An Alternative to the Classical α-Arylation: the Transfer of an Intact 2-Iodoaryl from ArI(O2CCF3)2.
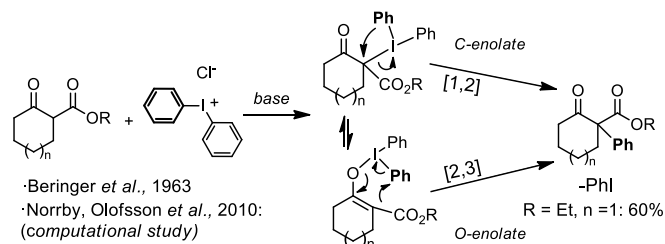
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((Dedication----optional))

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 ArI(O2CCF3)2 as the source of a 2-iodoaryl group. The reaction is applicable to activated ketones, such as α-cyanoketones and works with substituted aryliodanes. This formal CH functionalization reaction is thought to proceed via [3,3] rearrangement of an iodonium enolate. The final α-(2-iodoaryl)ketones are versatile synthetic building blocks.*
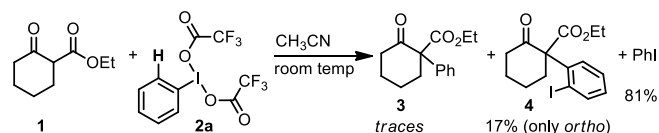
The transfer of an aryl group to a position α to a carbonyl is an important class of the C-C bond-forming reactions, popularized with the introduction of the metal-catalysed (mainly Pd and Cu) coupling of the aryl halides (or equivalent) to enolates.[1,2] Predating these advances, the metal-free α-arylation has been in use since the 1960's, following reports by Beringer *et al.* on the ability of the diaryl-λ^3-iodanes (*e.g.* [Ph2I]Cl) to transfer an aryl ligand to an enolate (Scheme 1).[3,4] Recent studies revealed that both the *C*- and the *O*-iodonium enolate intermediates can lead to the product *via* a [1,2] or [2,3] shifts, respectively.[5]

This methodology, including its asymmetric versions,[6] has since gained importance as complementary to the cross-coupling, in turn stimulated further research into diaryl λ3-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 group (*e.g.* mesityl) is often the key to a selective arylation using asymmetric diaryliodoanes.[7b] Although the use of the mono-aryl iodonium species (*i.e.* PhIX2) 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 mono-aryl iodonium species, exemplified by phenyliodine bis(trifluoroacetate) (PIFA, **2a**).

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

We found that exposing the β-ketoester **1** to **2a** in CH3CN led to an unexpected *ortho*-iodoaryl species **4** in 17% yield (Scheme 2); in contrast, none of **4** was obtained using PhI(OAc)2 or PhI(OH)(OTs) (entries 1-3, Table 1). The formation of **4** was found to be solvent-dependent (entries 1, 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 2h at room temp.; other additives proved detrimental (entries 7-9). Under the new conditions, the use of other hypervalent iodine reagent was now possible (entries 10-12), likely *via* the *in situ* formation of **2a**. Oxidative degradation of **1** accounts for the reaction mass balance.

**Scheme 2.** The outcome of treating the β-ketoester **1** with PhI(O2CCF3)2, **2a**.

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Table 1. Screening of conditions in the arylation of **1** with **2a** (from Scheme 3).[a]

Entry	Solvent	PhIX2	Additive[b]	%4[c]
1	CH3CN	**2a**	-	17
2	CH3CN	PhI(OAc)2	-	--
3	CH3CN	PhI(OH)(OTs)	-	--
4	CH2Cl2	**2a**	-	14
5	CF3CO2H	**2a**	-	34
6	CH3CN-CF3CO2H	**2a**	-	48
7	CH3CN-CF3CO2H	**2a**	(CF3CO)2O	**57**[d]
8	CH3CN-CF3CO2H	**2a**	(CF3SO2)2O	<5
9	CH3CN-CF3CO2H	**2a**	H2O	<5
10	CH3CN-CF3CO2H	PhI(OAc)2	(CF3CO)2O	23
11	CH3CN-CF3CO2H	PhI(OH)(OTs)	(CF3CO)2O	26
12	CH3CN-CF3CO2H	PhIO	(CF3CO)2O	**52**

[a] Using 1.0 mmol **1**, 1.3 mmol **2a** in 4 mL of solvent for 4h at rt; [b] 1.5 equiv; [c] GC yield corrected *vs* int. C6H11CN; [d] % Isolated yield.

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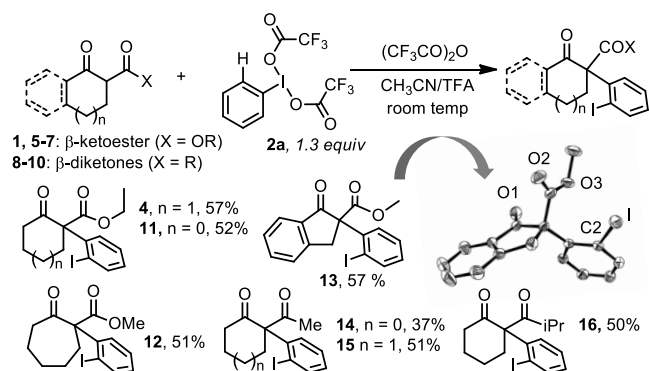
**Scheme 3.** The α-iodoarylation of β-dicarbonyl compounds using PIFA.

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 6-8h.[11] Next, **17** was exposed to eight additional ArI(O$_2$CCF$_3$) 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 derivatives **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, while the *p*-NO$_2$ derivative **20g** was isolated in a 68% yield. The transfer of a 2-iodo-3-Me-phenyl group took place with a 49% yield (prod. **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 (Supp. Info). Interestingly, while secondary cyanoketones, including benzoylacetonitrile, proved unsuitable, the 2-benzoylpropionitrile, which only differs by a 2-Me group, gave the expected **23** in 60% yields. Finally, the protocol was used to prepare a 19 g batch of **20a** (74%, Scheme 4).[13]

**Table 2.** Iodoarylation of the α-cyanoketones.[a]
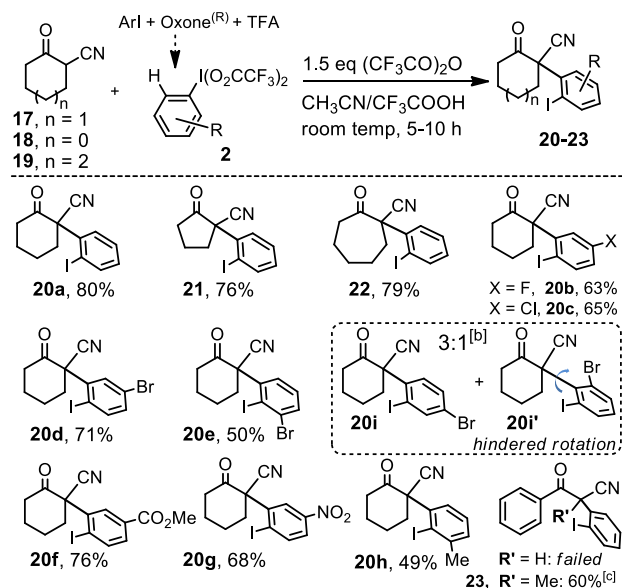
[a] 1.3:1 ratio of **2**:**17**. Using 1 mmol **17** in CH$_3$CN/CF$_3$COOH (1:1, 4 mL).
[b] From *m*-Br-C$_6$H$_4$I(O$_2$CCF$_3$), **2i**. [c] at 60 °C for 48 h.
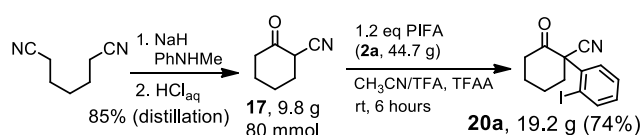
Scheme 4. Gram-scale preparation of **20a**; α-arylation conditions as in Table 2.

Although a mechanistic study is currently underway, this formal CH alkylation may arise *via* 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**.
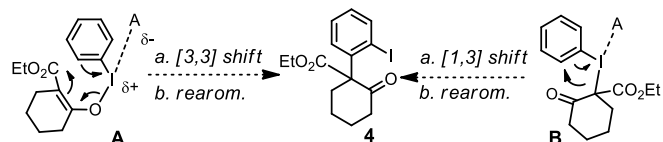
Scheme 5. Two of the possible enolate rearrangement paths leading to **4**.

A priori, the [1,3] shift appears less likely. Indeed, while the *C*-enolates are intermediates in the formation of the iodonium ylides[15,16], the quaternary analogs (such as **B** in Scheme 3) are 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 phenyliodoodium ylide PhCOC(=IPh)CN, expected to give a C-enolate upon protonation,[15c] failed to undergo the aryl transfer under the reaction conditions. Thus, we favour a [3,3] shift of an iodonium *O*-enolate (Scheme 3), akin the *iodonio-Claisen rearrangement* introduced by Ochiai *et al.* in 1990's.[17,18] Despite our efforts, such 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-arylative oxidation processes (Scheme 6A). We note that the iodine-free 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.
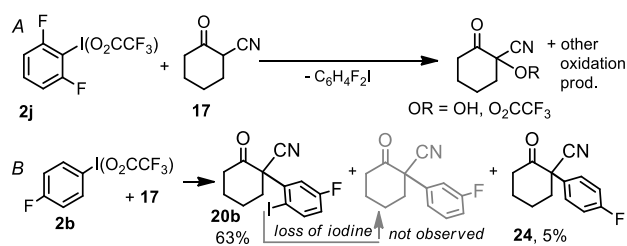

Scheme 6. Additional observations in the arylation of **17**.

The cyanoketones **20a** and **21** were readily converted to the amides **25** and **26**. While PIFA was unsuitable for the arylation of parent cyclohexanone, the arylketone **27** could, nevertheless, be obtained *via* the decarboxylation of **25** (Scheme 7, top). The substrates also underwent the Suzuki (Supp. Info) and Sonogashira coupling reaction (Scheme 7, bottom, prod. **28-30**).
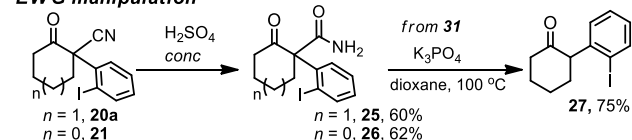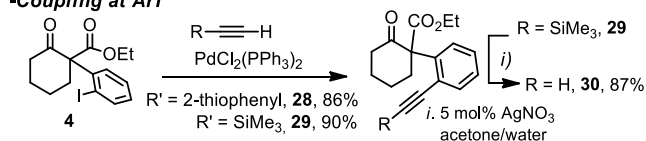
**Scheme 7.** Functional group manipulation in the α-(2-iodoaryl) derivatives.

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 equatorial *o*-iodophenyl group.[20] Preliminary tests showed that **31** can be converted to the hydroxy-spiroxindole **32** (X-Ray structure shown for ***trans***) using Cu-catalyzed *C-N* coupling,[21] with **32-*cis*** representing the spiroxindole portion of Gelsemine, a synthetically interesting natural product target (Scheme 8).[22,23]

In summary, the ArI(O₂CCF₃)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 new method is complementary to the metal-catalyzed arylation, and could overcome the issues of the aryl loss associated with the use of the diaryliodonium salts. In a more general sense, the concept of a *reversible* formation of iodonium-based Claisen precursor, shown here with *O*-enolates, might open the door to the development of a range of new synthetic methods.
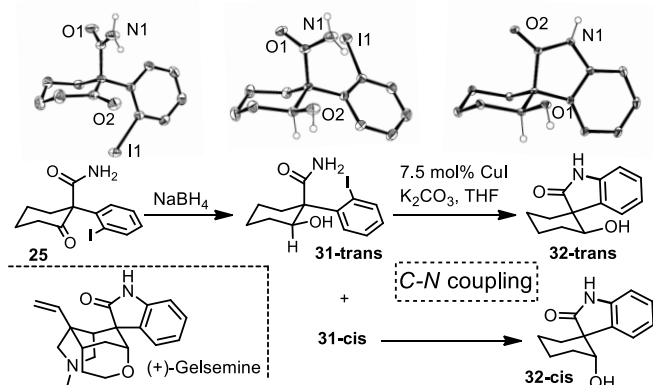
**Scheme 8.** Some simple transformations of the ketoamide **25**.

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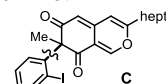
[19] Only the PhI(O₂CCF₃)₂ and the coupling product detected by NMR.

[20] CCDC 1005725 -1005728 contains the supplementary crystallographic data for this paper.

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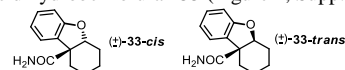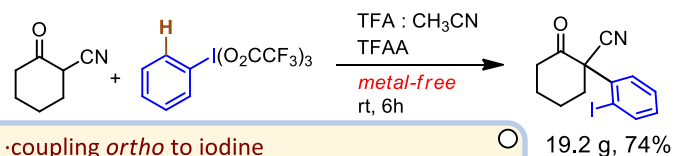
An Alternative to the Classical α-Arylation: the Transfer of an Intact 2-Iodoaryl from $ArI(O_2CCF_3)_2$

·coupling *ortho* to iodine
·likely *Iodonio-Claisen* mechanism
·complementary to metal-catalyzed arylation

19.2 g, 74%

Activated ketone derivatives, including β-dicarbonyl and α-cyanoketones, react with $ArI(O_2CCF_3)_2$ reagents to give an α-arylated product with the iodine atom retained *ortho* to the new C-C bond. The reaction takes place under acidic conditions. This formal CH functionalization reaction is thought to proceed via [3,3] rearrangement of an iodonium enolate. The final α-(2-iodoaryl)ketones are versatile synthetic building blocks.