

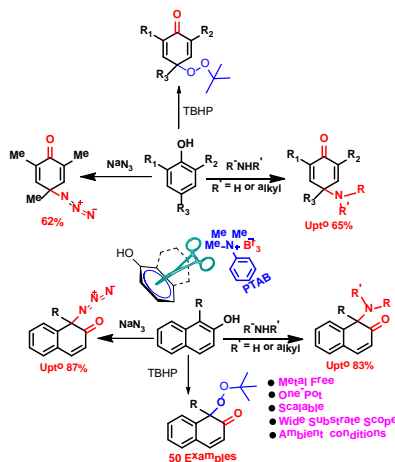
# “A Jack of Trio”- Facile One-pot Metal free Oxidative Amination, Azidation and Peroxidation of Phenols

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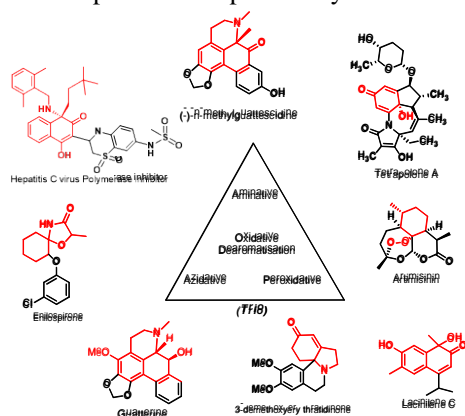
Supporting Information Placeholder



**ABSTRACT:** A highly efficient methodology for generation of nitrogen containing Quarternary Carbon centres via aminative and azidative oxidative dearomatization of phenols has been explored. The same protocol has also been successfully employed to achieve oxidative peroxidation of Phenols. The simplest metal free reaction conditions delineates an easy break through to the “Trio”- of oxidative amination, azidation and peroxidation. An array of diverse polyfunctionalised heterocycles has been synthesized in one pot

Dearomatization is a versatile synthetic tool for transformation of a simple planar molecule to a more functionalised diverse non-planar molecular skeleton allowing a fast access to synthetic complexity<sup>1</sup>. Cyclohexadieneones and naphthalenones are important structural motifs which serve as effective molecules towards complex natural product synthesis<sup>2</sup>.

These important motifs are normally achieved from the direct dearomatization of arenes. There has been continued reports for accomplishing these molecules via oxidative dearomatization reactions using varied hypervalent iodine<sup>3</sup> and transition metal complexes<sup>4</sup>. Notably, the last decade has seen a tremendous urge to develop sustainable versions of this transformation which can be applied to a wider context. Important functionalisation along with conversion of these planar molecules to three dimensional molecules like Aminocyclohexadieneones, azido-naphthalenones and Peroxo-cyclohexadieneones constitute the central core for a vast set of medicinally important molecules and thus create an extreme focus of attention. Certainly, a generalised oxidative strategy which carefully accomplishes this “trio” of reactions aminative, azidative and Peroxidative dearomatisations can be a reaction of tremendous synthetic importance<sup>5</sup>. Interestingly extensive literature survey has fetched us scanty reports focussing on discrete aminative and peroxidative dearomatization of naphthols<sup>6,7</sup>. Nevertheless, there has been no reports on oxidative amination & azidation of phenols, which possess elevated aromatic energy levels than naphthols. Thus suitable design of a



**Fig. 1: Biologically active Natural Products with amino- naphthalenones, amino-cyclohexadieneone, peroxides and azaspiro structural cores**

Sl. No.	Solvent	Base/ Nucleophile	Yield(%)
1	Dioxane	Cyclohexyl amine	40
2	DCM	„	45
3	Toluene	„	35
4	Benzene	„	40
5	DCE	„	40
6	DMF	„	30
7	THF	„	>60
8	DMSO	„	25
9	Et <sub>2</sub> O	„	35
10		„	No reaction
11		„	No reaction
12		„	No reaction
13		„	No reaction
14		„	No reaction

syn- methodology demands for an appealing intervention into this area.

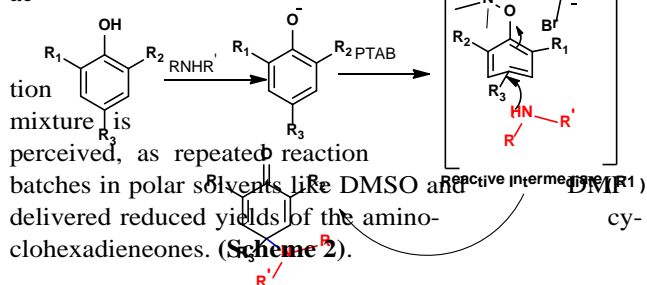
Herein, we report an easy and economic protocol for achieving the “*Trio*” - aminative, azidative and peroxidative dearomatization of naphthols as well as Phenol derivatives employing Phenyl trimethyl ammonium tribromide (PTAB) as the effective reagent. Initially, We began our study using 2,4,6-trimethyl phenol as the model substrate and on reaction with cyclohexylamine as the incoming nucleophile in presence of PTAB at room temperature delivered 4-(cyclohexylamino)-2,4,6-trimethylcyclohexa-2,5-dieneone (**1**) as the sole product in overwhelming yields in 12 hrs.(Scheme-1).

**Scheme-1: Reaction “*Trio*”**

The reactions on suitable optimisation required for 1 equivalent of PTAB for completion. Solvent Screening as listed in Table 1 puts up an impression, that THF fits as the best solvent for these reaction.(Table 1).

**Table 1: Optimization of aminative dearomatization mentioned in scheme 1.**

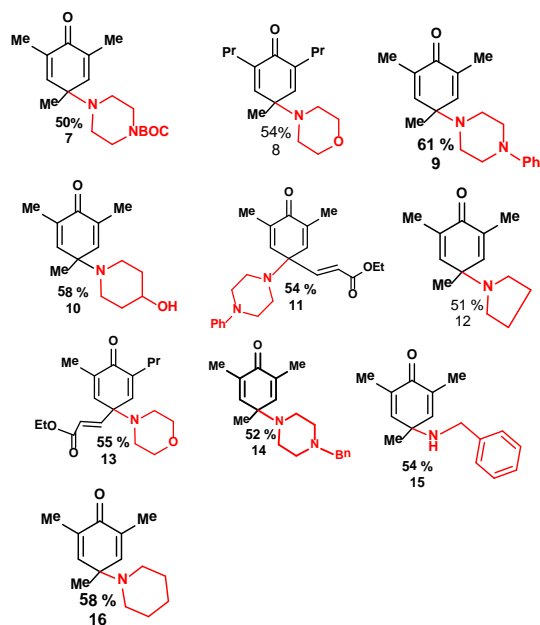
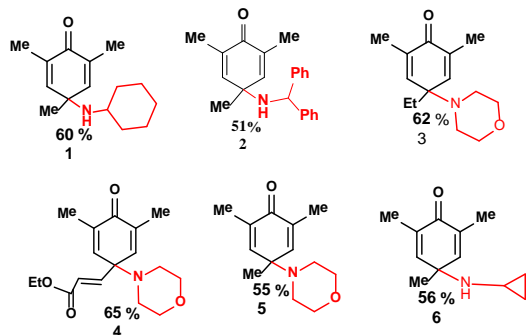
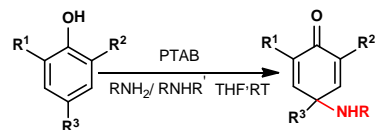
The reaction mechanism is perceived to be a straight forward one and proceeds with the initial generation of Phenoxide which intum activates the ammonium counterpart of PTAB with the concomitant attack of the nucleophile maintaining a perpendicular trajectory towards the partially planar reactive intermediate (R1) with minimal stereo electronic interaction. (Scheme-2). Presence of a moderately tight ion-pair the reactive intermediate in the re-



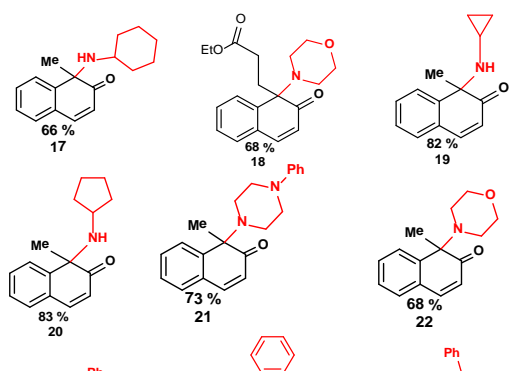
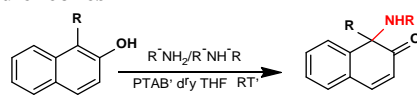
**Scheme 2**

To re-investigate this proposal further, several controlled experiments were carried out. It was concluded that secondary amines delivered better yields compared to primary amines, thus highlighting nucleophilicity to be a dominant factor in this reaction. Cyclic amines prompted higher yields as compared to acyclic amines and the acyclic ones were found to be better than the aromatic amines. Exposure of a wide range of amines with 2,4,6-trimethyl phenol in similar experimental condition delivered corresponding aminocyclohexadieneones in good yields. The substrate scope of this reaction is noteworthy as a wide range of phenols delivered the desired products in fantastic yields. Satisfactory functional group tolerance (Table-2, entry- 4, 11, 13) like unsaturated esters is also revealed. Not only phenols, the substituted naphthols derivatives also delivered the corresponding  $\alpha$ -aminonaphthalones in appreciable yields. Labile functionalities like cyclopropanes,

esters are left intact in the reaction (Table-3, entry- 18, 19, 27 ) making this protocol for aminative dearomatisation best of the available lot. The reaction proceeds impressively well with unprotected alcohols (Table-2, entry-10, Table-3, entry-28,).

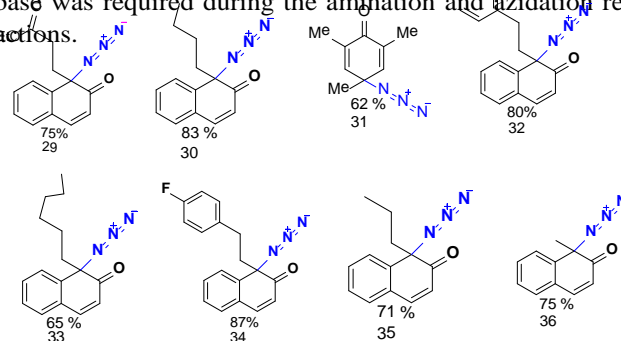


**Table-2: Substrate Scope for the synthesis of aminocyclohexadienones**

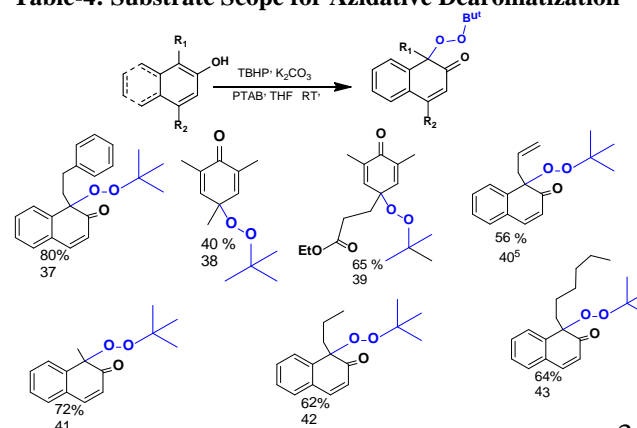


**Table-3: Substrate Scope for the synthesis of  $\alpha$ -aminonaphthalones**

To evaluate further applicability of this methodology, azides and peroxides were treated as potential nucleophiles with the above phenolics under similar reaction conditions. To our delight, both the azidative and peroxidative dearomatisations turned out to be fruitful with enhanced yields further attesting our proposal for dominant nucleophilicity in this reaction. No external base was required during the amination and azidation reactions.

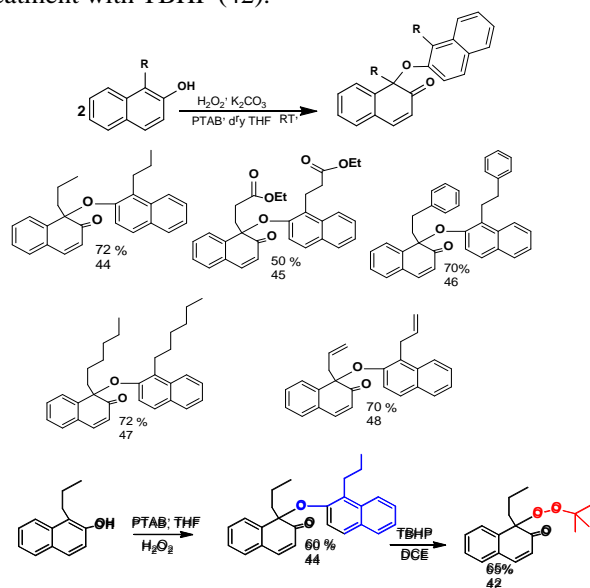


**Table-4: Substrate Scope for Azidative Dearomatization**



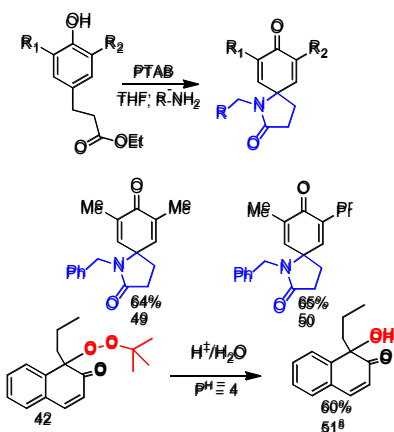
### Table-5: Substrate Scope for Peroxidative Dearomatization

The naphthols delivered oxidative etherification in presence of other non-nucleophilic co-oxidants like *m*-CPBA, and hydrogen-peroxide which interestingly delivered the tert-butylperoxy-naphthalene-2-one in good yields on treatment with TBHP (42).



### Table-6: Substrate Scope for Oxidative-dimerization

The products obtained from this generalised methodology can be diverted towards important synthetic transformations. For e.g. the aminative dearomation of phenols with ester functionalities result onto aza-spiranones whereas the peroxo-naphthalones can be hydrolysed to  $\alpha$ -ketols.



### Table-7: Substrate Scope for Spirolactamization

In summary, we have realized an unique and simplest “trio” of aminative, azidative and peroxidative dearomatisation of Phenols. The generalisability,

substrate scope and the associated simplicity of the reaction conditions undoubtedly makes this methodology a helpful one to the chemist community around the globe. The facile generation of a quaternary centre with amine, azide and the peroxide substitutions from easily available phenolics, labile functional group tolerance has given a special attention to this synthetic protocol. Above all, it supersedes the existing discrete methodologies being not limited only to naphthols rather is applicable to the entire phenolic community along with labile functionalities. The diverse range of amino, azido and peroxo-cyclohexadienones as well as naphthalones synthesised in one pot can be easily extended towards generation of synthetically important heterocyclic motifs, thus solving molecular intricacy to greater extents.

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