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PIFA-Promoted, Solvent-Controlled Selective Functionalization of C(sp^2)−H or C(sp^3)−H: Nitration via C−N Bond Cleavage of CH_3NO_2, Cyanation, or Oxygenation in Water

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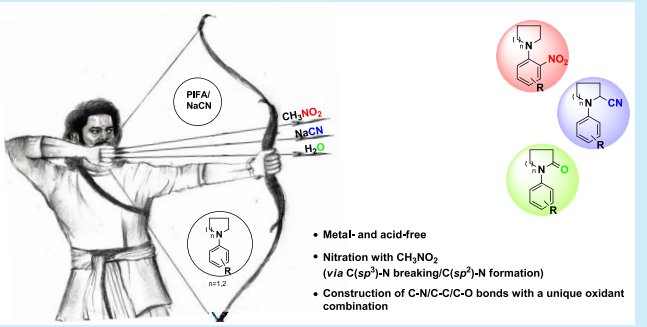
Supporting Information

ABSTRACT: A novel nitration (via C(sp^3)−N breaking/C(sp^2)−N formation with CH_3NO_2) mediated by [bis-(trifluoroacetoxy)iodo]benzene (PIFA) is described. The NO_2 transfer from CH_3NO_2 to the aromatic group of the substrate is possible with careful selection of the solvent, NaX, and oxidant. In addition, the solvent-controlled C(sp^2)−H functionalization can shift to an α-C(sp^3)−H functionalization (cyanation or oxygenation) of the α-C(sp^3)−H of cyclic amines.



The development of efficient methods for selective C(sp^2)−H or C(sp^3)−H functionalizations, which involve the formation of new C−C and C−heteroatom bonds, has recently attracted substantial attention.[1] In particular, nitro and cyano groups are the most prevalent functional groups in natural products,[2b,d] and they are important precursors in chemical transformations to access other pharmaceutically and biologically active compounds.[2]

Nitroarenes are one of the most important motifs in organic synthesis. Nitric acid in the presence of another strong acid is frequently and traditionally used for nitration;[3] however, a variety of metal-based methods[4] and some metal-free approaches have also been developed.[5] The above protocols have several drawbacks, such as requiring harsh conditions (strong acids), limited substrate scope, overnitration, or the formation of a mixture of isomers. Thus, the development of new nitrating agents for regioselective mononitrations has attracted considerable attention. Recently, organo-nitrating agents,[6] such as ^{t}BuONO, CH_3ONO_2, and urea nitrate, have become attractive and emerged as effective nitrating agents to overcome these difficulties. These are simpler, more readily available, less toxic, more direct, and more selective nitrating agents compared to other reagents.[6e−m]

Generally, CH_3NO_2 is used as a polar solvent in organic conversions. Otherwise, it can serve as a nitro-methylating agent in cross-coupling reactions[7a,b] and conjugate additions under basic conditions.[7c−f] Surprisingly, we observed that the combination of PIFA with a NaX can facilitate nitration instead of cross-coupling (see Scheme S1 in the Supporting Information). To the best of our knowledge, there have been no reports of nitrations[8] with CH_3NO_2, which encouraged us to develop CH_3NO_2 as an organo-nitrating reagent.

Hypervalent iodine can facilitate metal-free functionalizations as well as oxidations.[9] Among the derivatives of iodine(III), PIFA has been successfully applied in oxidative intra- and intermolecular C−C and C−heteroatom bond formations.[10,11] Recently, the Nachtsheim group[11e] obtained a nitro product by employing $NaNO_2$ under additive-free conditions[11] (Scheme 1, eq 1). In 2015, Shen et al.[10d] reported the cyanation of amines using TMSCN as a cyanide source promoted by PIFA/additives (eq 2), and the oxygenation of cyclic amines could be achieved

Scheme 1. Iodine(III)-Supported Functionalizations

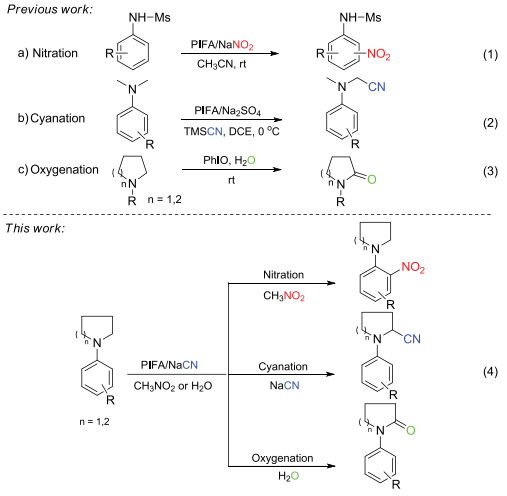


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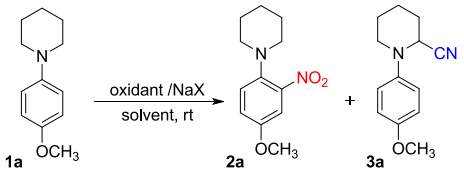
Table 1. Nitration Optimization[a]



entry	oxidant	NaX	solvent	time (h)	yield[b] (%) 2a	3a
1	PIFA	NaCN	CH_3NO_2	10	nd	
2	PIFA	NaCN	CH_3NO_2/H_2O(9:1)	3	87	trace
3	PIFA	NaCN	$C_2H_5NO_2/H_2O$(9:1)	6	79	
4	PIFA	NaCN	$PhNO_2/H_2O$(9:1)	10	nd	
5	PIFA		CH_3NO_2	10	nd	
6[c]	PIFA	NaCN	CH_3NO_2/H_2O(9:1)	10	61	
7	PIFA	NaCN	CH_3NO_2/H_2O (1:1)	6	53	32
8	PIFA	NaCN	H_2O	6		93
9	PIFA	NaOH	CH_3NO_2/H_2O(9:1)	6	77	
10[d]	PIFA	NaOMe	CH_3NO_2/MeOH(9:1)	6	57	
11[d]	PIFA	NaO^{t}Bu	CH_3NO_2/MeOH(9:1)	6	46	
12[d]	PIFA	NaH	CH_3NO_2/MeOH(9:1)	6	57	
13[d]	PIFA	NaOPh	CH_3NO_2/MeOH(9:1)	6	23	
14[d]	PIFA	$NaBH_4$	CH_3NO_2/MeOH(9:1)	10	nd	
15	PIFA	NaOAc	CH_3NO_2/H_2O(9:1)	10	nd	
16	PIFA	$NaHCO_3$	CH_3NO_2/H_2O(9:1)	10	trace	
17	PIFA	Et_3N	CH_3NO_2	6	47	
18	PIFA	NH_4OH	CH_3NO_2	10	trace	
19	(diacetoxyiodo)benzene	NaCN	CH_3NO_2/H_2O(9:1)	10	nd	
20	2-iodoxybenzoic acid	NaCN	CH_3NO_2/H_2O(9:1)	10	nd	
21	Dess−Martin periodinane	NaCN	CH_3NO_2/H_2O(9:1)	10	nd	
22	PhI	NaCN	CH_3NO_2/H_2O(9:1)	10	nd	

[a]Reaction conditions: **1a** (1.0 equiv), oxidant (2.0 equiv), NaX (2.0 equiv) at room temperature (rt). [b]Isolated yield. [c]PIFA (1.0 equiv), NaCN (1.0 equiv). [d]MeOH was used as a cosolvent for water-sensitive bases. nd = not detected.

in moderate yields using PhIO in water (eq 3).[12e] Unfortunately, the investigations showed limited substrate scopes and poor regioselectivities. In most cases, while iodine(III)-catalyzed reactions require additives and fluorinated solvents to activate the oxidant,[10] large-scale syntheses using such methods will never be environmentally friendly. Herein, we report (1) a nitration via C(sp^2)−H functionalization, (2) a cyanation, and (3) an oxygenation[12] via C(sp^3)−H functionalizations under metal-free PIFA/NaCN conditions (eq 4).

Initially, we chose aromatic ring-bound cyclic tertiary amine **1a** as the substrate to investigate the nitration conditions (Table 1). Using 2.0 equiv of PIFA and 2.0 equiv of NaCN in CH_3NO_2, no desired product was observed, and the NaCN was poorly soluble (entry 1). To our delight, when water was used as a cosolvent along with CH_3NO_2 (9:1), NaCN was completely soluble, and the desired C(sp^2)−H nitration product **2a** was exclusively obtained in 87% yield within 3 h (entry 2). This nitration occurred due to the basicity of CN^- (see mechanism). Next, by screening various nitro solvents, nitroethane was also found to be a suitable solvent but provided the product in a lower yield (entry 3), and the reaction did not proceed in the presence of nitrobenzene (entry 4). Removing NaCN led to no reaction, and only the elimination of PhI was observed (entry 5). Finally, a lower yield of **2a** was observed with lower loadings of PIFA and NaCN (entry 6). Our further studies focused on searching for optimal conditions to generate cyano product **3a** efficiently. When the reaction was conducted in CH_3NO_2/H_2O (1:1), **2a** and alternative C(sp^3)−H cyanation product **3a** were obtained. In fact, the reaction of **1a** under the above conditions afforded a 3:1 mixture of **2a**:**3a** with a promising 53% yield of **2a** (entry 7). Gratifyingly, the use of water as solvent led to a dramatic increase in the yield of **3a**, which was selectively formed as the major product (93% yield, entry 8). Additional studies focused on changing the sodium salt. Notably, nitration was also possible using NaOH as a NaX (entry 9). In addition, replacing NaOH with related sodium bases, such as NaOMe, NaO^{t}Bu, NaH, and NaOPh, resulted in no observable improvements (entries 10−13). $NaBH_4$ (a mildly basic reducing agent) or NaOAc (less basic than NaCN) did not furnish the desired products (entries 14 and 15). Finally, the reaction was tested with $NaHCO_3$, Et_3N, and NH_4OH (near the pK_a of CN^-), but nitration was only observed in the condition of organic base Et_3N (entries 16−18). A subsequent screening of other oxidants showed they were completely ineffective (entries 19−21), proving the key role of PIFA as a superior agent for this C−H functionalization, as it promoted both selective nitration and cyanation.

Scheme 2 describes the applicability of our method into versatile amines for the late-stage nitration of functional molecules. First, a variety of activating and deactivating aromatic rings of cyclic amines were examined. All transformations were performed in the presence of PIFA (2.0 equiv) and NaCN (2.0 equiv) in CH_3NO_2/H_2O (9:1). Surprisingly, substrates with electron-donating and electron-accepting groups at the *para*-

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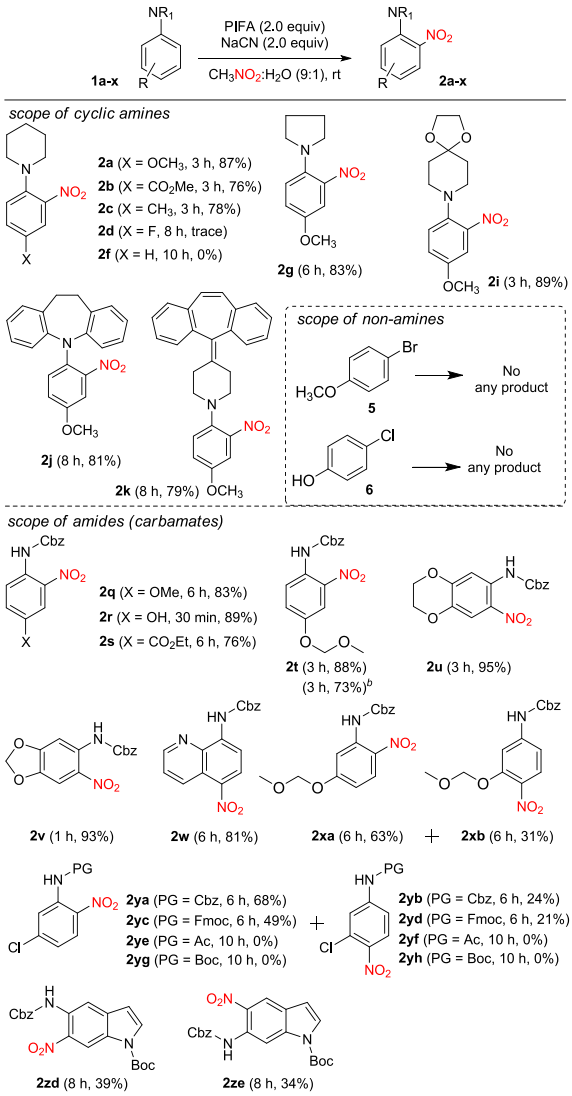
Scheme 2. Substrate Scope of the Nitration[a]



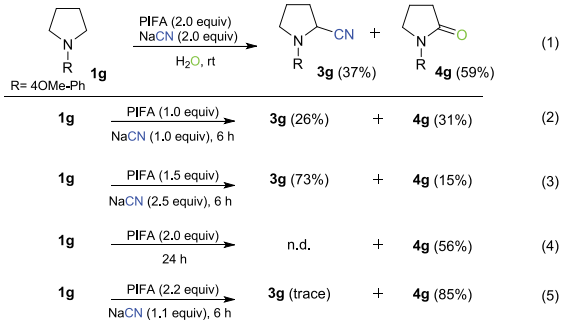
[a]Reaction conditions: **1a–x** (1.0 equiv) in CH_3NO_2/H_2O (9:1). [b]1 mmol scale.

position efficiently underwent the reaction and reached complete conversion within 3 h, giving nitro compounds **2a–c** in excellent yields (76–87%), but when the 4-F-derived substrate was employed, only trace **2d** was obtained. After the effect of a substituent at the *para*-position of the aromatic ring was tested, a *meta*-Me group on the aromatic ring (**1e**) was tested to show the oxidative biaryl coupling product as the major product (Scheme S2).[13] When **1f** was used as a substrate, the formation of **2f** was not observed despite a longer reaction time (10 h). The above results indicate that selective *ortho*-nitration requires a substituent at the *para*-position to achieve satisfactory results. In addition, we were happy to find that substrates with azepine and annulen-5-ylidene skeletons (**1j** and **1k**) gave nitro products **2j** and **2k** with high yields (ca. 80%).

With the established reaction condition in hand, we could assess the scope and generality of the present process. First, nonamine substrates were examined, including compound **5**, a precursor to cyclic amines. Unfortunately, this protocol did not tolerated any nonamine substrates. Our investigation extended the substrate scope from cyclic amines to amides (carbamates). Benzyl chloroformate (Cbz)-protected 4-methoxyaniline (**1q**) was selected as the first substrate for our nitration, and it afforded the corresponding nitro product **2q** in 83% yield (Scheme 2). To our delight, substitution at the *para*-position substantially improved the reaction outcome. Thus, carbamates with a donating group at the *para*-position were smoothly converted into the corresponding nitro products in excellent yields (**2q–v**). When the scale was adjusted from 0.1 to 1 mmol, the yield slightly decreased due to the reduced reaction rate in the heterogeneous system (**2t**). Surprisingly, when **1r** (4-OH) was used as the substrate, complete conversion to desired product **2r** within 30 min (89% yield) was observed without oxidative dearomatization of the phenol ring. This indicates that electron-donating groups at the *para*-position increase the efficiency of the amine group attack on PIFA and lead to the rapid formation of the required products. In contrast, when **1za** (3-OH) and **1zb** (2-OH) were used for this nitration, unidentified side reactions including oxidative dearomatization caused the substrates to decompose within 5 min.[13a] When **1w** was used as the substrate, regioselective formation of *p*-nitro **2w** was observed (isolated in 81% yield).[14] Next, it is worth mentioning that when 3-OCH_2OCH_3 substituted **1x** was tested as the substrate, a mixture of two regioisomers was obtained. The two products, **2xa** and **2xb**, were isolated in 63% and 31% yields, respectively. At this juncture, when the PIFA and NaCN loadings were decreased from 2.0 to 1.2 equiv, the regioselectivity increased, but the isolated yield of **2xa** was moderate (43%), and trace amounts of **2xb** were obtained after 8 h. In addition, the reactions of **1ya** and **1yb** were similar to that of **1x**.

Based on the optimal conditions for C(sp^3)-cyanation (Table 1, entry 8), we next examined the cyanation of the same substrates. Surprisingly, when the reaction was conducted with five-membered or fused aromatic cyclic amines as substrates, undesired products (i.e., oxidation product) were generated along with cyano products **3**. In particular, our preliminary experiment with the optimized conditions revealed that the cyanation reaction of **1g** afforded the desired cyano product in 37% along with 59% of the oxidation product (Scheme 3, eq 1).

Scheme 3. Cyanation and Oxygenation Selectivity[a]



[a]Reaction conditions: **1g** (1.0 equiv). nd = not detected.

We then investigated the reaction selectivity between the cyanation (**3g**) and the oxygenation (**4g**) to reveal the necessary ratio of PIFA and NaCN (Scheme 3). In other words, while equimolar amounts of PIFA and NaCN (same ratio as the first series of experiments) also show poor selectivity between **3g** and **4g** with slightly decreased yields, cyanation occurred more

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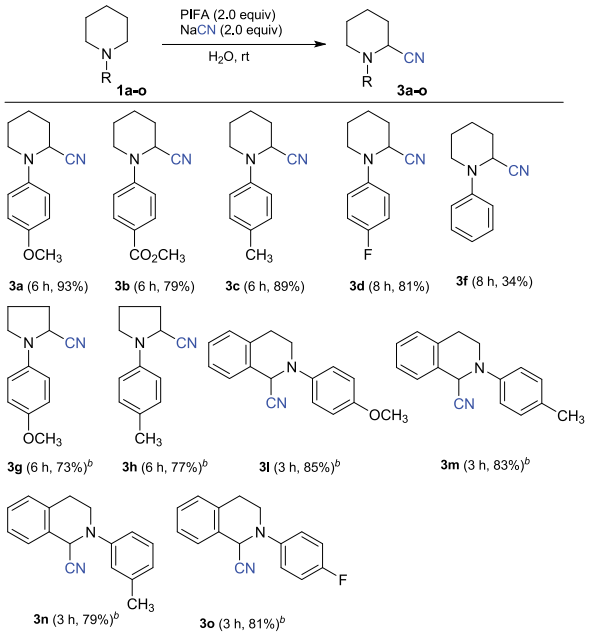
selectively with 1.5 equiv of PIFA (modified ratio of PIFA to NaCN 1−0.6).

Six-membered cyclic amines **1a−f** were compatible with these conditions and resulted in high yields (Scheme 4). Notably,

Scheme 4. Scope of the Cyanation[a]



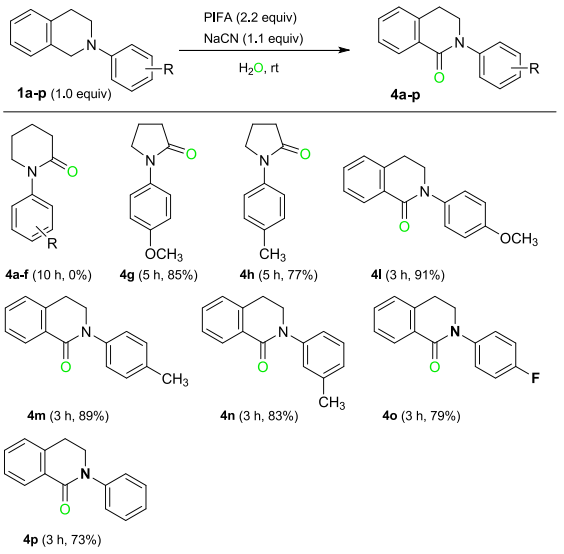
[a]Reaction conditions: **1a−o** (1.0 equiv). [b]PIFA (1.5 equiv), NaCN (2.5 equiv).

when tetrahydroisoquinoline derivatives **1l−o** were used as substrates, the reaction proceeded to complete conversion to cyanation products **3l−o** in H_2O/CH_3NO_2 as well as the optimal condition. Finally, the cyanations of **1g−o** proceeded with excess NaCN (2.5 equiv) in the presence of PIFA (1.5 equiv) to provide cyano products **3g−o** in high yields (73−85%, Scheme 4).

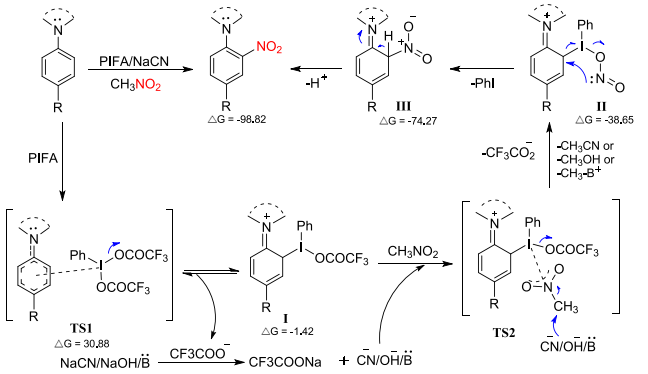
After the demonstration of the cyanation, we should remind ourselves of the oxygenations described in Scheme 3. When the reaction was conducted without NaCN, **4g** was isolated in 56% yield after 24 h (Scheme 3, eq 4). To quickly and selectively obtain oxidation products, higher quantities of oxidant and NaCN were essential to afford better results. The reaction at a higher loading of PIFA (2.2 equiv), using a lower loading of NaCN (1.1 equiv), selectively provided oxidation product **4g** in 85% yield along with traces of **3g** (Scheme 3, eq 5). After optimization of the reaction conditions, we tested the scope of the oxygenation and the reactivity of various cyclic amines (Scheme 5). All monosubstituted five-membered and fused aromatic cyclic amines **1g−p** underwent the reaction smoothly and afforded corresponding oxidation products **4g−p** in high yields (73−91%). However, when less reactive six-membered cyclic amines were tested, none of the oxygenation products were observed (**4a−f**).

The mechanism in the Scheme 6 starts with the coordination of PIFA to *N*-aryl cyclic amine to obtain the intermediate **I** via halogen−π interactions between benzene and iodine. The slight energy gap can permit reversible reaction between cyclic amine and the intermediate **I**. The eliminated ligand ($CF_3CO_2^-$) and NaCN or NaOH reach the equilibrium between ion pairs to produce the conjugate base (CN^- or OH^-). The attack of CN^-/

Scheme 5. Scope of the Oxygenation



Scheme 6. Plausible Mechanism



OH^-/Lewis base (:B) to the methyl group in nitromethane can be assisted or concerted by I−O formation to produce the intermediate **II** with $\Delta G = -38.65$ kcal/mol. Even though the nitro (I−N) or nitrite (I−O) transfer from CH_3NO_2 can be considered, I−O intermediate was selected on the basis of the literature.[15a] The intermediate **II** can be converted into the intermediate **III** via the four-membered TS. Finally, the aromaticity can be regenerated by the loss of a proton from intermediate **III**, which gives final nitro product **2**. The DFT calculations (see Figure S1 in the Supporting Information) and previous literature reports[11e,15] elucidate the proposed mechanism at the B3LYP-D3(6-31G**/ LAVCP) level of theory in the Poisson−Boltzmann solvent model (CH_3NO_2, $\varepsilon = 36.56$). In order to support the proposed mechanism, a nucleophile receiving methyl group from CH_3NO_2 was traced. When NaCN was replaced with NaOPh due to the detectability, anisole (PhOMe) could be detected in TLC, crude NMR, and LCMS.

In conclusion, we have reported the first nitration reaction with CH_3NO_2 under PIFA/NaCN conditions via a novel $C(sp^3)$−N breaking/$C(sp^2)$-N formation mechanism. Notably, the same composition of PIFA/NaCN can dramatically alter the reaction: (1) from $C(sp^2)$−H to α-$C(sp^3)$−H functionalization (changing the solvent) and (2) from cyanation to oxygenation of α-$C(sp^3)$−H bonds of cyclic amines (changing the ratio of PIFA to NaCN). The use of a low toxic, inexpensive PIFA as the oxidant for these three functionalizations, which are compatible

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with a wide range of amines, makes this methodology very attractive and practical. The major highlight of our strategy is that one reaction system (PIFA/NaCN) could facilitate three types of functionalizations in a facile and efficient manner.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00751.

General information; nitration instead of the cross-coupling reaction; synthesis of substrates; general procedures for the nitration, cyanation, and oxygenation reactions; computational methodology (DFT); reference; spectral data of synthesized compounds; ^{1}H and ^{13}C NMR spectra of the products (PDF)

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Notes

The authors declare no competing financial interest.

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