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Aerobic, Transition-Metal-Free, Direct, and Regiospecific Mono-α-arylation of Ketones: Synthesis and Mechanism by DFT Calculations

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Supporting Information

ABSTRACT: We disclose a facile, aerobic, transition-metal-free, direct, and regiospecific mono-α-arylation of ketones to yield aryl benzyl and (cyclo)alkyl benzyl ketones with substitution patterns that are currently inaccessible or challenging to prepare using conventional methods. The transformation is operationally simple, scalable, and environmentally friendly. There is no need for pre-functionalization (i.e., α-halogenation or silyl enol ether formation) or the use of specialized arylating agents (i.e., diaryliodonium salts). DFT calculations suggest that the *in situ*-generated enolate undergoes direct C−C bond formation with the nitroarene followed by regioselective O_2-mediated C−H oxidation.

The α-arylated carbonyl structural motif appears in a large number of biologically active natural products as well as in active pharmaceutical ingredients (APIs). α-Arylated carbonyl compounds also often serve as key intermediates for the synthesis of substituted heterocycles such as indoles, furans, imidazoles, oxazoles, and pyrazoles. Thus, it is not surprising that the selective installation of an aryl group in the α-position of a carbonyl group has received considerable attention from the synthetic community over the past 40 years.[1] While the formation of $C(sp^3)-C(sp^3)$ bonds at the α-position of electron-withdrawing groups is now considered routine,[2] the direct installation of $C(sp^3)-C(sp^2)$ bonds has proven to be far more challenging. The efficient transition-metal (TM)-catalyzed α-arylation of ketone enolates with aryl halides and pseudo-halides, did not emerge until the first reports by Kuwajima,[3] Buchwald, and Hartwig,[4] in the early 1980s and late 1990s. Today, enolates derived from other electron-withdrawing functional groups—aldehydes, esters, amides, nitriles, and imines—are also efficiently arylated, even in an enantioselective fashion, using TM catalysis.[5] Several TM-free α-arylation processes of enolates and enolate equivalents have been also developed (see Figure 1 for a sampling of previous work): (i) S_NAr reaction with highly activated aryl halides;[6] (ii) addition to electron-deficient arenes, followed by oxidation (Figure 1A);[7] (iii) addition of enolates derived from α-halogenated carbonyls to heterocycles and various electron-deficient arenes via vicarious nucleophilic substitution (VNS, Figure 1B);[8] (iv) reaction with aromatic iodine(III) derivatives (Figure 1C);[9] (v) reaction with aromatic Bi(V) and Pb(IV) derivatives;[10] (vi) reaction with benzynes;[11] (vii) reaction with aryl diazonium salts mediated by base or visible light;[12] (viii) organocatalytic enantioselective approaches that utilize various electrophilic arylating agents;[13] and (ix) miscellaneous other methods[14] including addition of triarylaluminum reagents to *N*-alkoxyenamines[14d] and reaction of activated sulfoxides[14c] with β-keto esters.

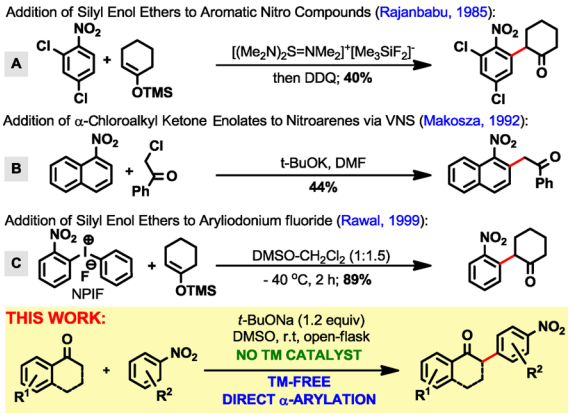

Figure 1. A sampling of methods for the TM-free synthesis of α-arylated ketones. Our direct and regiospecific mono-α-arylation process that delivers structurally diverse ketones is highlighted.

Although TM-catalyzed α-arylations are currently the most widely used, they suffer a number of drawbacks, such as use of expensive ligands and catalyst, use of a variety of additives, need to employ harsh conditions (e.g., elevated temperatures for extended periods of time), and generation of a toxic waste of heavy metals that is expensive to remove, especially in production of APIs, in which residual metal contamination must meet stringent specifications.[15] On the other hand, current TM-free α-arylation processes are also far from being ideal since the carbonyl compounds often require pre-functionalization (e.g., formation of enol ethers and enol carboxylates as well as α-halogenated or α-alkoxy derivatives) and the arylating agents are prepared via multi-step processes.

There is a need for the development of TM-free direct arylation[16] reactions that are operationally simple, utilize readily available and inexpensive starting materials, achieve C−C bond formation with high regioselectivity, build molecular complexity rapidly (i.e., in one-pot), and complement existing methods by allowing the preparation of currently inaccessible compounds.

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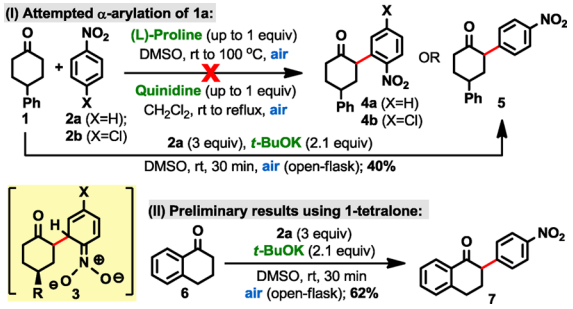
Scheme 1. Preliminary Direct α-Arylation Results



We decided to examine the possibility of α-arylating ketones directly (not via an S_NAr reaction!) in the absence of TMs. Our initial plan (Scheme 1, I) was to desymmetrize 4-substituted cyclohexanone **1** in the presence of chiral amine catalysts and nitroarenes; the *in situ*-generated C-nucleophile was expected to add to the nitroarene to form an anionic σ^H adduct (**3**) which, upon oxidation, would furnish the α-arylated ketone **4**. But none of the conditions we tried yielded even trace amounts of the expected **4** or **5**; the starting materials were recovered unchanged. We suspected that the nucleophilicity of the α-C in these reactions was insufficient to achieve addition to the nitroarene coupling partners. A thorough study of the literature on VNS[8] and NSH[17] (nucleophilic substitution of hydrogen) reactions made us realize that the formation of anionic σ^H-adducts like **3** is usually a fast and reversible process and the equilibrium is shifted toward σ^H-adducts due to either the high electrophilicity of the arenes or the high nucleophilicity of nucleophiles. We chose to increase the nucleophilicity of the α-C in **1** by utilizing KO*t*-Bu, a strong base. To our delight, a rapid reaction took place in an open flask, and α-arylated ketone **5** was isolated in 40% yield. We next reacted 1-tetralone (**6**) with nitrobenzene (**2a**) in DMSO; α-arylated tetralone **7** was isolated in 62% yield (Scheme 1, II). Surprisingly, the arylation of both ketones **1** and **6** was very clean (only a single product spot on the TLC) and no trace of *ortho*-substituted nitrobenzene regioisomers (such as **4a**) could be isolated.

Encouraged by these results, we next conducted a thorough solvent screen using the reaction **6** + **2a** (3 equiv) → **7** as the model (Table 1). DMSO and DMF were found to be the best solvents (entries 7 and 8), giving arylated product **7** in 62% and 48% yields, respectively. The reaction in DMA was significantly slower (entry 6); only 50% of ketone **6** was converted after 18 h and 30% yield of **7** was isolated. Nonpolar solvents (entries 1 and 2) led to no reaction (i.e., recovered **6**), while ethereal solvents (entries 3 and 4) yielded complex mixtures.

Screening various organic (TMG, DBU) and inorganic bases (*t*-BuONa, NaOH, NaH, *t*-BuOLi, KOH) in DMSO indicated that organic bases are ineffective even at elevated temperatures (80 °C), while sodium salts gave the best product yields. *t*-BuONa gave the highest yield of **7** (68%, 30 min).[18] Thus we selected *t*-BuONa as our preferred base and DMSO as the preferred solvent, and set out to find the optimum number of equivalents of base and nitroarene reaction partner that would furnish the maximum yield of the α-arylated product (see SI). These studies showed that the amount of **2a** could be reduced from 3 to 2 equiv without any effect on the isolated yield of **7**. Further decreasing the stoichiometry of **2a** (<2 equiv) led to significant erosion of the yield (<30%). We also found that 1.2 equiv of *t*-BuONa was sufficient.[19]

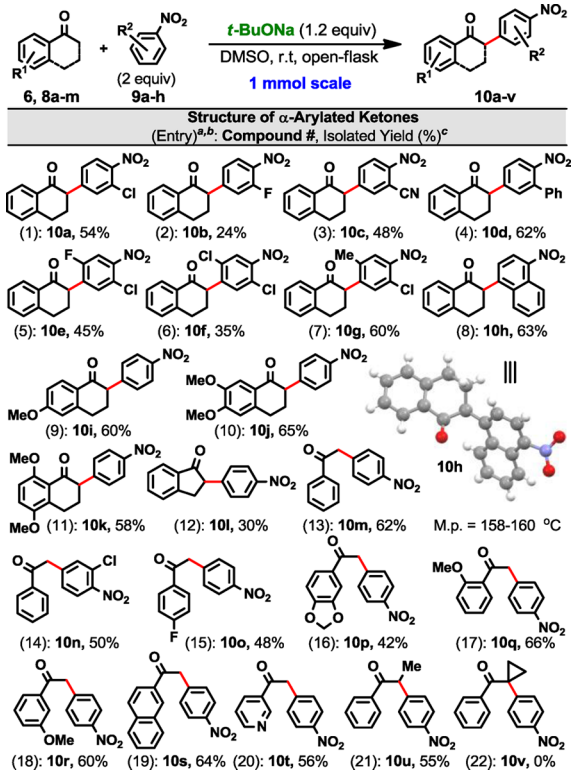
With the optimized reaction conditions in hand, we first examined the scope of alkyl aryl ketones and nitroarene substrates (Table 2). 1-Tetralone (**6**) was an excellent substrate for eight different substituted nitroarenes (entries 1–8) in addition to nitrobenzene (**2a**) itself. Halogens (Cl, F) as well as cyano and phenyl groups are apparently well-tolerated in the 2-position of the nitroarene substrates. Surprisingly, products of an S_NAr process were not present in the reaction mixture (discussed below). *Para*-substitution is exclusive as no traces of the corresponding *ortho*-alkylated nitroarene products were detected or isolated. 1-Nitronaphthalene (entry 8) was exclusively substituted at the 4-position, in contrast with the *ortho*-selective regiochemistry observed in a VNS reaction[8] (Figure 1B). Electron-rich 1-tetralones (entries 9–11) also reacted readily with **2a** to afford the corresponding α-arylated products (**10i–k**)

Table 1. Solvent Screen for the α-Arylation of 6 with 2a

Entry[a]	Solvent	Time[b] (h)	Conv.[c] (%)	Yield[d] (%)	Comment
1	DCM or DCE	5	0	0	No reaction
2	toluene	4	0	0	No reaction
3	Et_2O or THF	4	100	0	Complex
4	dioxane	0.5	100	0	Complex
5	MeCN or NMP	0.5	100	<5	Complex
6	DMA	18	50	30	Clean
7	DMF	0.5	100	**48**	Clean
8	DMSO	0.5	100	**62**	Clean
9	EtOH	17	100	0	No reaction

[a,b]Reactions conducted at 0.2 M concn in an open flask for the indicated time. [c]Conversion based on TLC analysis and amount of recovered starting material. [d]Isolated yield after column chromatography.

Table 2. α-Arylation of Alkyl Aryl Ketones



[a,b]Reactions conducted at 0.2 M concn in an open flask. [c]Isolated yield after column chromatography.

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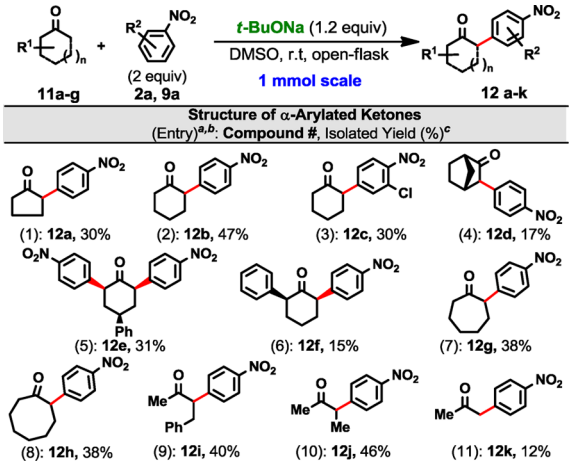
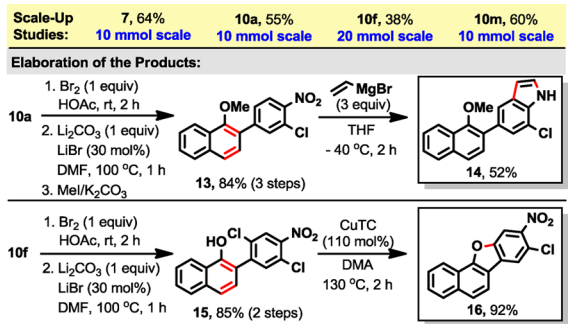
Table 3. α-Arylation of Alkyl Alkyl Ketones



[a,b]Reactions conducted at 0.2 M concn in an open flask. [c]Isolated yield after column chromatography.

Scheme 2. Scale-Up Studies and Unique Heterocycles

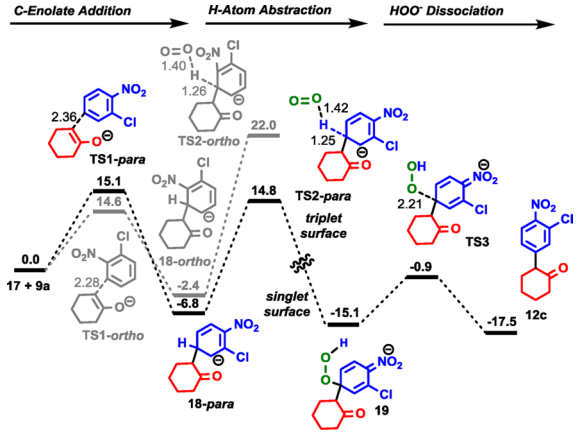


in good isolated yields; however, indanone was arylated only in fair yield (entry 12). Electron-rich as well as electron-poor aryl methyl ketones underwent smooth α-arylation (entries 13−21). Interestingly, phenyl cyclopropyl ketone (entry 22) did not undergo α-arylation even with a large excess (5 equiv) of **2a**; it is conceivable that deprotonation at the α-position of this substrate is challenging. Remarkably, all the alkyl aryl ketones that we subjected to our α-arylation protocol (Table 2) gave rise exclusively to mono-arylated products; no traces of α,α-diarylated ketones were detected or isolated. One limitation of this method is that α,α-dialkyl ketones (e.g., 2-Me-1-tetralone) do not undergo α-arylation.

Next we investigated the reactivity of cyclic as well as acyclic ketones (Table 3). Alkyl alkyl ketones gave rise to α-arylated derivatives in fair isolated yields; the exclusive *para*-selectivity as well as the formation of only mono-α-arylated ketones remained the same as for the substrates presented in Table 2. The fact that only the more highly substituted α-position was arylated in products **12i,j** (entries 9 and 10) is noteworthy. Acetone (entry 11) was a poor substrate, presumably because the competing self-condensation reaction is faster than the α-arylation process.

To demonstrate the synthetic utility of this facile, aerobic, TM-free, regiospecific, direct mono-α-arylation of ketones on a multigram scale, we chose a combination of two ketones and three substituted nitroarenes to prepare four α-arylated products: **7**, **10a**, **10f**, and **10m** (Scheme 2). We also showed that compounds **10a,f** could be readily aromatized to biaryls **13** and **15**, respectively, which in turn could be converted to unusually substituted heterocycles **14** and **16** in a single step.

Scheme 3. Free Energy (kcal/mol) Surface of Proposed Mechanism (Bond Lengths in Å)



We also used DFT calculations to examine the mechanism and regioselectivity of C−C bond formation and aerobic oxidation. (U)M06-2X/6-31+G(d,p) calculations were carried out in Gaussian 09 (see SI) using the SMD solvent model for DMSO.[20]

Several mechanisms for C−C bond formation between cyclohexenolate (**17**) and **9a** were considered (see SI).[21] One involves O-enolate addition at the *ortho*-position of **9a** followed by a [3,3] rearrangement. For O-enolate addition at the *ortho*-position of **9a**, $\Delta H^{\ddagger}$ = 7.5 kcal/mol and $\Delta G^{\ddagger}$ = 19.3 kcal/mol. A lower energy pathway was found for direct C-enolate addition via **TS1-*para*** at the *para*-position of **9a** with $\Delta H^{\ddagger}$ = 3.2 kcal/mol and $\Delta G^{\ddagger}$ = 15.1 kcal/mol (Scheme 3). We also considered electron transfer (ET) from **17** to **9a** followed by C−C bond formation. The computed ΔH for ET between enolate **17** and **9a** is 8.9 kcal/mol, suggesting that ET is less viable than C-enolate addition.[22] However, a Marcus−Hush estimate of $\Delta G^{\ddagger}$ for ET is 13−14 kcal/mol, which may be competitive with C-enolate addition.

No S_NAr product is formed because the Cl atom increases the $\Delta H^{\ddagger}$ for C-enolate addition by ~10 kcal/mol compared to **TS1-*para***.[23] Surprisingly, C-enolate addition *ortho* to the nitro group of **9a** via **TS1-*ortho*** (Scheme 3) has a lower $\Delta G^{\ddagger}$ than **TS1-*para***.[24] However, experimentally, ketone addition was found to occur exclusively with *para*-selectivity. This suggests that *ortho* C-enolate addition is reversible. In accordance with this hypothesis, the ΔG for formation of **18-*ortho*** is close to zero, and the barrier for subsequent oxidation is higher in energy than reversion back to reactants.

Scheme 3 also shows our proposed mechanism for aerobic oxidation. From **18-*para***, oxidation involves $^3O_2$-mediated H-atom abstraction with $\Delta G^{\ddagger}$ = 14.8 kcal/mol. Importantly, H-atom abstraction at the *ortho* position of **18** via **TS2-*ortho*** requires several kcal/mol more energy. This reaction step is likely irreversible and sets the regiochemistry. After H-atom abstraction, the resulting hydroperoxyl and carbon radicals can combine to give **19**.[25] Oxidation is completed after hydroperoxide anion dissociation via **TS3**.

We also considered whether oxidation proceeds by electrophilic addition of $^3O_2$ to the *meta*-positions of **18-*para*** followed by intra- or intermolecular deprotonation and elimination of reduced O_2. Although addition of $^3O_2$ to **18-*para*** is favorable, subsequent base elimination of reduced O_2 requires a large barrier. We also considered oxidation via ET between **18-*para*** and $^3O_2$ followed by H-atom abstraction. The ΔH for ET

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requires 12.1 kcal/mol, and so an ET-stimulated oxidation mechanism cannot be ruled out.

In conclusion, we demonstrate that mono-α-arylation of ketones is feasible under aerobic and TM-free conditions to yield products that are challenging or impossible to obtain using conventional methods. The transformation is operationally simple and scalable, the scope of substrates is wide, and there is no need for pre-functionalization or the use of specialized arylating agents. DFT calculations suggest that the *in situ*-generated enolate undergoes direct C−C bond formation with the nitroarene followed by regioselective O_2-mediated C−H oxidation. Studies to expand this direct α-arylation process to other classes of carbonyl compounds are currently under way.

■ ASSOCIATED CONTENT

Supporting Information

Procedures and characterization, and ref20a. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(18) Other bases performed as follows: NaH, 63%, 30 min; NaOH, 31%, 17 h; KOH, trace, 17 h; and *t*-BuOLi, 34%, 30 min.

(19) When the flask is closed (i.e., capped) or Ar gas is used, the α-arylation reaction shuts down. Using an O_2-filled balloon instead of just air does not result in higher isolated yield of the product.

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(21) We also explored the interaction of *t*-BuO$^-$ with 2-chloronitrobenzene (**9a**). In DMSO, *t*-BuO- addition to **9a** to give a Meisenheimer adduct has $\Delta G \approx -8.0$ kcal/mol.

(22) For ET between enolate **17** and $^3O_2$, $\Delta H = 12.1$ kcal/mol.

(23) The IRC from the TS for C-enolate addition at the 2-position of **9a** leads directly to the S_NAr product without an intermediate.

(24) Na^+-coordinated transition states also show a preference for addition at the *ortho* position (see SI).

(25) It is possible that another $^3O_2$ reacts with the carbon radical.

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