Tandem Cooperative Friedel-Crafts Reaction of Aldehydes with Electron Deficient Arenes Through Catalyst-Activation *via* Hydrogen Bonding Network

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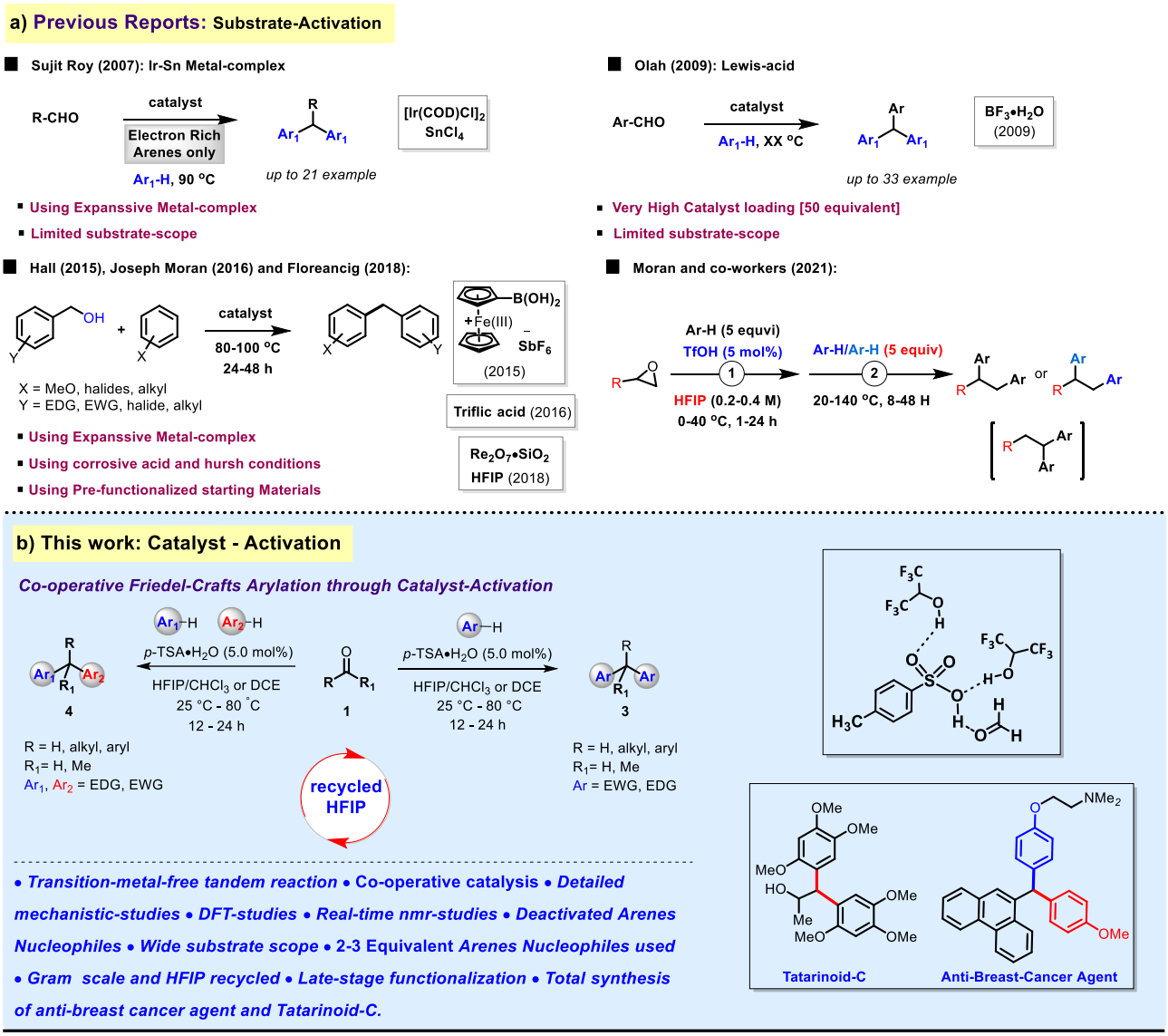
Since its discovery in 1877, the Friedel-Crafts alkylation reaction has been the method of choice to prepare various aryl hydrocarbons. Recent developments for this reaction have resulted in the synthesis of these compounds in one pot process with various metal as well as metal free protocols. However, the alkylation of common feedstock aldehydes using electron deficient arenes and also with two different arene nucleophiles are quite challenging and scantily explored. Herein, we provide a solution to these problems by a new concept, *"catalyst activation"* accomplished by increasing the Brønsted acidity of *p*-toluenesulfonic acid (*p*TSA) through strong hydrogen bonding with hexafluoroisopropanol (HFIP). The real-time NMR titration as well as computational studies reveal multiple roles of HFIP in increasing the Brønsted acidity of para-toluene sulphonic acid (*p*TSA) and stabilization of the transition states formed during the electrophilic aromatic substitution. The developed process has a great potential for industrial application reflected from the synthesis of various bio-active natural products like arundine, tartarinoid C, and several other bioactive molecules. Also, the used HFIP was recovered in a gram-scale synthesis making this protocol highly cost-effective and conducive for industrial production.

The Friedel-Crafts reaction (FC reaction) involving the C─C bond formation between an electrophile and aromatic arene is considered one of the most important strategies to synthesize various bio-active aromatic hydrocarbons[1]. The classical FC reaction involves synthesis of aryl hydrocarbons using alkyl halides as electrophiles which has various limitations like the formation of side products and liberation of corrosive and toxic hydrogen halides. Further, this reaction is carried out under harsh reaction conditions hence having huge environmental impact[2]. In fact, the need to develop an atom economic process under environmentally benign conditions is considered one of the primary focus of research in this field[3]. Recent developments in FC reaction focuses on using other electrophiles such as epoxides[4-5], benzyl alcohols[6-10] & their derivatives[11], benzyl fluorides[12], aldehydes and ketones etc[13-18]. For example, in a seminal work by Hall and coworkers a ferrocenium boronic acid catalyst was developed for the FC arylation of deactivated benzylic alcohols[6]. Also, a rhenium oxide catalyzed FC alkylation of benzyl alcohols has been reported for the synthesis of the diaryl alkanes[8]. Generally, in these methods the reaction occurs via substrate activation through direct coordination with the catalyst. However, "*substrate-activation*" strategy goes well only with the strong nucleophiles. Also, these protocols were explored to limited substrates and requires pre-functionalized starting materials.

Recently our group has published several protocols for typical FC reaction by using activated nucleophiles[19-22]. We were curious to investigate and develop a general protocol for FC reaction which can be used with both activated and deactivated arene nucleophiles under *"green reaction conditions"*. So, we directed our efforts on using aldehydes and ketones as substrates for classical FC reaction. The FC reaction on these substrates is highly atom economical and leave behind water as the sole by-product. Also, the corresponding synthesis of biologically important unsymmetrical hydrocarbons through this protocol is highly challenging and relatively unexplored[15].

To address these challenges, we thought of using a strong acid catalyst which would activate the electrophiles[17] and allow the FC reaction with weak nucleophiles. Towards such pursuits, here in this work, we have developed a new strategy where the reaction proceeds via "*catalyst-activation*"[23] followed by "*substrate-activation*". Here the catalyst was activated by the solvent, HFIP, through hydrogen bonding network[23-27]. Further, recent literature reports also suggests that HFIP interacts with the arene molecules through OH-π and CH-π interactions[24]. The combined effect of catalyst activation by HFIP followed by substrate activation resulted in achieving our goal as discussed in this paper.

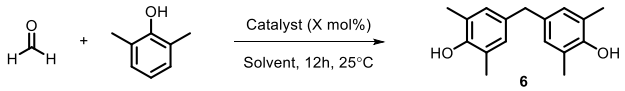


Scheme 1 | Strategies for metal-free Friedel-Crafts arylation reactions - a) substrate activation and (b) catalyst-activation (this work).

Results and Discussion

Reaction development. We began our study through optimizing different reaction parameters taking formaldehyde and 2,6-dimethylphenol as the model substrates. At first, we screened the reaction with various Lewis acid catalysts like BF_3•Et_2O, TMS•OTf, iodine, and Brønsted acid catalysts like triflic acid, trifluoroacetic acid, *p*TSA in chloroform to observe low to high yield of the corresponding diarylmethane (**6**) in 48-87% yield (Table 1). However, the mild Brønsted acid catalyst, L-Proline essentially gave a trace amount of the desired product indicating the reaction to be dependent on the Brønsted acidity of the catalyst. Further to this, we screened different solvents to observe dichloroethane (DCE) and chloroform ($CHCl_3$) to have higher yields compared to that with the other solvents (see Table 1). Thus, at room temperature, using 10.0 mol% *p*TSA, the diarylmethane (**6**) could be synthesized in excellent yield (87%) within 10 h. However, interestingly, when the reaction was performed in fluorinated alcohols like HFIP, the reaction was very clean and essentially gave the quantitative yield of the product analyzed by NMR studies.

Table 1: Optimization of Reaction Conditions[a]



Entry	Catalyst	Cat (X mol%)	Solvent	Yield (%)[a]
1	BF_3•OEt_2	10	$CHCl_3$	70
2	Triflic acid	10	$CHCl_3$	77
3	TMSOTf	10	$CHCl_3$	80
4	I_2	10	$CHCl_3$	52
5	*L*-Proline	10	$CHCl_3$	NR
6	TFA	10	$CHCl_3$	48
7	*p*-TSA	10	$CHCl_3$	87
8	*p*-TSA	10	DCE	75

9	*p*-TSA	10	-	30
10	*p*-TSA	10	H_2O	trace
11	*p*-TSA	10	MeOH	trace
12	*p*-TSA	10	Ethanol	trace
13	*p*-TSA	10	CF_3CH_2OH	70
14	*p*-TSA	5	$CHCl_3$	78
15	*p*-TSA	5	Toluene	72
16	*p*-TSA	5	PhCl	70
17	*p*-TSA	5	HFIP	97%
18	*p*-TSA	5	HFIP/$CHCl_3$	96%
19	-	-	HFIP	NR

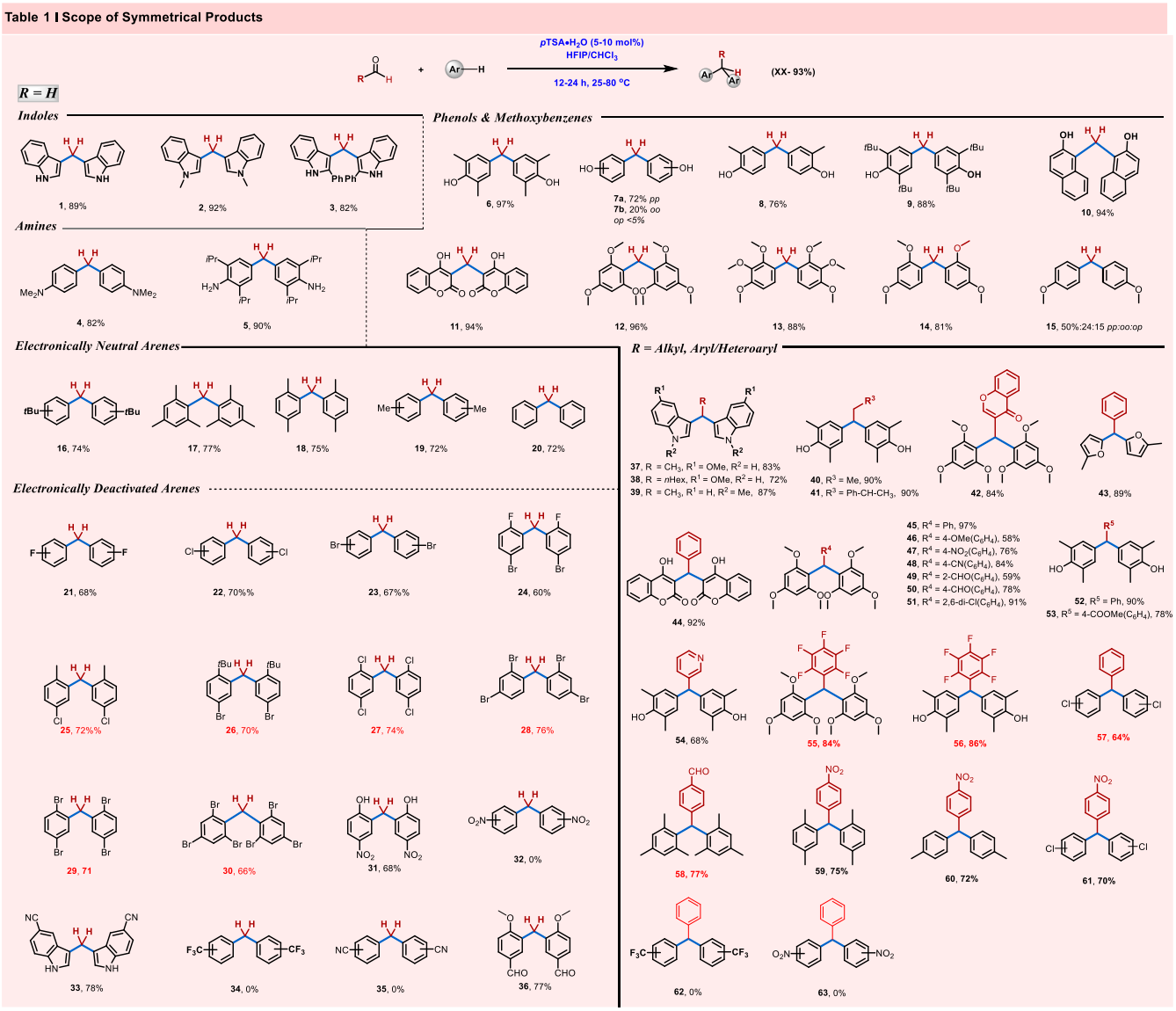
[a] Reaction conditions: a) **1a** (0.5 mmol), **2a** (1.2 mmol), Solvent, 25 °C, 12 h

This could either be due to the enhanced hydrogen bond donor ability of the fluoroalcohols compared to common alcohol solvents like methanol (MeOH) or ethanol (EtOH) or maybe due to the strong ionizing power of the fluoroalcohol and hence stabilizing the polar intermediates (thus enhancing the reaction rate) formed during the course of the reaction[24-27]. The polarity effect might not be important in this case since no significant improvement in the reaction rate as well as the yield was observed when HFIP was replaced by EtOH or 2,2,2-trifluroethanol (TFE), although the dielectric constant of these two polar protic solvents [ε(EtOH) = 24.3; ε(TFE) = 26.7] is higher than HFIP (ε = 16.7) (SI). Next, we optimized the catalyst loading to observe 5.0 mol% of the catalyst in $CHCl_3$/HFIP mixture (5:2) was sufficient to observe 96% yield of the product.

Reaction scope - symmetrical products. With the optimized reaction conditions in hand, we explored the generality of the developed protocol. Towards this goal, we applied the optimized reaction condition to various sets of arenes: a) Strongly nucleophilic electron rich arenes like indoles, phenols, and phenyl ethers, b) moderately nucleophilic electronically neutral arenes like mesitylene, xylene, toluene, and benzene and c) weakly nucleophilic electronically deactivated arenes like fluorobenzene, chlorobenzene, bromobenzene and strongly deactivating arenes like dihalobenzenes, nitrophenols, cyano phenols, trifluoromethyl arenes, and cyano arenes with formaldehyde as the electrophile[28-29].

As anticipated, the Friedel-Crafts alkylation of formaldehyde with the electron rich arenes were very smooth and gave the corresponding products in high yield (69-97%). The Friedel-Crafts alkylation of the heterocyclic phenol, 4-hydoxy coumarin resulted in the anticoagulant natural product, dicoumarol (**11**), in high yield (94%) demonstrating the applicability of the developed protocol for electron-rich heteroarenes. Interestingly, the Friedel-Crafts reaction of phenol resulted in the corresponding diarylmethanes, (**7a**) and **(7b**) with high para-selectivity (72:20:>5), and 2-naphthol gave the 1-substituted product exclusively. Also, the Friedel-Crafts reaction of 1,2,3-trimethoxy benzene resulted in the exclusive formation of compound (**13)** in high yield (88%).

The Friedel-Crafts alkylation of electronically neutral and deactivated arenes is considered a highly daunting task in synthetic organic chemistry[14]. In order to address this challenge, we applied the optimized conditions to these challenging substrates. Delightfully, electronically neutral substrates like mesitylene (**17**), *p*-xylene (**18**), *t*-Bu benzene (**16**), toluene (**19**), and benzene (**20**) were all successfully converted to the corresponding Friedel-Crafts alkylated products in good yields (72-77%) when these arenes were heated with formaldehyde at 80°C for 18-20 h under the optimized conditions. Interestingly, when sterically biased arene, *t*-Bu benzene, was used as the nucleophile, the corresponding Friedel-Crafts product was observed in high regioselectivity highlighting the formation of the sterically less encumbered product to be energetically more favorable. Moreover, we were also delighted to note that less nucleophilic aromatic hydrocarbons like benzene responded to the developed method resulting in the formation of the corresponding diphenylmethane in high yield (72%). The corresponding Friedel-Crafts alkylation with electronically deactivated arenes like aryl halides were performed next.



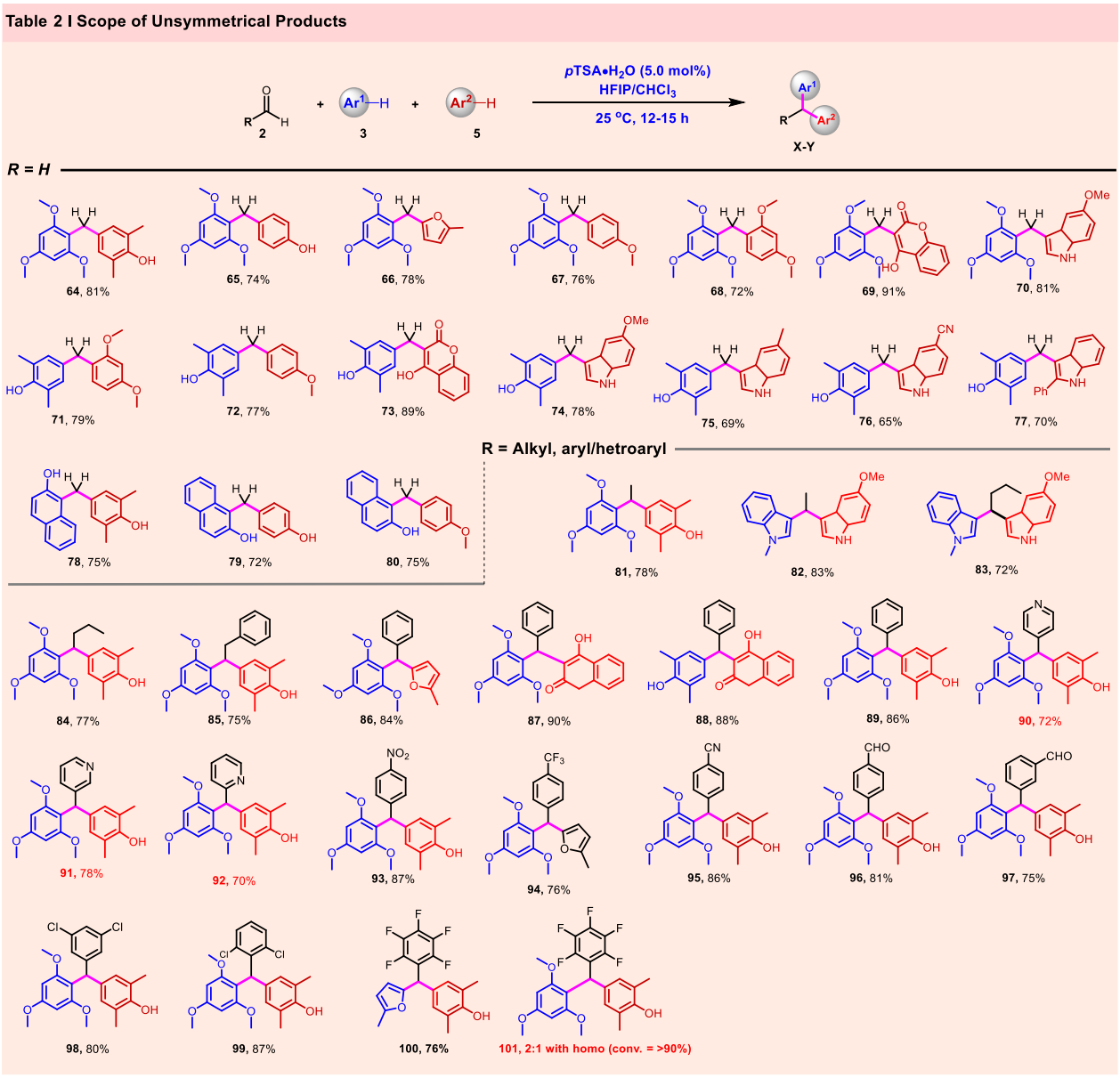
Scheme 2. [a] Conditions: *p*TSA (5-10 mol%), substrate (0.5 mmol), arene (Ar-H, 2-3 equiv.,) in 0.7 ml HFIP/$CHCl_3$ or DCE at 25-80 °C for 12-24 h. Yields of isolated products are presented. NR = No reaction.

Gratifyingly, the Friedel-Crafts alkylation of fluorobenzene, chlorobenzene as well as bromobenzene resulted in the halosubstituted diarylmethanes in an overall yield of (67-70%) respectively. The deactivated arene 4-chloro-toluene, also responded well to the reaction resulting in the corresponding diarylmethane (**25**) in high yield of (72%). Sterically biased aryl halide, 4-bromo-tert butylbenzene, resulted in the Friedel-Crafts product with high regioselectivity with **(26)** being the major product. Interestingly, without HFIP, no reaction was observed with the arene nucleophiles.

We further extended our interest in the FC alkylation of strongly deactivated arenes like di- and trihalobenzene, nitrophenol, and cyano-phenols. Importantly, earlier, in a similar work by Olah and coworkers, the Friedel-Crafts alkylation reaction with strongly deactivating arenes like dihalobenzenes were unsuccessful even with a very high catalyst loading (50 equivalents of boron trifluoride monohydrate), indicating the transformation to be highly challenging[14]. To address this challenge, we subjected the di- and poly-halogenated arenes to the optimized reaction conditions. Delightfully, we obtained the corresponding Friedel-Crafts products (**24**), (**27**), (**28**), (**29**) and (**30**) in moderate yield (60-76%), highlighting the first report on the Friedel-Crafts alkylation with very strongly deactivated arenes. Importantly, the Friedel-Crafts alkylation of 1,3,5-tribromo benzene resulted in the corresponding diarylalkane (**30**) with polyhalogen atoms. This provides a scope for further functionalization of the diarylmethane molecules and the synthesis of various polyarylated compounds through various metal catalyzed cross-coupling reaction.

To study the scope of the reaction with different aldehydes we applied our protocol to different sets of aldehydes: a) aliphatic aldehydes like acetaldehyde, propionaldehyde, butyraldehyde, phenyl acetaldehyde, and cyclopropyl carbaldehyde, b) aromatic aldehydes with electron releasing as well as electron withdrawing substituents, and c) heteroaromatic aldehydes. The Friedel-Crafts reaction of aliphatic aldehydes with electron rich arenes were very smooth and produced the corresponding trisubstituted products in high yields (72-87% yield). Further, both strongly electrophilic electron poor arylaldehydes as well as weakly electrophilic electron rich arylaldehydes was successful with electron rich arenes **(Scheme-2)**. Delightfully, the developed protocol tolerated wide variety of functional groups like ester, cyano, and nitro group when aldehydes with such functional groups were reacted with electron rich as well as poor arenes. Further, aromatic dialdehydes like phthalaldehyde and terephthaldehyde resulted in the selective condensation of one aldehyde group over the other resulting in the formation of the corresponding triarylmethane products with high efficacy (59 and 78% respectively). The pendant -CHO group in (**49**), (**50**) and (**58**) can be further utilized for the synthesis of other important compounds using routine nucleophilic substitution reaction of aldehydes. Moreover, the selective transformation of one aldehyde group allows for the challenging non-enzymatic desymmetrization process and hence can be used in the asymmetric synthesis of chiral molecules. The sterically congested 2,6-dichloro benzaldehyde also resulted in the corresponding Friedel-Crafts arylated product (**51**) in good yields (92%) highlighting the tolerance of the reaction to sterically bulky groups. However, electron rich aryl aldehydes like 4-methoxy benzaldehyde gave consistently low yield (58%) of the corresponding product **(46)** as anticipated from the low electrophilicity of such electron releasing aldehydes. The developed method was also successful with heteroaromatic aldehydes like furan-2-carboxaldehydes, as well as thiophene-2-carboxaldehydes without the cleavage of the thiophene or furan ring highlighting the importance of the developed method. Further, the method was also successful with the heteroaromatic aldehydes like 3-formylchromone, pyridine-3-carboxaldehyde etc. resulting in the formation of the corresponding triarylmethane (**42**) and (**54**) in high yield (84%), (68%) when treated with 1,3,5-trimethoxy benzene and 2,6-dimethylphenol respectively.

The Friedel-Crafts alkylation of aromatic aldehydes with electron neutral as well as electron withdrawing arenes were investigated next. Remarkably, benzaldehyde as well as 4-nitrobenzaldehydes resulted the corresponding Friedel-Crafts product (**59-61**) with electron neutral as well as electron-withdrawing arenes like para-xylene, toluene, chlorobenzene respectively in good yield (70-75%). However, electron rich aryl aldehydes like 4-methoxy benzaldehyde failed to respond to the developed protocol with electron neutral or electron withdrawing arenes probably due to the poor electrophilicity of such aldehydes.

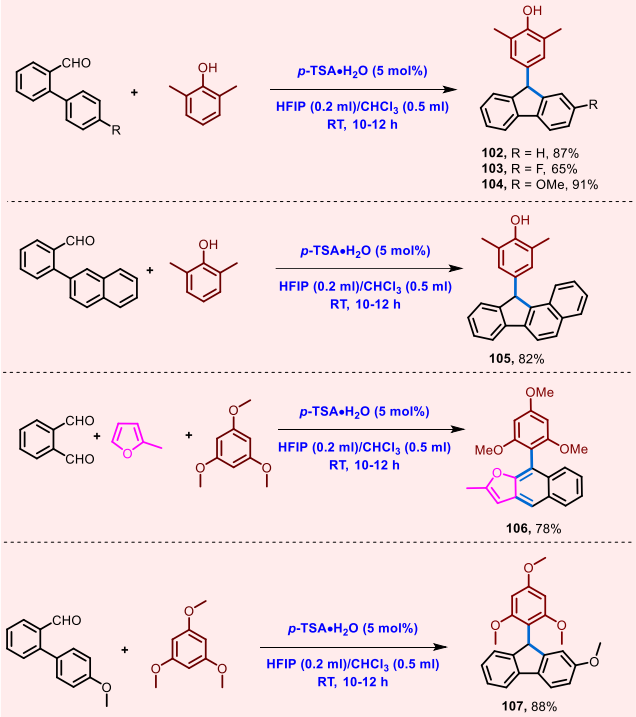


Scheme 3. [a] Conditions: *p*TSA (5.0 mol%), substrate (0.5 mmol), Ar_1-H (1.1 equiv., 0.55 mmol), Ar_2-H (1.1 equiv., 0.55 mmol) in 0.6 ml HFIP/$CHCl_3$ at 25 °C for 12-14 h. Yields of isolated products are presented. [b] Yields of isolated minor products are presented. [c] NMR yield of minor products are presented.

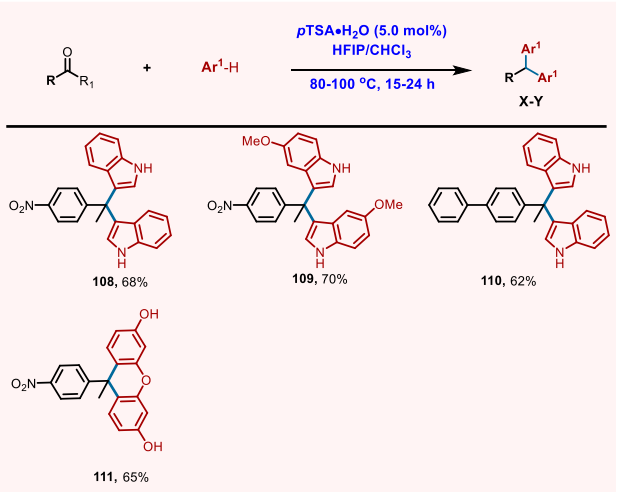
Unsymmetrical products. After the initial success with both electron-rich and electron poor arenes and a diverse set of aldehydes, we became interested in testing the possibility of using two different arene nucleophiles in a one-pot fashion. The FC reaction involving two different nucleophiles is challenging as there is always a finite possibility of the formation of homocoupled products [15]. This issue, however, can be alleviated by the use of our optimized reaction conditions. For example, we observed the formation of the unsymmetrical alkanes (**64-101**) in major amount (65-91%) along with minor amounts of respective symmetrical products when formaldehyde was treated with two different nucleophiles. Further, 4-hydroxycoumarin and 1,3,5-trimethoxy benzene resulted in (**69**) in 91% yield without significant formation of homo-coupled products. Moreover, aliphatic as well as aromatic aldehydes could be successfully arylated to the corresponding unsymmetrical products (**81-101**) in good yield (72-90%). Interestingly, two different indoles with similar nucleophilicity could also be used for this reaction without significant formation of homocoupled products as evident from the formation of compounds (**82**) and (**83**). Also, aromatic dialdehydes, terephthaldehyde, and isophthalaldehyde resulted in the selective arylation of one aldehyde group over the other similar to what has been observed in case of homocoupling reaction (*vide* supra).

Intra-inter-molecular Friedel-Crafts arylation. In the above reaction sequence, when ortho-phthaldehyde was used as the electrophile, with two different

arenes, the cyclic compound (**106**) was obtained in good yield (78%) that was characterized by ^{1}H, ^{13}C NMR as well as through HRMS. We proposed this reaction to proceed *via* a tandem reaction sequence involving both intermolecular followed by an intramolecular Friedel-Crafts reaction[18].



Scheme 4. [a] Conditions: *p*TSA (5.0 mol%), substrate (0.5 mmol), Ar_1-H (1.1 equiv., 0.55 mmol), in 0.7 ml HFIP/$CHCl_3$ at 25 °C for 10-12 h. Yields of isolated products are presented.



Scheme 5. [a] Conditions: *p*TSA (5.0 mol%), substrate (0.5 mmol), Ar_1-H (1.1 equiv., 0.55 mmol), in 0.6 ml HFIP/$CHCl_3$ at 80-100 °C for 15-24 h. yields of isolated products are presented.

Mechanistic studies - reaction profile and mechanism

To extend this tandem reaction protocol, we applied the proposed tandem reaction with various 2-arylbenzaldehydes intermolecular followed by intramolecular Friedel Crafts arylation with 2,6-dimethyl phenol and 1,3,5-trimethoxy benzene respectively to obtain compound (**102-105**) in good yield (65-91%). Importantly, this transformation result in the formation of various important 9-aryl fluoren based molecules which have been used as OLED materials[30].

Friedel-Crafts arylation with ketones. Due to low electrophilicity and high steric bulk of ketones, the corresponding Friedel-Crafts arylation of ketones are very challenging[13]. In order to address this challenge, we performed the Friedel-Crafts alkylation with the following ketones: a) ketones with electron withdrawing groups (4-nitroacetophenone and 4-nitrobenzophenone), b) ketones without any substituents (acetophenone and fluorenone), and c) sterically hindered ketones (benzophenone) with electron rich arenes like indoles, resorcinols, and phenols to give the respective products (**108-111**) in (62-70% yield) with our protocol. The 9-fluorenone with resorcinol resulted in the cyclic product (**xx**) in yy% through a tandem-Friedel-Crafts alkylation-intramolecular cyclization process.

Real-time NMR Studies, control experiments, and computational investigations

In order to elucidate the role of HFIP, we carried out various control experiments and density functional calculations. At first, we recorded the ^{1}H NMR of a mixture of benzaldehyde and HFIP with gradual addition of *p*TSA (0 mol%, 5.0 mol%, 10.0 mol%, 20.0 mol%, 30.0 mol%, 40.0 mol%, 50.0 mol%, and 100.0 mol%), and we observed a significant downfield shift of the -OH proton of HFIP from 3.1 ppm (blue coloured trace, no *p*TSA added) to 6.2 ppm (green coloured trace, with 1 equiv. of *p*TSA). Whereas, no significant shift was observed for aldehydic proton (Figure 1). This indicates that HFIP molecules interact with the *p*TSA molecules *via* a hydrogen bonding network formed between the oxygen atoms of *p*TSA and -OH protons of HFIP. A gradual chemical shift of the HFIP's -OH proton is because of the increased number of hydrogen bonds in the presence of more

*p*TSA molecules. Additionally, this hydrogen bonding effect also results in the increased acidity of *p*TSA (Brønsted acid catalyst). To complement this result, we have calculated *p*Ka of *p*TSA in the presence and absence of one explicit molecule of HFIP using DFT calculations (see SI). A significant decrease in the pKa value of *p*TSA was observed in the presence of one HFIP molecule that indicates increased acidity of *p*TSA.

From further DFT calculations it was observed that the *p*TSA first interacts with the formaldehyde via a hydrogen bond between *p*TSA proton and formaldehyde oxygen to form the Int_1. The distance between formaldehyde oxygen and *p*TSA proton is 1.72 Å. Whereas it decreased to 1.63 Å when calculations were performed with one explicit HFIP molecule and it decrease further to 1.56 Å with two explicit HFIP molecules (see SI). This suggests that the hydrogen bonding effect of HFIP on *p*TSA helps in activating the electrophile (HCHO). Then, in the next step a nucleophile (C_6H_6) attacks the carbonyl carbon of HCHO in such a way that the hydrogen of attacking nucleophilic carbon interacts with one of the oxygen atom of *p*TSA. This interaction in turn helps in activating the nucleophile (Figure 2 TS_1). In this way *p*TSA activates both electrophile as well as the nucleophile in a concerted way. The combined effect of concerted pathway and the hydrogen-bonding assistance of HFIP are responsible for a high catalytic activity of *p*TSA. The first step of the mechanism leads to the formation of benzyl alcohol intermediate (Int_2) which further interacts with the *p*TSA with a bond distance of 1.46 Å between O(Int_1) and H(*p*TSA). (Figure 2, Int_2) In the next step, another nucleophile (C_6H_6) attacks Int_2 to via TS_2 in a similar concerted way to give the final product ($PhCH_2Ph$). This step is accompanied by the removal of water as the byproduct and regeneration of *p*TSA catalyst. First step of the mechanism was found to be the rate determining step (RDS) with an activation free energy barrier of 22.8 kcal/mol whereas, the free energy barrier for the second step is 18.2 kcal/mol.

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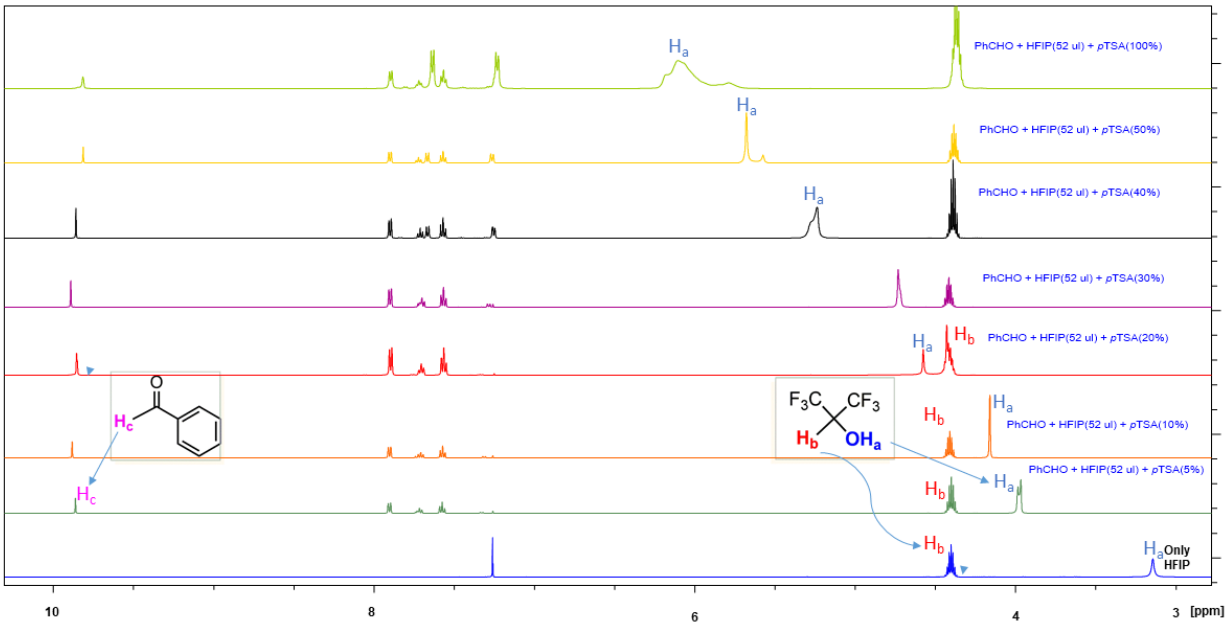


Figure 1. | Real time NMR studies showing the activation of the *p*TSA with HFIP

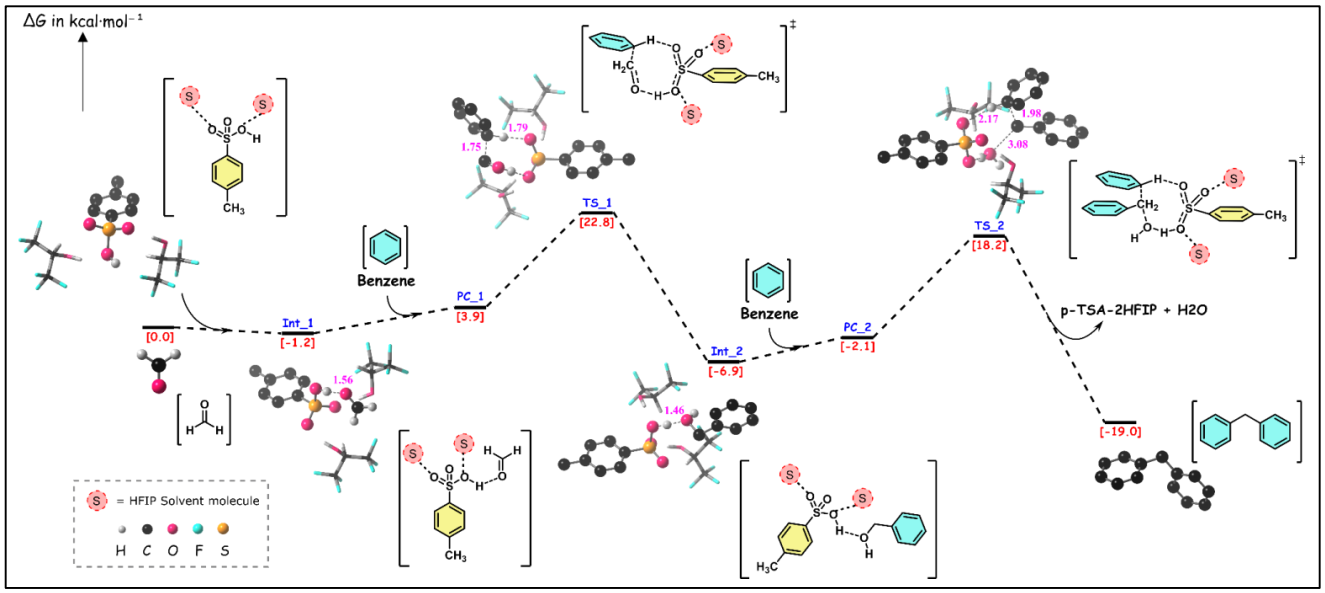


Figure 2. | Concerted reaction mechanism with cooperative effect of HFIP solvent (TS=Transition state, Int= Intermediate, PC= Pre-complex) *only hydrogens which are involved in the reaction are shown.

In order to understand the effect of HFIP solvent, we first did calculations using an implicit solvent model where we applied SMD solvation model based on density for DFT calculations. We calculated the reaction profiles in the presence of implicit $CHCl_3$ and HFIP solvents. In comparison to the $CHCl_3$, HFIP didn't showed any significant effect on the Gibbs free energy profile except a slight decrease in the free energy of both transition states and a slight increase in the energy of all intermediates.(see SI) This indicates that the implicit solvent models are inadequate in delineating the solvents role in the reaction. Additionally, the implicit solvent models do not consider the hydrogen bond effects making them ineffective in this case. Thus, we switched to using explicit solvents in our calculations. Firstly, we added one HFIP explicitly along with the implicit model, and a very prominent effect was observed on the Gibbs free energy profile showing a substantial decrease in the free energy of all the intermediates and transition states compared to that of the implicit solvent-based calculations (Fig. 2). The decrease in the activation free energy of the first step (RDS) from 34.4 to 27.6 kcal/mol was observed. Subsequently, using two explicit HFIP molecules showed further decrease in the activation free energy of RDS to 22.8 kcal/mol which is further accelerates the reaction. (Figure 2) On the contrary, when three explicit HFIP molecules were used, the Gibbs free energy change for the formation of Int_1 was found to be higher as compared to one and two equivalents of HFIP cases (Figure 2). This indicates that when two HFIP molecules are present in the vicinity of *p*TSA forming hydrogen bonds then the reaction is most favored. The presence of the third HFIP molecule is disadvantageous because it shows a destabilization effect. One would argue that in reality, there could be many HFIP molecules surrounding the reactants, however, we conjecture those HFIP molecules likely play a secondary role in the chemical reaction (beyond the scope of this investigation).

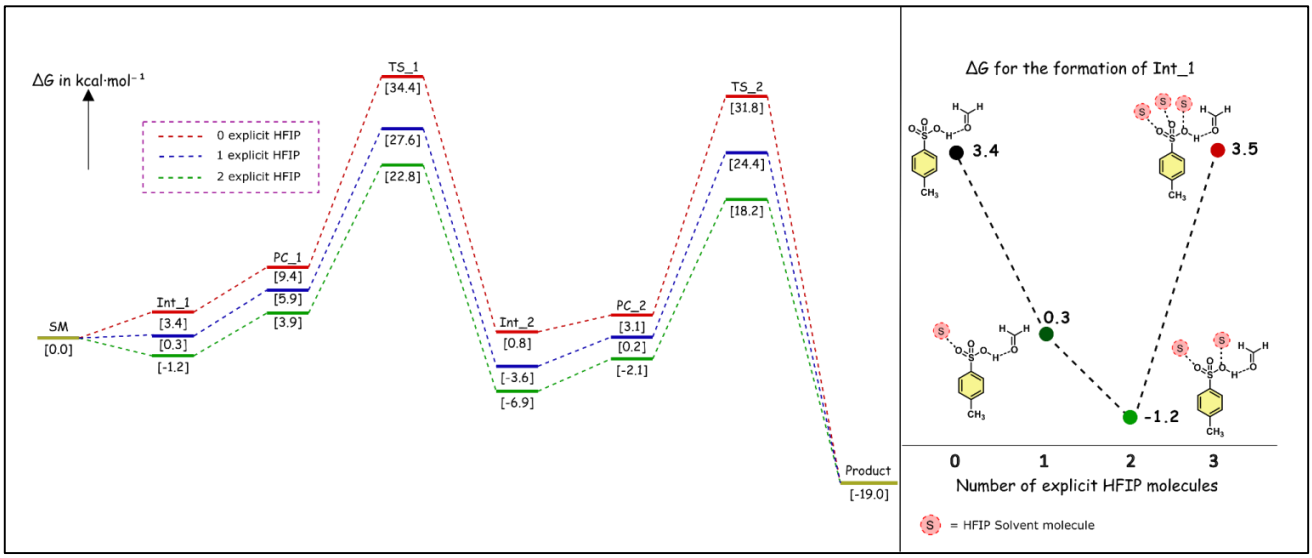
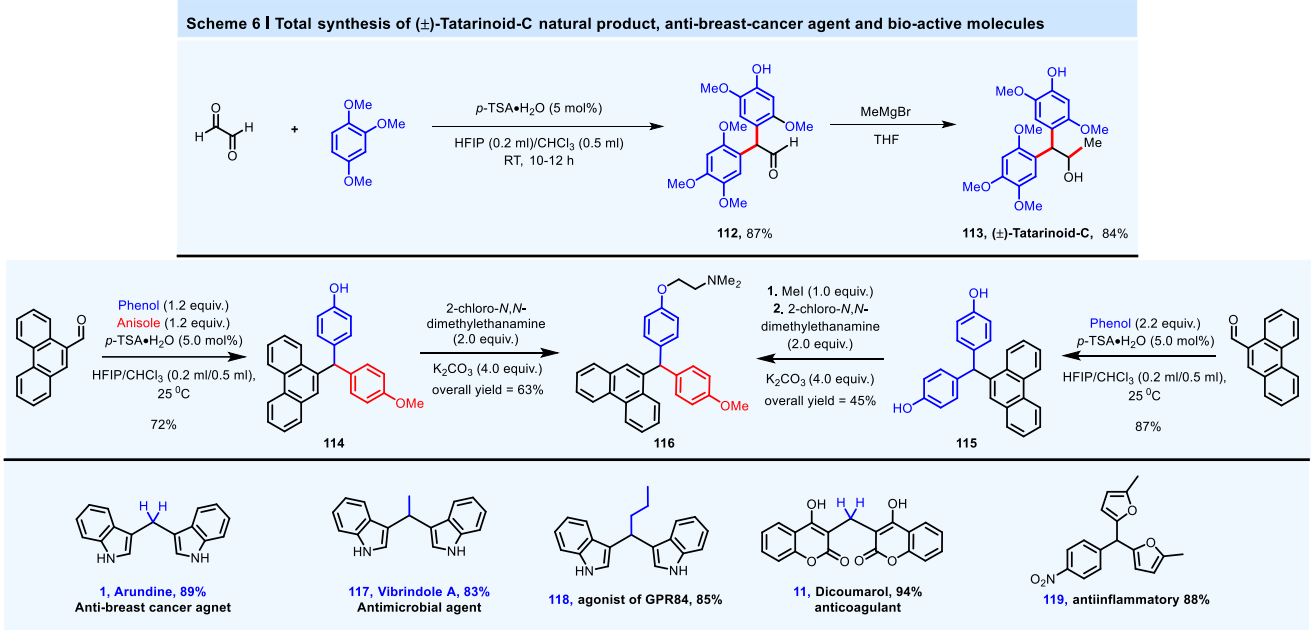
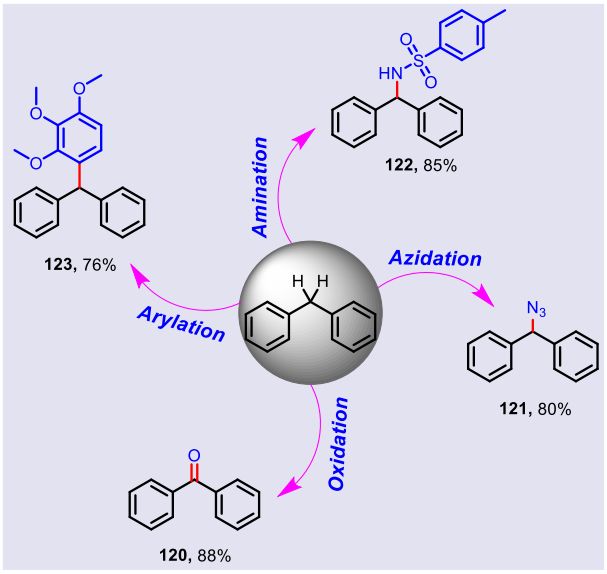


Figure 3. | DFT calculations for the reaction mechanism showing the effect of Hydrogen bond network of explicit HFIP solvent.

Applications. To show the potential utility of the protocol, we applied the developed process for the synthesis of various biologically important natural products like Tatarinoid C (**113**) and other pharmaceutically important compounds. At first, we attempted the synthesis of the natural product Tatarinoid C (**113**). Towards this, we carried out the Friedel-Crafts alkylation of commercially available glyoxal with 1,2,4-trimethoxy benzaldehyde under the optimized conditions resulting in the formation of the corresponding bisarylated compound in high yield. Interestingly, similar to the aromatic dialdehydes, aliphatic dialdehydes also underwent selective monoarylation yielding the diarylated compound with a pendant aldehyde group. Further, the Grignard reaction with MeMgBr yielded the natural product Tatarinoid C in racemic form. Finally, a kinetic resolution with vinyl acetate in the presence of an enzyme lipase may result in the formation of the optically pure natural product. Moreover, it is to be noted that till date, this is probably the shortest route for the synthesis of this natural product. The other complementary route involving the synthesis of Tatarinoid C from the chiral pool (*S*)- methyl lactate involves multiple steps involving silyl protection of the secondary hydroxy group of (*S*)- methyl lactate, conversion of the ester functional group to the aldehyde group, acid catalyzed Friedel-Crafts alkylation of the formed aldehyde, and further deprotection of the silyl group[16].This lengthy process has another disadvantage; it involves simultaneous deprotection of the protecting group that resulted in the oligomerization of the aldehyde, which eventually reduces the overall yield of the final product [16].

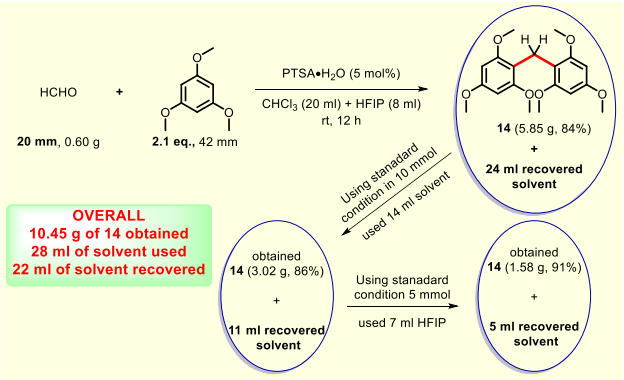


We further aimed at utilizing the developed method for the synthesis of various bioactive lead molecules. For example, the phenanthrene based triarylmethane (**116**) is an important lead molecule for the development of non-steroidal anti-breast cancer agents[31]. To synthesize this molecule in one pot fashion, we performed the Friedel-Crafts arylation of 9-anthraldehyde with phenol and anisole to yield the unsymmetrical triarylmethane (**114**) in 72 % yield along with some minor amounts of homocoupled products. A further base catalyzed alkylation of the phenolic hydroxy group in compound (**114**) resulted in the formation of the target molecule (**116**) in overall yield of 63%. This is the shortest, metal-free route for the synthesis of this type of compounds. Further, we developed an alternative approach for the synthesis of the same target molecule. A homocoupling of phenol and anthraldehyde resulted in the formation of the symmetrical triarylmethane (**115**) which was further desymmetrized through sequential methylation and alkylation with the amino alkyl chain to form the target anti-breast cancer agent molecule; (**Scheme 6**). The homocoupling of indoles, furans, and 4-hydoxycoumarin with formaldehyde, acetaldehyde, butraldehyde, and 4-nitro benzaldehyde, respectively also resulted in various bioactive molecules like aurindine (**1**), Vibrindole A (**117**), agonist of GPR84 (**118**) and Dicoumarol (**11**). We also could prepare other important molecules through benzylic C-H functionalization and other late stage functionalization (Scheme 7)[32].



Scheme 7 Benzylic C-H bond functionalization for organic synthetic transformation.

Recycle and reusability of HFIP Solvent. The high cost of HFIP is a major hurdle for the large scale use of this *"magic solvent"* and the scale-up of the developed protocol. So, we probed into the fact that whether we can recover and reuse this solvent. Towards this goal, we carried out the developed Friedel-Crafts reaction in a gram scale (0.6 g formaldehyde, ~ 7 g 1,3,5-trimethoxy benzene) using 28 ml $CHCl_3$ HFIP mixture. After the completion of the reaction, we could distill the solvent and reuse it for 3 other cycles. Thus a total of 24 ml of the solvent was recovered from the reaction mixture (used 28 ml) and an overall 10.45g of (**14**) was obtained. This indicates the process can be used for the industrial scale synthesis of these molecules.



Scheme xx: Recycle and reusability of the solvent

Conclusions. In summary, we report a tandem cooperative Friedel-Crafts reaction of aldehydes with electron rich and *more challenging* electron deficient arenes enabled through catalyst activation by hydrogen bonding network of HFIP. Both real-time NMR and computational studies indicated HFIP was more than a solvent that activates the Brønsted acid catalyst, *p*TSA through hydrogen bonding. Also, a profound role of HFIP in stabilizing all the transition states and reactive intermediates through hydrogen bonding was concluded from the computational studies. It was found that two molecules of HFIP formed hydrogen bonds with the S=O group of the Brønsted acid, *p*TSA and activated the catalyst to the fullest. This hydrogen bonded HFIP-*p*TSA complex further activates the aldehyde group through stronger hydrogen bonds thus enabling the nucleophilic attack by electron deficient arenes like fluorobenzene. Further, from computational studies, we proposed a cooperative Friedel-Crafts alkylation through a cyclic transition state wherein *p*TSA activates the carbonyl group while its counter anion interacts with the arene C-H. The utility of this protocol was demonstrated by synthesizing various bio-active symmetrical and unsymmetrical diaryl and triarylmethanes, and gram scale reactions. The used HFIP could be recycled and reused making the reaction protocol economical. Further utilization of the method for the development of other reactions with more challenging substrates such as ketones and esters, and also their enantioselective versions are currently underway in our laboratory.

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Conflict of Interest

The authors declare no conflict of interest.

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