Silylium Ion-Catalyzed *α*-Arylation of Carboxylic Acids, Amides, and Esters: Efficient Synthesis of Anesthetic and Anti-inflammatory Drugs

Jabir Khan,[a] Aparna Tyagi,[a] and Chinmoy Kumar Hazra*[a]

Abstract: A metal-free strategy has been developed for the *α*-arylation of carboxylic acids, secondary amides, and esters employing arenes as key reagents. This process entails the Lewis-acid catalyzed reductive Friedel–Crafts alkylation of aromatic and heterocyclic arenes with *α*-ketoacids, facilitated by silane as a reductant in HFIP solvent. The transformation is highly efficient and mild, providing significant advantages over existing protocols. Notably, the method exhibits exceptional tolerance towards various functional groups, enabling late-stage functionalization of pharmaceutical compounds and natural products such as Thymol, and Sesamol. The reaction mechanism has been studied through control experiments, providing valuable insight. This one-step reductive Friedel–Crafts type protocol has been successfully used in the synthesis of various commercially available drugs, such as Adiphenine, Piperidolate, derivatives of Ketoprofen, Ibuprofen, and Flurbiprofen, and Bromopropylate pesticide. Furthermore, after the gram-scale synthesis, the solvent (HFIP) was recovered, demonstrating the method's suitability for industrial applications.

Introduction

The carboxyl group (CO_2H) is widespread in various organic compounds, encompassing biologically active natural products and pharmaceuticals.[1] In chemical synthesis, forming a C–C bond between an aryl group and the *α*-carbon of the carboxylic acid group is challenging.[2]

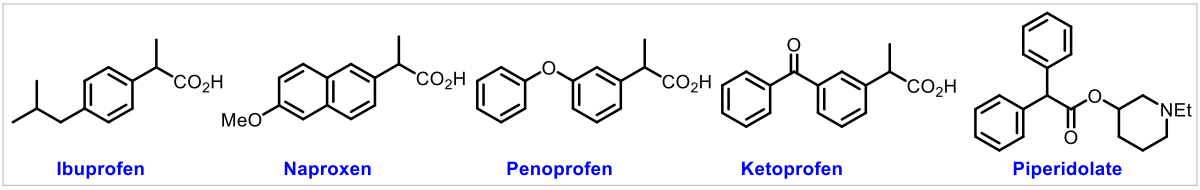

Figure 1. Commercial drugs containing *α*-aryl free carboxylic acids.

Aromatic electrophilic substitution reactions are indispensable for functionalizing aromatic compounds to make C–C bonds. Pioneered by Charles Friedel and James Crafts, the Friedel−Crafts reaction stands out for its straightforward introduction of carbon substituents to arenes without needing prior functionalization.[3-5] *α*-Aryl carboxylic acid derivatives are crucial in various natural products. Additionally, they serve as essential building blocks in the pharmaceutical industry. Notably, the well-established class of nonsteroidal anti-inflammatory drugs (NSAID), including Naproxen, Ibuprofen, Penoprofen, and Ketoprofen, deserve special mention in this context (Figure 1).[6] Hence, the appendage of an aryl group to the *α*-position of a carbonyl carbon (carboxylic acid group) is a highly substantial technique in synthetic organic chemistry. Given the significant importance of these compounds,

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extensive progress in α-arylation technology has predominantly arisen over the past two decades, heavily dependent on the advancement of efficient transition-metal catalysts.[7] The high cost, stringent reaction conditions, and potential contamination with heavy metals pose challenges for industrial and pharmaceutical applications, leading to developing "metal-free" arylation methods.[8] Despite being one of the effortless and ubiquitous carbonyl derivatives, the direct α-arylation of free aliphatic carboxylic acids has not been accomplished. Similarly, the α-arylation of common secondary amides bearing an acidic N-H bond has not been documented.[9] Instead, the α-arylation of esters, which frequently serve as masked carboxylic acids, and tertiary amides containing a narrow range of nitrogen groups has been described.[10] Since carboxylic acid is frequently the desired product, a typical strategy is to change the acid into an ester prior to α-arylation and then converting it back to the acid after the catalytic process. Despite these impressive strides, the pursuit of establishing metal-free direct arylations of carboxylic acids continues to enthral the synthetic chemistry community.

In 2015, Walsh and co-workers devised another approach for the α-arylation of aryl acetic acids using palladium catalysts with aryl bromides and chlorides (Scheme 1a).[11] The depicted arylations of α-aryl carboxylic acids showed limited functional group tolerance and were also restricted to carboxylic acids with an inherent α-aryl group. Additionally, the exclusive use of acetic acid as substrate and solvent required a very high reaction temperature. Hartwig *et al.* recently established a widely adaptable method for palladium-catalyzed α-arylation of carboxylic acids (Scheme 1b).[12] This protocol involves the *in-situ* installation of silyl groups on the carboxylate under basic conditions, followed by subsequent palladium-catalyzed α-arylation using zinc fluoride as an additive. As an alternative approach, Zhang and his coworkers have utilized gold catalysis to directly modify C−H bonds in phenols and *N*-acyl anilines without protection, using α-aryl α-diazoacetates and diazo oxindoles (Scheme 1c).[13] This approach necessitated using noble metals (Au and Ag) and pre-functionalized substrates. Inspired by these works, we hypothesized that α-arylation of carboxylic acids and amides may be achievable *via* a metal-free process with arenes and silanes. Herein, we report our latest work on reductive Friedel-Crafts alkylation of α-ketoacids towards synthesizing α-arylated carboxylic acids using silane as a reductant. Our methodology seeks to provide a straightforward pathway to synthesize Adiphenine, an antispasmodic drug used to treat pain in colic and cramps, and a dactil drug used for chemoprevention effects and scurvy treatment. We have applied our methodology to synthesize Bromopropylate, an acaricide primarily utilized for mite control. The practical value of this method is shown by a one-pot, gram-scale synthesis of commercially available drugs and pesticides, as well as the tolerance of a broad range of functional groups and enabling late-stage functionalization of pharmaceutical compounds and natural products (Scheme 1d).

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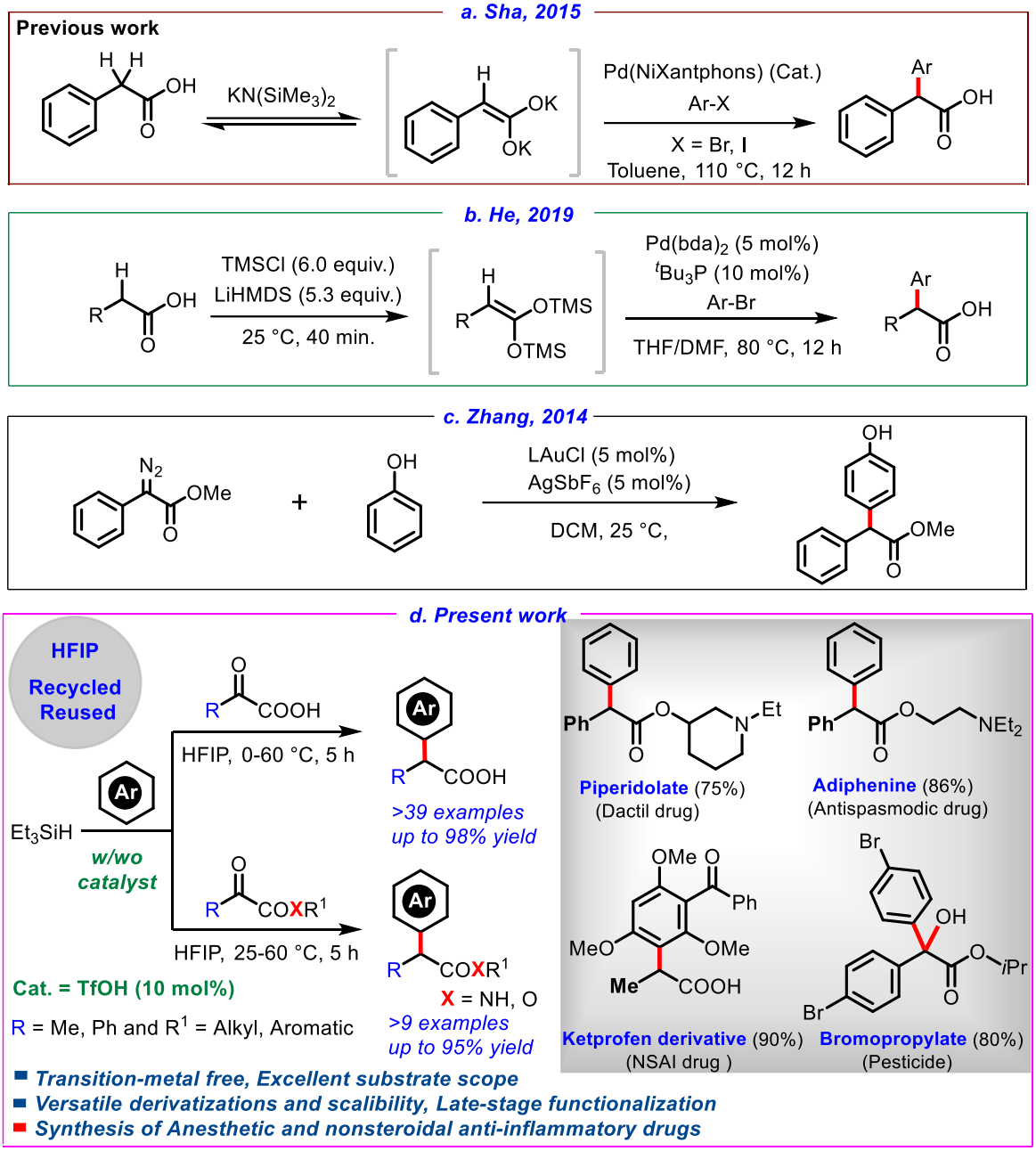

Scheme 1. a→c) Previous work. **d**) Present work.

Results and Discussion

Primarily, we focused on screening a high-yielding synthetic procedure for preparing *α*-arylated carboxylic acid (**3a**, Table 1). We discovered through initial exploration that the reductive Friedel–Crafts alkylation of *α*-ketoacid **1a** using mesitylene **2a** could not be realized without a catalyst (entry 1). As silylium ions are useful for forming a wide range of C−C bonds, although they have only recently beenapplied to the Friedel–Crafts alkylation process.[14] Therefore, we sought to determine if catalytic silylium ions could activate the carbonyl groups and enable the synthesis of *α*-arylated carboxylic acids. A practical synthesis of *α*-arylated acid was observed (**3a**, 86%, entry 2) using triflic acid (TfOH, 10.0 mol%) as a catalyst with 1.5 equiv. of dimethylchlorosilane as a reductant in HFIP solvent at 60 °C for 12 h via *in-situ* production of silylium ion ($R^1R^2R^3Si$)(OTf) by the activation of the Si−H bond of

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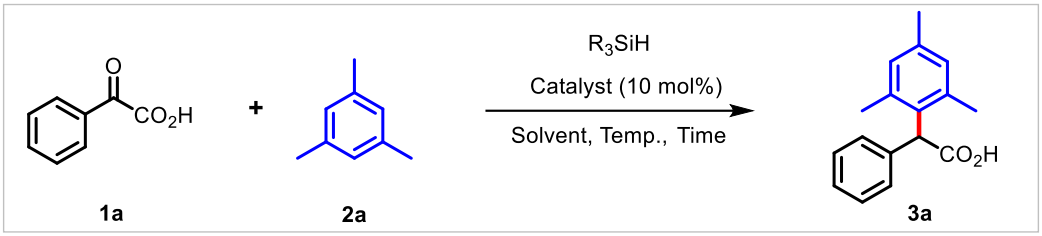
$R^1R^2R^3SiH$ using triflic acid (TfOH).[15] Replacement of HFIP with other solvents, such as DCE, $PhCF_3$, and TFE, had an unfavorable effect on product yield (entries 3-5), as did performing the reaction in other Brønsted acid catalysts, *viz. p*TSA and TFA (entries 6 and 7); hence, HFIP was chosen as a standard reaction solvent. TfOH was taken as the standard reaction catalyst since it displayed good catalytic activity compared to others. The screening of another silane, such as Et_3SiH revealed an enhanced yield of 88% (entries 8), whereas only a 20% yield of **3a** was isolated with Ph_3SiH (entries 9). Thus, Et_3SiH was chosen as the optimized silane for the reaction. Subsequently, we switched the reaction temperature from 60 °C to 25 °C and observed only a 55% yield (entry 10). Strikingly, the desired product was observed upon lowering the reaction time to 5 h (**3a**, 86%, entry 11).

Table 1: Optimization of Reaction Conditions. [a]



S. N.	Catalyst (10 mol%)	Solvent	Silane	Yield (3a%)
1	-	HFIP	Me_2SiHCl	<5
2	TfOH	HFIP	Me_2SiHCl	86
3	TfOH	DCE	Me_2SiHCl	10
4	TfOH	$PhCF_3$	Me_2SiHCl	12
5	TfOH	TFE	Me_2SiHCl	<5
6	pTSA	HFIP	Me_2SiHCl	15
7	TFA	HFIP	Me_2SiHCl	<5
8	TfOH	HFIP	Et_3SiH	88
9	TfOH	HFIP	$PhSiH_3$	20
10[b]	TfOH	HFIP	Et_3SiH	55
11[c]	TfOH	HFIP	Et_3SiH	86

[a] Reaction conditions 1a (0.5 mmol), 2a (0.75 mmol), Silane (0.75 mmol), HFIP (0.5 mL), 60 °C for 12 h. [b] 25 °C. [c] 5.0 h.

With the optimized condition in hand, we sought to investigate the generality of the presented protocol for the scope of different arenes as a coupling partner with 2-oxo-2-phenylacetic acid **1a** (Table 2). We concentrated on four types of arenes: a) moderately nucleophilic and electrically neutral arenes producing products (**3b-3f**), b) weakly nucleophilic electronically deactivated arenes such as halogen-

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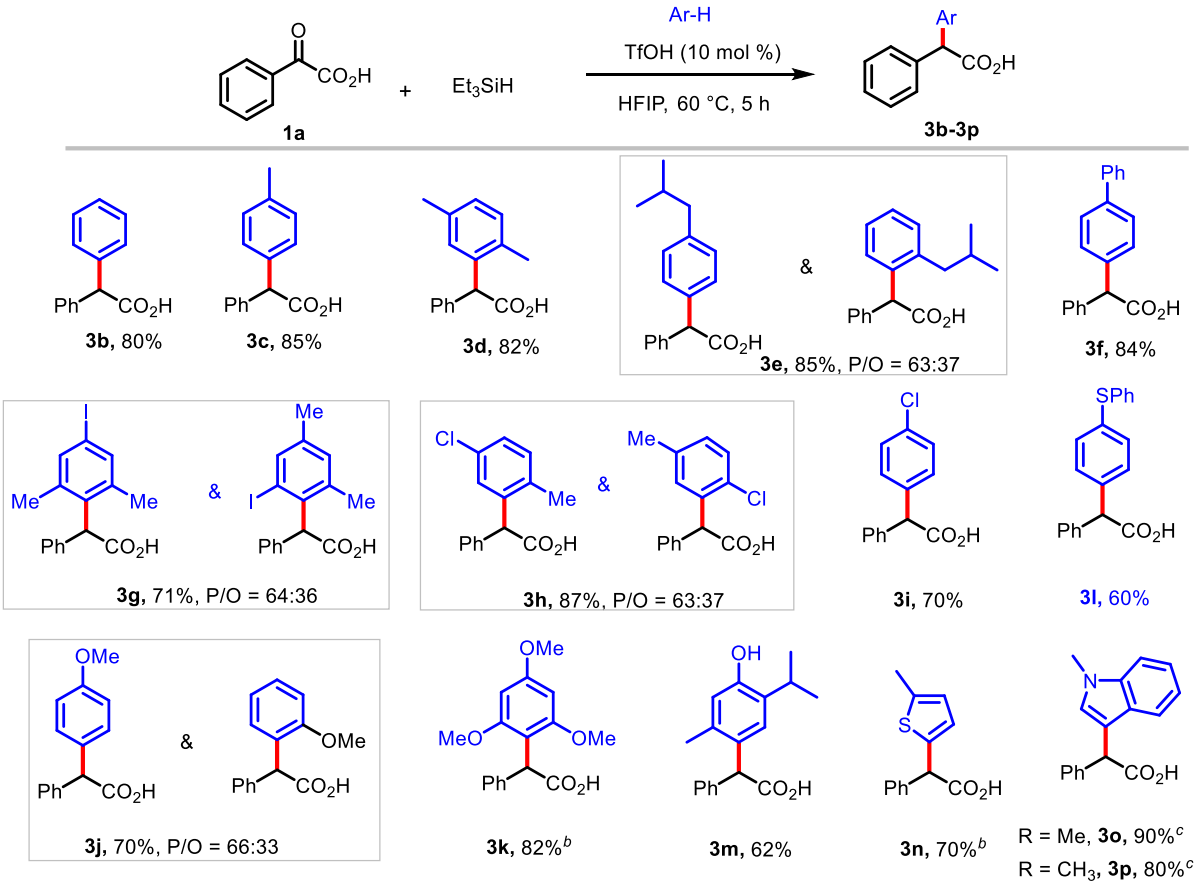
substituted alkyl arenes and halobenzenes generating products (**3g-3i**), c) strongly nucleophilic electronically rich arenes (**3j-3m**), and d) electron-rich heterocycles (**3n-3p**). When treated with **1a**, the electronic neutral benzene, toluene, and *p*-xylene were effectively converted into the corresponding *α*-arylated acid product (**3b-3d**; 80-85%) in good to excellent yield. Interestingly, the sterically hindered isobutyl benzene resulted in the expected isomeric product (*p*/*o* = 1.0/0.65, **3e**, combined yield = 85%). Biphenyl nucleophile was also effectively utilized to furnish the respective product **3f** in 84% yield under the optimized reaction condition. Subsequently, we investigated the applicability of our developed approach for the reductive Friedel–Crafts reaction involving arenes with poor nucleophilicity. The halogen-substituted alkyl arene *viz.* 1-iodo-3,5-dimethylbenzene and 1-chloro-4-methylbenzene were successfully converted to the desired *α*-arylated acid products (**3g**, 71%, and **3h**, 87%) in a regioselective ratio (*p*/*o* = 1.0/0.58; *ortho of Me*/*ortho of Cl* = 1.0/0.65), respectively.

Table 2. Scope of arenes with 2-oxo-2-phenylacetic acid (1a).[a]



[a] Reaction conditions **1a** (0.5 mmol), Ar-H (0.75 mmol), Silane (0.75 mmol), HFIP (0.5 mL), 60 °C for 5 h. [b] 25 °C, DCE solvent. [c] 25 °C, 1 h

Pleasingly, aryl halides such as 4-chlorobenzene delivered the single regioselective product **3i** in 70% yield. Significantly, the presence of halogen atoms in these compounds offers opportunities for additional modification using diverse metal-catalyzed cross-coupling reactions.[16] Next, arenes-bearing electronically rich methoxy groups were used, and the arylation occurred (**3j-3k**) in good to excellent

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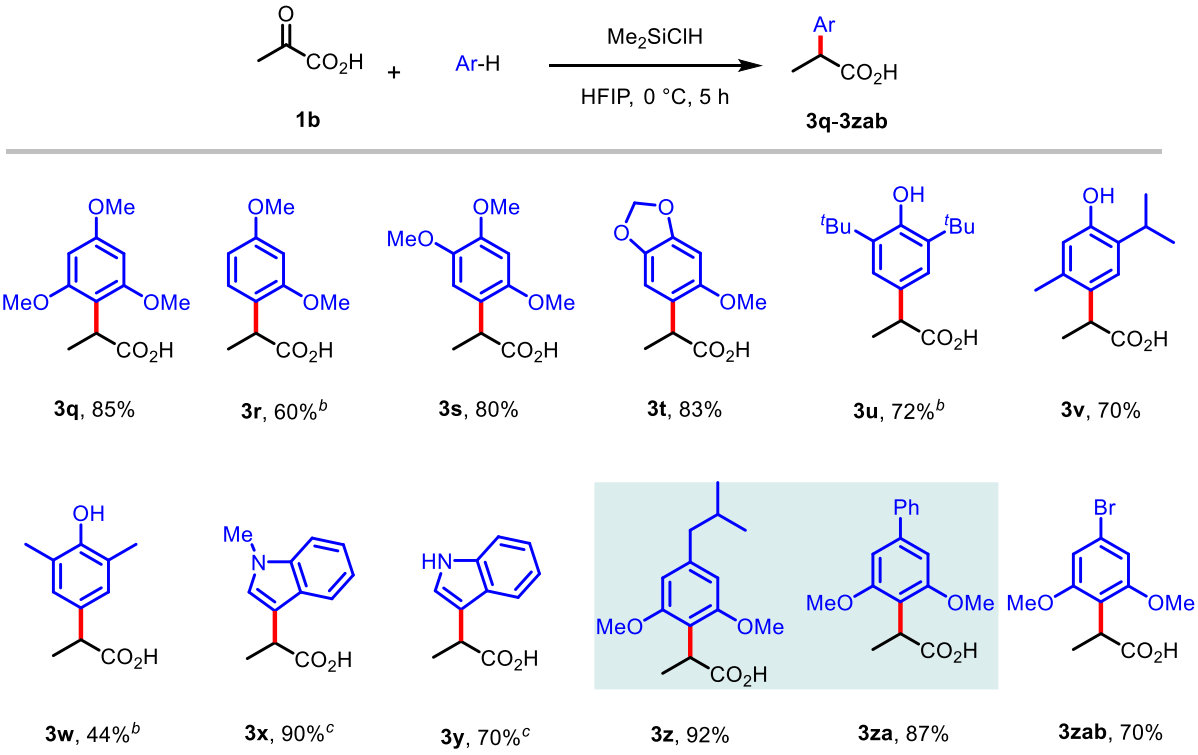
yield (70-82%). In the case of anisole, a mixture of regio isomers formed (*p*/*o* = 1.0/0.53). Further, diphenylsulfane also worked well under the devised protocol, providing the product (**3l**, 60%) with a single regio isomer. Of utmost importance, the natural product Thymol with subtle hydroxy group exhibited excellent performance in the optimized reaction while preserving complete regioselectivity and delivered the desired product **3m** in 62% yield. We were pleased to discover that the established protocol was compatible with heterocyclic nucleophiles. 2-methyl-thiophene, *N*-methyl-indole, and indole effectively reacted and delivered the corresponding product **3n-3p** with remarkable yields. Interestingly, the deuterated benzene showcased good nucleophilicity under the standard reaction condition and gave the product (**3q**, 70%).

Next, we explored the suitability of different arenes with aliphatic carboxylic acids (**1b**, 2-oxo propanoic acid) for this reaction (Table 3). When we used our optimized reaction conditions with mesitylene (**2a**), we did not observe product formation. However, we isolated undesired α, *α*'-diarylated carboxylic acid as a major product with 1,3-dimethoxybenzene under the standard reaction conditions. Hence, we realized that we needed to optimize the reaction conditions to get the desired results. Therefore, after optimizing several parameters, we have found that the reaction of 2-oxo-propanoic acid with arenes worked well without any catalyst. Notably, a wide range of electronically rich arenes proved to be strong substrates, exemplified by the successful reaction with Me_2SiClH at 0 °C in HFIP solvent.

Table 3. Scope of arenes with 2-oxopropanoic acid (1b).[a]



[a] Reaction conditions **1b** (0.3 mmol), Me_2SiClH (0.4 mmol) and Ar-H (0.2 mmol), HFIP (0.5 mL), 0 °C for 5 h. [b] -25 °C, 2 h. [c] Et_3SiH, 0 °C, 1 h.

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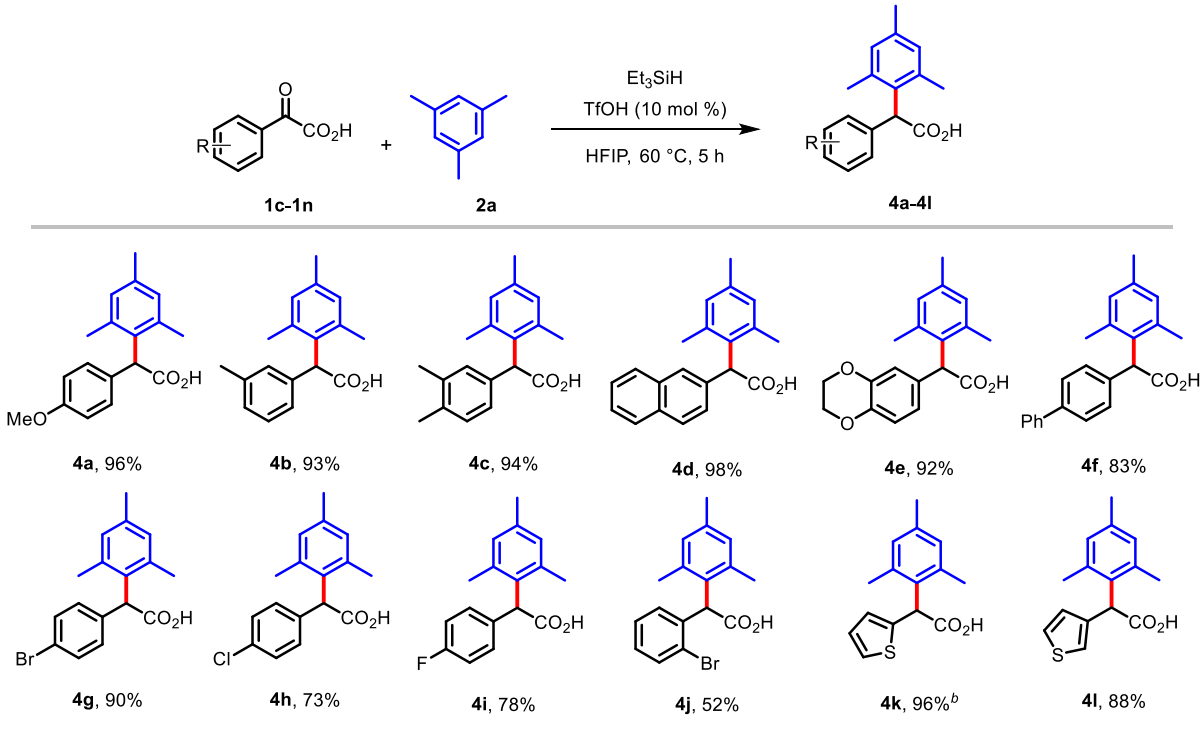
The trisubstituted and disubstituted arenes having methoxy substituents at different positions underwent successful reductive Friedel–Crafts arylation, yielding products (**3r-3u**, 60-85%). Even the sterically hindered phenol *viz.* 2,6-di-*tert*-butylphenol, 3-isopropyl-5-methylphenol, and 2,6-dimethylphenol demonstrated high effectiveness as a nucleophile in this transformation while upholding complete regioselectivity (**3v-3x**, 44-72%). Also, the method was applied for the late-stage functionalization of various natural products such as Thymol and Sesamol (**3u** and **3w**). Delightfully, the medicinally privileged heterocyclic arenes such as *N*-methyl-indole and indole also worked well using Et_3SiH instead of Me_2SiClH at 0 °C and delivered the respective products (**3y-3z**, 70-90%). Elegantly, we have successfully synthesized Ibuprofen and Flurbiprofen derivatives (**3za-3zb**) with high efficacy (87-92%) using 1-isobutyl-3,5-dimethoxybenzene and 3,5-dimethoxy-1,1'-biphenyl respectively. Further, this Csp^2–OMe bond could be cleaved to obtain Ibuprofen and Flurbiprofen using the already developed methodology,[17] (Table 3). These commercial anti-inflammatory drugs could be easily prepared in two steps (Table 3) to highlight the synthetic efficiency of the present method. For example, the well-known, nonsteroidal anti-inflammatory drug Ibuprofen, has been prepared commercially in 6 steps (Boot process) or 3 steps (Hoechst process) from iso-butylbenzene.[18] This transformation enables a practical and adaptable approach to producing valuable synthetic transformations and commercial drugs. Hence, it marked the notable feature of our study.

Table 4. Scope of *α*-Ketoacids with mesitylene (2a).[a]



[a] Reaction conditions *α*-ketoacid (0.5 mmol), Et_3SiH (0.75 mmol), and **2a** (0.75 mmol) in HFIP (0.5 mL) solvent for 5 h. [b] 0 °C solvent, 1 h.

Next, we probed the diversity of *α*-ketoacids **1c-1n** with **2a** for the established protocol (Table 4). The 2-(4-methoxyphenyl)-2-oxoacetic acid provided the arylated product (**4a**, 96%) under the standard

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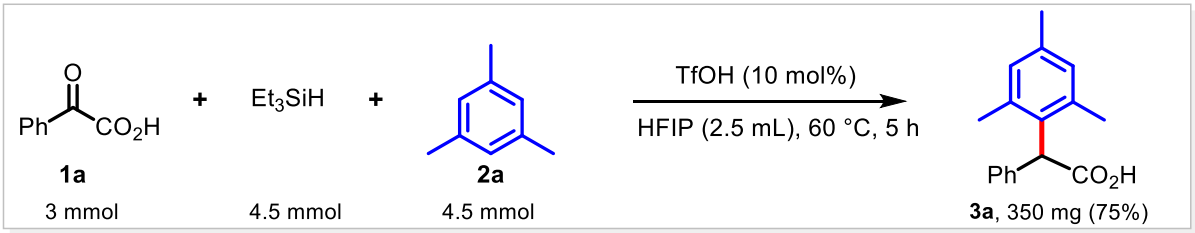
reaction condition. Furthermore, the α-ketoacid containing methyl substitutions at different positions effectively participated in the reductive Friedel–Crafts reaction, forming products **4b-4c** with remarkable yields. This methodology also evaded the steric hindrance posed by 2-(naphthalene-2-yl)-2-oxoacetic acid, 2-oxo-2-(2,3,4a,8a-tetrahydrobenzo[*b*][1,4] dioxin-6-yl)-aceticacid and 2-([1,1'-biphenyl]-4-yl)-2-oxoacetic acid and furnished the corresponding products **4d-4f** in excellent yields. We were gratified to discover that despite their partial nucleophilic properties, the halo-substituted α-ketoacids effectively served as reactive counterparts in the reaction and contributed deliberately in yielding the respective products with excellent yields (**4g-4j**) ranging from 52-90% yield. This protocol proved good reactivity with pharmacologically valuable heterocyclic constituents such as 2-thiophene-glyoxylic acid and 3-thiophene glyoxylic acid and successfully delivered the intended products **4k-4l** with satisfactory yields.

To show the synthetic efficiency of our designed protocol, a scale-up reaction was performed using 2-oxo-2-phenylacetic acid (**1a**, 3.0 mmol), mesitylene (**2a**, 4.5 mmol), and Et_3SiH (4.5 mmol) in the presence of TfOH (10 mol%) catalyst, and obtained the desired product in 75% yield (**3a**, 350 mg, Scheme 2).



Scheme 2. Scale-up synthesis of **3a**.

The products obtained have broad synthetic utility, facilitating a wide range of convenient organic transformations (Scheme 3). The synthesized acid molecules might undergo extension to a framework denoted as **5a**, which has more structural complexity, through a process of substitution of chlorine atom from 1,2-dichloroethane in the presence of K_2CO_3. The esterification was done using ethanol under DCC (dicyclohexylcarbodiimide) coupling[19] reaction conditions (**5b**, 90%). Interestingly, the carboxylic unit of the compound was efficiently converted into an amide through DCC coupling[19] with diethylamine and gave the product **5c** in 94% yield. Furthermore, the DCC coupling of **3a** leads to the amide using aniline as a coupling partner. Subsequently, the amide group can be transformed into β-functionalized amine **5d** with a 70% yield when subjected to $LiAlH_4$ as the reducing agent. The β-functionalized amines are fascinating structural motifs significant in drug design.[20] The carboxylic component can be converted into an anhydride using acyl chloride, eventually constructing a more complex structural framework **5e**. In addition, aryl esters are highly significant motifs in organic chemistry as they are widely utilized in pharmaceuticals, agrochemicals, and polymers.[21] Therefore, it is imperative to introduce three different arenes at the α position of the ester group. Delightfully, we have successfully synthesized the unsymmetrical tri-arylated ester product (**5f**, 70%) *via* three consecutive steps.

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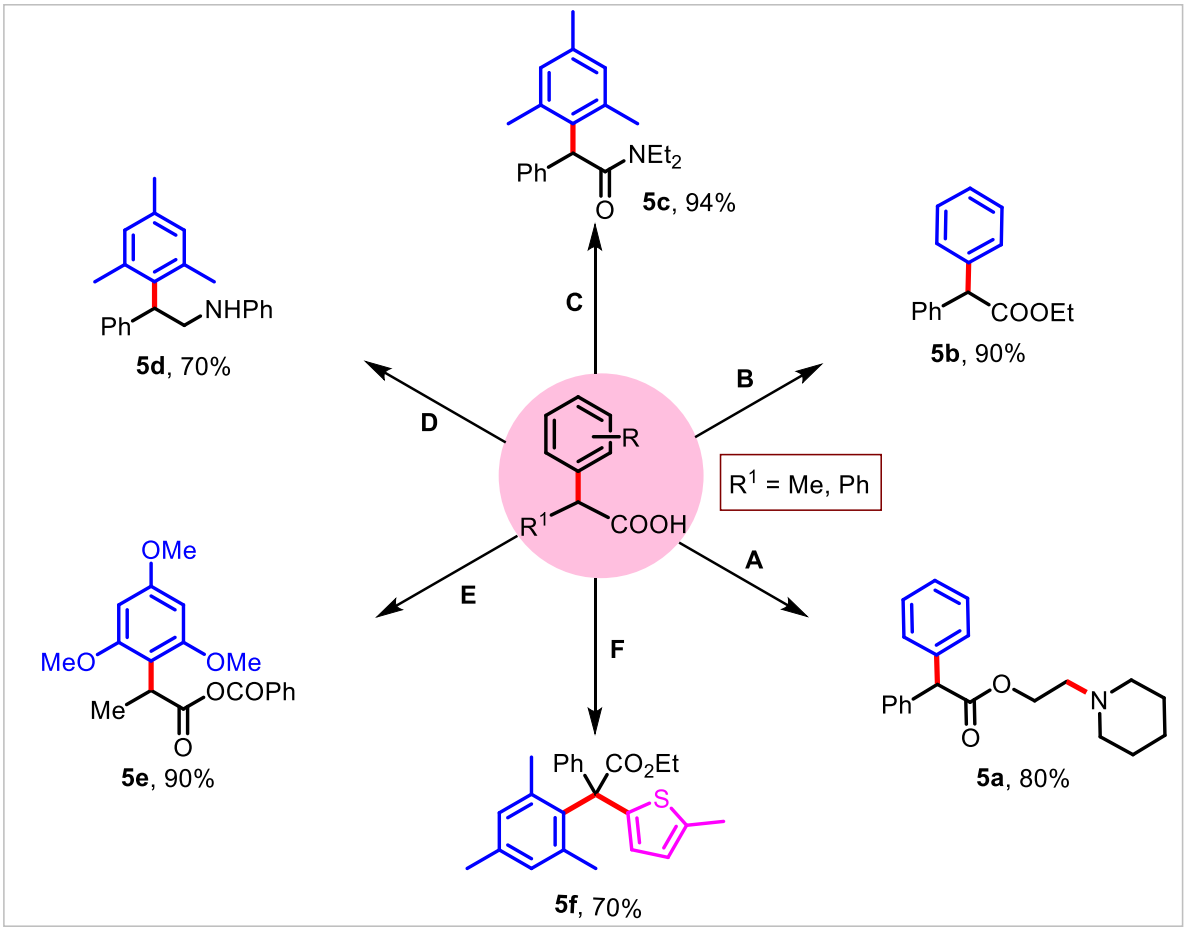

Scheme 3. Synthetic transformations. **A**) Piperidine (10 equiv.), K_2CO_3 (5 equiv.), DCE, 80 °C, 16 h. **B**) CH_3CH_2OH (5 equiv.), DMAP (20 mol%), DCC (1.1 equiv.), DCM, 25 °C, 2 h. **C**) Et_2NH (5.0 equiv.), DMAP (20 mol%), DCC(1.1 equiv.), DCM, 25 °C, 2 h. **D**) (i) Aniline (1.5 equiv.), DMAP (20 mol%), DCC (1.1 equiv.), DCM, 25 °C, 2 h; (ii) $LiAlH_4$ (5.0 equiv.), THF, 70 °C, 5 h. **E**) PhCOCl (1.0 equiv.), $AlCl_3$ (1.5 equiv.), DCM, 25 °C, 12 h. **F**) (i) CH_3CH_2OH (5.0 equiv.), DMAP (20 mol%), DCC (1.1 equiv.), DCM, 25 °C, 2 h; (ii) Cs_2CO_3 (20 mol%), $P(OEt)_3$ (2.0 equiv.), DMSO, O_2 balloon, 25 °C, 12 h; (iii) 2-Methylthiophen (1.1 equiv.), HFIP, 25 °C, 12 h, TfOH (10 mol%).

Significantly, the bioactive molecule Adiphenine (**5g**, 86%), an excellent marketed antispasmodic drug used to treat pain in colic and cramps, was synthesized by the esterification of **3b** with 2-(diethylamino)-ethan-1-ol. Subsequently, the esterification of the **3b** with 1-ethylpiperidin-3-ol enabled the synthesis of dactil drug (**5h**, piperidolate) in 75% yield. Next, to synthesize Bromopropylate (**5i**), we start the reaction with 2-(4-bromophenyl)-2-oxaacetic acid with bromobenzene under our optimal reaction condition. After the completion reaction, we obtained **4a'** in excellent yield. Later, we did esterification of **4a'** with DCC coupling using isopropyl alcohol and, product **4a''** was observed after purification. Then we introduced the hydroxy group at the α-position of the ester (**4a''**) by using a reported procedure[22] to attain **5i** in 80% yield (Scheme 4). Moreover, 2-(2,4,6-trimethoxyphenyl) propanoic acid (**3s**) was smoothly converted to ester derivative (**3s'**) under the reported method of DCC coupling.[19]

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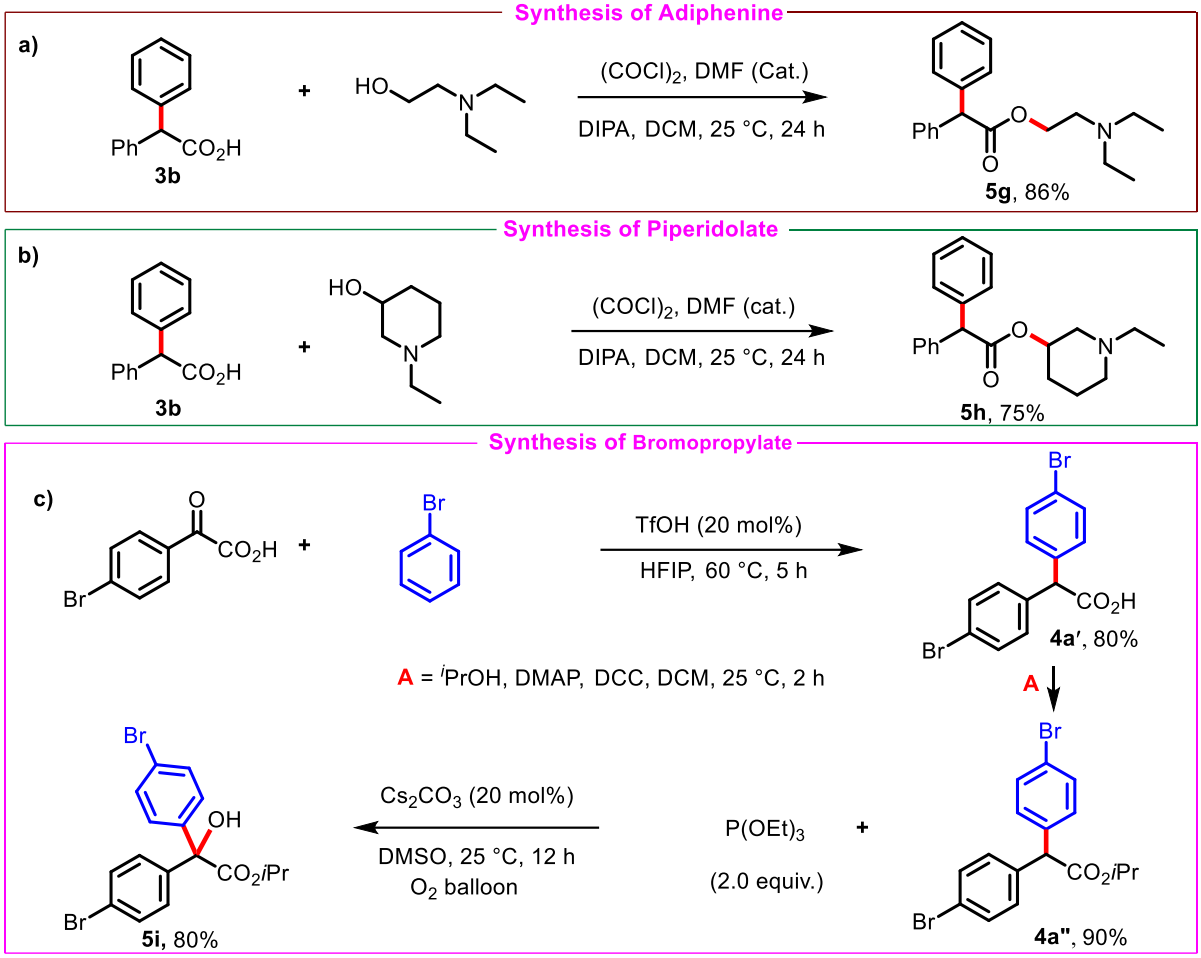
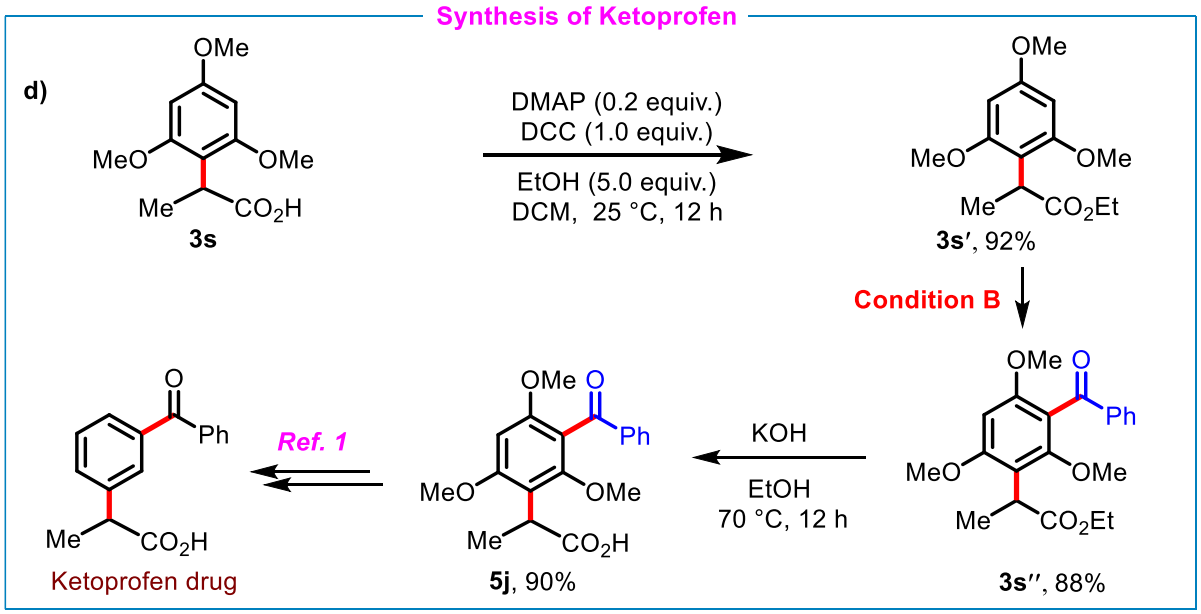


Consequently, **3s''** was easily isolated *via* Friedel–Crafts acylation reaction. After basic hydrolysis, the desired Ketoprofen derivative (**5j**, 90%, *lower part*, Scheme 4) was obtained. Intriguingly, Ketoprofen (an NSAID that is widely used to treat acute and chronic inflammation and pain and as a pyretic agent in clinical practice)[23] can be achieved by cleavage of Csp^2–OMe bond by following the developed precedents.[17]



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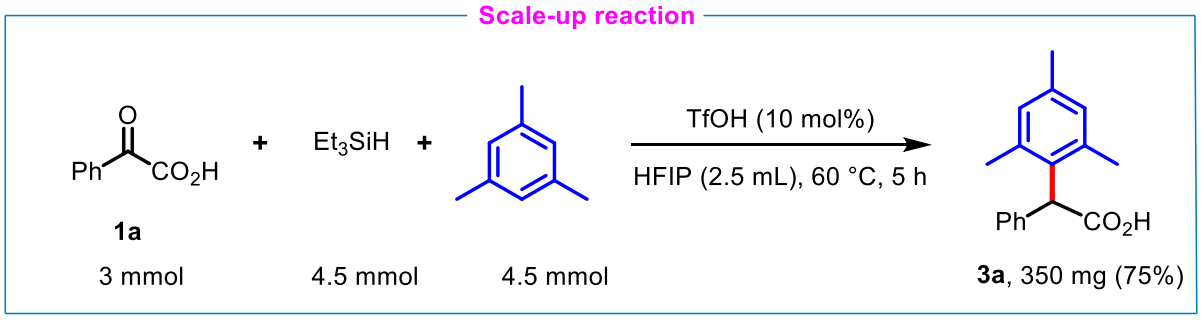
A scale-up reaction was performed according to the general procedure (A) to show the synthetic efficiency of our designed protocol. For this, a reaction was carried out using 2-oxo-2-phenylacetic acid (1a, 3.0 mmol, 1.0 equiv), mesitylene (2a, 4.5 mmol, 1.5 equiv), and Et3SiH (4.5 mmol, 1.5 equiv) in the presence of 10 mol % catalyst under the optimal reaction condition. After completion of the reaction, the reaction mixture was evaporated in vacuo, and the residue was purified by column chromatography using a gradient of DCM−MeOH (97:03) to afford the product 3a as a white solid (350 mg, 75% yield)



Scheme 4. Synthesis of drug molecules. **Condition A** = **3s** (1.0 equiv.), DMAP (20 mol%), DCC (1.1 equiv.), $(CH_3)_2CHOH$, 25 °C, 2 h. **Condition B** = **3s'** (1.0 equiv.), $AlCl_3$ (1.5 equiv.), PhCOCl (1.0 equiv.), Dry DCM, 25 °C, 12 h under N_2.

Next, we conducted control experiments to understand the reaction mechanism. Initially, the arylation process utilized **6a** (mandelic acid) instead of **1a** under optimized reaction conditions. The resulting 50% yield of the desired product **3a** suggested that **6a** could be one of the intermediates formed by reducing the carbonyl group in **1a** using silane (Scheme 5a). To verify the initial formation of **6a** as an intermediate, substrate **1a** underwent reduction with silane, yielding a trace amount of product **6a** (Scheme 5b). Based on these two control experiments, we can conclude that our reaction involves FC alkylation followed by reduction. To prove this further, we synthesized tertiary alcohol **6b** (a kind of intermediate of FC alkylation). When we subjected this **6b** to 10 mol% TfOH and Et_3SiH, we observed product **5b** in 95% yield, which depicted that the reaction pursued arylation followed by reduction (Scheme 5c). To check the reactivity of tertiary alcohol towards a competitive arylation or reduction we performed a reaction of **6b** with **2a** and Et_3SiH under standard conditions and only the reduced product **5b** was observed in 99% yield indicating that tertiary alcohols are more susceptible to reduction rather than arylation (Scheme 5d). This could be the reason for the selective mono-arylation of the keto group under standard conditions. Next, 2-oxo propionic acid was treated with mesitylene using TfOH (50 mol%), and the alkene **6d** was formed by arylation followed by dehydration (Scheme 5e). This result further supported the initial attack of arene to the carbonyl group **1a**, followed by a reduction with Et_3SiH.

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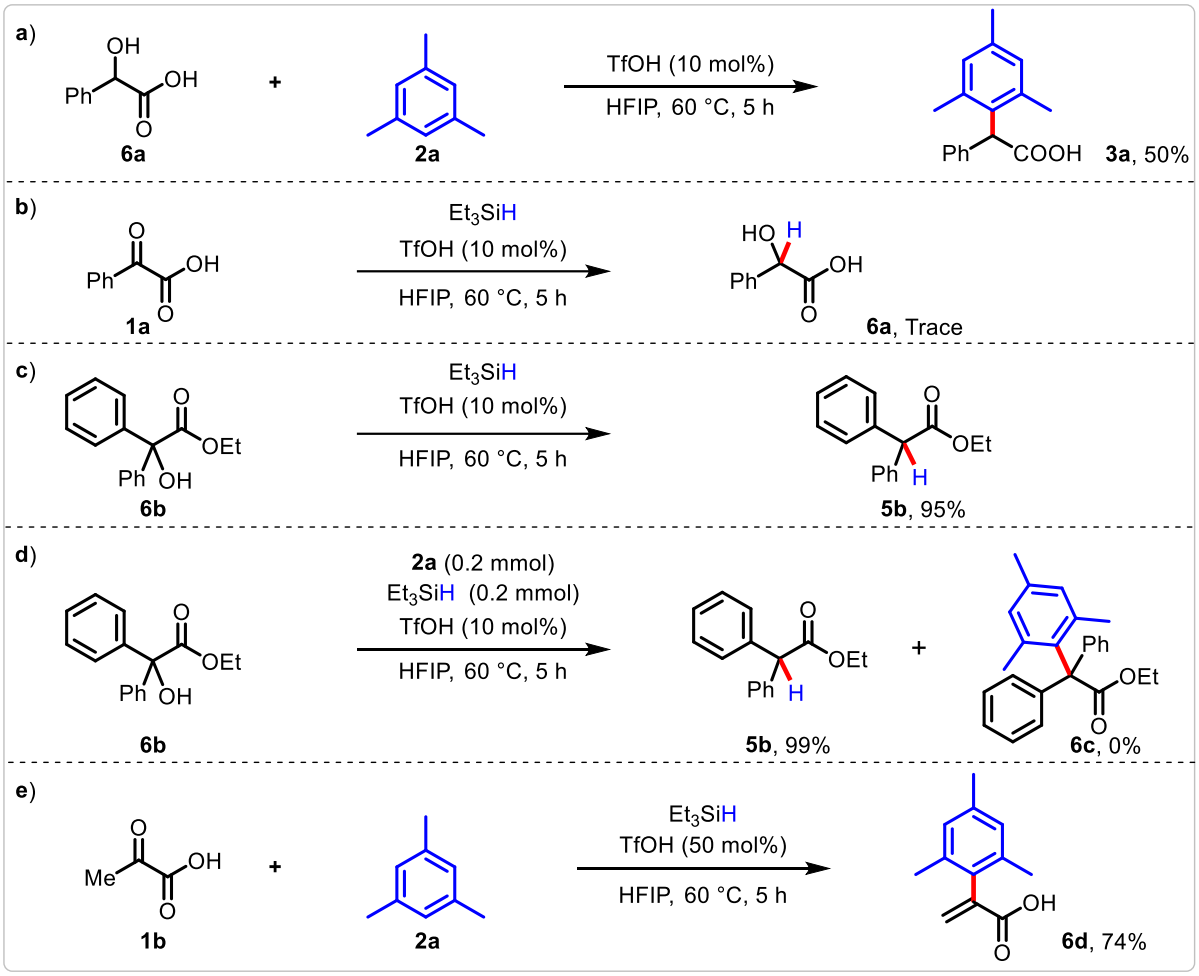

Scheme 5. Control experiments.

We have devised a possible mechanism based on the control experiments illustrated in Figure 2. Initially, TfOH reacts with Et_3SiH, resulting in the formation of $TfOSiEt_3$ and the release of hydrogen gas.[15] $TfOSiEt_3$ then activates the carbonyl group of **1a**, producing species **I**. This species is then attacked by the nucleophile **2a**, leading to the formation of **II**. After re-aromatization, **II** regenerates the catalyst and gives rise to species 2-mesityl-2-phenyl-2-((triethylsilyl)oxy) acetic acid (**III**). Next, species **III** is activated by a $TfOSiEt_3$ catalyst. This leads to the liberation of $Et_3SiOSiEt_3$ through the electron push from arene nucleophile, forming species **IV**. Finally, a hydride attack from Et_3SiH occurs at the electrophilic center of species **IV**, which provides product **3a** and regenerates $TfOSiEt_3$.

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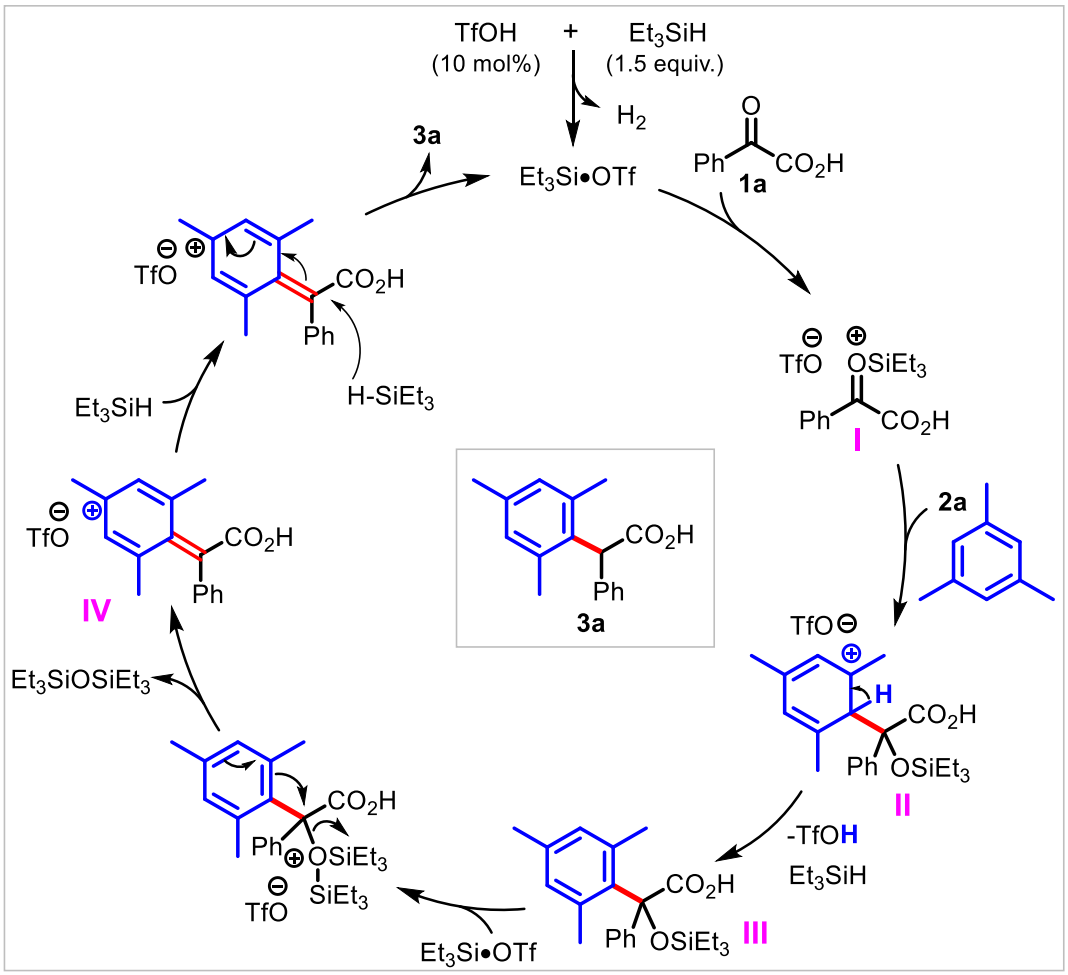
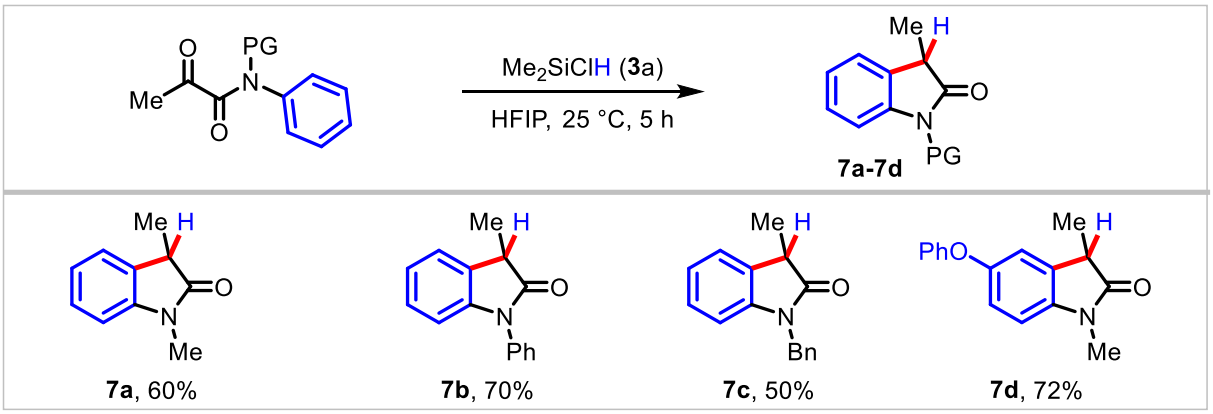


Figure 2. Plausible reaction mechanism.

Oxindoles are commonly found in biologically active molecules.[24] However, methylation them directly can be challenging due to the limited availability of direct methods. To address this, Pulis and his team have developed a catalytic approach for the direct C3 methylation of a wide range of oxindoles. They employed amine-based alkylating agents with 10.0 mol%



Scheme 6. Intramolecular reductive Friedel crafts alkylation of α-ketoamide. [a] ketoamide (0.2 mmol) and Me_2SiClH (0.3 mmol) in HFIP (0.3 mL) at 25 °C for 5 h.

Lewis acidic borane catalyst (expensive and air-sensitive) to achieve the desired result.[25] Alternatively, a catalyst-free protocol for methylated oxindoles is highly desirable. To pursue this hypothesis, we

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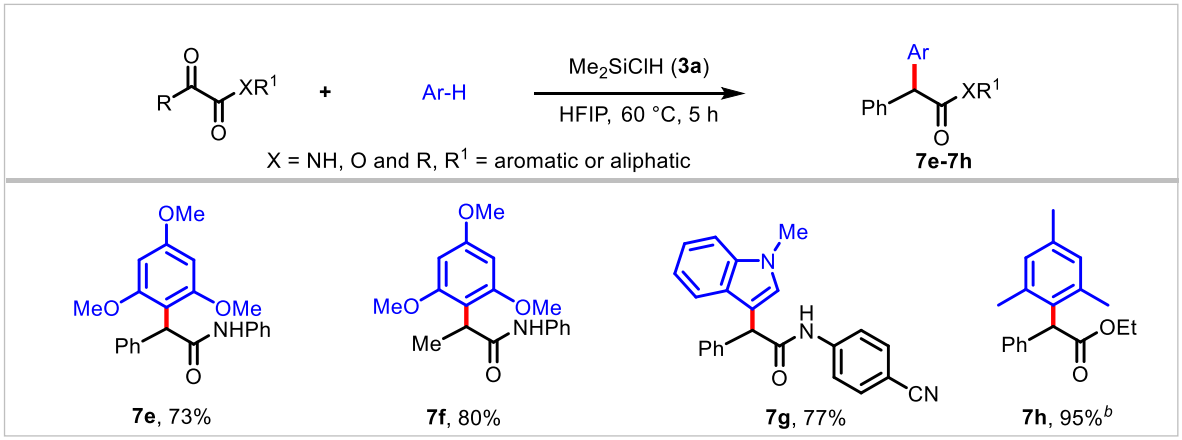
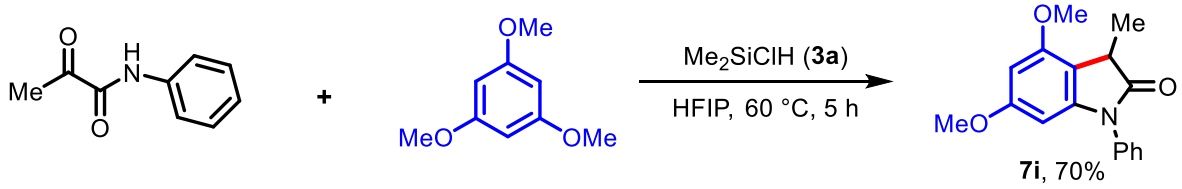
developed a mild metal-free intramolecular reductive Friedel–Crafts alkylation process to access C3 methylated oxindoles (Scheme 6). It has been discovered that *N*-protected *α*-ketoamides that have protecting groups like methyl, phenyl, and benzyl groups can produce corresponding cyclized products **7a**-**7d** (50-70%) when subjected to chlorodimethylsilane in HFIP solvent at 25 °C. Our designed protocol has been expanded to allow for a catalyst-free intermolecular reductive Friedel–Crafts alkylation of *α*-ketoamides. We found that the electron-rich 1,3,5 trimethoxybenzene was compatible with aromatic and aliphatic *α*-ketoamides, resulting in excellent yields of products **7e** and **7f** (73-80%). Additionally, the *α*-ketoamide *N*-(4-cyanophenyl)-2-oxo-2-phenylacetamide reacted well with the heterocyclic *N*-methyl-indole, producing **7g** in a 77% yield. We have also observed that ethyl 2-oxo-2-phenylacetate also worked well for this intermolecular reductive FC reaction with **2a** (moderately nucleophilic) and gave **7h** in 95% yield (Scheme 7).



Scheme 7. [a] Intermolecular reductive Friedel-Crafts alkylation of *α*-ketoamide. [b] TfOH (10 mol%).

Our established procedure proved operational in delivering the medically valuable oxindole derivative **7i** with a reasonable yield. This was accomplished through the intermolecular reductive Friedel-Crafts alkylation of *α*-ketoamide, followed by cyclization with the nitrogen of the amide bond. Herein, we have demonstrated that C–C and C–N bonds formed in one pot when 2-oxo-*N*-phenylpropanamide (unprotected) and 1,3,5-trimethoxybenzene were subjected to chlorodimethylsilane in HFIP at 60 °C (Scheme 8).



Scheme 8. Intermolecular reductive Friedel-Crafts alkylation of *α*-ketoamide followed by cyclization with *NH* of amide bond. [a] 2-oxo-*N*-phenylpropanamide (0.2 mmol), 1,3,5-trimethoxybenzene (0.22 mmol), and Me_2SiClH (0.3 mmol) in HFIP (0.3 mL) at 60 °C for 5 h.

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Conclusion

In summary, we have developed a strategy for the synthesis of α-aryl carboxylic acid derivatives *via* a Silylium ion-catalyzed reductive Friedel–Crafts arylation by utilizing silane as a reductant in HFIP solvent. This arylation method is notable for its broad functional group tolerance, including challenging and medicinally important aromatic and heterocyclic arenes. It has been successfully applied to the late-stage derivatization of natural products. The presented protocol was extended for inter- and intramolecular reductive Friedel–Crafts arylation of α-ketoamides. Additionally, the developed methodology allowed the short and efficient synthesis of Adiphenine drug, Piperidolate drug, derivatives of Ketoprofen, Ibuprofen, Flurbiprofen, and Bromopropylate pesticide. This simple and practical method of arylation should facilitate the discovery of new drugs and enable the rapid construction of diverse ring systems.

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