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**To be cited as:** *Chem. Eur. J.* 10.1002/chem.201903816

**Link to VoR:** http://dx.doi.org/10.1002/chem.201903816

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10.1002/chem.201903816


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# Deoxygenative Arylation of Carboxylic Acids via Aryl Migration

Rehanguli Ruzi†, Junyang Ma†, Xiang-Ai Yuan†, Wenliang Wang, Shanshan Wang, Muliang Zhang, Jie Dai, Jin Xie* and Chengjian Zhu*

**Abstract:** An unprecedented deoxygenative arylation of aromatic carboxylic acids has been achieved, allowing the construction of an enhanced library of unsymmetrical diaryl ketones. The synergistic photoredox catalysis and phosphoranyl radical chemistry allows for precise cleavage of a stronger C-O bond and formation of a weaker C-C bond via 1,5-aryl migration under mild reaction conditions. This new protocol is independent of substrate redox-potential, electronic and substituent effects. It affords a general and promising access to 60 examples of synthetically versatile *o*-amino and *o*-hydroxy diaryl ketones under redox-neutral conditions. Furthermore, it also brings one concise route to the total synthesis of quinolone alkaloid, (±)-Yaequinolone A2 and Viridicatin derivative in satisfying yield.

*o*-Aminobenzophenone moiety is widely presented in a broad range of biologically important molecules, pharmaceuticals and nature products, such as nepafenac, bromfenacum and mitoxantrone (Figure 1). In organic synthesis, this skeleton is a versatile building block leading to indoles[4a,b] or quinolines[4c] and is also a privileged synthetic linchpin for a wide variety of diazepinone-based pharmaceuticals, including currently heavily used drugs such as clonazepam, alprazolam and valium (Scheme 1b).[4d]

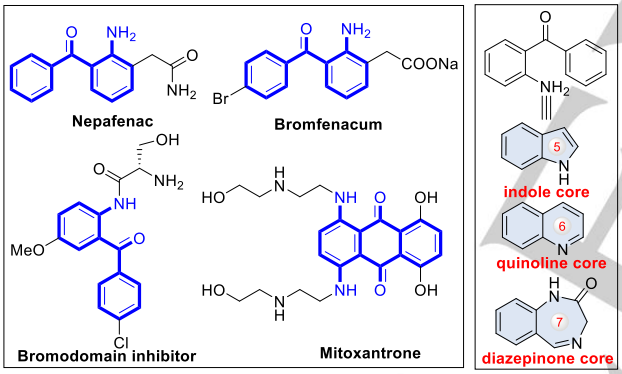
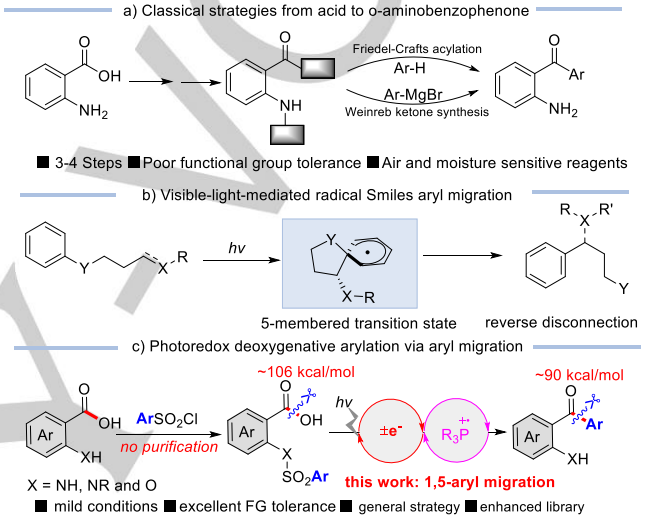



***Figure 1***. The significance of *o*-aminobenzophenone moiety.

Ketones are a class of compounds important in organic synthesis.[1] The development of efficient routes for the synthesis of ketones from carboxylic acids or their derivatives is a subject of interest. The classical synthetic strategies, from 2-aminobenzoic acids to *o*-aminobenzophenones, usually require 3-4 steps, involving amino group protection, carboxylic group activation and subsequent Friedel-Crafts arylation or Weinreb ketone synthesis (Scheme 1a). While powerful, the employment of $AlCl_3$/$PCl_5$ or Grignard reagents would compromise functional group compatibility. A new synthetic methodology to address previous synthetic limitations and enhance the structural diversification of the products is highly desirable.




***Scheme 1.*** General strategy for ketone synthesis from acids and our work hypothesis.

In 2018, our group[5] and Doyle et al.[6] have independently developed photoredox phosphoranyl radical chemistry for redox-potential independent deoxygenation of carboxylic acids. This affords a promising route for construction of aryl-alkyl ketones and aldehydes directly from carboxylic acids. In the last five years, visible-light-mediated radical Smiles aryl rearrangement has been recognized as a powerful structural reversal tactic to construct new C-C bonds (Scheme 1b).[7] Although the radical Smiles rearrangement[8] *via* a five-membered transition-state has been recently established for 1,4-aryl migration,[9] photoredox 1,5-aryl migration leading to C-C bond formation[10] has been rarely developed possibly due to the higher energy barrier that is involved. We questioned if an unprecedented deoxygenative arylation protocol *via* photoredox-catalyzed 1,5-aryl migration could be a reliable method to furnish versatile *o*-aminobenzophenones as well as the synthetically useful *o*-hydroxybenzophenones (Scheme 1c).

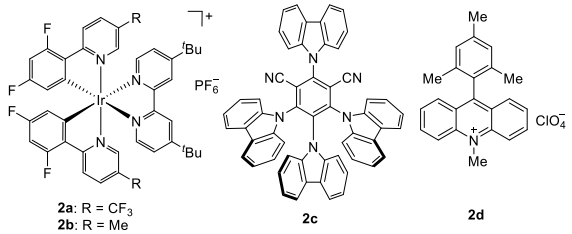



***Table 1***: Optimization of the reaction conditions.[a]

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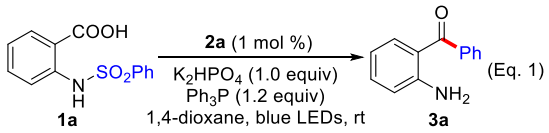
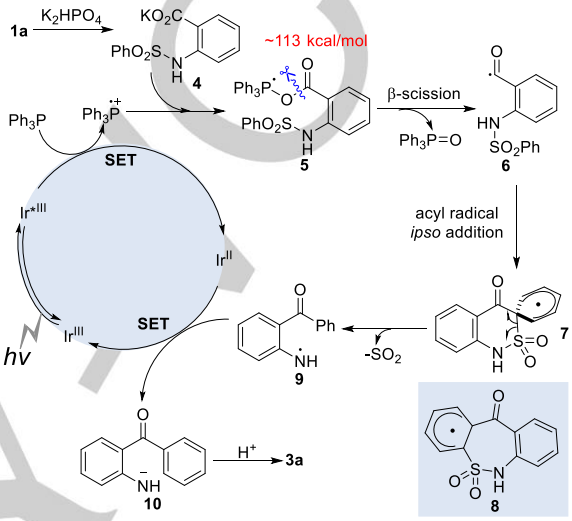



| Entry | Variation of standard conditions | Yield[b] |
|---|---|---|
| **1** | **none** | **74%** |
| 2 | **2b** instead of **2a** | 30% |
| 3 | **2c** instead of **2a** | 69% |
| 4 | **2d** instead of **2a** | nd |
| 5 | THF instead of dioxane | 71% |
| 6 | DCM instead of dioxane | 17% |
| 7 | no $Ph_3P$ | nd |
| 8 | no PC or no light | nd |

[a] Standard conditions: **1a** (100 µmol), **2a** (1 µmol), $Ph_3P$ (120 µmol), $K_2HPO_4$ (100 µmol), 1,4-dioxane (1.0 mL), blue LEDs, 25 °C, 8 h. [b] Isolated yield of **3a**. nd = not detected; DCM = dichloromethane.

Our study was initiated with substrate **1a** coupled with an effort to optimize the photoredox deoxygenative arylation reaction conditions. Representative results are summarized in Table 1. The optimized conditions require 1 mol% of photocatalyst (**2a**), 1.0 equiv of $K_2HPO_4$, 1.2 equiv of $Ph_3P$ as a deoxygenation reagent, dioxane as solvent and irradiation with blue LEDs. In this case, the desired *o*-aminobenzophenone was obtained in 74% yield (Entry 1). The use of other photocatalysts (**2b-d**) instead of **2a** resulted in lower yield (Entries 2-4). Among the solvents that were screened, 1,4-dioxane gave the best result (Entries 1, 5 and 6, see Supporting Information for details). In the absence of $Ph_3P$, the deoxygenative arylation reaction cannot take place (Entry 7). The control experiments indicate that both light and photocatalyst are crucial for a successful deoxygenative arylation (Entry 8). The addition of radical scavengers TEMPO (2,2,6,6-tetramethylpiperidin-1-yl)oxyl) or BHT (butylated hydroxytoluene) can significantly inhibit the reaction, indicating that a radical mechanism is possible (See Supporting Information for details). In addition, the quantum yield of the model reaction (Eq. 1) was determined to be 0.39 and thus a radical chain pathway for intramolecular deoxygenative arylation is less likely.




***Scheme 2***. Proposed mechanism.

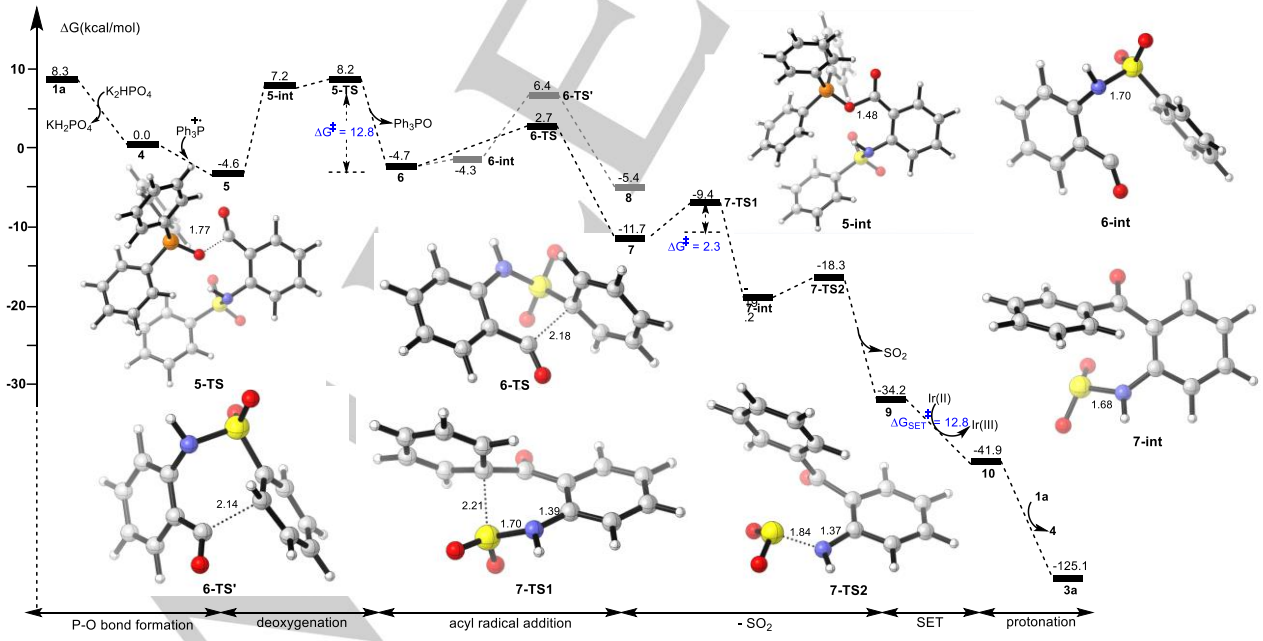



***Figure 2.*** Gibbs free energy profile of the deoxygenative arylation of carboxylic acids via aryl migration.

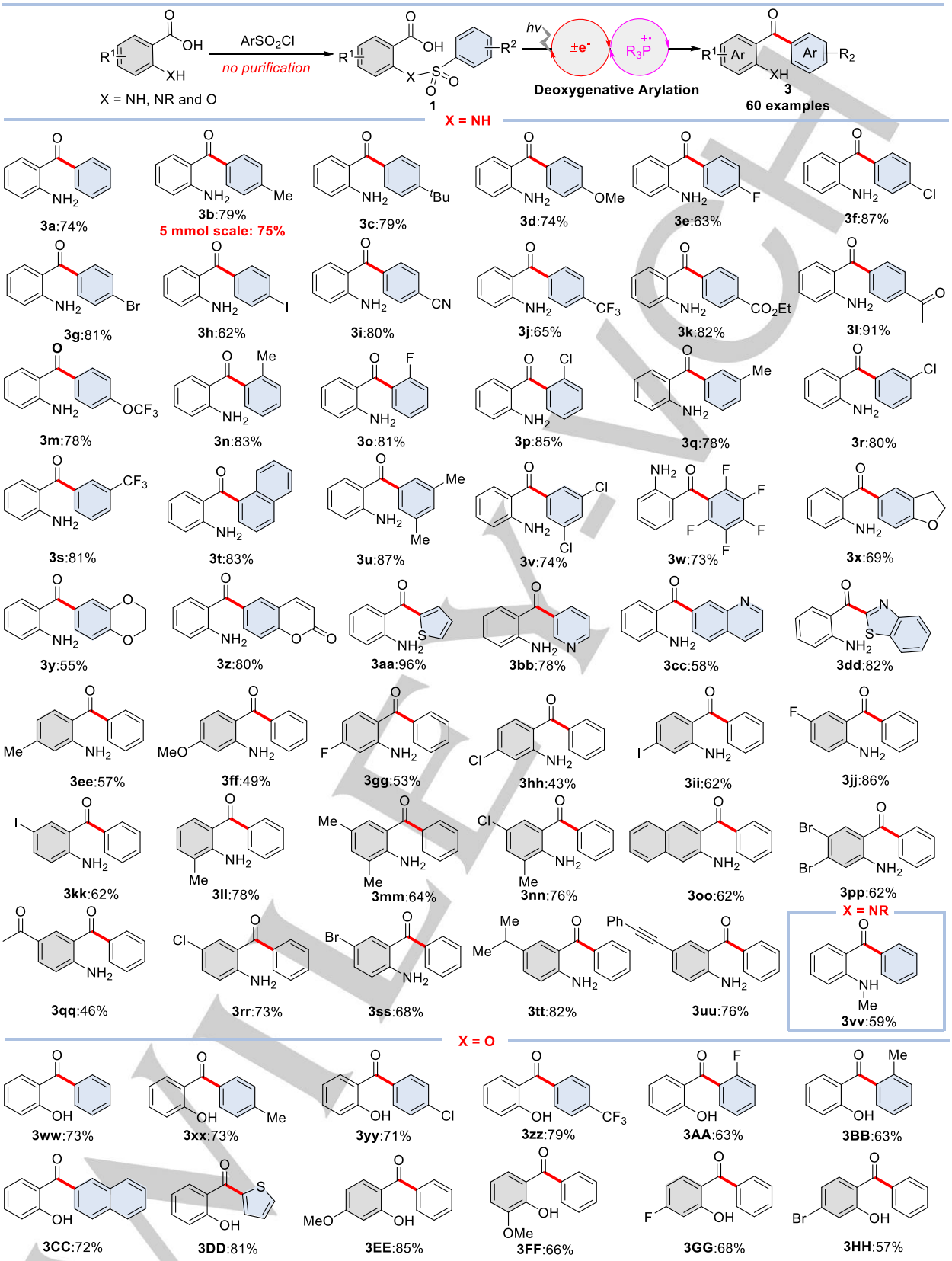
According to our previous report, a possible reaction mechanism is shown in Scheme 2. The photoexcited Ir-complex [$^{1/2}E_{red}$ ($^{*}Ir^{III}/Ir^{II}$) = + 1.21 V vs SCE τ = 2.3 μs] [11], can undergo single electron oxidation of triphenylphosphine ($^{1/2}E_{red}$ = + 0.98 V vs SCE)[5] to form triphenylphosphine radical cation, which can be trapped by the carboxylate (**4**) to give intermediate (**5**). Due to the strong affinity between phosphine and oxygen atoms, it proceeds β-scission C(acyl)-O bond cleavage to produce acyl radical (**6**), which undergo an intramolecular 1,6-*ipso* addition to give intermediate (**7**) rather than 1,7-*ipso* addition for intermediate (**8**). The resulting 6-membered transition state (**7**) would undergo radical rearrangement to generate the N-centered radical species (**9**). Subsequent SET with $Ir^{II}$ and followed by protonation finally affords the desired product (**3a**). Interestingly, this deoxygenative arylation is featured by its precise cleavage of a stronger C-O bond of carboxylic acid (106 kcal mol$^{-1}$) and formation of a weaker C-C bond (90 kcal mol$^{-1}$).

To have an insightful mechanistic picture, we used DFT calculations to understand the mechanism. The calculation result indicates that the photoexciting process of $Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ is endoergic by 58.0 kcal mol$^{-1}$, which is feasible with blue LEDs irradiation. The SET process between photoexcited *Ir-complex and $Ph_3P$ is calculated to be exergonic by 0.8 kcal mol$^{-1}$ with a very low SET energy barrier of 0.01 kcal mol$^{-1}$ (See Supporting Information). The calculated free energy profile for the full picture of deoxygenative arylation of carboxylic acids via aryl migration is shown in Figure 2 and it comprises the following sections: (1) Both reactions of carboxylic acid (**1a**) with $K_2HPO_4$ to form carboxylate (**4**) and triphenylphosphine radical cation and **4** to produce intermedaite (**5**) are calculated to be exergonic by 8.3 kcal mol$^{-1}$ and 4.5 kcal mol$^{-1}$, respectively. (2) The resulting radical intermediate (**5**) can undergo the homolytic C-O bond cleavage (113 kcal mol$^{-1}$) via the transition state **5-TS** with a free energy barrier of 12.8 kcal mol$^{-1}$. (3) Interestingly, the DFT calculation clearly demonstrates that the free energy barrier for 1,7-acyl radical *ipso* addition (**8**) is much higher than 1,6-acyl *ipso* addition (**7**) (11.1 versus 7.4 kcal mol$^{-1}$ relative to **6**), which can account for its exclusive product selectivity. (4) It is calculated that excursion of $SO_2$ process is highly exergonic by 23.0 kcal mol$^{-1}$ with two energy barriers of only 1.8 kcal mol$^{-1}$ (relative to **7**) and 0.9 kcal mol$^{-1}$ (relative to **7-int**) respectively. It indicates that release of $SO_2$ may be one driving force for the radical rearrangement process. (5) The SET process from N-centered radical species (**9**) to intermediate (**10**) with strongly reducing Ir(II)-species is calculated to be exergonic by 7.7 kcal mol$^{-1}$, with a SET energy barrier of 11.0 kcal mol$^{-1}$, completing the photoredox cycle. (6) The resulting N-centered anion is a strong base and it can abstract one proton from carboxylic acid (**1a**) to afford the desired product (**3a**). This process is calculated exergonic by 83.2 kcal mol$^{-1}$. From the above DFT calculation results, we can conclude that the whole deoxygenative arylation of carboxylic acids via aryl migration process is strongly exergonic by 125.1 kcal mol$^{-1}$ (relative to carboxylate **4**) and thus it is thermodynamically and kinetically feasible under room temperature with blue LEDs.

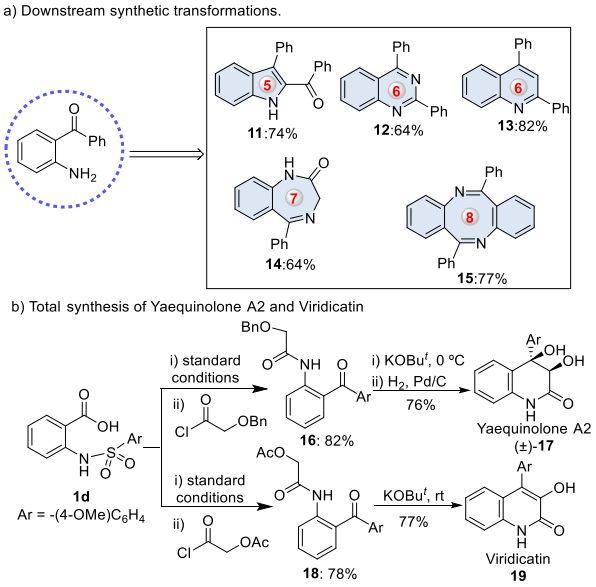
With the optimized reaction conditions in hand, we investigated the scope of photoredox deoxygenative arylation reaction (Scheme 3). The reaction of *o*-aminobenzoic acids with aromatic sulfonyl chlorides at room temperature can afford, upon aqueous workup, substrate **1** which can be directly used in photoredox deoxygenative arylation reactions without further chromatographic purification. Thus, the practicality of this method for the synthesis of divergent unsymmetrical diaryl ketones is enhanced. We explored the substituent effect on the migrating phenyl ring (Scheme 3). In general, various substituted aromatic and heteroaromatic moieties tolerate the deoxygenative arylation conditions well, uniformly delivering the desired *o*-amino diaryl ketones (**3a-dd)** with yields up to 96%. Both electron-donating and electron-withdrawing functional groups in either the *o*-, *m*- or *p*-position are compatible (**3a-v**). The strongly electron-deficient pentafluorophenyl group appeared to be a good migratory functional group, leading to **3w** in 73% yield. The heterocycle-containing substrates support a smooth deoxygenative arylation and the desired diaryl ketones (**3x-dd**) are obtained in 55-96% yield. When the migratory aryl group is coumarin (**3z**), pyridine (**3bb**), quinoline (**3cc**) or benzo[d]thiazole (**3dd**), the 1,5-aryl migration still proceeds readily. The electron-rich thiophene (**3aa**) proved to be a good migratory heteroarene in this radical process, which competes with the ionic Smiles rearrangement.[8c,d] The reaction can be easily scaled up to 5 mmol in satisfying yield (**3b**) under standard conditions (See SI for details).

Next, we investigated the generality of *o*-aminobenzoic acid in this transformation. As shown in Scheme 3, the introduction of different functional groups on the phenyl ring of the *o*-aminobenzoic acid hardly influences the reaction efficiency and the diaryl ketones (**3ee-uu**) are obtained in 43-82% yield. The tolerance of useful C-I and C-Br bonds would allow for downstream Pd- or Ni-catalyzed coupling transformations of the *o*-amino diaryl ketones (**3ii**, **3kk**, **3pp**, **3ss**). Methyl-substituted *o*-amino diaryl ketone (**3vv**) can also be synthesized by photoredox deoxygenative arylation.

*o*-Hydroxybenzophenones are a prevalent structural motif in natural products and biologically important molecules.[12] To further expand the practicality of this deoxygenative 1,5-aryl migration, we sought to construct *o*-hydroxybenzophenones by direct deoxygenation of carboxylic acids by means of photoredox catalysis and phosphoranyl radical synergism. Two elegant acyl radical Smiles examples[13] have been reported, but both required the use of external oxidants, such as di-*t*-butyl peroxides (DTBP) or hypervalent iodine(III) reagents, to trigger the generation of acyl radicals. Our deoxygenative arylation strategy reflects a significant synthetic advance because it is a redox-neutral process, has mild reaction conditions and uses readily accessible starting materials. By changing the solvent from dioxane to THF (see Table 1), many *o*-hydroxybenzophenones (**3ww-HH**) bearing different functional groups were obtained in satisfying results (Scheme 3, lower part).




***Scheme 2.*** Reaction scope: The reaction was performed in 0.2 mmol scale. See SI for detailed reaction conditions. The yields are after column chrom atography on $SiO_2$.




***Scheme 4.*** Synthetic application: a) Downstream synthetic transformations. See SI for detailed reaction conditions; b) Total synthesis of Yaequinolone A2 and Viridicatin derivative.

Starting with *o*-aminobenzophenones, several important 5- to 8-membered heterocyclic skeletons can be easily obtained. As shown in Scheme 4a, indole (**11**), quinoline (**12**), quinazoline (**13**), diazepinone (**14**), dibenzodiazocine (**15**) can be constructed, further underscoring the synthetic value of the *o*-aminobenzophenones. Yaequinolone A2 (**17**), isolated from *Penicillium janczewskii* or *Penicillium sp. FKI-2140,* is one class of biologically important compounds in the family of 2-quinolone alkaloid.[14a] With our developed deoxygenative arylation strategy, it affords a concise access to (±)-Yaequinolone A2 in two steps and 63% total yield. Similar strategy can also afford another quinolone alkaloid derivative, 4-OMe Viridicatin (**19**)[14b] in two steps and 60% total yield (Scheme 4b).

In conclusion, we have developed a general deoxygenative arylation method for the synthesis of a wide range of *o*-amino and *o*-hydroxy diaryl ketones from commercially available aromatic acids via 1,5-aryl migration. The synergistic photoredox and phosphoranyl radical chemistry can cleave strong C-O bond of carboxylic acids site-selectively. The mechanism is studied by DFT calculations and the results demonstrate that the deoxygenative arylation reaction is thermodynamically and kinetically feasible under standard conditions. The significant synthetic advantage of this method is supported by the mild reaction conditions, practical operating procedure, scalable preparation and excellent functional group compatibility. The versatility of the products of this reaction in synthetic chemistry will result in an enhanced library of small molecules for lead optimization and screening.

## Acknowledgements

We gratefully acknowledge National Natural Science Foundation of China (21702098, 21672099, 21732003 and 21703118), Shandong Provincial Natural Science Foundation (No. ZR2017MB038), “1000-Youth Talents Plan”, start-up funds from NJU for financial support.

## *Conflict of interest*

The authors declare that one patent has been been applied.

**Keywords:** carboxylic acids • ketones • aryl migration • deoxygenation • synergistic catalysis

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Layout 2:

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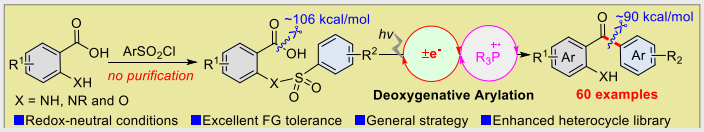


*Rehanguli Ruzi, Junyang Ma, Xiang-Ai Yuan, Wenliang Wang, Shanshan Wang, Muliang Zhang, Jie Dai, Jin Xie* and Chengjian Zhu**

***Page No. – Page No.***
**Deoxygenative Arylation of Carboxylic Acids *via* Aryl Migration**

**Unified strategy:** A general deoxygenative arylation tactic has been developed for the construction by 1,5-aryl migration of an enhanced library of unsymmetrical diaryl ketones. The photoredox catalysis and phosphoranyl radical synergism allows for precise cleavage of the stronger C-O bond and formation of a weaker C-C bond under mild reaction conditions.