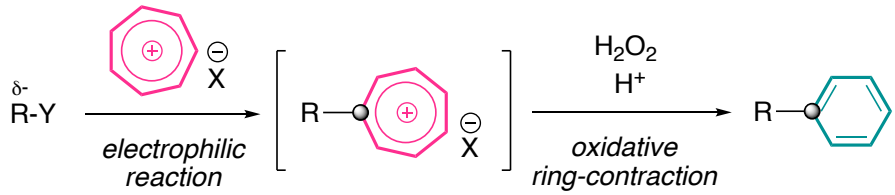
Formal Electrophilic Phenylation Reaction with Tropylium Ion

Demelza J. M. Lyons,[§] An H. Dinh,[§] Reece D. Crocker,[§] Binh Khanh Mai,[†,*] Thanh Vinh Nguyen[§,*]

[†]*School of Chemistry, University of New South Wales, Sydney, NSW 2052, Australia*

[§]*Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, United States*

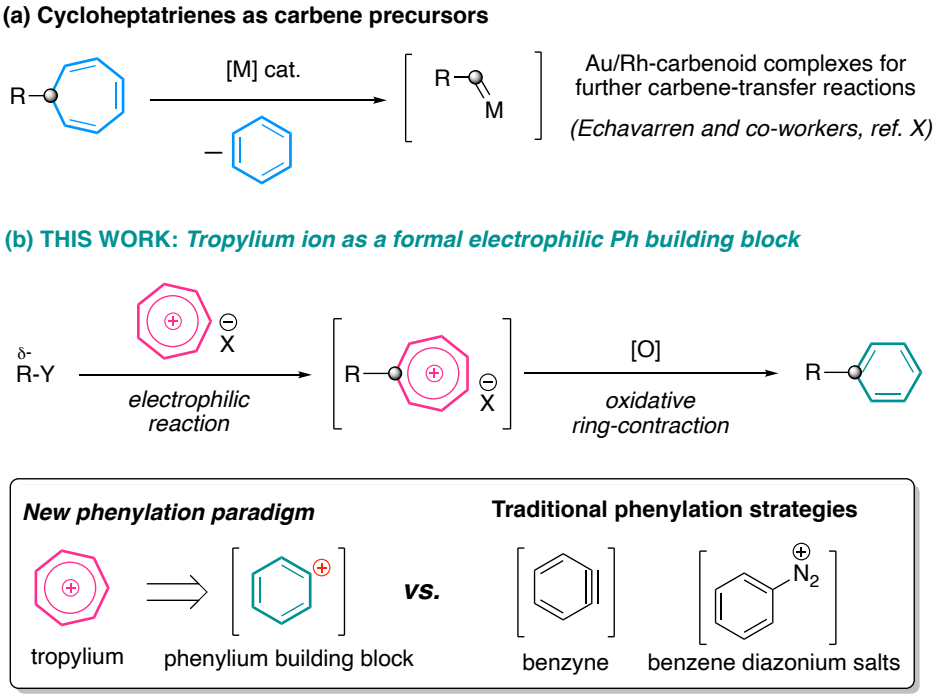
Tropylium ion as a formal electrophilic Ph building block



Abstract: Arylation reaction is an important transformation in synthetic chemistry as aryl building blocks are ubiquitous in valuable organic frameworks. Traditionally, this type of reaction has been carried out either via biaryl coupling reactions or with the use of reactive intermediates such as arynes or aryl radicals. Direct electrophilic arylation reactions have been rarely reported in literature, as the required arenium building blocks are often unstable or inaccessible. To develop a new strategy for such transformation, we herein introduce the development of a formal phenylation reaction, which proceeds via an electrophilic cycloheptatrienylation with tropylium ion, followed by an oxidative ring-contraction.

As aryl moieties are ubiquitous in many synthetic organic structures and biologically valuable compounds, installation of aryl substituents becomes one of the most frequently used chemical transformations in organic chemistry.[1] There have been numerous approaches for arylation reactions, most notably transition metal-catalyzed coupling methods such as the Ullmann,[2] Kumada,[3] Negishi,[4] Stille,[5] Suzuki-Miyaura,[6] Hiyama,[7] and other reactions.[8] Due to their excellent efficiency and broad scope, these reactions have been extensively used for biaryl couplings or arylation of aliphatic substrates in organic syntheses.[8] However, they are not without drawbacks, which include the use of specifically designed precursors and precious transition-metal catalysts, highly toxic reagents, or harsh reaction conditions.[8] Transition-metal residues remaining in target products also pose significant interference to their downstream synthetic or biological applications.[9] These issues led to recent efforts to develop transition metal-free aryl-aryl coupling methods, many of them are however with disputable outcomes.[10]

For phenylation reactions in particular, it is possible to avoid transition metal coupling chemistry by treating substrates with highly reactive phenylating reagents such as benzyne[11] or phenyl radical, which can be generated from phenyldiazonium or phenyliodonium salts (Scheme 1).[12] However, the synthetic precursors of these reactive intermediates normally require lengthy synthetic sequences to prepare; and their high reactivity often leads to unwanted side reactions. It is therefore of great interest to develop a new synthetic paradigm for the phenylation reaction.



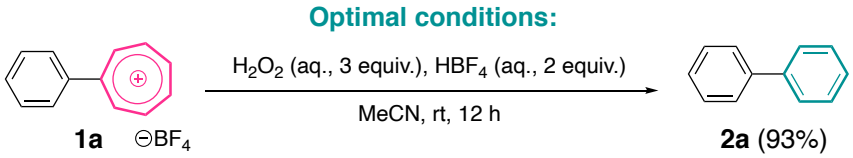
Scheme 1. Tropylium as an electrophilic phenyl building block.

During the course of our recent investigations on the synthetic utility of the non-benzenoid aromatic tropylium ion,[13] we found that it can efficiently couple with a broad range of nucleophilic substrates such as alkenes, arenes, or organometallic reagents to form cycloheptatriene derivatives. The cycloheptatriene moiety can also be easily converted to a tropylium ion again by simple hydride abstraction. We believe that an oxidative ring contraction reaction[14] can be performed on the electron deficient seven-membered ring of the tropylium ($-C_7H_6^+$) ion to transform it into a phenyl ring ($-C_6H_5$). The cleavage of one carbon from the seven-membered ring,[15] to retain a phenyl group on the original organic framework, is directly opposite but complementary to the elegant cycloheptatriene chemistry developed by the Echavarren group, in which they use Au(I) or Rh(II) catalysis to eliminate a benzene ring from cycloheptatriene derivatives to produce organometallic carbenoid complexes for further carbene-transfer cycloaddition and insertion reactions (Scheme 1a).[16]

Our approach would allow a novel strategy to formally install phenyl group in an electrophilic fashion without transition metal catalysis, which will have tremendous potential in synthetic chemistry. It is also an interesting transformation at fundamental level that the non-benzenoid aromatic tropylium ring is converted to the aromatic benzene ring. Our calculations of the nucleus-independent chemical shifts ($NICS(1)_{zz}$) values[17] for tropylium ion and benzene are –27.7 and –30.8 ppm,[18] respectively, which indicate that benzene ring has higher aromaticity than tropylium ion. Hence the ring contraction transformation from a tropylium ion to a phenyl group should be energetically favorable. Herein, we report the development of an experimental protocol to couple nucleophiles with the tropylium ion. This electrophilic building block was then subjected to an oxidative ring-contraction to afford a *formal* phenylation process (Scheme 1b).

We started our investigation of this *formal* phenylation reaction by screening the reaction conditions to ring contract phenyl tropylium tetrafluoroborate **1a** into biphenyl **2a** in an oxidizing environment, as the tropylium moiety is electrophilic. After an extensive optimization study,[18] we established that the reaction was best carried out in aqueous/acetonitrile environment with H_2O_2 (3 equiv.) as the oxidant in the presence of HBF_4 (2 equiv.) to give the product in excellent yield of 93% (Table 1). The use of less HBF_4 or a different Brønsted acid led to lower product yields. Similarly, replacing H_2O_2 with other commonly used oxidants such as Oxone®, $(NH_4)_2Ce(NO_3)_6$, ^{t}BuOOH or even bleach also resulted in poorer efficiencies.[18]

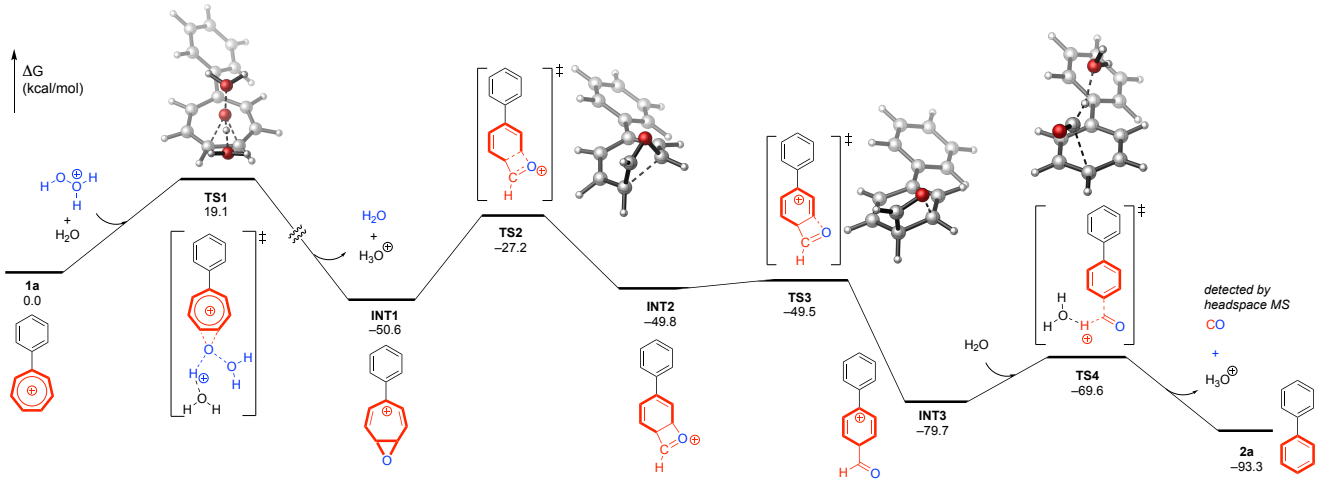
Table 1. Optimization of the oxidative ring-contraction.



[a]	Variations from optimal conditions[b]	Yield[c]
1	no HBF_4	56%
2	H_2O_2 (1 equiv.), no HBF_4	28%
3	only 1.0 equiv. of HBF_4	81%
4	H_2SO_4 (2 equiv.) instead of HBF_4	52%
5	Oxone® (3 equiv.) instead of H_2O_2	52%
6	Oxone® (3 equiv.), no HBF_4	59%
7	CAN (3 equiv.) instead of H_2O_2	31%
8	^{t}BuOOH (3 equiv.) instead of H_2O_2	69%

[a] Conditions: **1a** (0.5 mmol), acid and oxidant in MeCN (2 mL) under ambient conditions at room temperature. [b] For further experiments on optimization studies, see page S28 in the experimental SI. [c] Yield of the isolated product **2a**.

We were curious to understand the mechanistic insights of these reactions, with the hope that they will lead to direct synthetic applications for this reaction as well as inform future developments in chemistry of non-traditional aromatic compounds. However, we were met with little success in our attempts to trap reaction intermediates in the conversion of **1a** to **2a**, as the reaction was in partially aqueous and oxidative environment. Thus, density functional theory (DFT) calculations[19] were carried out to locate a plausible pathway for this oxidative ring contraction. The computational studies were initiated by locating transition states for the reaction between the tropylium salt **1a** (Scheme 2) and neutral hydrogen peroxide H_2O_2. However, all transition states that we could locate are calculated to associate with very high activation barriers (> 30 kcal/mol, see Figure S1 in the computational SI).



Scheme 2. Computational mechanistic elucidation of the oxidative ring-contraction reaction.

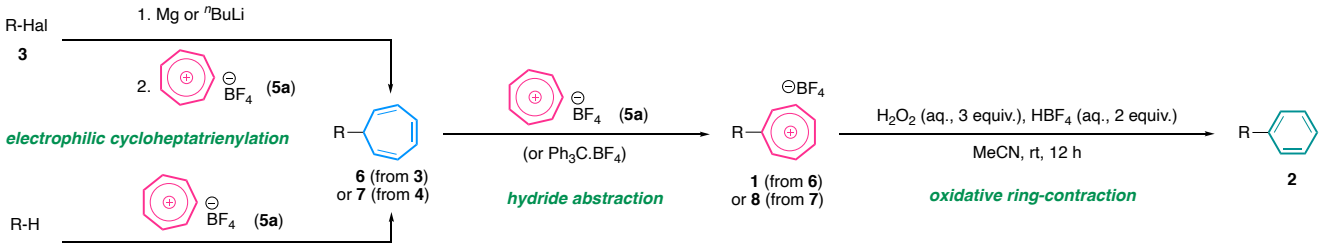
This result is inconsistent with the experimental finding in Table 1 where we found that the reaction can occur efficiently at ambient temperature, albeit in a strongly acidic environment. We then carried out calculations with the assumption that under these reaction conditions, H_2O_2 is protonated by fluoroboric acid to generate a highly reactive species $HOOH_2^+$,[20] which indeed led to a feasible reaction pathway. The computed free energy profile and optimized structures of transition states for the reaction between the tropylium ion **1a** and the protonated hydrogen peroxide $HOOH_2^+$ are shown in Scheme 2. The reaction starts with the electrophilic addition of the $HOOH_2^+$ species to tropylium ion **1a** via transition state **TS1**, giving oxirane intermediate **INT1**. The activation energy of **TS1** is calculated to be 19.1 kcal/mol relative to **1a**. The feasible barrier of **TS1** is primarily initiated by the relatively low energy of LUMO of $HOOH_2^+$.[20a]

To proceed, calculations suggested that skeletal rearrangements[21] via transition states **TS2** and **TS3** take place, generating cyclohexadienylium intermediate **INT3**. Subsequent decomposition of **INT3** can then occur via **TS4**, giving product **2a** and CO. The formation of CO molecule (M = 28) from the reaction mixture was detected by headspace mass-spectrometry, supporting this proposed mechanism of our oxidative ring contraction reaction. Our DFT calculations show that the rate-determining step is **TS2** with an overall barrier of 23.5 kcal/mol (Scheme 2). This energy barrier is consistent with our mild reaction conditions. The overall reaction is calculated to be exergonic by 93.3 kcal/mol, which explains why the reaction can proceed to transform the non-benzenoid aromatic tropylium ion into the aromatic benzene ring.

Having the mechanistic insights of the tropylium moiety to the phenyl ring (Scheme 2) and the optimal conditions of the oxidative ring-contraction (Table 1) in hand, we subsequently applied this

reaction to a synthetic sequence to formally introduce the phenyl group onto a range of aryl halide, alkyl halide and arene substrates (**3** or **4**, Table 2). The synthetic sequence started with the electrophilic cycloheptatrienylation of the organometallic reagents derived from halides **3** to form intermediates **6**, which is a typical procedure to make cycloheptatrienyl derivatives.[16a] Electron-rich arenes **4** could also be directly cycloheptatrienylated via the Friedel-Craft type reaction between them and tropylium tetrafluoroborate **5a** (Table 2).[13p]

Table 2. Substrate scope of the *formal* phenylation reaction.[a]



SM	6[b]	1[b]	Product 2[b]	SM	6/7[b]	1/8[b]	Product 2[b]
3a	**6a**: 91%	**1a**: 93%	**2a** 93%	**3i**	**6i**: ~35%	**1i**: 57%	**2i** 71%
3b	**6b**: 87%	**1b**: 90%	**2b** 83%	**3j**	**6j**: 42%	**1j**: 51%	**2j** 73%
3c	**6c**: 81%	**1c**: 92%	**2c** 88%	**4k**	**7k**: 88%	**8k**: 80%	**2k** 64%
3d	**6d**: 81%	**1d**: 75%	**2d** 74%	**4l**	**7l**: 90%	**8l**: 80%	**2l** 68%
3e	**6e**: 73%	**1e**: 59%	**2e** 47%	**4m**	**7m**: 84%	**8m**: 81%	**2m** 63%
3f	**6f**: 47%	**1f**: 85%	**2f** 89%	**4n**	**7n**: 75%	**8n**: 70%	**2n** 61%
3g	**6g**: 89%	**1g**: 95%	**2g** 72%	**4o-u**	**R' = H** R = H: **7o**, 64%; R = Cl: **7p**, 53%; R = CN: **7q**, 49%; R = OEt: **7r**, 56%; R = NO_2: **7s**, 47% **R = H** R' = Me: **7t**, 53%; R' = CO_2Et: **7u**, 78%		**8o-u** not formed
3h	**6h**: 82%	**1h**: 81%	**2h** 86%	**4v**	**7v**, 35%		**8v** not formed

[a] Further details about the synthesis of **1**, **6**, **7,** and **8** can be found in the experimental SI. [b] Yield of the isolated product from the previous precursor in the synthetic sequence.

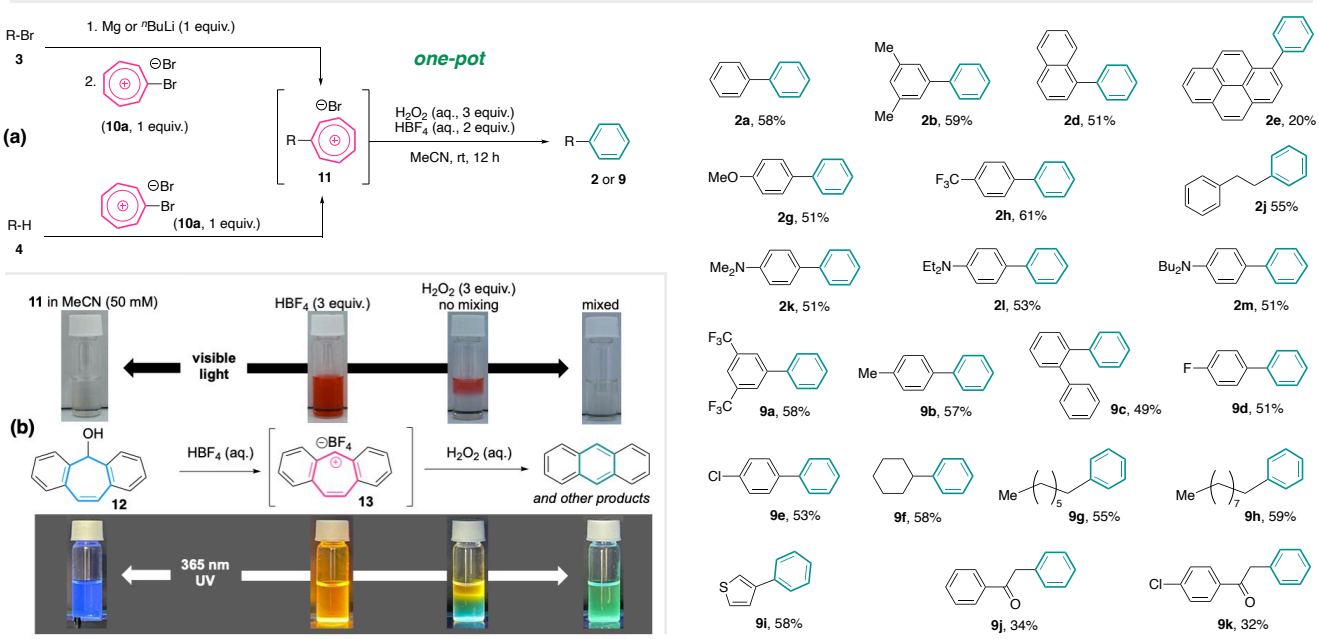
Cycloheptatrienes **6** or **7** were then subjected to a hydride abstraction reaction[13p] with tropylium or tritylium salts to turn them into aryl tropylium salts **1** or **8**. Subsequently, **1** or **8** were oxidized using

our optimal conditions developed in Table 1 to obtain the *formal* phenylated products **2**. Yields of isolated intermediates and products for each synthetic step are documented in Table 2. We could also carry out direct a-cycloheptatrienylation reactions on a range of ketones and ketoesters (**4o**-**v**). Unfortunately, this cycloheptatriene moiety on **7o**-**v** is quite labile in the presence of Lewis acid, hence the subsequent hydride abstraction step was unsuccessful. Overall, however, we can use this synthetic sequence to install phenyl onto a range of aryl halides and electronic arenes in a transition metal-free fashion with good efficiencies (Table 2).

Undoubtedly, the synthetic sequence in Table 2 is lengthy for the installation of a phenyl ring. The hydride abstraction step from cycloheptatrienes **6**/**7** to tropylium salts **1**/**8** is also not very atom economic. We envisioned that if we could form some intermediates being synthetically equivalent to **1**/**8** in one step and carry out the oxidative ring contraction in the same reaction pot, the protocol would be more practical. Thus, we decided to explore this new approach by employing halotropylium halide **10** (Scheme 3a), which we previously used as halogenating or esterification/amidation reaction promoters.[13a-c] After an extensive reaction optimization study, we found out that bromotropylium bromide **10a** was the best reagent for this purpose. A stoichiometric amount of **10a** could react with the organometallic reagents from aryl halides **3** or react directly with arenes **4** to form intermediates **11**. As the second bromine was able to dissociate off from the newly formed cycloheptatriene ring,[22] **11** can serve a synthetic equivalent of tropylium salts **1**/**8**, eliminating the need for the hydride abstraction step. Subsequently, **11** was directly subjected to the oxidative ring contraction conditions developed in Table 1 to form the phenylated products (Scheme 3a).

Using this new one-pot protocol, we were able to convert a selected number of previously investigated aryl halides and arenes (**3a**-**j** and **4k**-**4m** in Table 2, respectively) to their corresponding phenylated products (**2a**-**2m**, Scheme 3a). The product yields of this new protocol were comparable to the overall yields of synthetic sequences in Table 2. We also further investigated a range of new aryl and alkyl halide substrates, most of them worked efficiently with this *formal* phenylation procedure to give products **9a**-**9i** in good yields. Most interestingly, this one-pot protocol was applicable to ketone substrates, which did not work with the synthetic sequence in Table 2. Indeed, acetophenone **4o** and 4'-chloroacetophenone **4p** gave phenylated products **9j** and **9k**, albeit in low yields. This type of a-phenylation reaction on carbonyl compounds is not straightforward and normally required transition metal-catalyzed or complex umpolung processes.[23]

Our oxidative ring contraction process could potentially be used in other applications than the formal phenylation reaction. For example, when we subjected suberenol **12** to similar reaction conditions (Scheme 3b), we observed an interesting shift in colors and photoluminescences of the solution. Suberenol **12** solution in acetonitrile is colorless under visible light but weakly light-blue luminescent under 365 nm UV irradiation. When an acid was introduced, a protonation and dehydration process occurred to generate a cationic dibenzosuberenylium species **13**, which has similar reactivity to the tropylium ion. This solution immediately turned bright red under visible light and yellow luminescent under 365 nm UV light upon acidification. When being exposed to an oxidizing environment such as H_2O_2, **13** was oxidized to anthracene, and a number of other polyaromatic by-products, which instantly turned the solution colorless and green luminescent (Scheme 3b). Further studies to adapt this simple redox-sensitive system to sensing or imaging application of oxidants in biological environments are currently underway.



Scheme 3. One-pot *formal* phenylation reaction substrate scope.

In conclusion, we have developed a new protocol to allow *formal* phenylation reactions of aryl halides and electron-rich arenes in a transition-metal free manner. This protocol exploited the versatile electrophilicity and oxidizing ability of tropylium ion to construct the seven-membered ring framework and subsequently contract one carbon from that to produce the phenyl ring. It is also an interesting transformation at fundamental level in that the non-benzenoid aromatic tropylium ring is converted to the aromatic benzene ring. We are currently working on the incorporation of

substituted tropylium ions onto organic structures and transforming them into polysubstituted arylated frameworks and will report the outcomes in due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge: Experimental details and spectroscopic data for all products, full Gaussian reference, Cartesian coordinates, electronic and free energies.

AUTHOR INFORMATION

Correspondence

*T. V. N. E-mail: t.v.nguyen@unsw.edu.au (general enquiries)

*B. K. M. E-mail: binh.mai@pitt.edu (computational enquiries)

CONFLICTS OF INTEREST

There is no conflicts of interest to declare.

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