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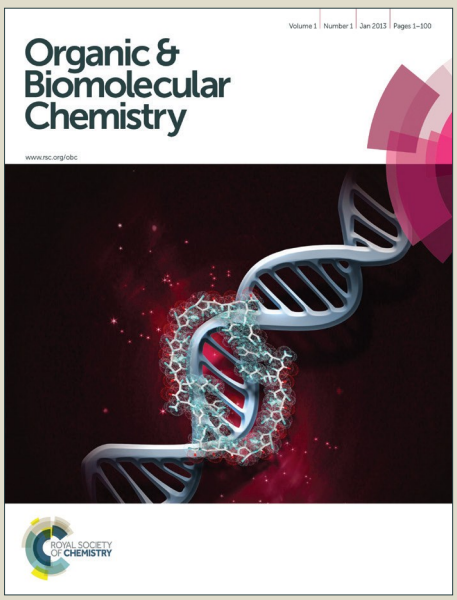

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ARTICLE

Metal-Free Cascade Cyclization of Alkenes toward Polyfluorinated Oxindoles

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A simple AIBN-mediated cyclization reaction of activated alkenes toward perfluorinated was developed. In the presence of readily available AIBN, *N*-arylacrylamide and perfluoroalkyl iodides underwent perfluorination reaction to give perfluoroinated oxindoles in good to excellent yields under metal-free conditions.

The incorporation of fluorinated substituents into potential pharmaceuticals and agrochemical agents has recently attracted considerable attention from synthetic chemists.[1] Oxindoles are common structural motifs in pharmaceutical agents and natural products,[2] and the incorporation of fluorinated groups into these scaffolds by using Togni reagent,[3] $TMSCF_3$,[4] or CF_3SO_2Na[5] has attracted increasing interest. But successes have mainly been limited to the incorporation of the CF_3 moiety. Therefore, increasing the diversity of available methods for incorporation of other fluorinated groups (e.g., perfluorinated groups) into the oxindole scaffold is in high demand. It was well-known that perfluorinated radicals can be generated in many ways,[6] and photosensitized approaches to the generation of fluorinated radicals from inexpensive R_fI have currently received much attention due to the excellent reductive ability of a photocatalyst in the excited state under mild conditions.[7] However, these approaches suffer from an apparent drawback that precious Ru/Ir photocatalysts were required for high reaction efficiency. Alternatively, treatment of R_fI with AIBN (azodiisobutyronitrile) was a viable strategy to generate perfluorinated radicals, which has been used for the incorporation of both R_f and I functional groups into an alkene or alkyne.[8] Significant progress has been achieved in the construction of oxindoles via radical difunctionalization of *N*-arylacrylamides in the past years.[9] Consistent with these findings, we envisage that incorporation of perfluorinated groups into oxindole *via* cascade radical addition/C(sp^2)-H cyclization initiated by AIBN is possible. However, there are, to our best knowledge, only two reported examples for this purpose to date.[10] Moreover, these

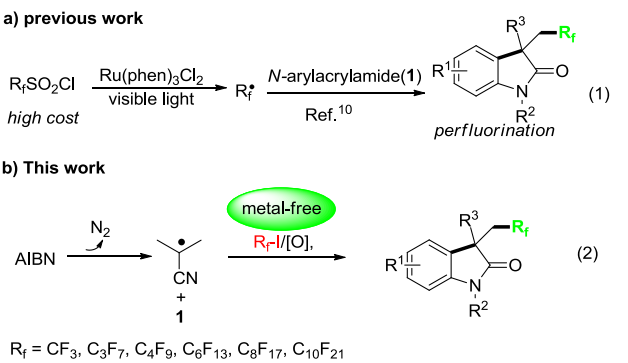


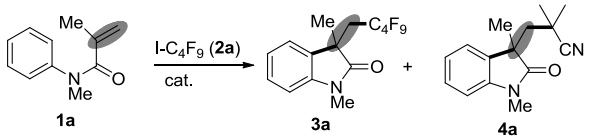
Figure 1 Fluoroalkylation of alkenes toward oxindoles

reactions were realized by using precious $Ru(Phen)_3Cl_2$ photocatalyst and/or high cost fluoroalkylsulfonyl chloride (Figure 1, eq 1). In addition, only limited perfluorinated reagents (e.g., $C_4F_9SO_2Cl$) have been applied in these reactions. In general perfluoroalkyl iodides were commercially available, and much less expensive than fluoroalkylsulfonyl chlorides and Togni reagent in large scale productions.[11,12] Therefore, replacement of R_fSO_2Cl with R_f-I, as well as the application of metal-free conditions for this perfluoroalkylation reactions are of highly practical interest. As a continuation of our interest in the synthesis of oxindoles,[13] we herein demonstrate a novel controllable AIBN-mediated alkylarylation reaction of *N*-arylacrylamide, which could allow for highly practical incorporation of perfluorinated groups (Figure 1, eq 2).

Initially, the reaction between *N*-methyl-*N*-phenylacrylamide **1a** and AIBN was employed as the model reaction to explore optimal conditions (Table 1). At the outset, the catalytic combinations of metal with an oxidant were examined, which failed to yield desired oxindole 3a efficiently (entries 1-3). Thus, some radical initiators were added to improve the yield (entries 4 and 6). Expectedly, the yield of desired product **3a** was improved to 32% when the reaction was conducted in the presence of CuBr and AIBN, and a cyanated product

4a was also observed *via* the addition of radical NC(CH$_3$)$_2$C• produced by AIBN onto the double bond of activated alkene (entry 4).[13d] Unexpectedly, the yield was improved to 81% when CuBr was removed, and the product **4a** was also suppressed efficiently (entry 5). Notably, lowering the amount of AIBN to 1.0 equiv could exactly suppress cyanoalkylation leading to **4a**, but decreased the yield of **3a** simultaneously (entry 6). Another radical initiator, $Na_2S_2O_3$, turned out to be less efficient (entry 7). Further screening shown that using an oxidant was beneficial for the reaction, and DTBP was optimal. Other oxidants, such as TBPB and TBHP, as well as the absence of oxidant, generally resulted in inferior yields (entries 8-10). Sequential screening of solvents revealed CH_3CN as the best choice (entries 11-12). The optimal temperature for the perfluoroalkylation reaction was 105 °C. Further raising the temperature (>120 °C) led to a side-reaction[14] triggered by the methyl radical produced by DTBP (entries 13 and 14).

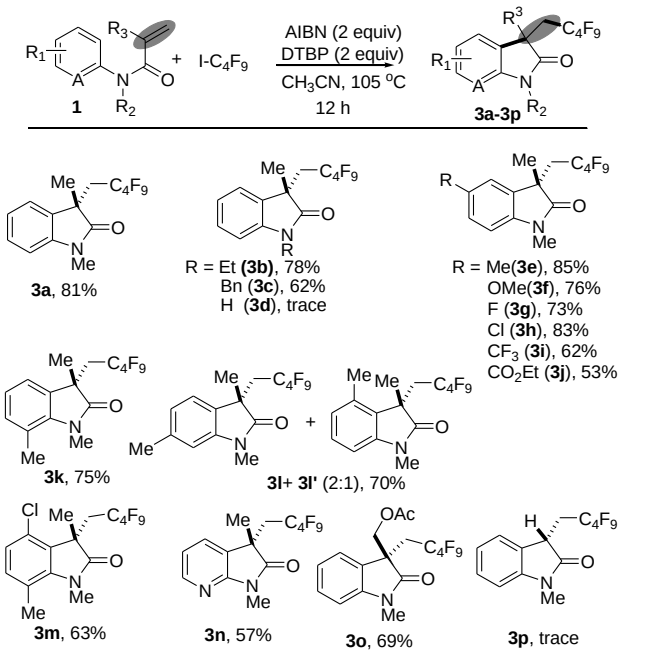
Table 1 Optimization of reaction conditions[a]



entry	initiator	oxidant	yield **3a** (%)[b]	yield **4a** (%)[b]
1	$FeBr_2$	DTBP	trace	0
2	CuBr	DTBP	trace	0
3	$AgNO_4$	$K_2S_2O_8$	trace	0
4	CuBr/AIBN	DTBP	32	45
5	AIBN	DTBP	81	10
6[c]	AIBN	DTBP	70	6
7	$Na_2S_2O_3$	DTBP	trace	0
8	AIBN	TBPB	43	15
9	AIBN	TBHP	17	10
10	AIBN	none	trace	trace
11[d]	AIBN	DTBP	22	trace
12[e]	AIBN	DTBP	55	trace
13[f]	AIBN	DTBP	26	trace
14[g]	AIBN	DTBP	37	trace

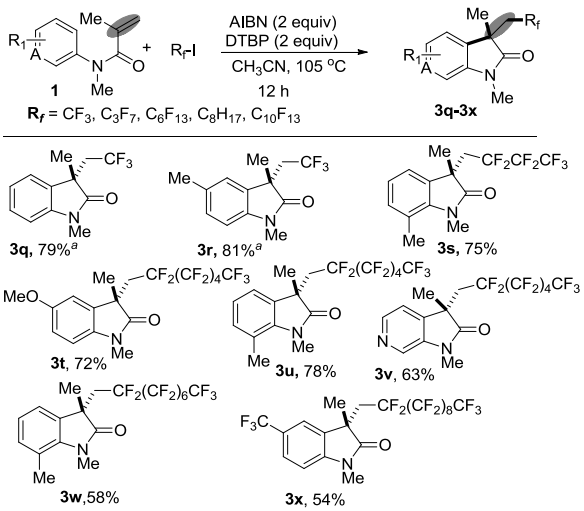
[a] Reaction conditions: **1a** (0.3 mmol), C_4F_9I (2 equiv), metal (10 mol %), initiator (2 equiv), oxidant (3 equiv), and solvent (2 mL) at 105 °C for 12 h. DTBP = Di-*tert*-butyl peroxide, AIBN = azodiisobutyronitrile, TBPB = *tert*-butylperoxyl benzoate, TBHP = *tert*-butyl hydrogenperoxide (70% aqueous solution). [b] Yield of the isolated product. [c] Using 1 equiv of AIBN. [d] Toluene instead of CH_3CN. [e] Dioxane instead of CH_3CN. [f] At 80 °C. [g] At 120 °C.

With the optimal conditions to hand, we set out to investigate the substrate scope in the perfluorinated reaction (Scheme 1). Initial screening revealed that *N*-substituents of acrylamides had an obvious effect on the reaction. For example, *N* arylacrylamides with a benzyl or ethyl group on the *N*-atom were found to be compatible with the reaction conditions, whereas unprotected *N* arylacrylamide (R^2 = H) was less efficient (**3a-d**). Next, we embarked upon investigating the substitution effect on the *N* aryl moiety in the reaction. A wide variety of substituents including Me, MeO, Cl, F, CF_3, 105 Et at the 4-, 3- or 2-position of the aromatic ring displayed good reactivity irrespective of steric and electronic character of the substituent groups (**3e-m**). The reaction of *meta* methyl substituted *N*-arylacrylamide afforded a mixture of two regioselective products **3l** and **3l'** in a total yield of 70%. In addition, *N*-pyridyl acrylamides was also a viable substrate for the cyclization, and afforded *N*-containing heterocycle **3n** in 57% yield. Sequential investigations revealed that the substituent CH_2OAc at the 2-position of the acrylamide moiety was compatible with the optimal conditions to afford **3o** in 69% yield. Nevertheless, mono-substituted olefin (R^3 = H) were inefficient for the perfluoroalkylation process (**3p**).



Scheme 1 Scope of *N*-arylacrylamines. Reaction conditions: **1** (0.3 mmol), C_4F_9I (2 equiv), AIBN (2 equiv), DTBP (2 equiv), and CH_3CN (2 mL) at 105 °C for 12 h

Next, the scope of perfluoroalkyl iodide in the reaction was also investigated (Scheme 2). Gratefully, the perfluoroalkylation process turned out to be well compatible with various perfluoroalkyl

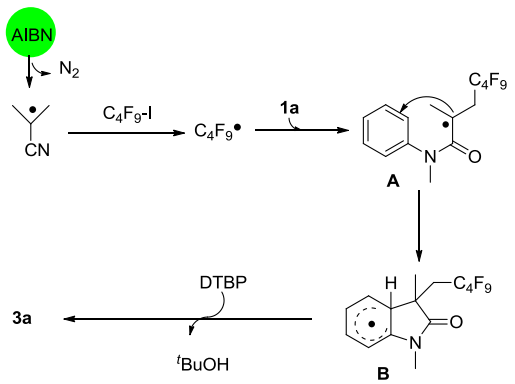


Scheme 2 Scope of perfluoroalkyl iodides. Reaction conditions: **1** (0.3 mmol), R_fI (2 equiv), AIBN (2 equiv), DTBP (2 equiv), and CH_3CN (2 mL) at 105 °C for 12 h. [a] CF_3I (3 equiv)

iodides including C_3F_7I, $C_6F_{13}I$, $C_8F_{17}I$, and etc., and afforded the corresponding perfluorinated oxindoles in moderate to good yield (**3q-x**). It is worth noting that CF_3I, a fluorinated reagent rarely applied in metal-free trifluoromethylation reactions,[12] could also be well tolerated under

optimal conditions (**3q** and **3r**), which required a slightly larger excess of fluorinated reagent.

Based on above experimental results and previously reported mechanism,[3-6,8,10,12,13] a possible radical cyclization routes to the oxindoles for the reaction with C_4F_9I was proposed as outlined in Scheme 3. Firstly perfluorinated radical C_4F_9• was generated from C_4F_9I by the initiation of AIBN, followed by its addition onto the C=C bond of acrylamide 1a yielding an alkyl radical **A**. Intramolecular cyclization of intermediate **A** with an aryl ring forms intermediate B, and then abstraction of an aryl hydrogen in intermediate **B** by DTBP takes place to afford perfluorinated oxindole **3a**.



Scheme 3 Proposed mechanism for the reaction with C_4F_9I.

In summary, we have discovered a controllable alkylarylation reaction of alkenes toward perfluorinated oxindoles by simple AIBN for the first time. The use of readily available and comparatively low cost RfI as fluorine sources and readily available AIBN as an initiator or reactant, broad substrate scope and mild temperature conditions, as well as simplicity of preparation and handling make this protocol a highly practical means to perfluorinated oxindoles. The detaileq mechanism and application of the reaction to more complex targets are currently under investigation in our laboratory.

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