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Transition metal-free aroylation of diarylmethanes with *N*-Bn-*N*-Boc arylamides and *N*-acylpyrroles

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Abstract. In the last 20 years, efficient transition metal catalysts for the α-arylation of enolates have been introduced. Despite the popularity and utility of these reactions, there remains room for improvement (reduced costs, elimination of transition metals and specialized ligands). Herein is reported a general, scalable and green method for aroylation of simple diarylmethane pronucleophiles through direct acyl C–N cleavage of *N*-Bn-*N*-Boc arylamides and *N*-acylpyrroles under transition metal-free conditions. Importantly, a 1 : 1 ratio of the amide to the pronucleophile is employed. Unlike use of Weinreb amides, this method avoids preformed organometallics (organolithium and Grignard reagents) and does not employ cryogenic temperatures, which are difficult and costly to achieve on scale. The operationally simple protocol provides straightforward access to a variety of sterically and electronically diverse 1,2,2-triarylethanones, a group of compounds with high-value in medicinal chemistry.

Keywords: transition metal-free; aroylation; amide, enolate diarylmethane

Introduction

α-Aryl carbonyl compounds, such as 1,2-diaryl- and 1,2,2-triarylethanones, have attracted considerable attention as important synthetic targets due to their presence in natural products[1] and bioactive molecules.[2] In addition, these structural motifs have been used as chemical intermediates in the production of marketed drugs, such as Tamoxifen, Daidzein, Oxcarbazepine, and Droloxifene.[3] The most popular route for the synthesis of these privileged carbonyl compounds largely relies on palladium-catalyzed α-arylation of ketone enolates,[4] which was pioneered simultaneously by Buchwald, Hartwig, and Miura in 1997 (Fig. 1A, i).[5] Subsequently, several other α-arylations with different metals (Fig. 1A. ii-iv) were developed for the synthesis of 1,2,2-triarylethanones by the groups of Taillefer (Cu-catalyzed with Ar-I),[3b] Itami (Ni-catalyzed with carbonates and carbamates),[6] and Zhang (Fe-catalyzed C–H functionalization).[7]

Despite the importance of metal-catalyzed α-arylation reactions, there remains room for improvement. These include avoidance of precious metals (that ultimately generate metal waste) and the use of expensive ligands. Towards these objectives, Grimaud, Ciofini, Ollevier, Taillefer and co-workers developed a transition metal-free method for the α-arylation of enolizable aryl ketones with aryl iodides via a free radical process (Fig. 1A, v).[8] Kürti and co-workers also developed a transition metal-free arylation of ketones using nitro aromatics as the aryl electrophiles (Fig. 1A, vi).[9] In addition to α-arylations, other methods to prepare 1,2,2-triarylethanones are known.[10]

The present synthesis of 1,2,2-triarylethanones was inspired by the work of Szostak and co-workers, who demonstrated the transamidation of activated and unactivated amides with non-nucleophilic amines under transition metal-free conditions (Fig. 1B).[11a,b] We were curious if related activated amides (with decreased amidic resonance[11c]) could be employed

with different classes of nucleophiles. In particular, we have built a program around reversible *in situ* deprotonation of weakly acidic pro-nucleophiles. Among these, the *in situ* deprotonation of toluene derivatives for metal catalyzed arylations,[12] aminobenzylation of aldehydes,[13] and a new indole synthesis from 2-fluoro toluenes are notable.[14] For the current study, we became interested in the use of amides as electrophiles with *in situ* generated organometallic reagents to afford 1,2,2-triarylethanones.

Traditionally, the conversion of amides to ketones relies on the use of Weinreb amides (Fig. 1C),[15] which have been applied with great effect in the coupling of elaborate fragments in complex natural product synthesis. Typically, Weinreb amides are subjected to addition of preformed organometallic nucleophiles, such as organolithiums, Grignard reagents or hydride sources. Weinreb amides largely solved the problem of over addition of the organometallic reagent to the newly formed ketone or aldehyde. Despite their overwhelming success, Weinreb amides do have limitations, including decreased reactivity of the amide C=O carbonyl toward nucleophiles, requiring the use of strongly nucleophilic organometallic reagents with reduced functional group tolerance, and side reactions that take place at the N(Me)OMe unit.[16] A significant improvement over use of traditional Weinreb amide chemistry would be use of air and moisture stable pro-nucleophiles that could be readily converted to nucleophiles under experimentally convenient conditions. Less well-known approaches to conversion of amides to ketones, such as Wolfe's use of 2-methyl pyridine based nucleophiles with *N,N*-dimethyl amides[17] or Katritzky's use of *N*-acylbenzotriazoles[18] have some advantages, because they use pro-nucleophiles. These approaches, however, are typically performed with the strong base LDA at temperatures that are costly and challenging to access on scale (below –70 ºC).

Given that amides are common place in chemical synthesis, biology, and drug discovery,[19] extension of the Weinreb ketone synthesis beyond the confines of the Weinreb amide could, in principle, significantly broaden the potential of this strategy. Furthermore, by diversifying the amides that are effective substrates in Weinreb-type ketone syntheses, it may be possible to engender chemoselectivity among amide coupling partners with amides bearing different *N*-substituents.

Herein we present the results of our efforts to identify amides that participate in the ketone synthesis under conditions with *in situ* generation of the organometallic nucleophile. We have discovered that both *N*-Bn-*N*-Boc arylamides and *N*-acylpyrroles react with diarylmethane-based pro-nucleophiles under conditions where the pro-nucleophiles are reversibly deprotonated by $KN(SiMe_3)_2$ (Fig. 1D). The advantages to this synthesis of 1,2,2-triarylethan-1-ones over enolate arylation is that expensive transition metals and ligands, along with their accompanying waste, can be avoided.

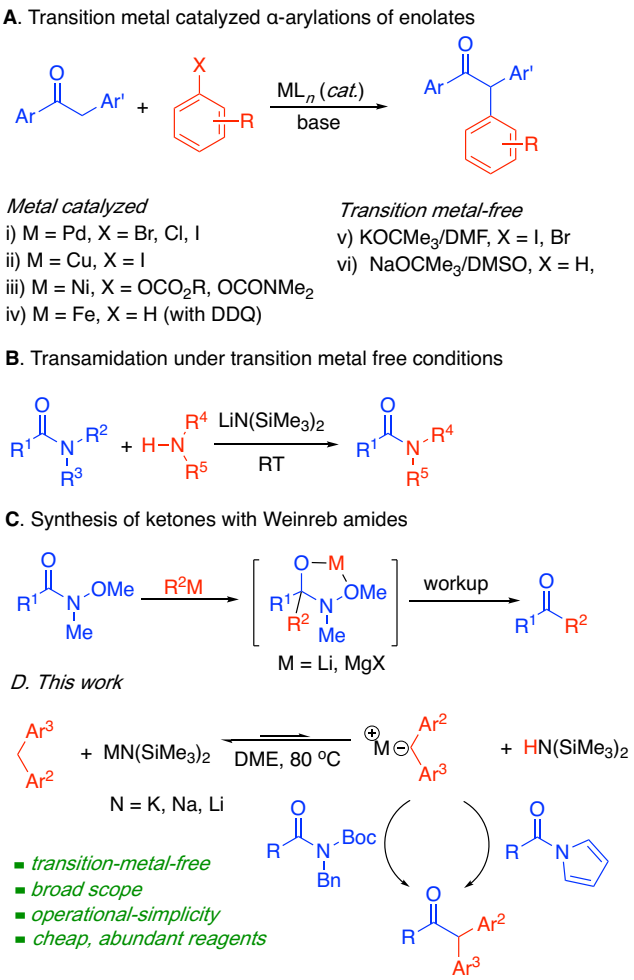


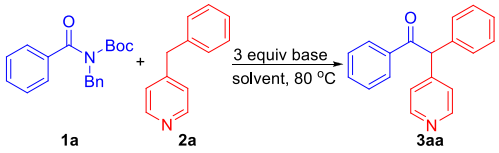
Fig. 1 Reactions of carbonyl compounds. A. Methods for α-arylation of enolates catalyzed by transition metals and in the absence of transition metal catalysts. B. Transamidation reactions. C. Weinreb's ketone synthesis. D. Synthesis of 1,2,2-triarylethanones under transition metal-free conditions (this work).

Results and Discussion

Reaction optimization. In our prior investigations, we studied the use of diphenylmethane and related pronucleophiles in palladium[20] and nickel[21] catalyzed cross-coupling processes with aryl halides. In these reactions, the weakly acidic C(sp^3)–H bonds of diarylmethanes and toluene derivatives (pK_a 25~43 in DMSO)[22] were reversibly deprotonated under basic reaction conditions [usually with silylamides: $MN(SiMe_3)_2$, M = Li, Na, K and in some cases with additives[23]]. The resulting carbanions then acted as nucleophiles toward the transition metals, undergoing transmetallation. In the present investigations, under transition metal-free conditions, amides are used as the electrophiles with the goal of generating 1,2,2-triarylethanones.

We initiated our studies with *N*-Bn-*N*-Boc benzamide **1a** and 4-benzylpyridine **2a**. The pro-nucleophile, 4-benzylpyridine **2a**, was chosen because the pK_a in DMSO is 26.7, facilitating deprotonation. Additionally, pyridines are among the most prevalent heterocycles in medicinal chemistry, increasing the value of the products.[24] Five different bases were tested in DME [LiN(SiMe$_3$)$_2$, NaN(SiMe$_3$)$_2$, KN(SiMe$_3$)$_2$, NaO^{t}Bu, and KO^{t}Bu] at 80 °C for 12 h (Table 1, entries 1–5). The silyl amide bases yielded the desired product (32–86%), with KN(SiMe$_3$)$_2$ the most promising. In contrast, both NaO^{t}Bu and KO^{t}Bu failed to afford the product (Table 1, entries 4–5). Solvents [dioxane, toluene, THF, and CPME (cyclopentyl methyl ether), Table 1, entries 6–9] were next examined, but the reaction in DME outperformed the other solvents by ≥30%. Lowering the temperature was next examined, but only 32% yield was observed at 60 °C, and no desired product was detected at 40 °C (Table 1, entries 10–11). We note that benzamides with *N*-Me-*N*-Boc and NBoc$_2$ gave lower yields than *N*-Bn-*N*-Boc benzamide. Based on these reactions, the optimized reaction conditions employ equal amounts of the amide and 4-benzylpyridine with 3 equiv KN(SiMe$_3$)$_2$ at 80 °C for 12 h in DME (Table 1, entry 3).

Table 1. Reaction Optimization Studies[a]



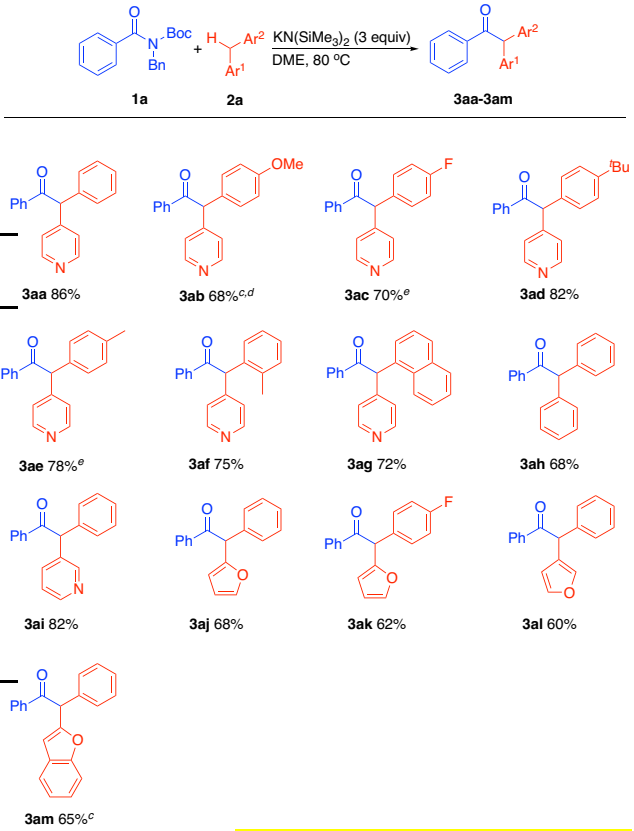
entry	base	solvent	temp. (°C)	Yield[b] (%)
1	LiN(SiMe$_3$)$_2$	DME	80	54
2	NaN(SiMe$_3$)$_2$	DME	80	32
3	KN(SiMe$_3$)$_2$	DME	80	86
4	NaO^{t}Bu	DME	80	0
5	KO^{t}Bu	DME	80	0
6	KN(SiMe$_3$)$_2$	dioxane	80	trace
7	KN(SiMe$_3$)$_2$	toluene	80	trace
8	KN(SiMe$_3$)$_2$	THF	80	56
9	KN(SiMe$_3$)$_2$	CPME	80	52
10	KN(SiMe$_3$)$_2$	DME	60	32
11	KN(SiMe$_3$)$_2$	DME	40	0

[a]Reactions were conducted with **1a** (0.1 mmol), **2a** (0.1 mmol), and base (0.3 mmol) with solvent (1 mL) for 12 h. [b]Isolated yields.

Substrate scope. The substrate scope of 4-benzylpyridine derivatives was explored with *N*-Bn-*N*-Boc benzamide **1a**. As shown in Table 2, substrates bearing electronically-diverse substituents on the phenyl group of 4-benzylpyridine (4-OMe, 4-F, 4-^{t}Bu, 4-Me, 2-Me, and 1-naphthyl) afforded the desired ketones (**3ab**, **3ac**, **3ad**, **3ae**, **3af**, **3ag**) in 68–82% yield. It is noteworthy that sterically-hindered substrates bearing a 2-tolyl or 1-naphthyl reacted with similar efficiency as less hindered substrates. In the case of **3ab**, LiN(SiMe$_3$)$_2$ was superior to KN(SiMe$_3$)$_2$ while NaN(SiMe$_3$)$_2$ outperformed KN(SiMe$_3$)$_2$ with **3ac** and **3ae**. The reason for the observed reactivity is not clear at this point.

In addition to 4-benzyl pyridines, less acidic diarylmethane analogues were successfully employed. Both the parent diphenylmethane (**2h**, pK_a 32 in DMSO) and 3-benzylpyridine (**2i**, pK_a 30.1 in DMSO) proved to be suitable substrates, with desired products isolated in 68 (**3ah**) and 82% (**3ai**) yield, respectively. Furans bearing benzyl groups at the 2- (**2j**, **2k**) or 3-position (**2l**) were also examined. The isomeric substrates all underwent the base-mediated transformation to give the product in 60–68% yield (**3aj**, **3ak**, **3al**). Furthermore, 2-benzyl benzofuran **2m** was successfully benzoylated to afford **3am** in 65% yield. Under the conditions outline here, both *N*-Bn-*N*-Boc acetamide and *N*-Bn-*N*-Boc pivalamide did not provide the desired products. Overall, a variety of 1,1,2-triaryl ethanones were readily assembled in good yields without the assistance of transition metal catalysts and using equal amounts of both coupling partners.

Table 2. Scope of diarylmethane derivatives[a,b]

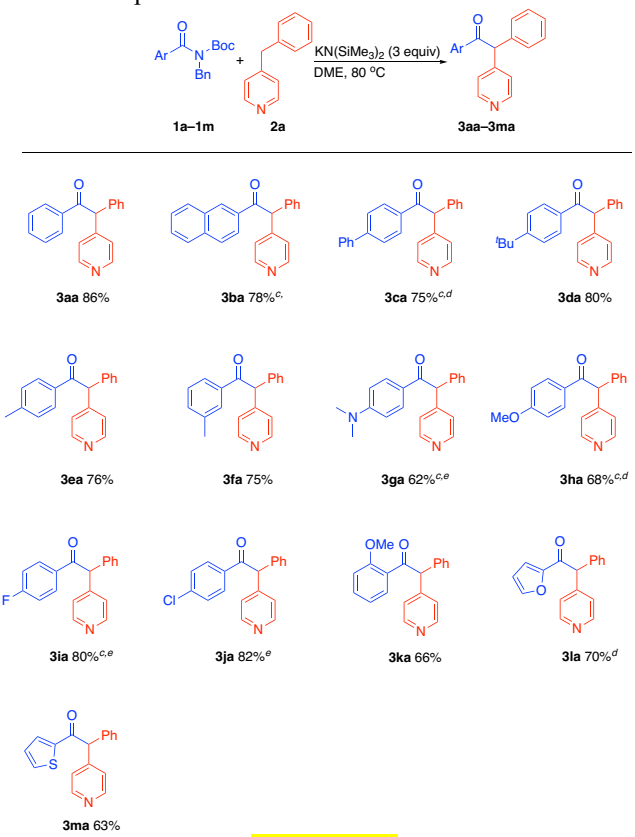


[a]Reaction conditions: *N*-Bn-*N*-Boc benzamide (0.2 mmol), diarylmethane (0.2 mmol), KN(SiMe$_3$)$_2$ 0.6 mmol, DME (0.2 M), 80 °C, 12 h. [b]Isolated yields. [c]Reaction conducted in tetrahydrofuran (THF). [d]0.6 mmol of LiN(SiMe$_3$)$_2$. [e]0.6 mmol of NaN(SiMe$_3$)$_2$.

Next, we examined the substrate scope of amides in benzoylation of 4-benzylpyridine (**2a**). Beyond the

parent reaction to give **3aa** with the benzamide (**1a**), various arylamides bearing different substituents on the aryl group gave the expected products in moderate to good yields (62–86%, Table 3). 2-Naphthylamide and biphenyl-4-amide furnished **3ba** and **3ca** in 78% and 75% yield, respectively. Benzamides possessing alkyl groups (4-^{t}Bu, 4-Me, and 3-Me) gave products **3da**, **3ea**, and **3fa** in 75–80% yield. Substrates bearing electron-donating groups (4-NMe_2, 4–OMe, 2-OMe) underwent addition in 62–68% yield to give the expected products (**3ga**, **3ha**, **3ka**). Benzamides supporting halides (4-F and 4-Cl) provided ketone products in 80–82% yield (**3ia** and **3ja**). These substrates are primed for further functionalization through cross-coupling strategies. Additionally, heterocyclic furylamide and thienylamide also participated in this protocol, affording the product **3la**–**3ma** in 70 and 63% yields, respectively. As outlined in Table 3, some substrates performed better with $LiN(SiMe_3)_2$ (**3ca**, **3ha**, **3la**) while others (**3ga**, **3ai**, **3ja**) gave better yields with $NaN(SiMe_3)_2$. This observation is surprising, because it is dependent on the amide electrophile. Overall, a wide range of 1,2,2-triaryl ethanones can be prepared by aroylation of simple diarylmethane derivatives with *N*-Bn-*N*-Boc arylamides.

Table 3. Scope of amides[a,b]



[a]Reaction conditions: *N*-Bn-*N*-Boc amide (0.2 mmol), 4-benzylpyridine (0.2 mmol), $KN(SiMe_3)_2$ 0.6 mmol, DME (0.2 M), 80 °C, 12 h. [b]Isolated yield. [c]Reaction conducted in cyclopentyl methyl ether (CPME). [d]6 mmol of $LiN(SiMe_3)_2$. [e]6 mmol of $NaN(SiMe_3)_2$.

The success of Weinreb amides for the synthesis of ketones and aldehydes is attributed to the stability of the tetrahedral intermediates formed upon addition of strong nucleophiles to the carbonyl groups of these substrates (Figure 1C).[15] Another class of amides that form stable tetrahedral intermediates is *N*-acylpyrroles.[25] An advantage of *N*-acylpyrroles is that the lone pair is delocalized into the pyrrole and less available for delocalization into the carbonyl group. As a result, the carbonyl group is significantly more electrophilic than Weinreb amides and also more reactive than amides in general. The reactivity of *N*-acylpyrroles is on par with that of ketones.[26] Another advantage of *N*-acylpyrroles, also stemming from the delocalization of the *N*-lone pair, is that the pyrrole does not readily bind to metals, reducing its ability to act as a leaving group. Thus, stable tetrahedral intermediates can be isolated.[25g] Of relevance to this work, examples using *N*-acylpyrroles for the synthesis of ketones are known, but usually require inconveniently low temperatures[27] (–48 to –78 °C) to insure the tetrahedral intermediate does not break down, allowing a second addition to take place.[27b] These additions often furnish the pyrrolylcarbinol product.

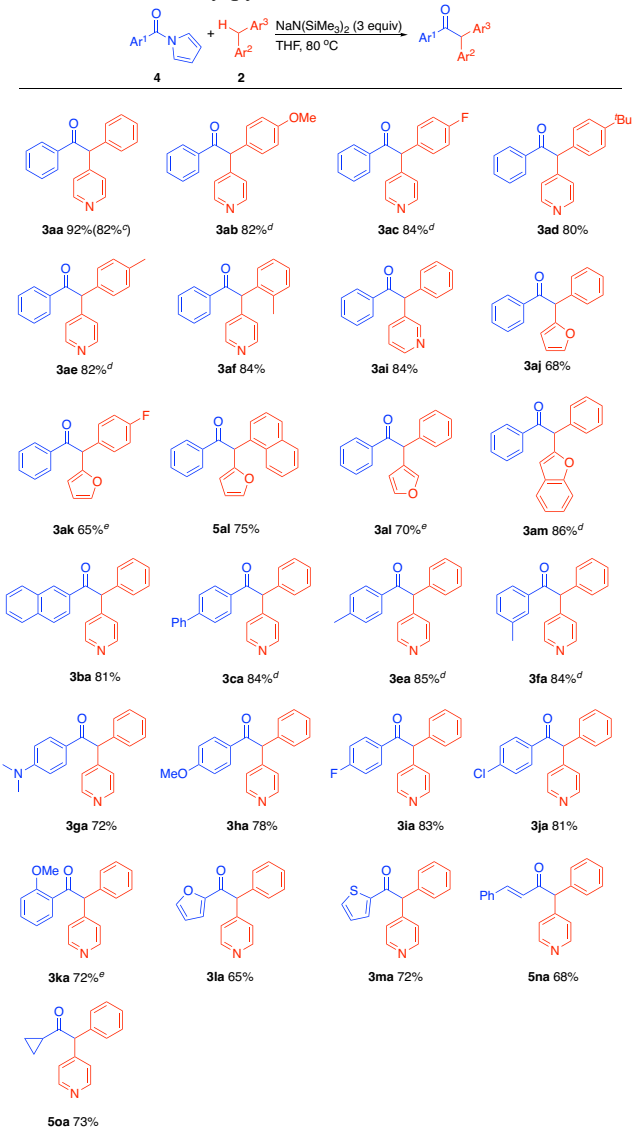
Based on the reactivity of *N*-acylpyrroles, we decided to examine the aroylation of diarylmethanes with these substrates to expand the generality of our method. We were pleased to find that aroylation could be successfully extended to encompass *N*-acylpyrroles under conditions similar to those used in the reactions described earlier (see the Supporting Information for reaction optimization). Examination of the scope indicated that a broad range of diarylmethanes and *N*-acylpyrroles were viable substrates in this transformation (Table 4). Using 4-benzylpyridine with a variety of substituents on the benzyl group (4-OMe, 4-F, 4-^{t}Bu, 4-Me, 2-Me, **3ab**–**3af**) provided products in 80–84% yields. It is interesting that the sterically demanding 2-tolyl derivative did not exhibit diminished reactivity. Less acidic 3-benzylpyridine was also a fine substrate, furnishing the product in 84% yield. Pronucleophiles 2- and 3-benzyl furans also participated in the reaction (65–75% yield). 2-Benzyl benzofuran proved to be a very good substrate, providing the product in 86% yield.

The *N*-acylpyrroles could also be varied, as demonstrated with a series of reactions using 4-benzylpyridine as the pronucleophile. Aryl *N*-acylpyrroles bearing aryls with 2-naphthyl, or phenyl groups substituted with 4-Ph, 4-Me, 3-Me, 4-NMe_2, 4-OMe, 4-F, and 4-Cl reacted to furnish the products in 72–85% yield. Only the more sterically hindered 2-methoxy phenyl *N*-acylpyrrole proved to be a challenging substrate, furnishing the product in 40% yield. However, the yield was improved when 6 equiv of 18-crown-6 was added, generating the product in 72% yield. The 2-furanyl and 2-thiofuranyl *N*-acylpyrroles were also good substrates, providing the

products in 65 and 72% yield. To illustrate the practicality of our method, we conducted the reaction of 4-benzylpyridine (**2a**) with *N*-benzoylpyrrole (**4a**) on a 4 mmol scale. The aroylation product **3aa** was isolated in 82% yield. Like the previous reactions of *N*-Bn-*N*-Boc amides, reactions with *N*-acylpyrroles were performed with only one equiv of the pronucleophile.

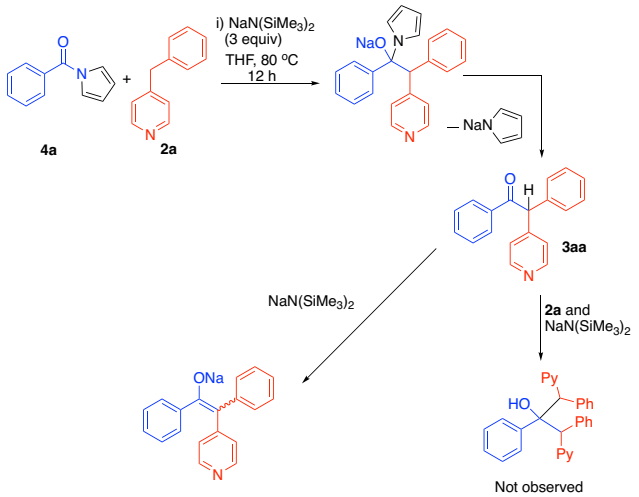
We next employed the *N*-acylpyrrole derived from cinnamic acid. We were pleased to find that the product **5na** could be generated under the standard conditions in 68% yield. For aliphatic acid derivatives, we employed the *N*-acylpyrrole prepared from cyclopropane carboxylic acid. This substrate reacted to give **5oa** in 73% yield.

Table 4. Transition metal-free aroylation of heteroaryl aryl methanes with *N*-acylpyrroles[a,b]



[a]Reaction conditions: *N*-Acylpyrrole (0.2 mmol), diarylmethane (0.2 mmol), $NaN(SiMe_3)_2$ (0.6 mmol), THF (0.1 M), 80 °C, 12 h. [b]Isolated yields. [c]Reaction performed on 4 mmol scale. [d]The reactions were executed in 1,4-dioxane. [e]1.2 mmol of 18-crown-6.

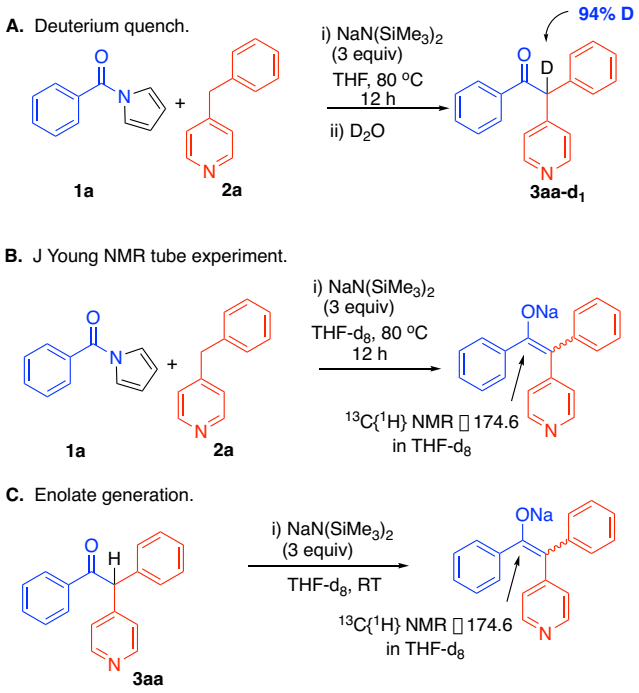
Mechanistic Experiments. We next wanted to understand the reason that the addition reactions give high selectivity for mono-addition products. With the *N*-acylpyrroles, we envisioned that the deprotonated pronucleophile derived from **2a** would add to the *N*-acylpyrrole to form a tetrahedral intermediate (Scheme 1). From here, two possibilities were considered. The first was that the tetrahedral intermediate formed upon addition of the nucleophile to the *N*-acylpyrroles was stable, as was observed by others.[25g] We viewed this possibility as less likely, because the reaction was conducted at 80 °C. The second possibility was that the tetrahedral intermediate underwent collapse to afford the ketone **3aa**. The ketone **3aa** could undergo a second addition of the deprotonated pronucleophile, however, this product was not observed. Alternatively, the ketone could be deprotonated by the excess $NaN(SiMe_3)_2$ to generate an enolate that would be inert to further reaction with the deprotonated pronucleophile.



Scheme 1. Possible reaction pathways.

To explore these key features of the reaction mechanism, experiments were conducted. When the reaction between 4-benzyl pyridine (**2a**) and *N*-acylpyrrole **4a** with $NaN(SiMe_3)_2$ (3 equiv) was performed under the standard conditions, but worked up with D_2O, the crude reaction product and contained 94% deuterium at the α-carbon (**3aa-d$_1$**, Scheme 2A). This is the product expected if the enolate were generated under the reaction conditions. We next desired to explore the possibility of enolate formation by directly examining the reaction products before workup. Thus, the reaction between 4-benzyl pyridine (**2a**) and *N*-acylpyrrole **4a** with $NaN(SiMe_3)_2$ (3 equiv) was performed in a degassed and sealed J Young NMR tube in THF-d_8 (Scheme 2B) The sealed tube was heated for 12 h at 80 °C in an oil bath before cooling to room temperature and analysis by NMR spectroscopy. The ^{1}H NMR spectrum of

this reaction solution consisted of a mixture of compounds, including sodium pyrrol-1-ide [which was verified by independent synthesis from pyrrole and $NaN(SiMe_3)_2$, see Supporting Information for details]. To determine if the enolate was also present in the reaction mixture, the independently synthesized ketone (**3aa**) was treated with $NaN(SiMe_3)_2$ (3 equiv) in THF-d_8 at room temperature (Scheme 2C). Analysis of the ^1H NMR of this solution indicated the majority of the resonances were identical to the reaction mixture when the reaction was conducted in the J Young NMR tube (Scheme 2b), suggesting that the product before workup was an *E/Z* mixture of the enolates. Examination of the $^{13}C\{^1H\}$ NMR spectrum of the ketone treated with $NaN(SiMe_3)_2$ and comparison with the $^{13}C\{^1H\}$ NMR of the reaction mixture in the J Young NMR tube indicated that the major components were the same. Among other resonances (see Supporting Information for details), both the deprotonated ketone and the reaction mixture in the J Young tube contained resonances at 174.6 ppm. A resonance at this location is not characteristic of a ketone, but instead is in the expected range for an O-*C*=C oxygen-bound enolate carbon (which in related systems appear at 165–175 ppm).[28] These results indicate that the enolate is the product of the reaction, which undergoes protonation on workup with water to generate the observed ketones.



Scheme 2. A. Deuterium quenching studies and B. Analysis of the reaction mixture in THF-d_8 before workup.

Conclusion

We have developed a transition metal-free and operationally-simple method for aroylation of diarylmethanes with *N*-Bn-*N*-Boc arylamides and *N*-acylpyrroles to afford a variety of 1,2,2-triarylethanone derivatives. 1,2,2-Triarylethanones belong to a class of privileged carbonyl compounds with various applications and biological activities. The scope of the aroylation is broad with high functional group compatibility and enables rapid incorporation of heteroaryl groups. In most cases, the reagents used are commercially available and inexpensive. Mechanistic studies indicate the product of the reaction before workup is the enolate, explaining why a second addition does not take place. This approach is complementary to popular palladium catalyzed α-arylations, and more economical. The novelty and advantages are: 1) the use of air stable pronucleophiles and amide electrophiles, 2) in situ reversible deprotonation to reveal reactive nucleophiles, and 3) the avoidance of transition metals. An important feature of this method is it circumvents the use of preformed air- and moisture-sensitive organometallic reagents. Given the significant role of amides in modern chemistry, we envision that this process will be of interest in chemical sciences and medicinal chemistry.

Experimental Section

Synthesis of 1,2,2-triarylethanones

General Procedure A

An oven-dried 10 mL vial equipped with a stir bar was charged with *N*-Bn-*N*-Boc arylamide (0.2 mmol) and $KN(SiMe_3)_2$ (120 mg, 0.6 mmol) under a nitrogen atmosphere. A solution of 4-benzylpyridine (33.8 mg, 0.2 mmol) in 2 mL of dry DME was added to the reaction by syringe at room temperature. Note that solid diarylmethanes were added to the reaction vial prior to $KN(SiMe_3)_2$, followed by addition of the solvent. The reaction mixture was stirred for 12 h at 80 °C. After cooling to room temperature, the reaction mixture was quenched with three drops of H_2O, passed through a short pad of silica gel and eluted with ethyl acetate (1 mL × 3). The combined organic solution was concentrated under reduced pressure. The crude material was loaded onto a silica gel column and purified by flash chromatography.

General Procedure B

An oven-dried 10 mL vial equipped with a stir bar was charged with *N*-acylpyrroles (0.2 mmol) and $NaN(SiMe_3)_2$ (110 mg, 0.6 mmol) under a nitrogen atmosphere at room temperature. A solution of 4-benzylpyridine (33.8 mg, 0.2 mmol) in 2 mL of dry THF was added to the reaction by syringe. Note that solid diarylmethanes were added to the reaction vial prior to $NaN(SiMe_3)_2$, followed by addition of the solvent. The reaction mixture was stirred for 12 h at 80 °C. After cooling to room temperature, the reaction mixture was quenched with three drops of H_2O, passed through a short pad of silica gel and eluted with ethyl acetate (1 mL × 3). The combined organic solution was concentrated under reduced pressure. The crude material was loaded onto a silica gel column and purified by flash chromatography.

General Procedure C

An oven-dried 10 mL vial equipped with a stir bar was charged with *N*-acylpyrroles (0.2 mmol) and $LiN(SiMe_3)_2$ (100 mg, 0.6 mmol) under a nitrogen atmosphere. A solution of 4-benzylpyridine (33.8 mg, 0.2 mmol) in 2 mL of dry THF was added to the reaction by syringe at room temperature. Note that solid diarylmethanes were added to the reaction vial prior to $NaN(SiMe_3)_2$, followed by addition of the solvent. The reaction mixture was stirred for 12 h at 80 °C. After cooling to room temperature, the reaction mixture was quenched with three drops of H_2O, passed through a short pad of silica gel and eluted with ethyl acetate (1 mL × 3). The combined organic solution was concentrated under reduced pressure. The crude material was loaded onto a silica gel column and purified by flash chromatography.

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Transition metal-free aroylation of diarylmethanes with *N*-Bn-*N*-Boc arylamides and *N*-acylpyrroles

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