

Article

N-Iodosuccinimide as a Precatalyst for C–N Bond-Forming Reactions from Alcohols under Mild Reaction Conditions

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Abstract: We report an efficient and selective methodology for the direct cross-coupling of alcohols with *N*-nucleophiles mediated by *N*-iodosuccinimide (NIS) as the non-metal, commercially available, low-cost, and most effective precatalyst among the *N*-halosuccinimides (NXSs) under mild reaction conditions enhancing the green chemical profiles of these reactions. The scale-up procedure was accomplished with almost quantitative yield, verifying the presented method's synthetic applicability and potential for industrial application.

Keywords: alcohols; *N*-iodosuccinimide; cross-coupling; C–N bond formation; green chemistry



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1. Introduction

The development of new methodologies for C–N coupling reactions has attracted significant interest in academia and industry due to their various biological activities and broad scope in the pharmaceutical industry, material science, and drug delivery [1–4].

Since alcohols are available, inexpensive, and could serve as alkylating agents, their direct cross-coupling with *N*-nucleophiles could be a desirable strategy from the perspective of green chemistry, as an additional synthetic step for the coupling reaction is avoided and the only by-product resulting from the associated coupling reaction is water.

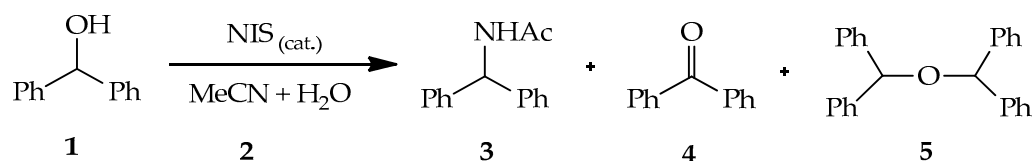
Catalytic direct activation of alcohols for nucleophilic substitution has become the preferred protocol among researchers; the different catalysts used include metal catalysts [5–8], Lewis acids [5,9,10], Brønsted acids [5,11], solid acids [12], and other promoters such as molecular iodine [5,13].

Despite being highly effective, these methods require expensive catalysts in many cases, environmentally inappropriate solvents, elevated temperatures, and prolonged reaction time, making such methods less attractive from a sustainability perspective. Regarding the environmental concerns and from an economic point of view, the desirable methodology should include the use of metal-free, low-cost, easily handled, water- and air-tolerant catalysts and solvent-free or safer reaction media, which remains an attractive research challenge in modern synthetic chemistry. Moreover, the methodology should be realizable for a broad substrate scope with high efficiency and selectivity, allowing a scale-up procedure.

Recently, we introduced *N*-halosuccinimides (NXSs) (chloro, bromo, and iodo), as the mediator for the direct transformation of a hydroxyl functional group, forming new carbon–carbon or carbon–heteroatom bonds [14]. *N*-Iodosuccinimide (NIS) in substoichiometric amounts was elevated as the most effective and selective precatalyst among the *N*-halosuccinimides. As part of our continuous research on developing environmentally friendlier synthetic methodologies, herein, we report the expanding role of NIS as a non-metal, accessible, and environmentally friendly precatalyst for direct cross-coupling of various alcohols with *N*-nucleophiles under mild reaction conditions.

2. Results

Initially, diphenylmethanol **1** was chosen as the model substrate to investigate the efficiency of NIS as a precatalyst of the process and to establish the reaction conditions for alcohol transformation (Scheme 1, Table 1). As shown in Table 1, no reaction occurred in the transformation of diphenylmethanol **1** in the presence of aqueous acetonitrile **2** without NIS as the precatalyst (entry 1, Table 1). In contrast, in the presence of NIS as the precatalyst, the corresponding amidation product **3** in nearly quantitative yield was observed, accompanied by the formation of a small amount of oxidized alcohol **4** (entry 2, Table 1) (entry 1, Table 2). The transformation of diphenylmethanol mediated by NIS in the absence of a nucleophile source under solvent-free reaction conditions (SFRC) provided dimeric ether **5** in quantitative yield [14]



Scheme 1. The conversion of diphenylmethanol **1** in the presence of acetonitrile solution mediated by NIS.

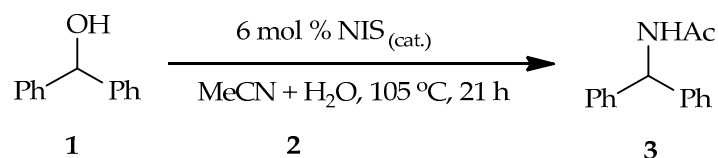
Table 1. Optimal reaction conditions for the highest conversion of diphenylmethanol **1** into the *N*-benzhydrylacetamide **3** mediated by NIS ¹.

Entry	NIS (mol%)	Reaction Conditions	Conversion ² (%) of 1	Relative Distribution ² (%)		
				3	4	5
1	/	MeCN (1/2 mL), H ₂ O (0.5 mmol), 105 °C, 21 h	/	/	/	/
2	6	MeCN (1/2 mL), H ₂ O (0.5 mmol), 105 °C, 21 h	100	96	4	/

¹ Reaction conditions: diphenylmethanol **1** (0.5 mmol), MeCN **2** (1/2 mL), H₂O (0.5 mmol), 105 °C, 21 h. ² Determined from ¹H NMR spectra of isolated crude reaction mixtures.

In search of optimal reaction conditions, different parameters, including the loading of the NIS as the precatalyst, reaction temperature, reaction time, and effect of adding water for the reaction of diphenylmethanol **1** with MeCN/H₂O **2**, were first studied, and the results are given in the Supplementary Materials (Tables S1–S4).

Screening on precatalyst loading, reaction temperature, reaction time, and effect of adding water showed that 6 mol% NIS, 105 °C, 21 h, and 0.5 mmol H₂O were the best conditions ensuring complete conversion of **1** into the corresponding amidation product **3** (Scheme 2).



Scheme 2. Optimal reaction conditions for the conversion of diphenylmethanol **1** into the *N*-benzhydrylacetamide **3** mediated by NIS.

Having established the optimal conditions for amidation products, we next sought to check the scope of this transformation with various alcohols (Scheme 3), and the results are collected in Table 2.

Table 2. Nucleophilic substitution of alcohols using NIS as a precatalyst ^a.

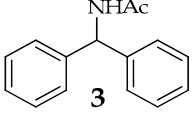
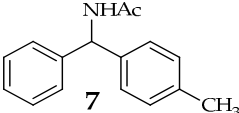
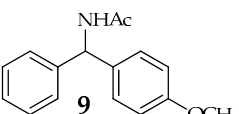
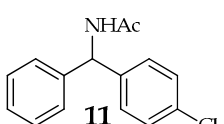
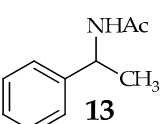
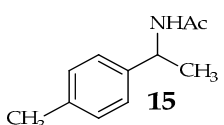
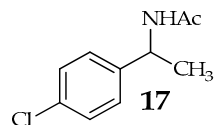
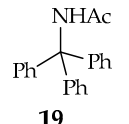
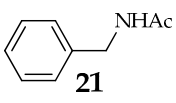
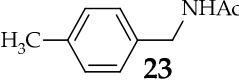
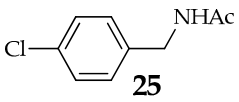
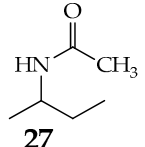
Entry	R ¹ , R ² , R ³	NuY	Product	Conversion ^b (%) (Yield ^c (%))
1	R ¹ = R ² = H, R ³ = Ph 1	MeCN/H ₂ O 2	 3	100 ^d (94)
2	R ¹ = Me, R ² = H, R ³ = Ph 6	MeCN/H ₂ O 2	 7	100 ^d (94)
3	R ¹ = OMe, R ² = H, R ³ = Ph 8	MeCN/H ₂ O 2	 9	92 ^e (73)
4	R ¹ = Cl, R ² = H, R ³ = Ph 10	MeCN/H ₂ O 2	 11	100 ^d (92)
5	R ¹ = R ² = H, R ³ = Ph 12	MeCN/H ₂ O 2	 13	100 ^d [14] (93)
6	R ¹ = Me, R ² = H, R ³ = Me 14	MeCN/H ₂ O 2	 15	93 ^{d,f} (80)
7	R ¹ = Cl, R ² = H, R ³ = Me 16	MeCN/H ₂ O 2	 17	96 ^d (86)
8	R ¹ = H, R ² = R ³ = Ph 18	MeCN/H ₂ O 2	 19	-
9	R ¹ = H, R ² = R ³ = Ph 20	MeCN/H ₂ O 2	 21	46 ^e
10	R ¹ = Me, R ² = R ³ = H 22	MeCN/H ₂ O 2	 23	96 ^e (73)
11	R ¹ = Me, R ² = R ³ = H 24	MeCN/H ₂ O 2	 25	30 ^e
12	CH ₃ CH ₂ CHCH ₃ 26	MeCN/H ₂ O 2	 27	88 (85)

Table 2. Cont.

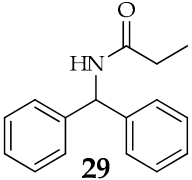
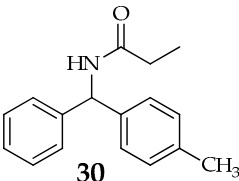
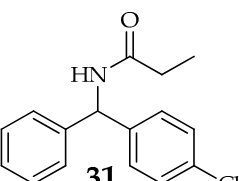
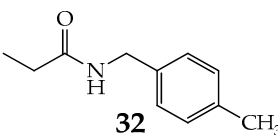
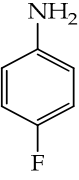
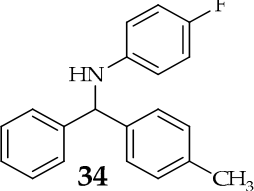
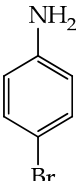
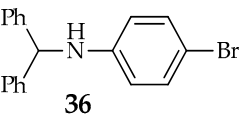
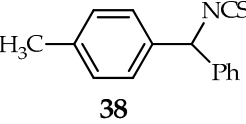
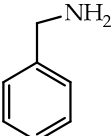
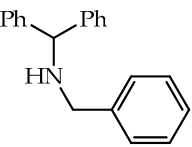
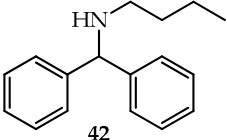
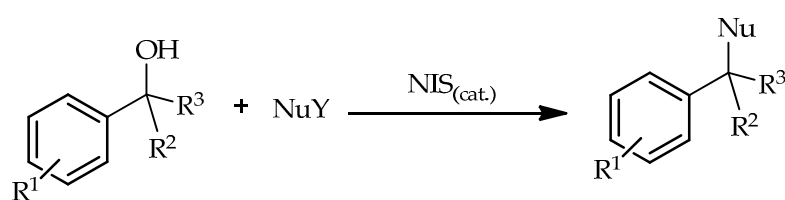
Entry	R ¹ , R ² , R ³	NuY	Product	Conversion ^b (%) (Yield ^c (%))
13	R ¹ = R ² = H, R ³ = Ph 1	CH ₃ CH ₂ CN/H ₂ O 28	 29	100 ^d (91)
14	R ¹ = Me, R ² = H, R ³ = Ph 6	CH ₃ CH ₂ CN/H ₂ O 28	 30	100 ^d (92)
15	R ¹ = Cl, R ² = H, R ³ = Ph 10	CH ₃ CH ₂ CN/H ₂ O 28	 31	100 ^d (93)
16	R ¹ = Me, R ² = R ³ = H 22	CH ₃ CH ₂ CN/H ₂ O 28	 32	98 ^e (74)
17	R ¹ = Me, R ² = H, R ³ = Ph 6	 33	 34	71 ^d (65)
18	R ¹ = R ² = H, R ³ = Ph 1	 35	 36	85 ^d [14] (79)
19	R ¹ = Me, R ² = H, R ³ = Ph 6	TMSNCS 37	 38	100 [14] (97)
20	R ¹ = R ² = H, R ³ = Ph 1	 39	 40	-

Table 2. Cont.

Entry	R ¹ , R ² , R ³	NuY	Product	Conversion ^b (%) (Yield ^c (%))
21	R ¹ = R ² = H, R ³ = Ph 1	<i>n</i> -BuNH ₂ 41	 42	-

^a Reaction conditions: alcohol (0.5 mmol), NuY (0.55 mmol–0.5 mL), H₂O (0.5 mmol), NIS (6–10 mol%), 85–115 °C, 21–24 h. ^b Determined from ¹H NMR spectra of the isolated crude reaction mixture. ^c Purified products. ^d Oxidized alcohol 2–10%. ^e Oxidized alcohol and dimeric ether 4–20%. ^f Eliminated product 8%.



Scheme 3. Nucleophilic substitution of alcohols mediated by NIS.

Effective transformation with acetonitrile solution **2**, mediated by NIS, was observed in the reaction with additional derivatives of diphenylmethanol bearing electron-donating groups (EDGs) or electron-withdrawing groups (EWGs) on the aromatic rings furnishing the corresponding amidation products in excellent yields. We checked the reaction of phenyl(*p*-tolyl)methanol **6** with NIS as the mediator in the presence of aqueous acetonitrile **2**, and the quantitative formation of the corresponding product **7** was observed, accompanied by a small amount of oxidized alcohol (entry 2, Table 2). Effective transformation with NIS as the mediator was observed in the case of (4-methoxyphenyl)(phenyl)methanol **8**, providing corresponding product **9** in good yield accompanied by the formation of dimeric ether and oxidized alcohol (entry 3, Table 2). Amidation of (4-chlorophenyl)(phenyl)methanol **10** with aqueous acetonitrile **2**, mediated by NIS, afforded the corresponding product **11** in nearly quantitative yield accompanied by a small amount of oxidized alcohol (entry 4, Table 2).

Under the typical reaction conditions, we extended the scope of the transformation to additional classes of secondary benzyl alcohols, including derivatives of 1-phenylethanol carrying EDGs or EWGs on the aromatic rings **12**, **14**, and **16**. These alcohols were quantitatively converted into the corresponding products **13**, **15**, and **17**, accompanied by a small amount of oxidized alcohol (entries 5–7, Table 2). In contrast, in the case of the bulky tertiary benzyl alcohol **18**, no product **19** was detected (entry 8, Table 2).

Furthermore, we checked the reactions of primary benzyl alcohols bearing EWGs and EDGs with aqueous acetonitrile **2** in the presence of NIS as the mediator. In the case of unsubstituted benzyl alcohol **20**, a low yield of the corresponding product **21** was observed, accompanied by a small amount of dimeric ether and oxidized alcohol (entry 9, Table 2). In the case of *p*-tolylmethanol **22**, the EDG on the aromatic ring enhanced the reaction efficiency providing the corresponding product **23** in good yield, while the EWG of benzyl alcohol **24** decreased the transformation, only a small amount of corresponding product **25** was observed, accompanied by a small amount of dimeric ether and oxidized alcohol due to lower reactivity (entries 10 and 11, Table 2).

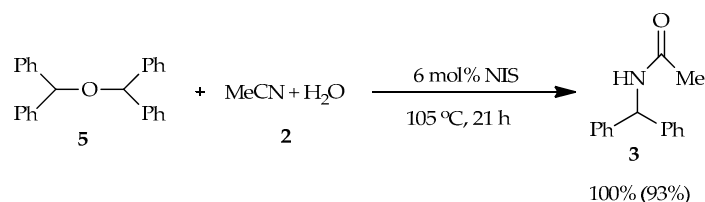
Effective transformation was observed in the case of secondary alkyl alcohols under typical reaction conditions. Butan-2-ol **26** was efficiently and selectively converted into the corresponding product **27** (entry 12, Table 2).

Inspired by these results, we further investigated the corresponding reactions of alcohols with other *N*-nucleophile sources, such as aqueous propionitrile **28**. In the case of

secondary benzyl alcohols, including derivatives of diphenylmethanol carrying EDGs or EWGs on the aromatic ring **1**, **6**, and **10**, efficient conversion into the corresponding products **29**, **30**, and **31**, accompanied by a small amount of oxidized alcohol were observed (entries 13–15, Table 2). In the case of primary benzyl alcohol bearing an EDG on the aromatic ring **22**, the formation of the corresponding product **32** in good yield was observed (entry 16, Table 2). Moreover, the direct coupling of substituted aniline bearing deactivated groups **33** and **35** with phenyl(*p*-tolyl)methanol **6** mediated by NIS afforded the corresponding products **34** and **36** in moderate to high yield accompanied by a small amount of oxidized alcohol and dimeric ether (entries 17 and 18, Table 2). On the other hand, we performed the reaction of phenyl(*p*-tolyl)methanol **6** as the model compound under the mentioned reaction conditions, using (trimethylsilyl)isothiocyanate (TMSNCS) **37** as the source of nucleophiles, where isothiocyanate was introduced successfully into organic molecule **38** (entry 19, Table 2). Additionally, no reaction occurred in the transformation of diphenylmethanol **1** as the model compound under the examined reaction conditions, using benzylamine **39** and *n*-butylamine **41** as the nucleophile sources in the presence of NIS as the precatalyst (entries 20 and 21, Table 2).

On the other hand, the following reaction was performed on the 10 mmol scale to establish the synthetic value of the reported methodology: coupling of phenyl(*p*-tolyl)methanol **6** with aqueous acetonitrile **2** in the presence of NIS as the mediator, which delivered the desired corresponding product **7** in excellent yield (93%).

To support the assumption that the dimeric ether **5** might be the intermediate of this dehydrative coupling [15], a control reaction was performed (Scheme 4). The dimeric ether **5** [16] was used as a starting material instead of diphenylmethanol **1** in the reaction with aqueous acetonitrile **2**, affording the corresponding product **3** in high yield accompanied by the formation of oxidized alcohol.



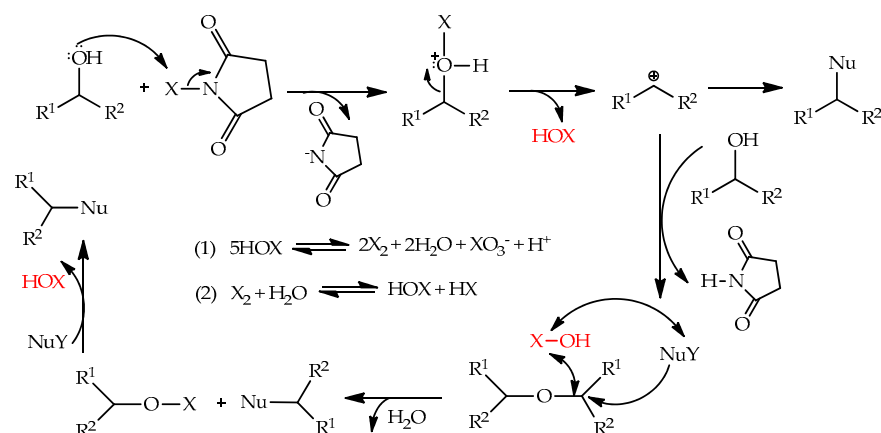
Scheme 4. Control experiment.

Based on the above observations, it could be speculated that the dimeric ether **5** might be the intermediate that can generate the benzylic carbocation, which MeCN can attack to release nitrilium ion followed by the presence of traces of H₂O providing the amide product **3**. Moreover, the direct reaction between carbocation and aqueous acetonitrile could be a possible pathway as well [17,18].

To gain mechanistic insight into the course of the reaction, the reaction of **1** with **2** in the presence of NIS as the precatalyst under the examined reaction conditions was performed, and the pH of the reaction mixture was measured (Table S5). The results show a drop in pH value from 6–7 to as low as 4–2 during the reaction.

Based on the result of the control experiment presented in Scheme 2, the proposed reaction pathway is presented in Scheme 5. It was reported that the R–X bond of organic molecules bearing an active *N*-halogen as the precatalysts was activated from its reaction with the addition of Lewis base by the interaction of a halogen atom X in one molecule with a negative site in another, such as the lone pair electrons of a Lewis base [19,20]. Therefore, it seems plausible that transient halogen bonding could be responsible for the catalytic effect of NIS [21,22]. Rather, halonium (X⁺) transfer will generate the intermediate and HOX, which further promotes the course of the reaction. HOX decomposes by disproportionation to X₂ and HXO₃. It is well known that X₂ forms HOX and HX in reactions with water, where HOX regenerates for the subsequent catalysis. Conversely, the water resulting as

the only by-product of the reaction might function as a supporter in the acceleration of the reaction.



Scheme 5. Plausible reaction course.

The assumption that NIS is a precatalyst forming HOX, X_2 , and protons during the process while these species could accelerate nucleophilic substitutions appears to be reasonable [23].

To check the NIS's thermal stability under reaction conditions, thermal gravimetric analysis (TGA) on the NIS precatalyst was performed. It was noticed that the degradation of the precatalyst did not occur at the temperature range 25–200 °C [14].

3. Materials and Methods

All alcohol substrates were commercially available and were used without further purification (Merck, Darmstadt, Germany; Sigma Aldrich, St. Louis, MO, USA; Fluka, Seelze, Germany). All reactions were performed in a Mettler-Toledo Easymax 102 Advanced Synthesis Workstation using 25 mL closed reactor tubes at 85–105 °C for 21–24 h. All reactions were monitored by TLC (mobile phase: dichloromethane/hexane 9:1) and visualized using a UV lamp (254 nm, Camag, Muttenz, Switzerland). pH was measured with Whatman Panpeha pH indicator strips (pH range 0–14). Column chromatography (CC) and flash chromatography (FC) were performed using silica gel 60 (particle size: 0.063–0.200 mm), and purification of certain products was accomplished on PLC Kieselgel 60 F254 preparative silica gel glass plates with 2 mm layer thickness. Spectroscopic methods included nuclear magnetic resonance (Varian INOVA 300 NMR instrument, Palo Alto, CA, USA, 300 MHz ^1H , 75 MHz ^{13}C , 285 MHz ^{19}F) at 25 °C. ^1H NMR spectra were obtained as solutions in CDCl_3 with TMS as an internal standard. ^{19}F NMR spectra were obtained as solutions in CDCl_3 with CFCl_3 as an internal standard. Melting points (open capillary tube methodology; uncorrected) were used for identification and structure elucidation employing Buchi-Melting Point M-560 equipment (BUCHI, Flawil, Switzerland).

The general procedure for new carbon–nitrogen bond formation in organic molecules mediated by NIS on a half-millimole scale is as follows:

In 25 mL reactor tubes, a mixture of benzyl alcohol (0.5 mmol), acetonitrile or propionitrile (0.5 mL), water (0.5 mmol), and NIS (6–10 mol%), or a mixture of solid reaction components previously powdered in a mortar, was transferred. The reactor tube was then heated at 85–115 °C for 21–24 h. The progress of the reaction mixture was monitored by TLC. After the completion of the reaction, the crude reaction mixture was cooled down to room temperature; diluted with ethyl acetate (15 mL); washed with $\text{Na}_2\text{S}_2\text{O}_3$ (6 mL), NaHCO_3 (6 mL), and water (10 mL); and dried over anhydrous Na_2SO_4 . The solvent was evaporated under reduced pressure, and the crude reaction mixture obtained was analyzed by ^1H NMR.

The scale-up procedure for the synthesis of *N*-(phenyl(*p*-tolyl)methyl)acetamide 7 is as follows: A mixture of phenyl(*p*-tolyl)methanol 6 (10 mmol, 1.98 g), 6 mol% NIS (135 mg,

0.06 mol), which had been powdered in a mortar, was transferred to a 25 mL reactor tube to which H₂O (10 mmol, 180 µL) and MeCN 2 (10 mL) were added, and the mixture was heated at 105 °C for 21 h, stirring at 300 rpm. The progress of the reaction mixture was followed by TLC. Upon completion of the reaction, the mixture was cooled to room temperature. Finally, the crude reaction mixture was purified by column chromatography to obtain a pure product in excellent yield (white solid, 2.2131 g, and 93%).

4. Conclusions

In summary, an efficient, selective, non-metal methodology for the direct C–N bond formation through the direct cross-coupling of secondary alkyl alcohols and benzylic alcohols (primary and secondary) with *N*-nucleophiles employing NIS as an accessible and environmentally friendly precatalyst has been developed. The synthesis has been performed under mild reaction conditions affording moderate to quantitative product yields. The large-scale synthesis of *N*-(phenyl(*p*-tolyl)methyl)acetamide **7** has been accomplished with excellent yield.

Supplementary Materials: The following are available online at <https://www.mdpi.com/article/10.3390/catal12111368/s1>, Table S1: The catalytic effect of NIS on the conversion of diphenylmethanol **1** with acetonitrile solution **2** based on temperature ¹, Table S2: The effect of loading of NIS as the mediator on the conversion of diphenylmethanol **1** with acetonitrile solution **2** ¹, Table S3: The catalytic effect of NIS on the conversion of diphenylmethanol **1** with acetonitrile solution **2** based on time ¹, Table S4: The catalytic effect of NIS on the conversion of diphenylmethanol **1** with acetonitrile solution **2** based on mmol of water ¹, Table S5: The pH measurements on the conversion of diphenylmethanol **1** with acetonitrile solution **2** mediated by NIS, Characterization Data of Isolated Final Products, ¹H NMR, ¹³C NMR, and ¹⁹F NMR spectra of isolated final products, Thermal Gravimetric (TG) analysis of the NIS. References [24–33] are cited in the supplementary materials.

Author Contributions: Conceptualization, S.S.; formal analysis, N.A. and S.S.; investigation, N.A. and S.S.; methodology, N.A. and S.S.; writing—original draft, N.A.; writing—review and editing, N.A. and S.S. All authors have read and agreed to the published version of the manuscript.

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