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para-Selective benzylation of aryl iodides via the *in situ* preparation of $ArIF_2$: a hypervalent iodine-guided electrophilic substitution

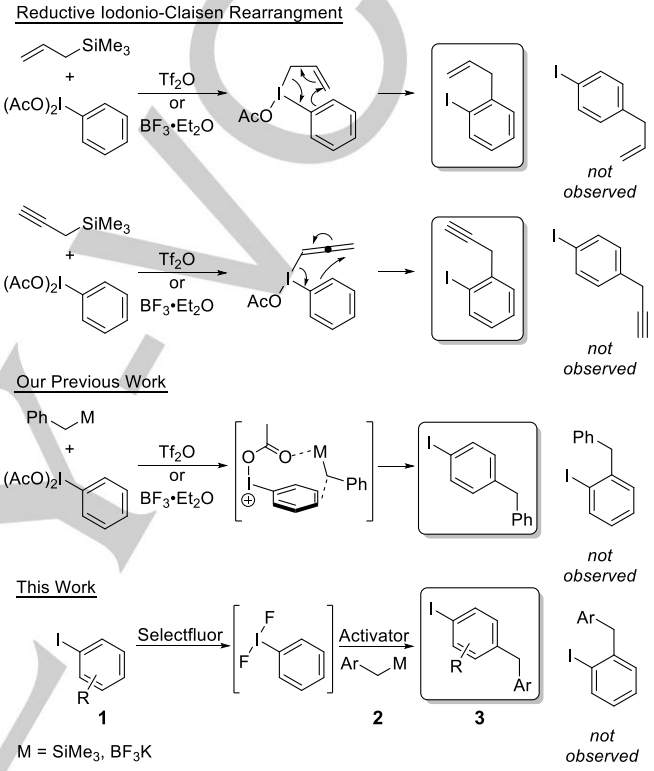
Jennifer Noorollah, Haram Im, Fatima Siddiqi, Nirvanie Singh, Nicholas R. Spatola, Azka Chaudhry, Taro J. Jones, and I. F. Dempsey Hyatt*

Abstract: Hypervalent iodine-guided electrophilic substitution (HIGES) was previously described for the *para*-selective benzylation of aryl-λ^3-iodane diacetates. One drawback of the method was the synthesis and isolation of hypervalent iodine starting materials. An improvement is reported herein in which the benzylation product can be afforded from an aryl iodide via an *in situ* oxidation. Hypervalent iodine's metal-like properties have been demonstrated in the transmetallation of metalloid groups such as silicon and boron and are compatible with multiple Lewis acid activators. A desirable facet of both the previous method and the newly reported procedure is that the iodine atom is incorporated into the product thus providing greater atom economy and a valuable functional group handle for further transformations. The following communication contributes to other articles in the field that imply there is a general HIGES mechanism yet to be fully understood.

The recent and rapid development of hypervalent iodine-guided electrophilic substitutions (Scheme 1) began from a series of papers by Khatri and Zhu in which they rediscovered and evaluated of the reductive iodonio-Claisen rearrangement (RICR).[1–3] RICR-type reactions have undergone review by Shafir and also in a section of a review on C-C bond forming reactions by Hyatt *et al*. in 2019.[4–6]

While allylic and benzylic groups often have similarities, substituting the allyl metalloid with a benzyl metalloid in the RICR would seem to theoretical fail due to their different π-systems and the theorized Claisen-type rearrangement.[7–12] However, when the allyl metalloid was replaced by a benzyl metalloid under the RICR reaction conditions, different regioselectivity was discovered; a *para*-selective substitution of the aryl iodine as opposed the RICR's *ortho* selectivity.[13,14]

The C-C bond forming methodology described herein hints at, and provides increasing evidence for, a new class of reactions involving HIGES. Elegant synthetic pathways incorporating HIGES have resulted in tetraasubstituted benzenes via four C-C bond forming reactions from iodobenzene,[13] the total synthesis of clopidogrel,[3] the total synthesis of broussin,[2] the synthesis of various heterocycles,[1] and the selective bromination of arenes.[15]



Scheme 1. Examples of the Reductive Iodonio-Claisen Rearrangement compared to previous work and the newly devised in-situ HIGES methodology.

DFT-calculations investigating the mechanistic aspects of RICR propargylation found an acid-activated hypervalent iodine intermediates was required.[16,17] Calculations have also shown that transition state energies are easier to achieve with $PhI(OAc)_2{\bullet}BF_3$ as opposed to $PhI(OAc)_2$ alone, a result congruent with experimental yields.[18] While the acid-activated hypervalent iodine intermediates are key to the reactivity of the RICR and the *para*-selective benzylation, the fundamental differences of how each π-system behaves varies the regioselectivity of products. Mechanisms for *para*-selective benzylation, both involving HIGES, have thus far withstood scrutiny by calculation and control experiments (Scheme 2).[14,19] One such critical control experiment revealed that the mechanism *cannot* be intermolecular electrophilic substitution similar to Friedel-Crafts reactivity; it must occur through a yet unknown intramolecular reaction or iodine coordination.

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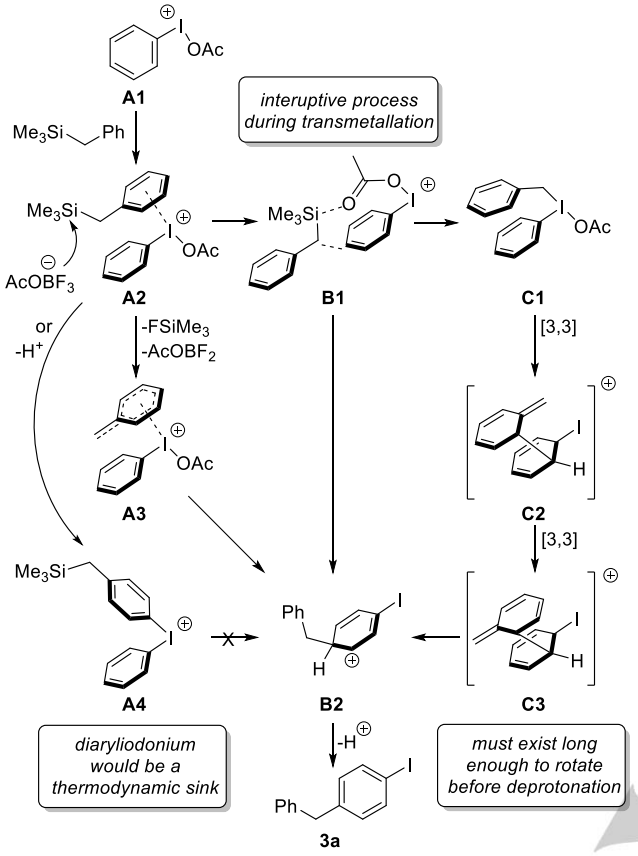


Scheme 2. Current mechanistic proposals of the HIGES *para*-selective benzylation

Three proposed mechanistic routes are shown in Scheme 2, with one being unlikely due to the high energy barrier associated with intermediates **C2** and **C3**.[20] The transmetallation of—or at least the interaction between—hypervalent iodine intermediates and metalloid groups is key to theorizing a mechanism for the benzylation shown in Scheme 2. From **A1**, if the benzylsilane interacts to coordinate to the HVI and form complex **A2**, the mechanistic path relies on the weak nucleophilicity of the $[AcOBF_3]^-$ anion to remove the metalloid group. Another issue is that, upon deprotonation, intermediate **A4** could result in a diaryl-λ^3-iodane which was shown not to produce benzylation products.[20] The mechanism resulting from the formation of intermediate **B1** relies on a large ring that occurs during a speculated transmetallation process. Note that the work herein does not use acetate anions and that the fluoride of $ArIF_2$ would be involved with the transmetallation step. Our group mentioned these differences in ring size between using an acetate and a fluoride in our previous report and it was determined that the fluoride could potentially still form the ring due to the negligible energy difference between a 8- and 10-membered ring.[14] The key conceptual leap that intermediate **B1** relies on is the positioning of the benzyl carbon as it rests over the *para* position of the aryl iodonium and causes an interruption in the transmetallation process that subsequently leads to product, **B2**.

The use of Selectfluor as a mild oxidant for the formation of $ArIF_2$ has been demonstrated in several articles,[21–23] yet in our lab the isolation of the $ArIF_2$ compounds encountered difficulty and impurities caused decomposition. The inability to isolate pure $ArIF_2$ compounds led us to develop an *in situ* process that could bypass isolation steps. Over 46 optimization conditions were explored and the most relevant ones are shown in Table 1. Several Lewis-acids and solvent systems were found to be tolerated. Another interesting fact is that the reactions can be performed at room temperature with moderate success.

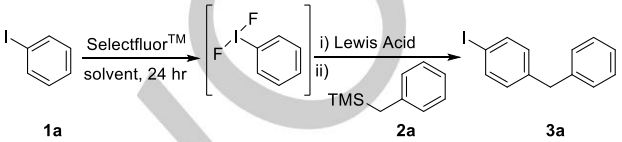


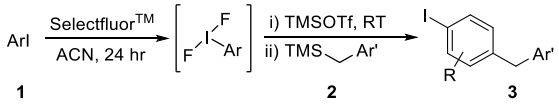
Table 1. Reaction optimization.[a]

Entry	Lewis Acid	Solvent	Temp.	Selectfluor	Yield
1	TMSOTf (2 equiv.)	ACN	-40 ˚C	2.6 equiv.	84%
2	TMSOTf (1 equiv.)	ACN	-40 ˚C	2.6 equiv.	48%
3	TMSOTf (1 equiv.)	ACN	-40 ˚C	1.3 equiv.	20%
4	TMSOTf (2 equiv.)	ACN	0 ˚C	1.1 equiv.	15%
5	TMSOTf (1 equiv.)	ACN	0 ˚C	2.6 equiv.	24%
6	Tf_2O (2 equiv.)	ACN	0 ˚C	2.6 equiv.	7%
7	Tf_2O (2 equiv.)	ACN	-40 ˚C	2.6 equiv.	13%
8	Tf_2O (0.5 equiv.)	ACN	-40 ˚C	2.6 equiv.	24%
9	Tf_2O (1 equiv.)	ACN	0 ˚C	2.6 equiv.	18%
10	$BF_3{\cdot}Et_2O$ (2 equiv.)	ACN	0 ˚C	2.6 equiv.	10%
11	$BF_3{\cdot}Et_2O$ (2 equiv.)	ACN	-40 ˚C	2.6 equiv.	10%
12	$BF_3{\cdot}Et_2O$ (1 equiv.)	ACN	-40 ˚C	1.3 equiv.	46%
13	TMSOTf (2 equiv.)	ACN	RT	2.6 equiv.	52%
14	TMSOTf (2 equiv.)	THF	0 ˚C	2.6 equiv.	0%
15	TMSOTf (2 equiv.)	$MeNO_2$	-40 ˚C	2.6 equiv.	53%
16	TMSOTf (2 equiv.)	TFE	-40 ˚C	2.6 equiv.	50%
17	TMSOTf (2 equiv.)	TFE	RT	2.6 equiv.	34%

[a] Iodobenzene (1.0 equiv) and Selectfluor™ (2.6 equiv) were dissolved in dry solvent and stirred for 24 h under nitrogen at room temperature. Varying amounts of Lewis-acid were then added to the reaction mixture followed by benzyltrimethylsilane (1.0 equiv).

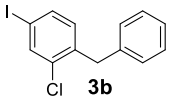
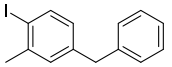
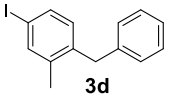
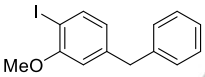
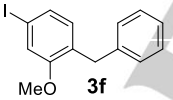
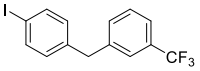
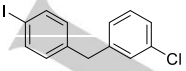
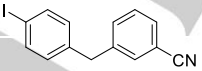
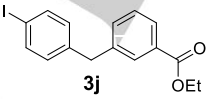
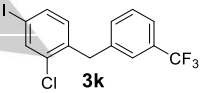
The substrate scope for the *in situ* benzylation of aryl iodides is shown in Table 2. Evidence seemed to imply that yields were dependent upon whether the groups on either substrate were electron-donating or electron-withdrawing. It was difficult to find a general method that worked with a range of substrates. The type of Lewis acid, the equivalents of Lewis acid, the temperature at which the Lewis acid was added, the time

allowed for the initial $ArIF_2$ formation, and solvent were different for each substrate attempted. We conclude that the dominating aspects of electron demand in the reaction largely govern the optimal reaction conditions for each substrate. With this in mind, we decided to run the substrate scope at room temperature to demonstrate the robustness of the method, with TMSOTF as the Lewis activator to better match our previous method in comparison, and acetonitrile for the solubility of the Selectfluor™.



1 2 3

Table 2. Substrate scope.[a]

Entry	ArI	Ar'	Product	Yield
1	1-chloro-3-iodobenzene (**1c**)	Ph (**2a**)	 **3b**	14%
2	2-iodotoluene (**1e**)	Ph (**2a**)	 **3c**	82%[b]
3	3-iodotoluene (**1f**)	Ph (**2a**)	 **3d**	31%
4	2-iodoanisole (**1h**)	Ph (**2a**)	 **3e**	14% 22%[c]
5	3-iodoanisole (**1i**)	Ph (**2a**)	 **3f**	8%[c]
6	Iodobenzene (**1a**)	3-CF_3 (**2b**)	 **3g**	19%
7	Iodobenzene (**1a**)	3-Cl (**2c**)	 **3h**	23%
8	Iodobenzene (**1a**)	3-CN (**2d**)	 **3i**	22%
9	Iodobenzene (**1a**)	3-COOEt (**2e**)	 **3j**	33%
10	1-chloro-3-iodobenzene (**1c**)	3-CF_3 (**2b**)	 **3k**	26%

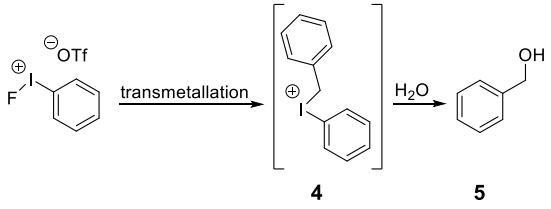
[a] Aryl iodide (1.0 equiv) and Selectfluor™ (2.6 equiv) were dissolved in dry acetonitrile and stirred for 24 h under nitrogen at room temperature. TMSOTf (2.0 equiv) was then added to the reaction mixture followed by a benzyltrimethylsilane derivative (1.0 equiv) at room temperature. [b] TMSOTf (1.0 equiv). [c] NMR yield.

The yields shown in Table 2 are higher than, or the similar to, the overall yields associated with our previous method. Since there is no need to oxidize the aryl iodide and isolate the aryl-λ^3-iodane diacetate, there is also a considerable amount of waste and time removed from the method. For example, the yield of synthesizing *m*-tolyl-λ^3-iodane diacetate was 80%, and our previous reported method afforded a yield of 45% for the same product (**3d**). The overall yield of the previous method was 36% while the new method afforded a similar 31% yield (Table 2, Entry 3). Other reactions such as *o*-tolyl-λ^3-iodane diacetate to the benzylated product, 3c, show a substantial increase in yield with the new method; a 42% overall yield for the previous method as opposed to the 82% yield (Table 2, Entry 2) of the in situ method described herein.

The difficulty in finding a suitable general procedure is also demonstrated by Entry 2 in that the reaction only required one equivalent of TMSOTf to produce a high yielding benzylation product. Within the substrate scope, varying amounts of TMSOTf were used and the highest yields are reported. The explanation to the varying optimal reaction conditions stems from the electron demands of the reaction. Entry 10 of Table 2 shows a reaction in which the methodology is extended to encompass mixed substituents on the aryl iodide as well as the benzyl-TMS derivatives.

Previous methods that isolated the aryl-λ^3-iodane diacetate precursor were capable of benzylating 2-iodothiophene, 2-iodobiphenyl, and 2-iodonapthalene while the *in situ* method described herein produced only trace amounts of benzylation. The poor benzylation of these substrates with the *in situ* method could be related to side reactions with Selectfluor or the Selectfluor byproduct, or from the reaction mechanism involving fluoride rather than acetate.

Electron-withdrawing groups on the aryl iodide that failed to achieve benzylation include 2-iodobenzoic acid, 2-iodohippuric acid, 2-iodonitrobenzene, 3-iodonitrobenzene, 3-iodobenzonitrile, 2-iodobenzotrifluoride, 3-iodobenzotrifluoride, 1-bromo-3-iodobenzene, and ethyl 3-iodobenzoate. The failure to benzylate the aryl iodide containing electron-withdrawing groups resulted in the benzyl-TMS converting to benzyl alcohol (**5**); a fact that provides evidence towards a complete transmetallation (**4**, Scheme 3) instead of our hypothesized interrupted transmetallation (**B1,** Scheme 2).



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Scheme 3. Possible mechanism to explain benzyl alcohol formation

Electron-donating groups on the benzyl-TMS derivatives failed to create benzylated aryl iodide products. The specific benzyl-TMS substituents that failed included: 4-methyl, 2,4-dimethyl, and 3-methoxy. The major product when the benzylation failed was the conversion of the benzyl-TMS derivatives to their corresponding benzyl alcohol (i.e. 4-methylbenzyl-TMS to *p*-tolylmethanol, and 3-methoxybenzyl-TMS to 3-methoxyphenylmethanol).

From the substrate scope, the optimal combination appears to be when electron-donating groups are on the aryl iodide and when electron-withdrawing groups are on the benzyl-TMS derivative. A hypothesized benzyl-aryl-iodonium (**4**) is a possible explanation for the formation of benzyl alcohols. The yields reported are higher than the previously reported yields over two-steps. Cross reactions (Entry 10 of Table 2) demonstrate the potential of the methodology to be incorporated into total synthesis targets.

Experimental Section

General procedure for the synthesis of benzylsilanes: Procedure is in accordance with that reported by Shafir *et al.*[20] Iodine(I) reagent (1.0 equiv) and $Ni(acac)_2$ (0.05 equiv) was dissolved in dry THF (25 mL) and stirred for a period of 5 min under nitrogen at room temperature. The reaction is cooled to 0 °C and a solution of Me_3SiCH_2MgCl in THF (1.0 equiv) was added to reaction mixture and was allowed to stir for 2 h. The reaction is then quenched with saturated NH_4Cl, filtered through Celite, and extracted with Et_2O. The combined organic layers were dried over anhydrous Na_2SO_4 and then concentrated in vacuo. The crude reaction mixtures were purified via silica gel flash column chromatography to give the desired benzyltrimethylsilane products.

General procedure for *para* benzylation: Iodine(I) reagent (1.0 equiv) and Selectfluor™ (2.6 equiv) was dissolved in dry acetonitrile (5 mL) and stirred for a period of 24 h under nitrogen at room temperature. At this point, trimethylsilyl trifluoromethanesulfonate (2.0 equiv) and benzyltrimethylsilane derivative (1.0 equiv) was added subsequently and was allowed to stir for 1 h. To the crude reaction, water was added and extracted with hexane. The combined organic layers were dried over anhydrous Na_2SO_4 and then concentrated in vacuo. The crude reaction mixtures were purified by PREP-TLC to give the desired Csp^2–Csp^3 products.

Acknowledgements

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Keywords: hypervalent iodine • C-C bond formation • HIGES • benzylation • Selectfluor

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Entry for the Table of Contents

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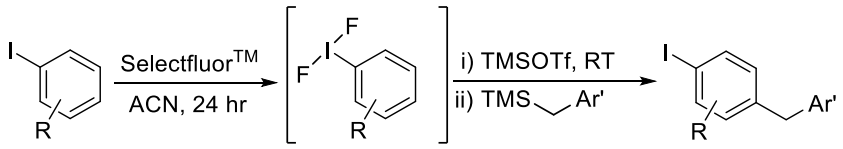

Delving into the HIGES: Hypervalent iodine-guided electrophilic substitution (HIGES) was previously described for the *para*-selective benzylation of aryl-λ^3-iodane diacetates. To make our methodology more accessible to the synthetic community, a procedure was developed in which the benzylation product can be afforded from an aryl iodide via an *in situ* oxidation with an overall higher yield for most substrates.

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***para*-Selective benzylation of aryl iodides via the *in situ* preparation of hypervalent iodine: a hypervalent iodine-guided electrophilic substitution**