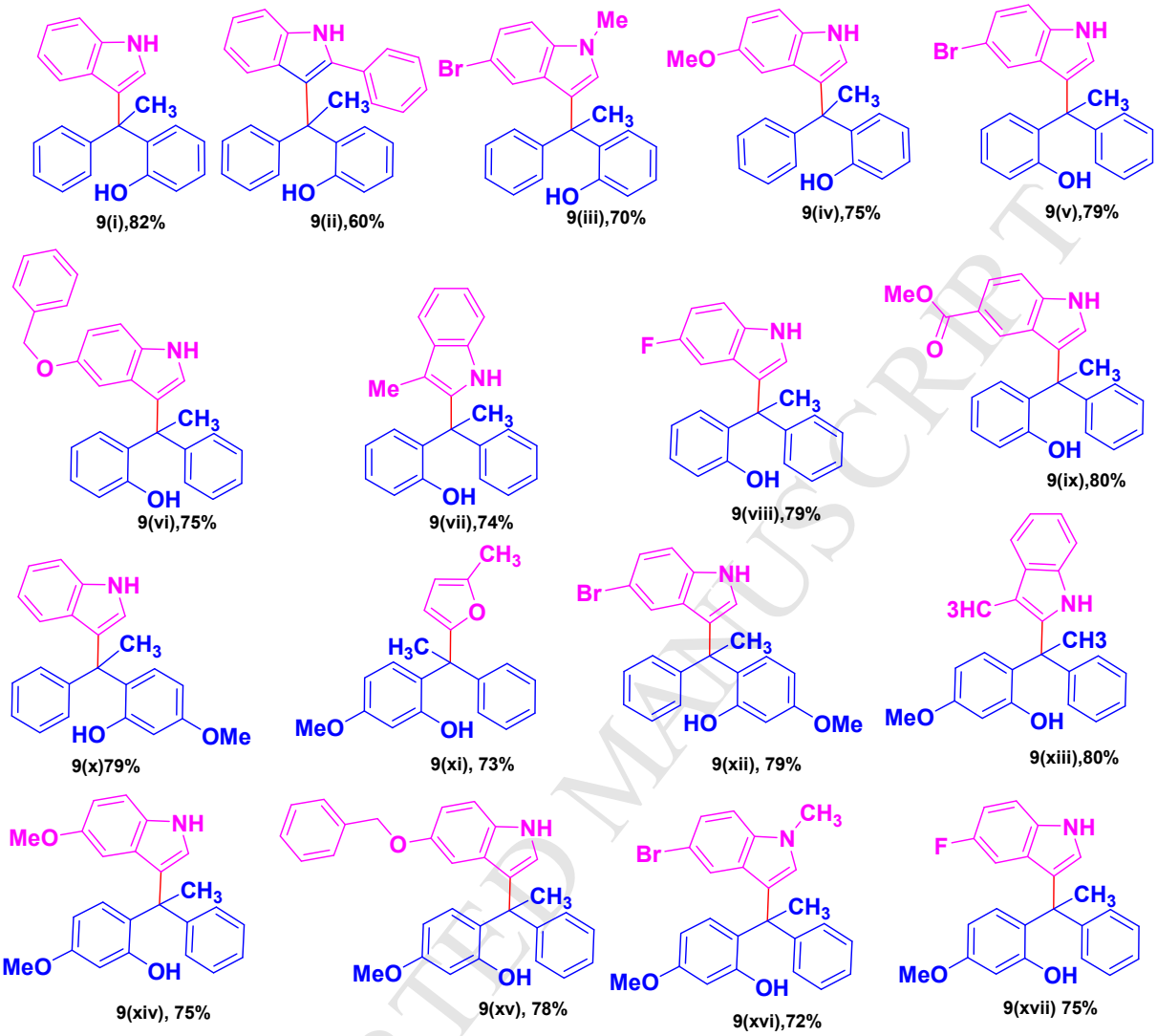
Under the optimized reaction conditions, the desired C-C and C-S bond formation with various arenes and thiol nucleophiles were attempted **(Scheme-2)**.

As evident from **Scheme-2**, both electron rich as well as electron poor carbinols were well suited for the C-C and C-S bond formation giving a wide array of tetraarylmethanes and triarylmethyl thioarenes respectively. Gratifyingly, we could prepare the indole derivatives with bulky phenyl group at the second position like in (**9xviii)** to **(9xxiii)**, thus highlighting the protocol to be tolerant to the steric effects of the nucleophile. Importantly, the reaction of the carbinol **(7)** with 5-fluoroindole and 4-fluorothiophenol gave the corresponding 1,1,1-triarylethanes and triarylmethyl thioarenes respectively having the important fluoro substituents in good yields; thus highlighting the applicability of the products in the drug discovery regime. Fluoro compounds provide additional point of binding to the receptor protein and are considered to be an important substituent in the drug discovery program.[19] Furthermore, the reaction of the carbinol **(7)** with 4-bromothiophenol gave the corresponding triarylmethyl thioarene with a handle for further diversification with various iterative metal catalyzed cross-coupling reaction.

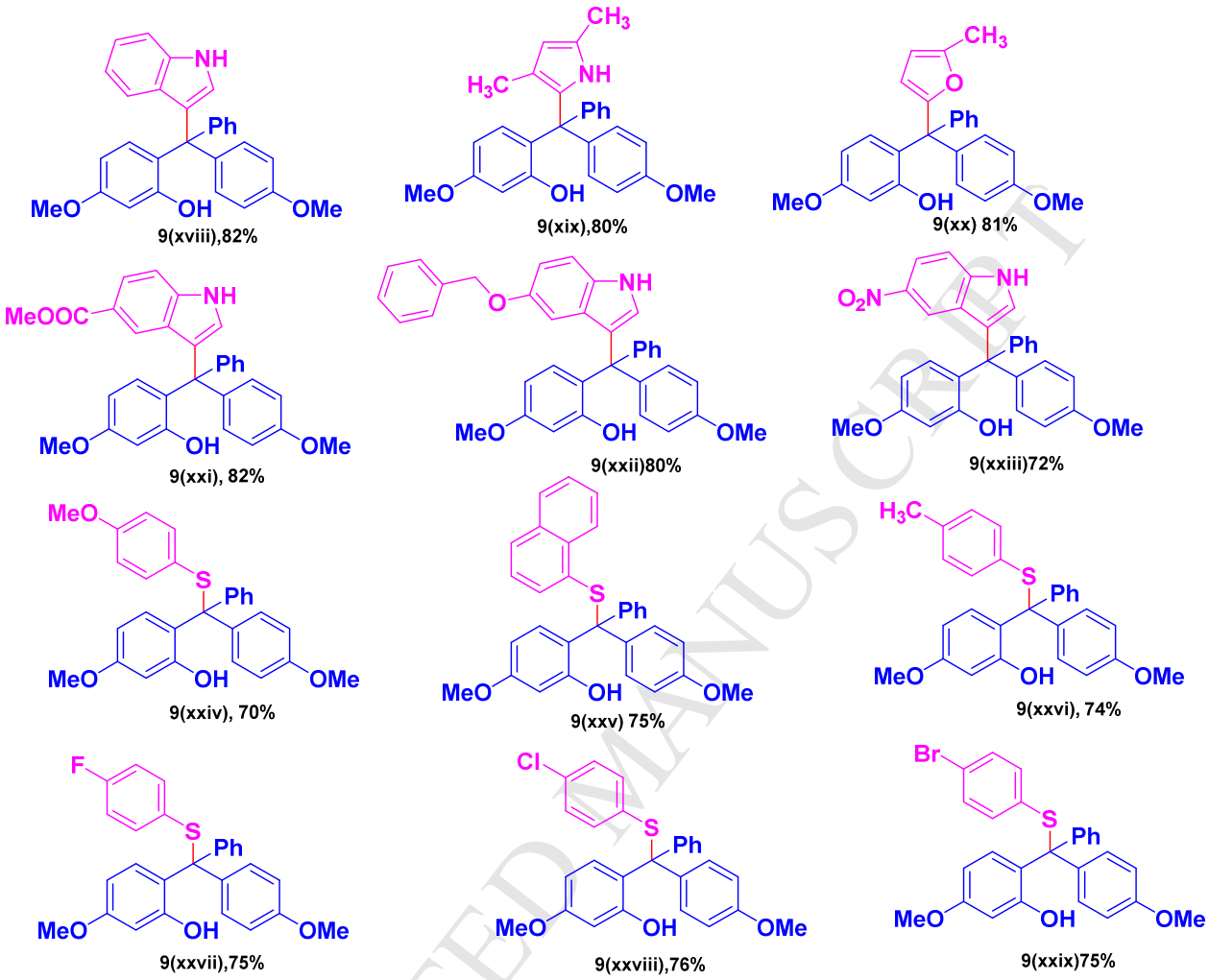
After the successful preparation of the indole derivatives and the triarylmethyl thioarenes, we became interested in the preparation of more challenging 1,1,1-triarylethanes, tetraarylmethanes containing all arene rings and also other heteroaromatic arenes. Though, we were successful in preparing furan containing triarylethanes and teraarylmethanes (compound **(9(xi))** and **(9(xx)** in **Scheme 2**), less nucleophilic arenes like 1,3,5-trimethoxy benzene, cresol, thiophene, pyrrole, benzothiophene, benzofuran did not give rise to the desired 1,1,1-triarylethanes, tetraarylmethanes and instead gave the corresponding elimination product as the sole product or were unchanged during the course of the reaction when we treated the carbinol **(7)** with those respective arenes.

Substrate scope[*]





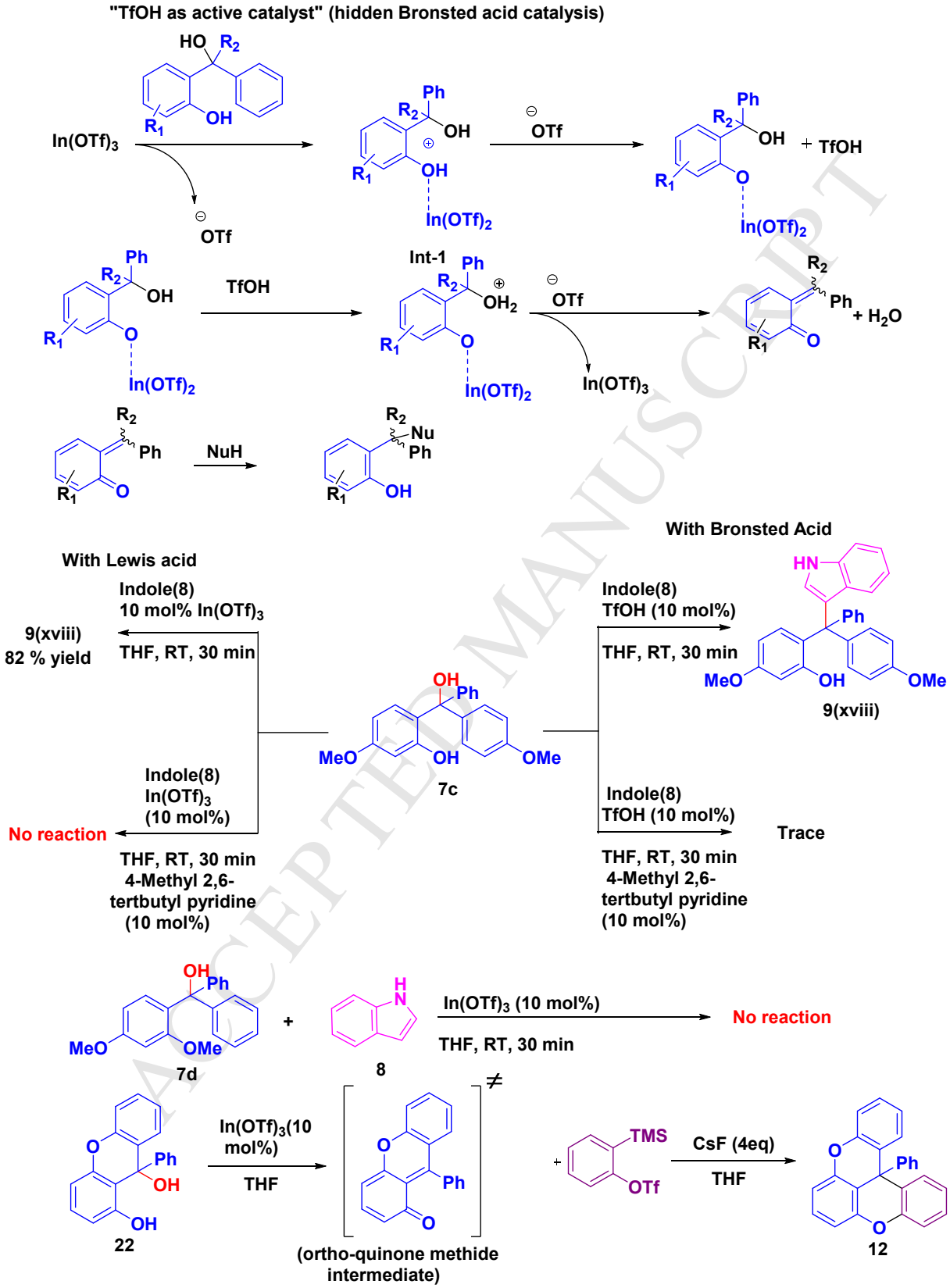
*Isolated yields; reactions conducted on a 0.1mmol scale using $In(OTf)_3$ (10 mol%), 7(1 eqiv) 8(1 equiv) in THF at Room temperature.



Scheme 2 Scope of synthesis of the proposed dehydrative arylation and thiolation of *ortho*-hydroxy tertiary alcohols with indoles, arenes, and heteroarenes.

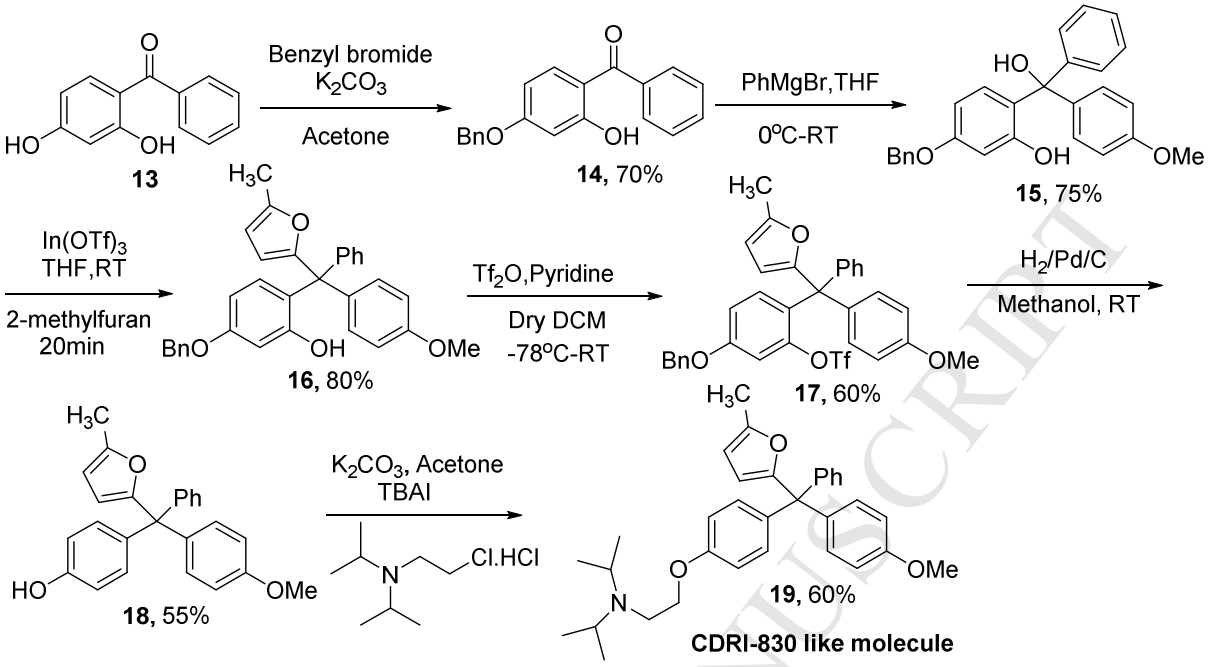
During further elaboration of the methodology towards C-N bond formation using nitrogen containing nucleophiles like piperidines, morpholines, we observed though the addition of Lewis acid catalyst to the starting carbinol generated the *ortho*-quinone methide, further addition of nitrogen nucleophile did not give any product. Further, treatment of the starting carbinols with the Lewis acid catalyst and the indole nucleophile in presence of the sterically hindered nitrogen base also did not give any product. Intrigued with such observations, we put various control reactions to gain insights into the reaction pathway. At first we investigated whether the metal triflates acted as Lewis acid catalysts or generated traces of proton which acted as Bronsted acid catalyst for the title transformation ("hidden Bronsted acid" catalysis).[20,21,22] Towards that goal we first carried out the reaction of carbinol **(7c)** with 10 mol% triflic acid in otherwise similar reaction conditions with **(8)** as the nucleophile to obtain the tetraarylmethane **9(xviii)** with

similar yield in the same reaction time. This indicates that the reaction could be carried out with Bronsted acid catalysis also. The reaction of the carbinol **(7c)** with 10 mol% triflic acid in presence of a non coordinating proton scavenger 4-methyl 2,6-ditertbutyl pyridine **(11)** with indole **(8)** as the nucleophile gave the triarylethane **9(xviii)** in much lower yield and requires prolonged reaction time. Further, the reaction of the carbinol **(7c)** with 10 mol% indium triflate in presence of the proton scavenger 4-methyl 2, 6-ditertbutyl pyridine with **(8)** as the nucleophile did not give the desired tetraarylmethane product. These results strongly indicated traces of triflic acid generated from metal triflates acted as the active catalysts for the reaction.[23] Furthermore, with the tertiary carbinol **(7d)** {the methoxy analogue of the carbinol **(7c)**} and indole nucleophile under otherwise similar reaction conditions, no product was observed **(Scheme 3)** indicating the important role of the hydroxy group in the coordination of the indium triflate with the substrate. Furthermore, when we added *in situ* generated benzyne to the mixture of the tertiary carbinol **(22)** and indium triflate; the Diels Alder cycloaddition product **(12)** could be generated **(Scheme 3)** and characterized. Recently, the Diels Alder cycloaddition of orthoquinone methides and benzynes have been established as a viable strategy for the preparation of 9-aryl xanthenes.[24] This indicated the intermediate formation of the ortho-quinone intermediate during the course of the reaction. So mechanistically the reaction may follow the following route, at first coordination of the carbinol with indium triflate may result in the generation of triflic acid which acted as the active catalyst and protonated the carbinol to generate the quinone methide intermediate. The *o*-quinone methide intermediate, thus generated participated in 1,4-Michael type addition reaction sequence to give the observed product **(Scheme 3)**.

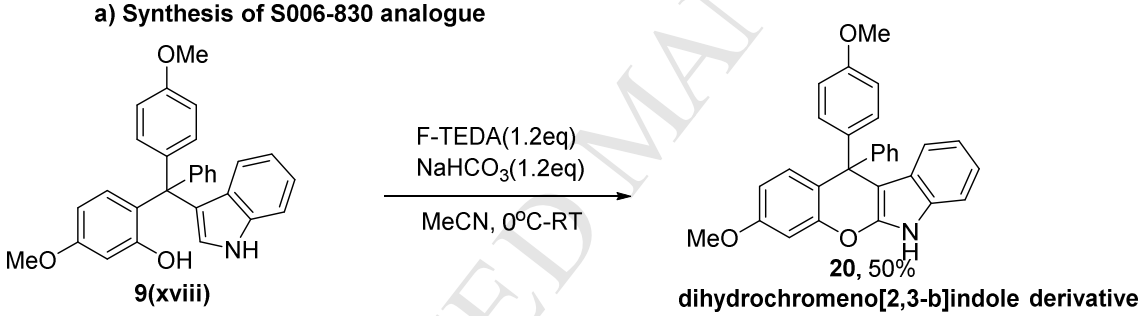


Scheme 3 Plausible reaction mechanism.

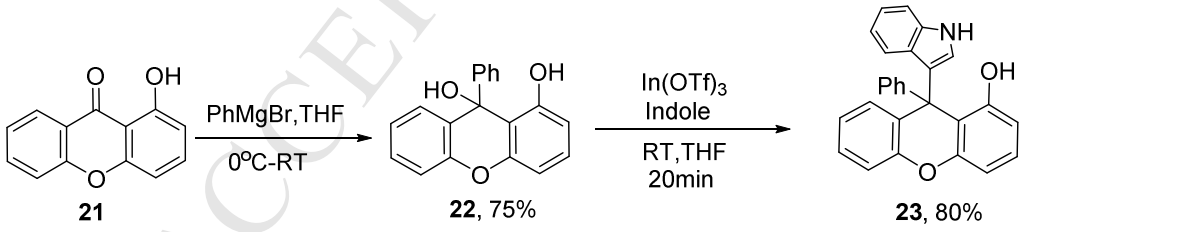
To further demonstrate the applicability of the protocol towards development of new bioactive molecules, we subsequently converted the tetraaryl methane compound **(16)** into an analogue of CDRI-S-006-830 through synthetic steps **(Scheme 4a)**. Thus **16** was reacted with triflic anhydride using pyridine as a base in DCM to give **(16)** in moderate yield (60%). The triflated compound **(17)** was then subjected to a global deprotection strategy involving debenzylation and removal of triflate group to give compound **(18)** in 55% yield which was converted to the CDRI-S-006-830 analogue **(19)** in overall yield 9% (total 6 steps) by treating with the dialkyl aminoethyl chain in presence of a base in refluxing acetone. Also few tetraaryl methanes were converted to biologically important indole containing compound dihydrochromeno[2,3-*b*]indole **(20)** derivatives in one step using the selective flourinating agent F-TEDA in 50% yield and the tetraarylmethane 9,9-diarylxanthene **(23)** in 80% yield **(Scheme 4b** and **4c)**.



a) Synthesis of S006-830 analogue



b) Synthesis of dihydrochromeno[2,3-b]indole derivative



c) Synthesis of 9, 9'-diarylxanthene analogue

Scheme 4 Synthesis of bioactive molecules [a) Synthesis of S-006-830**,** b) Synthesis of dihydrochromeno[2,3-*b*]indole derivative, c) Synthesis of 9,9'-diarylxanthene utilizing our protocol.

Conclusion

For the synthesis of tetraaryl methanes and triarylmethylthioarenes having quaternary benzylic stereocenters, we have developed an efficient strategy using tertiary benzylic alcohols as the starting material involving the intermediate formation of the *ortho*-quinone methide. The method is operationally simple, occurs in an open flask leaving behind water as the sole by product giving a diverse set of unsymmetrical tetraarylmethanes in high yields. The prepared tetraarylmethanes could further be converted to some interesting biologically important molecules like CDRI-S-006-830 analogue, dihydrochromeno[2,3-*b*]indole derivative and 9,9'-diarylxanthene. Preliminary mechanistic studies proved triflic acid generated *in situ* from metal triflates acted as the active catalyst for the generation of an orthoquinone methide intermediate, which takes part in the arylation/thiolation reaction. Application of this protocol for the synthesis of various other bioactive natural and unnatural products are currently underway in our lab and will be reported in due course.

Acknowledgements

This work was supported by MoES (09-DS/3/201P5C –IV), New Delhi, India. Instrumental facilities from SAIF, CDRI are highly acknowledged (CDRI Communication No. xx)

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