A New Reaction of Togni Reagent II: α-C–H Ester-Functionalization of Tertiary Amides

Md Imdadul H. Khan,[1,†] Jiaxin Yang,[1,†] Seong Jong Kim,[2] Hoang V. Le[1,*]

[1] Department of BioMolecular Sciences and Research Institute of Pharmaceutical Sciences, School of Pharmacy, University of Mississippi, University, MS 38677, U.S.A.

[2] Natural Products Utilization Research Unit, United States Department of Agriculture, Agricultural Research Service, University, MS 38677, U.S.A.

[†] These authors contributed equally to this work.

[*] Corresponding author: hle@olemiss.edu

ABSTRACT: Togni reagent II is a synthetically useful hypervalent iodine reagent for direct trifluoromethylation. Herein, we report a new reaction of Togni reagent II: α-C–H ester-functionalization of tertiary amides. This α-acyloxylation reaction proceeds smoothly in the presence of a mild base at 25–30 °C and produces moderate-to-high yields. This newly discovered reaction adds another dimension to the utility of Togni reagent II and provides direct and easy access to α-acyloxy amides and α-hydroxy amides.

Keywords: Togni reagent II; α-C–H ester-functionalization; benzoyloxylation; α-acyloxy amides; α-hydroxy amides

Our lab recently reported an efficient synthetic route to *L*-γ-methyleneglutamine and its amide derivatives.[1] We also showed that these *L*-γ-methyleneglutamic acid amides had potent anticancer activity against various breast cancer, glioblastoma, and head and neck cancer cell lines.[1,2] These compounds hold promise as novel therapeutics for broad applications in anticancer therapy.[2] As part of our ongoing effort to modify these glutamine-based compounds at the γ position, we serendipitously discovered a new reaction of Togni reagent II. Developed by Togni and coworkers, 1-trifluoromethyl-1,2-benziodoxol-3(1*H*)-one,[3] commonly known as Togni reagent II, is often used in organic synthesis for direct trifluoromethylation.[4,5]

Many important molecules in the pharmaceutical and agrochemical sectors contain one or more fluorine atoms. The inclusion of the fluorine atoms in these molecules often leads to an increase in their bioactivity, permeability, and, most importantly, metabolic stability resulting from the C-F bond's thermodynamic and kinetic stability.[6–8] In recent years, new synthetic methods to add a trifluoromethyl group to various molecules have been developed.[5,9] Besides the aforementioned benefits that the fluorine atom brings to the molecules, a trifluoromethyl group can also be used as a bioisostere for many different functional groups, including isopropyl, ethyl, and nitro.[10,11]

A trifluoromethyl group can be introduced into molecules through radical ($CF_3^{\cdot}$), electrophilic (CF_3^+), or nucleophilic (CF_3^-) trifluoromethylation reactions. Radical trifluoromethylation reactions are the most commonly used and often require the companion of transition metal catalysts or photocatalysts [common reagents include Umemoto's,[12] Togni II,[5] Langlois,[13] Baran,[14] CF_3I/triethylborane,[15] $(bpy)Cu(CF_3)_3$,[16] and $(bpy)Zn(CF_3)_3$[17]]. Some of these reagents can also participate in electrophilic trifluoromethylation reactions in the absence of metal catalysts or photocatalysts (common reagents include Togni I and Togni II).[5] Nucleophilic trifluoromethylation reactions are also popular, but the CF_3^- anion in these reactions tends to undergo rapid decomposition to a fluoride anion and difluorocarbene[5,9,18,19] (common reagents include Ruppert-Prakash,[9] Colby,[20] fluoroform,[21] and phenyl trifluoromethyl sulfone[22]).

Some of the most useful trifluoromethylation reagents were developed by Togni and coworkers. Togni reagent II (**Figure 1A**) generates a trifluoromethyl electrophile or a trifluoromethyl radical in the reactions, which can react with a variety of functional groups and rings, including alkyls and aryl alcohols,[23] ketene silyl acetals,[24] *N*,*N*-dialkylhydrazones,[25] oxindoles,[5,26] indoles,[27,28] unsaturated carboxylic acids,[29,30] electron-rich enamides,[31] electron-deficient alkenes,[32] allylic position of unactivated alkenes,[33,34] enones and related α,β-unsaturated carbonyls,[35] and quinones.[36,37] Togni reagent II is also used to introduce the trifluoromethyl group to a variety of natural products that contain a thiol, such as octreotide[38] and coenzyme A.[39] Togni reagent II can also react with allylsilanes,[40,41] arylsufinate sodium salt,[42] and phosphine.[43] Addition of the trifluoromethyl group to various heterocycles, such as lactone,[5,44] butenolide,[45] pyrazole,[46] and phenanthridine,[47] are also done by using Togni reagent II. Togni reagent II also reacts with terminal alkenes and alkynes in the presence of copper iodide, but it adds both the trifluoromethyl group and the 2-iodobenzoyloxy group to them[48] (the authors coined the term "trifluoromethyl-benzoyloxylation" for this transformation, [48] which is later also known as oxytrifluoromethylation).[5,49] Reactions between alkenes and Togni II in the presence of trimethylsilyl cyanide and copper(II) triflate add both the trifluoromethyl group and the cyano group to the molecules (cyanotrifluoromethylation).[50] A summary of these reactions is shown in **Figure 1B**.

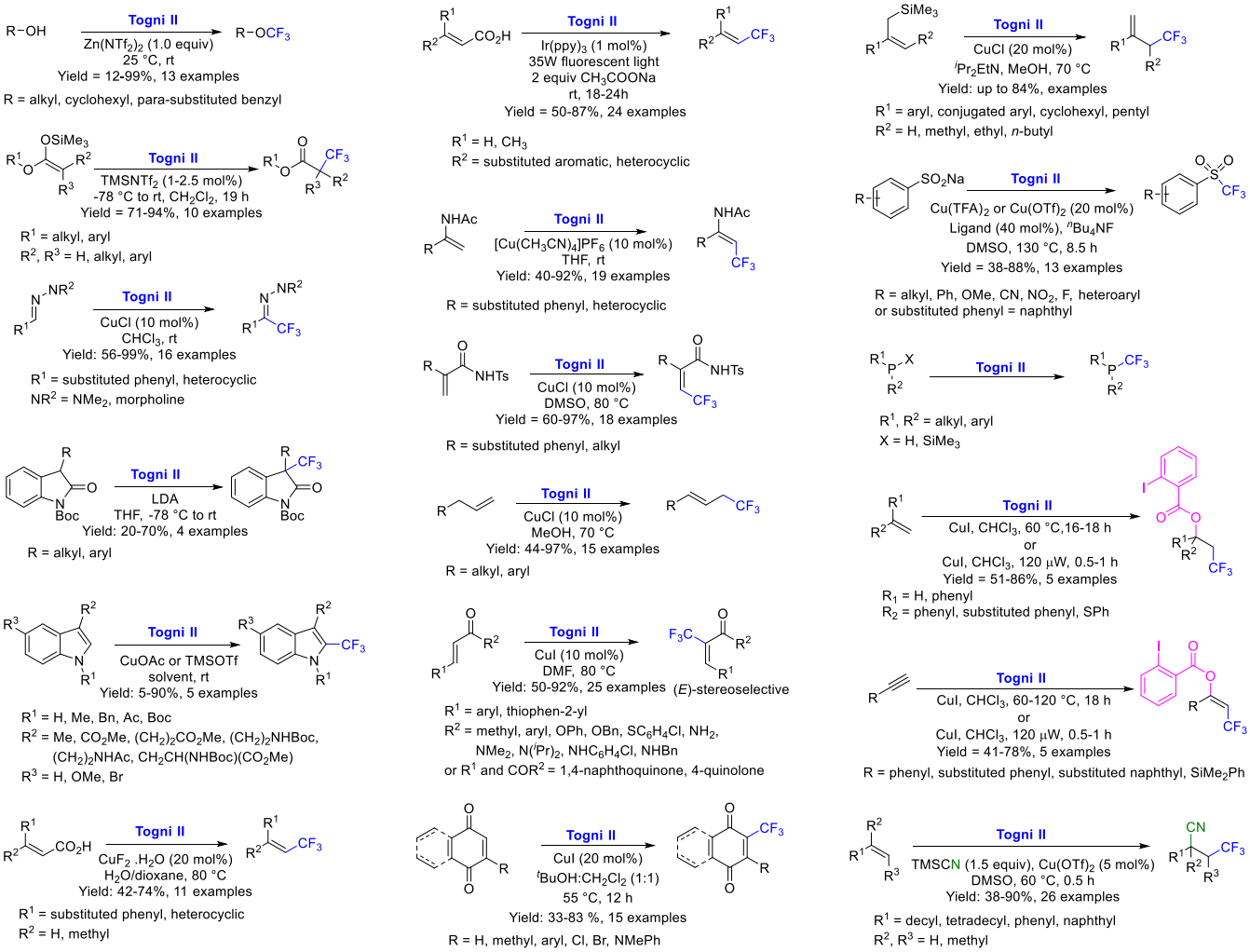
Herein, we report a new reaction of Togni reagent II: α-C–H ester-functionalization of tertiary amides (**Figure 1C**). This reaction proceeds smoothly in the presence of the mild base 2-iodopyridine, triflic anhydride, and 2,6-lutidine *N*-oxide in dichloromethane at 25–30 ºC for 15 h and produces α-(2-iodobenzoyloxy)amides in moderate-to-high yields. This newly discovered reaction of Togni reagent II provides direct and easy access to α-acyloxy amides, which can be hydrolyzed to α-hydroxy amides in almost quantitative yields. This new reaction expands the utility of Togni reagent II in synthetic methodology. α-Acyloxy amides[51] and α-hydroxy amides[51,52] are valuable molecules in pharmaceutical and agricultural fields.

We were inspired by the work of Maulide and coworkers on α-C–H functionalization of tertiary amides with heteroatom nucleophiles.[53] We used the same reaction condition, but replaced the heteroatom nucleophiles with Togni reagent II, expecting to obtain the α-C–H trifluoromethylated amide products. *N*,*N*-Dimethyl-4-phenylbutanamide was used as the starting material and stirred with 2-iodopyridine and triflic anhydride in dichloromethane for 10 min at 0 ºC. Then, 2,6-lutidine *N*-oxide was added and stirred for 5 min before adding Togni reagent II. The ice bath was removed, and the reaction solution was stirred at rt for 15 h. To our surprise, 1-(dimethylamino)-1-oxo-4-phenylbutan-2-yl 2-iodobenzoate, which is an α-C–H ester-functionalized amide, was obtained in 60% yield (**1**, **Figure 2**). No trifluoromethylated compounds were observed. We wondered if this new α-C–H ester-functionalization by Togni reagent II can be generalized for other amides. So, we synthesized various amides with different substituents (**Schemes S1–S3**, **Supporting Information**) and used them as starting materials under the reaction conditions mentioned above. Primary and secondary amides did not give any α-C–H ester-functionalized products (**2** and **3**, **Figure 2**). Only tertiary amides gave α-C–H ester-functionalized products in moderate-to-high yields (**1** and **4–10**, 10–70%, **Figure 2**). No trifluoromethylated products were observed in any of these reactions. Steric hindrance of the substituents on tertiary amides appeared to affect the yields of the α-C–H ester-functionalization. Going from *N*,*N*-dimethyl amide (**1**) to *N*,*N*-diethyl amide (**4**), the yield decreased from 60% to 28%. Similarly, going from pyrrolidine amide (**5**) to piperidine amide (**6**), the yield decreased from 67% to 27%. Pyrrolidine amide (**5**) had a slightly better yield than *N*,*N*-dimethyl amide (**1**), possibly due to the reduced steric hindrance of the constrained pyrrolidine ring. Shortening the linker between the benzene ring and the amide group from 3 carbons (**5**) to 2 carbons (**7**) and 1 carbon (**8**) led to a decrease in the yield from 67% to 32% and 10%, respectively. Furthermore, the reaction condition was observed to tolerate various reactive groups and rings, such

as 3,4-dimethoxyphenyl (**8**), terminal alkene (**9**), and 1,3-benzodioxole (**10**). Notably, **10** is the α-ester of the natural product tetrahydropiperine, which is found in *piper nigrum* L.[54] and in the dried fruits of *piper longum*.[55] Tetrahydropiperine has shown insecticidal activity.[54] Tetrahydropiperine also acts as a topical permeation enhancer for other compounds and is marketed as Cosmoperine© by Sabinsa Corporation for this purpose.[56] When included in formulations with other bioactive compounds, tetrahydropiperine was shown to enhance their bioavailability and utility.[56,57] Tetrahydropiperine can be synthesized from the natural product piperine using hydrogenation.[58] We followed the reported hydrogenation method to make tetrahydropiperine from piperine for this study (**Scheme S3**, **Supporting Information**). Piperine is the alkaloid responsible for the pungency of black pepper and long pepper.[59] We also carried out the α-C–H ester-functionalized reaction on piperine to see if α-unsaturated carbon can be functionalized under the above reaction condition, but the desired α-(2-iodobenzoyloxy) piperine **11** was not observed (**Figure 2**).

A) Structure of Togni Reagent II:

B) Known reactions of Togni reagent II



C) A new reaction of Togni reagent II

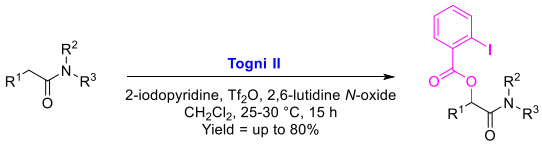


Figure 1. A) Structure of Togni reagent II; **B)** Known reactions of Togni reagent II; **C)** A new reaction of Togni reagent II

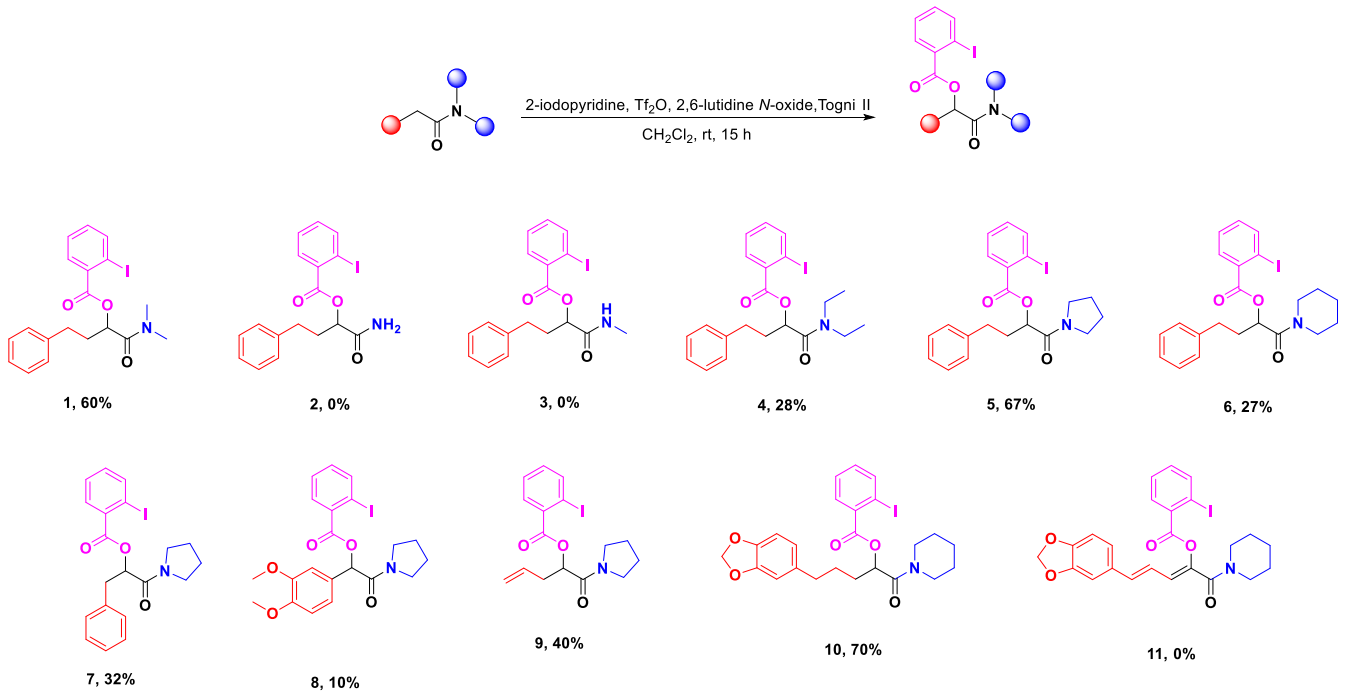
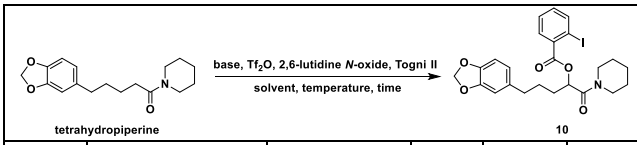


Figure 2. Scopes of α-C–H ester-functionalization of amides by Togni reagent II. Tf_2O, triflic anhydride; CH_2Cl_2, dichloromethane; rt, room temperature.

Table 1. Optimization of reaction condition for the synthesis of the α-(2-iodobenzoyloxy) tetrahydropiperine **10**



Entry	Base	Solvent	T (°C)	Time (h)	Yield (%)
1	2-I-pyridine	CH_2Cl_2	rt	15	70
2	pyridine	CH_2Cl_2	rt	15	25
3	2-F-pyridine	CH_2Cl_2	rt	15	15
4	2-Cl-pyridine	CH_2Cl_2	rt	15	40
5	2-Br-pyridine	CH_2Cl_2	rt	15	22
6	2-NH_2-pyridine	CH_2Cl_2	rt	15	0
7	2-I-pyridine	CH_2Cl_2	30	15	80
8	2-I-pyridine	CH_2Cl_2	40	15	5
9	2-I-pyridine	CH_2Cl_2	30	4	40
10	2-I-pyridine	CH_2Cl_2	30	24	60
11	2-I-pyridine	acetonitrile	30	15	55
12	2-I-pyridine	MeOH	30	15	0

Because tetrahydropiperine has insecticidal activity and useful applications, the α-(2-iodobenzoyloxy) tetrahydropiperine **10** could potentially have relevant biological activity and therapeutic applications of its own. Therefore, we optimized the reaction condition for its synthesis (**Table 1**). We performed the reaction with various bases, solvents, temperatures, and durations of time. When pyridine was used as the base, instead of 2-iodopyridine, in dichloromethane at rt for 15 h, the yield dropped from 70% to 25% (entry 2 vs. 1). When other 2-halopyridines (2-fluoro, 2-chloro, and 2-bromo) were used, the yield ranged from 15% to 40% (entries 3–5). When 2-aminopyridine was used, no desired product **10** was observed (entry 6). In general, 2-iodopyridine appeared to be the best among the bases that we screened, so we kept 2-iodopyridine as the base. When we increased the temperature from rt to 30 °C, the yield increased from 70% to 80% (entry 7 vs. 1). Interestingly, when the temperature was increased to reflux (at ~40 °C), the yield dropped dramatically to 5% (entry 8). When the reaction time was reduced to 4 h, the yield dropped to 40% (entry 9). When the reaction time was increased to 24 h, some degradation of the product was observed, and the yield dropped to 60% (entry 10). We then kept 2-iodopyridine as the base, the temperature at 30 °C, and the reaction time at 15 h, but used acetonitrile, another aprotic solvent, instead of dichloromethane (entry 11). The reaction, however, only gave a moderate yield of 55%. When methanol, a protic solvent, was used,

no desired product **10** was observed (entry 12). Notably, in all of the above entries, the starting material, tetrahydropiperine, was fully consumed; therefore, bases with a free amine (such as 2-aminopyridine) or protic solvents (such as methanol) appeared to interfere with the intermediates in the reaction progress (0% yield, entries 6 and 12, respectively).

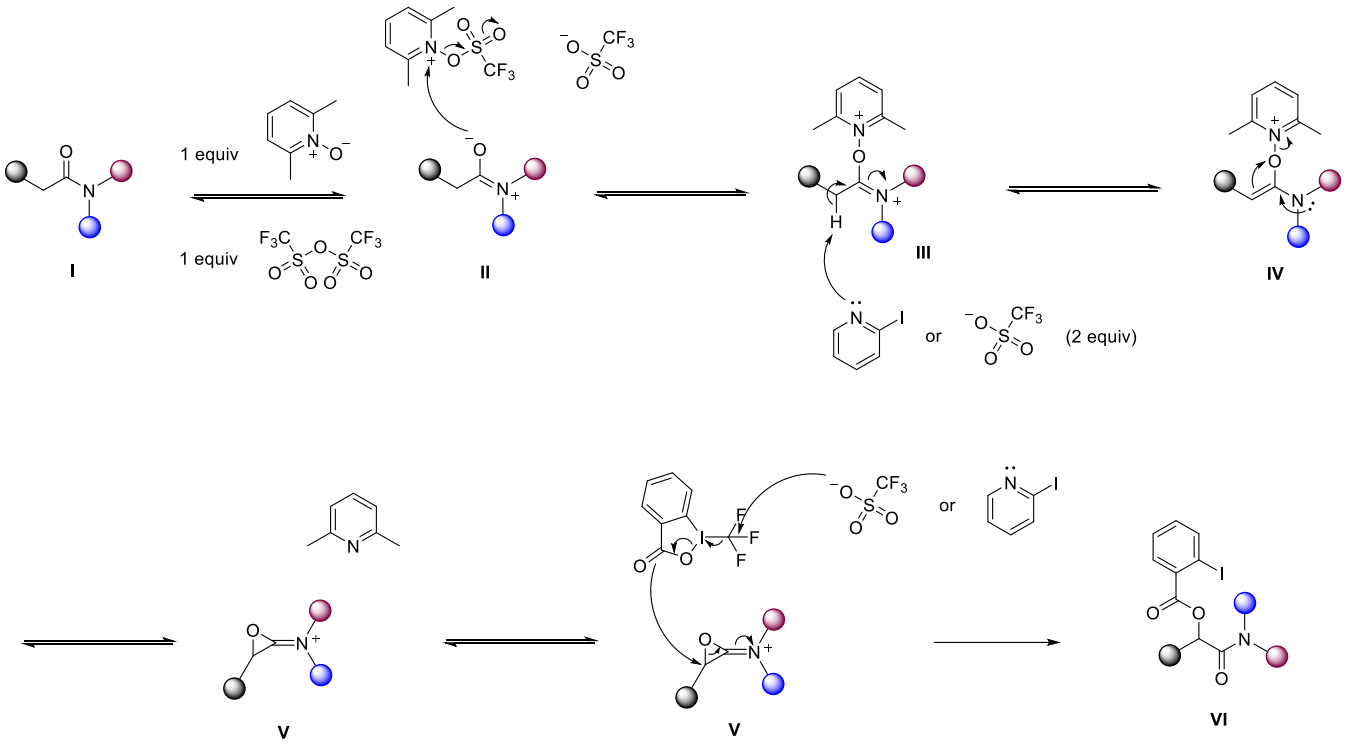


Figure 3. Proposed mechanism of the α-C–H ester-functionalization of tertiary amides by Togni reagent II

A proposed mechanism for the α-C–H ester-functionalization of tertiary amides by Togni reagent II is shown in **Figure 3**. 2,6-Lutidine *N*-oxide would first react and activate triflic anhydride to form triflate anion and triflated lutidine, which is immediately attacked by the nucleophilic oxygen atom in the C=N resonance structure of the amide (**II**) to form **III** and another triflate anion. 2-Iodopyridine or the newly formed and excessed triflate anion will abstract the proton on the α-carbon of **III** to form enolonium **IV**. The lone pair of electrons on the nitrogen atom in **IV** will trigger the production of epoxide **V** and the release of 2,6-lutidine. This formation of enolonium **IV**, epoxide **V**, and 2,6-lutidine were proposed by Maulide and coworkers when they worked with α-C–H functionalization of tertiary amides using 2,6-lutidine *N*-oxide, triflic anhydride, 2-iodopyridine, and heteroatom nucleophiles.[53] Maulide and coworkers reached this proposed mechanism after several rounds of revision and mechanistic studies.[53,60–62] In the next step of our proposed mechanism for the α-C–H ester-functionalization of tertiary amides, Togni reagent II is activated by 2-iodopyridine or triflate anion, which undergoes an SN2 nucleophilic substitution on the trifluoromethyl group and opens up the benzoate-iodo ring. The newly formed benzoate anion then attacks epoxide **V**, leading to the formation of α-(2-iodobenzoyloxy)amide **VI**. All steps up to the final step should be in equilibrium. The driving force for the overall transformation is the formation of the stable amide product.

Overall, the reaction proceeds smoothly in relatively non-polar aprotic solvents, like

dichloromethane, but does not proceed when a protic solvent, like methanol, was used. Both the type of the base and the equivalents of triflic anhydride play important roles in this reaction. Bases with a free amine, such as 2-aminopyridine, interfere with the reaction progress. When we repeated the reaction in entry 7 of Table 1 but used only 0.55 equiv of triflic anhydride, the yield decreased to 20%. α-C–H at an unsaturated carbon, such as in the case of piperine, is not compatible with this transformation. Furthermore, this transformation appears to be specific to Togni reagent II. When we repeated the reaction in entry 7 of Table 1 but replaced Togni reagent II with sodium benzoate, no desired α-benzoyloxyamide was observed, even though the amide starting material was consumed. Furthermore, unlike in the case of α-C–H functionalization of tertiary amides with heteroatom nucleophiles performed by Maulide and coworkers,[53] the reaction with Togni reagent II did not go through the α-triflated amide intermediates, despite our many attempts to detect by high-resolution mass spectrometry and isolate.

In conclusion, we have reported a new reaction of Togni reagent II: α-C–H ester-functionalization of tertiary amides. This new reaction adds a new dimension to the utility of Togni reagent II by providing direct and easy access to α-acyloxy amides and α-hydroxy amides (α-acyloxy amides were easily converted to α-hydroxy amides in almost quantitative yields by using K_2CO_3, **Scheme S4**, **Supporting Information**). Hypervalent iodine reagents, including Togni reagent II, can be synthesized in one pot.[63] α-Acyloxylation of amides has always been a difficult transformation to perform, and up until our report, it can only be applied to tertiary amides with a terminal α carbon.[64,65] In one report, aromatic carboxylic acids were oxidatively coupled with terminal α carbon of tertiary amides using a copper catalyst at a high temperature (150 °C) for 24 h, producing moderate yields.[64] In another report, oxy-alkynylation was performed on 2-diazo-*N*,*N*-diethylacetamide using various hypervalent iodine reagents and copper catalysts with both the alkynyl group and the 2-iodobenzoyloxy group being added to the compound.[65]

SUPPORTING INFORMATION

The Supporting Information is available free of charge at

Experimental procedures, full characterization of all prepared compounds, and copies of all spectral data.

CONFLICT OF INTEREST

The authors report no conflict of interest.

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GRAPHICAL ABSTRACT