

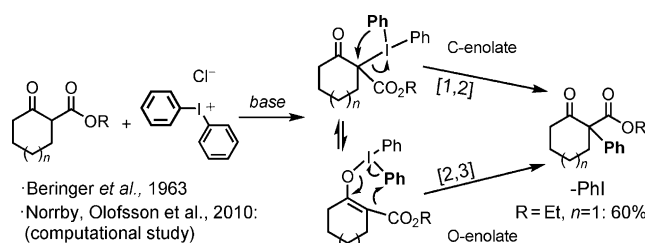
An Alternative to the Classical α -Arylation: The Transfer of an Intact 2-Iodoaryl from $\text{ArI}(\text{O}_2\text{CCF}_3)_2$ **

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Abstract: The α -arylation of carbonyl compounds is generally accomplished under basic conditions, both under metal catalysis and via aryl transfer from the diaryl λ^3 -iodanes. Here, we describe an alternative metal-free α -arylation using $\text{ArI}(\text{O}_2\text{CCF}_3)_2$ as the source of a 2-iodoaryl group. The reaction is applicable to activated ketones, such as α -cyano ketones, and works with substituted aryl iodanes. This formal C–H functionalization reaction is thought to proceed through a [3,3] rearrangement of an iodonium enolate. The final α -(2-iodoaryl)ketones are versatile synthetic building blocks.

The transfer of an aryl group to a position α to a carbonyl is an important class of C–C bond-forming reactions, popularized with the introduction of the metal-catalyzed (mainly Pd and Cu) coupling of aryl halides (or equivalent) to enolates.^[1,2] Predating these advances, the metal-free α -arylation has been in use since the 1960s, following reports by Beringer et al. on the ability of the diaryl- λ^3 -iodanes (e.g. $[\text{Ph}_2\text{I}]\text{Cl}$) to transfer an aryl ligand to an enolate (Scheme 1).^[3,4] Recent studies showed that both the C- and the O-iodonium enolate intermediates can lead to the product through a [1,2] or [2,3] shift, respectively.^[5]

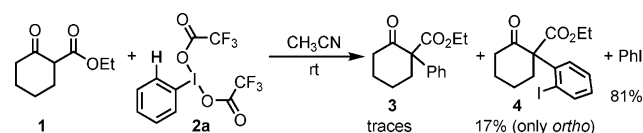
This methodology, including its asymmetric versions,^[6] has since then gained importance as complementary to the cross-coupling, in turn stimulating further research into diaryl λ^3 -iodanes.^[7,8] Despite the attractiveness of the method, one of the two aryl groups must act as a “spectator” ligand extruded in the form of ArI . The choice of such a group (e.g. mesityl) is often the key to a selective arylation using asymmetric



Scheme 1. The Beringer-type arylation of β -ketoesters using diaryliodonium salts.

diaryliodonanes.^[7b] Although the use of the monoaryl iodonium species (e.g. PhIX_2) would thus be attractive, examples of such usage are scarce.^[9] As part of our own research on hypervalent iodine reactivity,^[10] we wish to report an α -arylation protocol that employs monoaryl iodonium species, exemplified by phenyliodine bis(trifluoroacetate) (PIFA, **2a**).

We found that exposing the β -ketoester **1** to **2a** in CH_3CN led to an unexpected *ortho*-iodoaryl species **4** in 17% yield (Scheme 2); in contrast, none of **4** was obtained using $\text{PhI}(\text{OAc})_2$ or $\text{PhI}(\text{OH})(\text{OTf})$ (entries 1–3, Table 1). The



Scheme 2. The outcome of treating the β -ketoester **1** with $\text{PhI}(\text{O}_2\text{CCF}_3)_2$ (**2a**).

Table 1: Screening of conditions in the arylation of **1** with **2a** (from Scheme 2).^[a]

Entry	Solvent	PhIX_2	Additive ^[b]	4 [%] ^[c]
1	CH_3CN	2a	–	17
2	CH_3CN	$\text{PhI}(\text{OAc})_2$	–	–
3	CH_3CN	$\text{PhI}(\text{OH})(\text{OTf})$	–	–
4	CH_2Cl_2	2a	–	14
5	$\text{CF}_3\text{CO}_2\text{H}$	2a	–	34
6	$\text{CH}_3\text{CN}-\text{CF}_3\text{CO}_2\text{H}$	2a	–	48
7	$\text{CH}_3\text{CN}-\text{CF}_3\text{CO}_2\text{H}$	2a	$(\text{CF}_3\text{CO})_2\text{O}$	57^[d]
8	$\text{CH}_3\text{CN}-\text{CF}_3\text{CO}_2\text{H}$	2a	$(\text{CF}_3\text{SO}_2)_2\text{O}$	< 5
9	$\text{CH}_3\text{CN}-\text{CF}_3\text{CO}_2\text{H}$	2a	H_2O	< 5
10	$\text{CH}_3\text{CN}-\text{CF}_3\text{CO}_2\text{H}$	$\text{PhI}(\text{OAc})_2$	$(\text{CF}_3\text{CO})_2\text{O}$	23
11	$\text{CH}_3\text{CN}-\text{CF}_3\text{CO}_2\text{H}$	$\text{PhI}(\text{OH})(\text{OTf})$	$(\text{CF}_3\text{CO})_2\text{O}$	26
12	$\text{CH}_3\text{CN}-\text{CF}_3\text{CO}_2\text{H}$	PhIO	$(\text{CF}_3\text{CO})_2\text{O}$	52

[a] Using **1** (1.0 mmol) and **2a** (1.3 mmol) in 4 mL of solvent for 4 h at rt; [b] 1.5 equiv; [c] GC yield corrected versus the internal standard $\text{C}_6\text{H}_{11}\text{CN}$; [d] Yield of the isolated product.

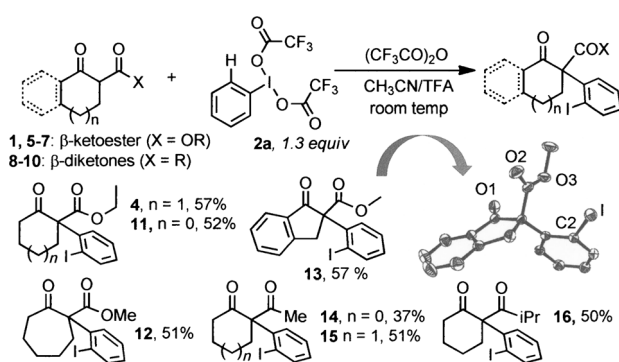
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formation of **4** was found to be solvent-dependent (entries 1 and 4–6), with a 48% yield achieved using a 1:1 CH₃CN/CF₃CO₂H mixture. The addition of the trifluoroacetic anhydride (1.5 equiv) led to a 57% yield of **4** after 2 h at room temperature; other additives proved detrimental (entries 7–9). Under the new conditions, the use of other hypervalent iodine reagents was now possible (entries 10–12), likely through the in situ formation of **2a**. Oxidative degradation of **1** accounts for the reaction mass balance.

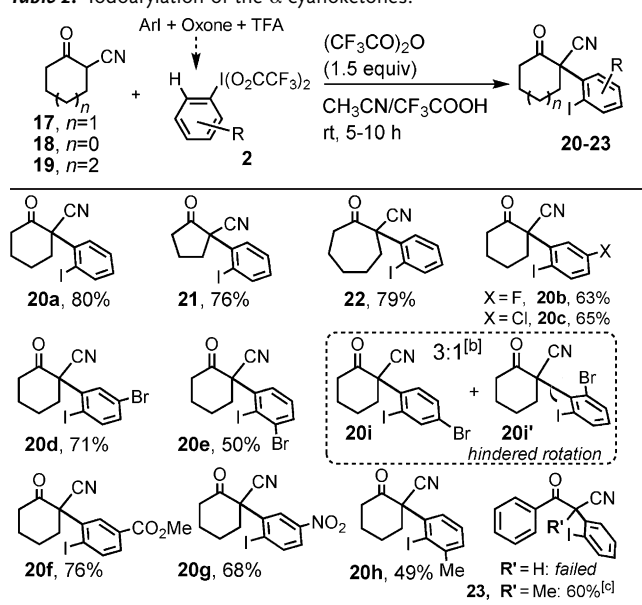
To probe the reaction scope, the cyclic β -ketoesters **5–7** were transformed into products **11–13** in 2 h at room temperature (Scheme 3, X-Ray structure of **13** shown). Similarly, α -(2-iodoaryl)-diketones **14–16** were synthesized from the corresponding β -diketones **8–10**.



Scheme 3. The α -iodoarylation of β -dicarbonyl compounds using PIFA.

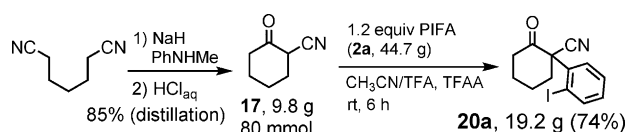
Particularly efficient was the arylation of α -cyanoketones (Table 2). Thus, the cyclic substrates **17–19** underwent a smooth reaction with PIFA to give a 76–80% yield of **20a**, **21**, and **22** after 6–8 h.^[11] Next, **17** was exposed to eight

Table 2: Iodoarylation of the α -cyanoketones.^[a]



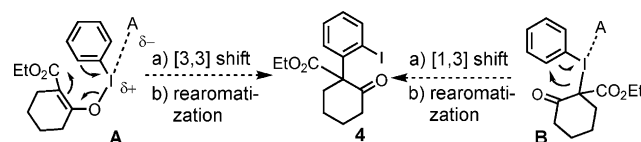
[a] 1.3:1 ratio of **2**/**17**. Using **17** (1 mmol) in CH₃CN/CF₃COOH (1:1, 4 mL). [b] From *m*-Br-C₆H₄I(O₂CCF₃)₂ (**2i**). [c] At 60 °C for 48 h.

additional ArI(O₂CCF₃)₂ reagents (**2b–2i**) prepared by a method developed by Zhdankin et al.^[12] The use of the halo derivatives **2b–2e** led to the formation of the dihaloaryl cyanoketones **20b** (63%), **20c** (65%), **20d** (71%), and **20e** (50%), with **20e** featuring the iodine flanked by a C–Br and a C–C bonds. A 76% yield of the carboxy-substituted **20f** was achieved and the *p*-NO₂ derivative **20g** was isolated in 68% yield. The transfer of a 2-iodo-3-methylphenyl group took place with a 49% yield (product **20h**). The coupling at the two *ortho* CH sites of the *meta*-Br iodane **2i** took place in a 3:1 ratio, with the minor isomer **20i'** (17%) observed as two rotamers (70:30) at –20 °C (see the Supporting Information). Interestingly, although the secondary cyanoketones, including benzoylacetonitrile, proved unsuitable, the 2-benzoylpropionitrile, which only differs by a 2-methyl group, gave the expected **23** in 60% yield. Finally, the protocol was used to prepare a 19 g batch of **20a** (74%, Scheme 4).^[13]



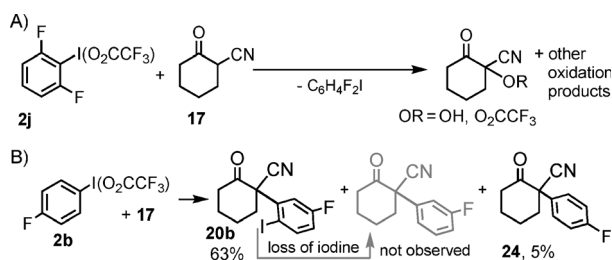
Scheme 4. Gram-scale preparation of **20a**; α -arylation conditions as in Table 2.

Although a mechanistic study is currently underway, this formal C–H alkylation may arise from a [3,3] shift of an O-enolate **A** (Scheme 5) as seen in a related sulfoxide-mediated α -arylation.^[14] Alternatively, the selectivity could be explained by a [1,3] shift of a C-enolate **B**.



Scheme 5. Two possible enolate rearrangement paths leading to **4**.

A priori, the [1,3] shift appears less likely. Indeed, while the C-enolates are intermediates in the formation of the iodonium ylides^[15] and can be isolated,^[16] the existence (or intermediacy) of the quaternary analogues (such as **B** in Scheme 5) is less frequent.^[5b] Furthermore, heating the isolated C-enolates typically leads to the formation of the α -C–O (e.g. C–OTs) bond.^[16] In our hands, the isolated phenyliodonium ylide PhCOC(=I)PhCN, expected to give a C-enolate upon protonation,^[15c] failed to undergo the aryl transfer under the reaction conditions. Thus, we favor a [3,3] shift of an iodonium O-enolate (**A**, Scheme 5), akin the iodonio-Claisen rearrangement introduced by Ochiai et al. in the 1990s.^[17,18] Despite our efforts, reaction intermediates have so far proven elusive, possibly due to the rearrangement proceeding faster than the I–O-enolate formation.^[19] Not even the *o,o*-disubstituted **2j** allowed for the trapping of the I-enolate, leading instead to non-arylate oxidation processes (Scheme 6A). It should also be noted that the iodine-free

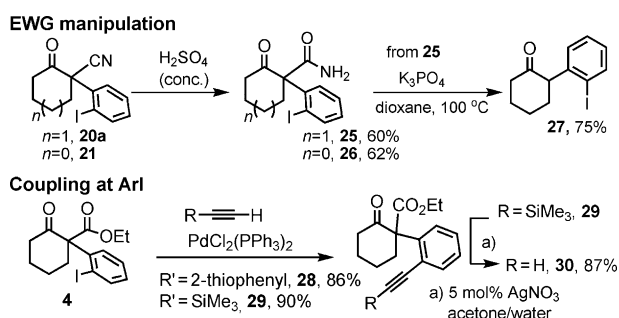


Scheme 6. Additional observations in the arylation of **17**.

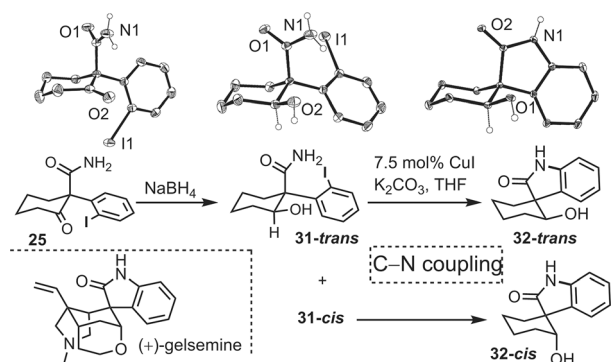
species **24** (5%), isolated during the synthesis of **20b**, proved to be the *para*-fluoro regioisomer, rather than the initially assumed *meta* (Scheme 6B); the steps leading to **24** remain to be investigated.

The cyanoketones **20a** and **21** were readily converted to the amides **25** and **26**. Although PIFA was unsuitable for the arylation of the parent cyclohexanone, the arylketone **27** could, nevertheless, be obtained through the decarboxylation of **25** (Scheme 7, top). The substrates also underwent the Suzuki (see the Supporting Information) and Sonogashira coupling reaction (Scheme 7, bottom, products **28–30**).

The reduction of **25** led to the alcohol **31** as a 4:1 *trans/cis* mixture (Scheme 8), with the solid state structures of both **25** and **31-trans** showing an equatorial *o*-iodophenyl group.^[20] Preliminary tests showed that **31** can be converted to the hydroxy-spiroindole **32** (X-ray structure shown for *trans*) using a Cu-catalyzed C–N coupling,^[21] with **32-cis** representing the spiroindole portion of Gelsemine, a synthetically interesting natural product target (Scheme 8).^[22,23]



Scheme 7. Functional group manipulation in the α -(2-iodoaryl) derivatives.



Scheme 8. Some simple transformations of the ketoamide **25**.

In summary, the $\text{ArI}(\text{O}_2\text{CCF}_3)_2$ reagents have been used in the α -arylation of β -dicarbonyls and α -cyanoketones. The aryl transfer takes place with retention of the iodide *ortho* to the newly formed C–C bond. The method is complementary to metal-catalyzed arylations, and could overcome the issues of the aryl loss associated with the use of diaryliodonium salts. In a more general sense, the concept of a reversible formation of an iodonium-based Claisen precursor, shown here with O-enolates, might open the door to the development of a range of new synthetic methods.

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