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Alkene Trifluoromethylation-Initiated Remote α-Azidation of Carbonyl Compounds toward Trifluoromethyl γ-Lactam and Spirobenzofuranone-Lactam

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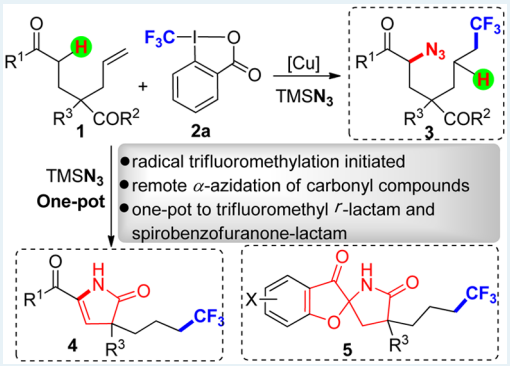
Supporting Information

ABSTRACT: The first unprecedented one-pot domino strategy toward diverse CF_3-containing γ-lactam and spirobenzofuranone-lactam scaffolds of antibacterial armeniaspirole from readily available acyclic precursors was developed. The key point of this transformation was the concurrent incorporation of CF_3 and azide into the alkene and remote carbonyl α-C−H position via carbonyl-stabilized radical intermediate triggered by alkene trifluoromethylation via a 1,5-H shift in a highly controlled site-selective manner. Furthermore, gram-scale synthesis and synthetic applicability of these compounds proved suitable.



KEYWORDS: *α-azidation, 1,5-H shift, trifluoromethylation, γ-lactam, spirobenzofuranone-lactam*

Spirofuranone-lactam cores are important structural motifs in many pharmaceuticals and natural products, such as cephalimysin A,[1a] strobilanthoside A,[1b] and armeniaspirols A−C[1c−e] (Figure 1). Specifically, armeniaspirol containing a unique spirobenzofuranone-lactam scaffold represents novel antibiotic lead structures[1d] and minor structural modifications of the substituents around such core result in markedly different antibacterial activity profiles.[1e] It is well-known that the selective incorporation of a trifluoromethyl (CF_3) group into drug molecules may give rise to significant improvement in the drug's pharmacokinetic properties, binding selectivity, and metabolic stability.[2] Consequently, much attention has been paid to the introduction of CF_3 groups into molecules for fine-tuning of the biological properties of the drug candidates.[3] Although endeavors have been devoted to spirobenzofuranone-lactam scaffold syntheses through some multistep sequences in recent years,[1d,e,4] so far, no general methodologies are available for the direct synthesis of this type with the concurrent incorporation of CF_3 group at a specific site in a domino version. Thus, to explore the structure−activity relationships (SAR) and considering the increasing importance of CF_3 group in improving potential antibacterial properties, the novel convergent one-pot method toward trifluoromethyl spirobenzofuranone-lactam scaffolds, preferably starting from readily available acyclic precursors, represents an unmet challenge and is in great demand.

Great advances have been made in trifluoromethylation of alkenes by using Togni's reagent[5] via a single-electron-transfer (SET) process[6] since the pioneering studies for allylic trifluoromethylation carried out by Buchwald,[7a] Liu,[7b] and Wang.[7c] In this regard, our group has been interested in the development of the radical domino process of using a radical trifluoromethylation of olefin to trigger a 1,5-H shift and further remote α-C−H bond functionalization of a protected amine.[8a] A unique feature of such a process resides in the marked preference for the generation of a lower-energy radical stabilized by the adjacent nitrogen atom, thus providing a driving force for 1,5-H atom abstraction by an inherently high-energy α-CF_3-alkyl radical generated in situ from trifluoromethylation of the alkene. On the basis of this mode of activation, similar capabilities can be envisioned for corresponding remote carbonyl-mediated processes because of the presence of a driving force for 1,5-H atom abstraction from such an α-CF_3-alkyl radical to generate a lower-energy radical stabilized by the π-electron of the adjacent carbonyl group, thus possibly rendering remote α-C−H bond functionalization of carbonyl group in a highly controlled site-selective manner. However, such transient α-CF_3-alkyl radicals have been identified as highly reactive intermediates, such as allylic trifluoromethylation,[7] hydrotrifluoromethylation,[9] trifluoromethylative 1,2-difuctionalization of trapping reagents,[6] and 1,2-carbotrifluoromethylation.[10] Thus, the proposed remote carbonyl α-C−H functionalization process must compete with such transformations involving identical intermediates, rendering the outcome of this endeavor uncertain. Considering the importance of azide group as among the most common and valuable building blocks

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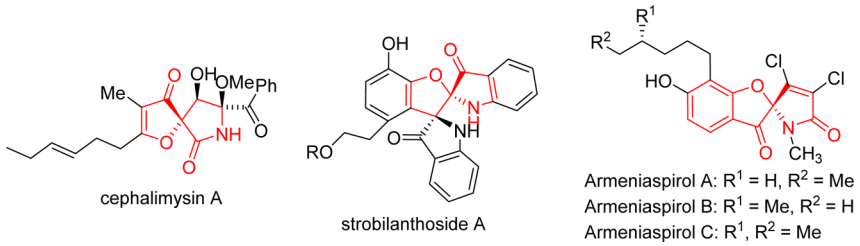
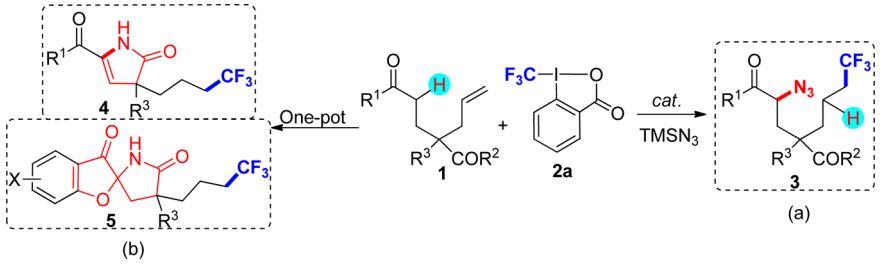


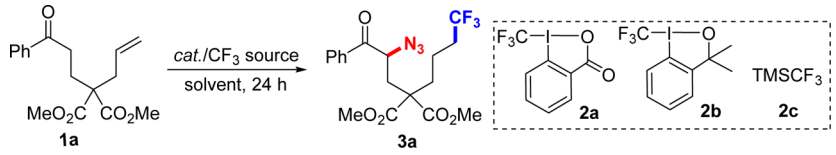
Figure 1. Natural products featuring the spirofuranone-lactam core.

Scheme 1. α-Azidation of Carbonyl Group Triggered by Trifluoromethylation of Olefin and Its Application[a]



[a](a) The formation of CF_3-containing α-azido ketone **3**. (b) One-pot construction of CF_3-containing γ-lactams **4** and spirobenzofuranone-lactams **5**.

Table 1. Screening Results of Reaction Conditions[a]



entry	catalyst	[CF_3]	solvent	T (°C)	**3a** [%][b]
1[c]	$PhI(OAc)_2$	**2c**	EtOAc	rt	0
2[d]	nBu_4NI	**2a**	CH_3CN	45	0
3	CuI	**2b**	CH_3CN	rt	43
4	CuBr	**2b**	CH_3CN	rt	35
5	CuCN	**2b**	CH_3CN	rt	37
6	$Cu(CH_3CN)_4PF_6$	**2b**	CH_3CN	rt	39
7	$Cu(OTf)_2$	**2b**	CH_3CN	rt	23
8	CuI	**2b**	EtOAc	rt	58
9	CuI	**2b**	DCE	rt	63
10	CuI	**2b**	DMSO	rt	17
11	CuI	**2b**	DCE	45	72
12	CuI	**2a**	DCE	45	83

[a]Reaction conditions: **1a** (0.1 mmol), $TMSN_3$ (0.3 mmol), CF_3 source (0.15 mmol), catalyst (10 mol %), solvent (2 mL) for 24 h under argon. [b]Determined by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard. [c]**1a** (0.1 mmol), $TMSCF_3$ (0.4 mmol), KF (0.4 mmol), $PhI(OAc)_2$ (0.2 mmol). [d]40 mol % of *n*-Bu_4NI was used.

in organic synthesis,[11] herein, we describe the first domino radical protocol for the concurrent incorporation of CF_3 and azide into alkene and remote carbonyl α-C−H position in a highly controlled site-selective manner (Scheme 1a). It is noteworthy that this reaction is also a potential alternative approach to α-azidation of carbonyl group.[12] Most importantly, owing to the excellent compatibility of various additional functional groups under the current methodology, the unprecedented one-pot domino transformation providing a convenient and step-economical access to diverse trifluoromethyl γ-lactam and spirobenzofuranone-lactam scaffolds was also accomplished (Scheme 1b).

To probe the feasibility of our proposed assumption, we started our investigation by reacting alkenyl ketone **1a** with azidotrimethylsilane ($TMSN_3$) as the model reaction, inspired by the seminal work about 1,2-azidotrifluoromethylation of alkenes reported by Liu and co-workers.[13] We initially examined such a reaction under metal-free conditions by using CF_3SiMe_3 as the CF_3 source and $PhI(OAc)_2$ as the oxidant,[9a,14] or Togni's reagent **2a** with *n*-Bu_4NI as the CF_3 radical initiator,[15] respectively. Unfortunately, in all cases, no desired product was observed (entries 1−2, Table 1). We had to turn our attention to the use of transition metals as the catalyst to initiate Togni's reagents. To our delight, the use of CuI as the catalyst initiated a sequential alkene/remote carbonyl α-C−H difunctionalization reaction of **1a** with **2b** to afford the desired CF_3-containing α-azido ketone **3a** in 43% yield (entry 3). Encouraged by this result, various reaction conditions were examined to improve the product yield. Upon optimization of the conditions through variation of the copper salt, solvent,

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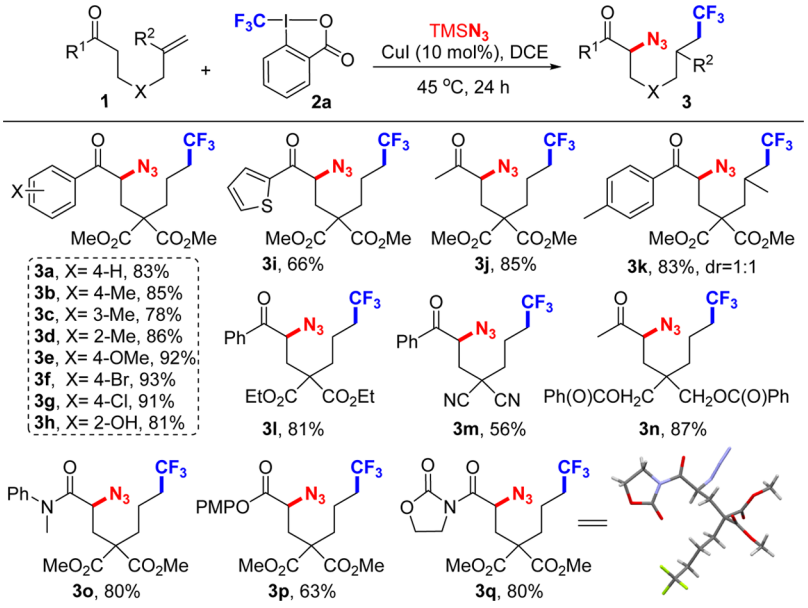
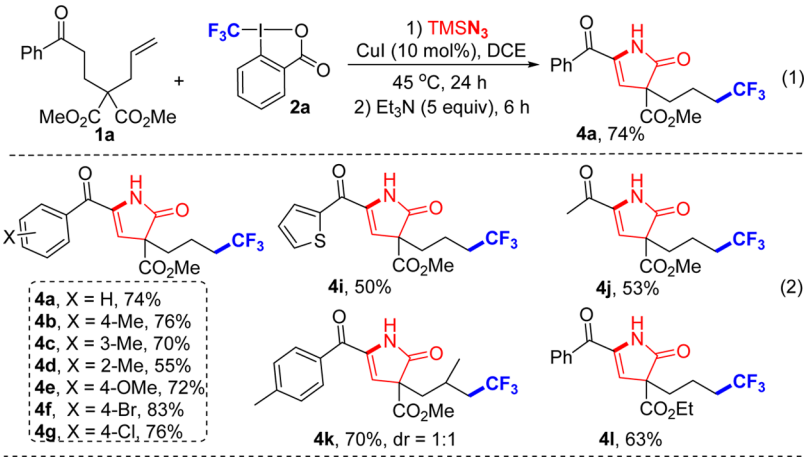
Table 2. Screening Results of Reaction Conditions[a,b]



[a]All the reactions were conducted on a 0.2 mmol scale. [b]Isolated yields based on the alkene.

Scheme 2. One-Pot Construction of CF_3-Containing γ-Lactams 4



reaction temperature, and Togni's reagent (entries 4−12), the optimal reaction conditions were determined to be 10 mol % of CuI with **2a** as the CF_3 source in DCE at 45 °C for 24 h, giving **3a** in 83% yield (entry 12).

We next investigated the substrate scope of alkenyl carbonyls with diverse substituents. As shown in Table 2, a variety of alkenyl aryl ketones, bearing electron-neutral (H), electron-donating (Me, OMe), or synthetically attractive electron-withdrawing (Br, Cl) groups at the different positions of the phenyl ring reacted smoothly with $TMSN_3$ and **2a**, affording the expected products **3a**−**3g** in 78−93% yields. Notably, the introduction of a reactive hydroxyl group at the ortho position did not affect the product yield (**3h**, 81% yield). The substrates with heteroaromatic and alkyl groups at the α position of carbonyl were also suitable to give **3i** and **3j** in good yields, respectively. The gem-disubstituted alkene **1k** also underwent this reaction to furnish **3k** in 83% yield as a mixture of two diastereomers (1:1 dr). Furthermore, changing the methyl ester to other tethered groups, such as ethyl ester (**1l**), nitrile (**1m**), and benzoate methylene (**1n**), had no significant influence on the reaction to give **3l**−**3n** in 56−87% yields. Most importantly, a variety of electronically distinct carbonyl groups, including amide (**1o**), ester (**1p**), or oxazolidinone (**1q**) in place of ketone, were also found to be compatible with the current reaction system, giving the expected products **3o**−**3q** in good yields. The structure of **3q** was further confirmed by X-ray analysis.[16]

To our great surprise, when Et_3N was used as the additive with DMSO as solvent during the course of the optimization of the reaction conditions, the unexpected trifluoromethyl γ-lactam **4a**, instead of **3a**, was obtained, albeit in only 15% yield. This finding can be attributed to the fact that **3a**, in situ generated by such a domino system, could further undergo an intramolecular cyclization in the presence of base via a cascade pathway. Although the product yield is very low, we recognized that further optimization of this reaction would offer a novel and promising method to synthesize trifluoromethyl γ-lactams containing a quaternary stereogenic center and various additional functional groups; such compounds could be potentially utilized in medicinal chemistry and serve as useful building

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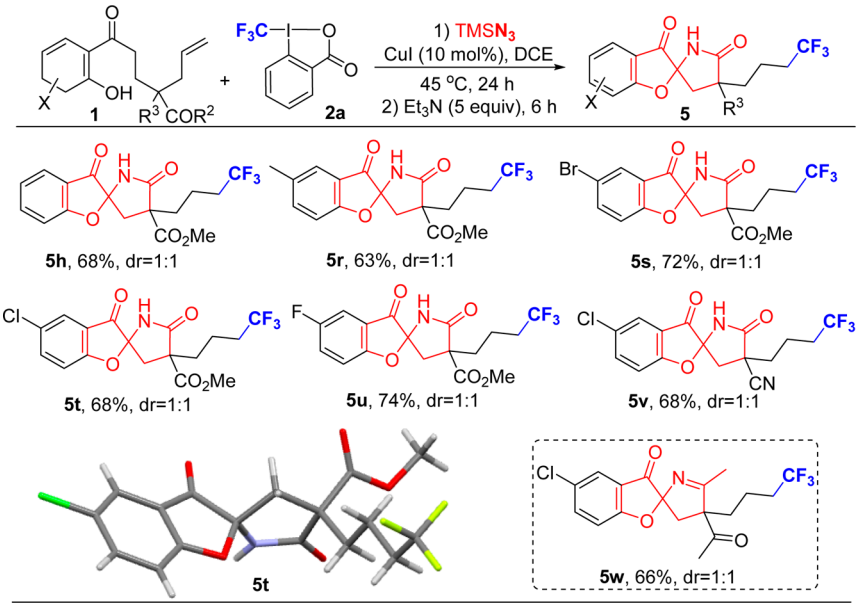
Table 3. Synthesis of Trifluoromethyl Spirobenzofuranone-Lactams 5

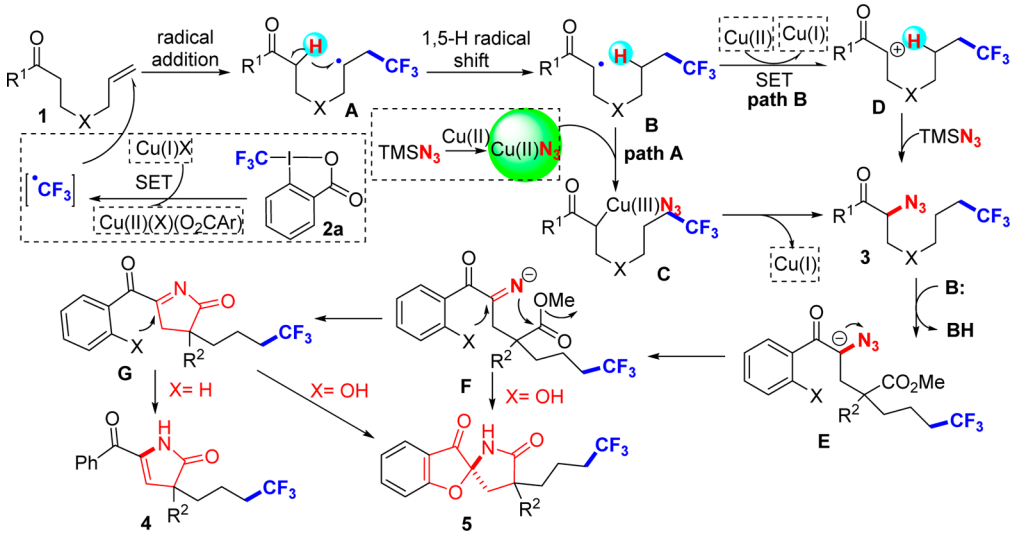


blocks for the synthesis of other biologically active compounds.[2,3] To address the issue, after systematic optimization of different reaction parameters, we are pleased to find that a very simple one-pot procedure was realized: **1a** was efficiently converted into **3a** within 24 h under the standard conditions, followed by the simple addition of Et_3N (5.0 equiv) without changing any reaction conditions for 6 h to afford **4a** in 74% yield (Scheme 2, eq 1). According to this one-pot procedure, which involves only simple sequential addition steps and a single purification, all of the CF_3-containing γ-lactams **4a**−**4l** bearing different functional groups were obtained in reasonable yield from readily available acyclic precursors with simple reagents under mild reaction conditions (Scheme 2, eq 2).

It should be noted that substrate **1h** bearing a hydroxyl substituent was very compatible with the current system. As such, we envisioned that such a hydroxyl group could further undergo intramolecular nucleophilic attack on the resultant γ-lactam from reaction of **1h** with **2a** promoted by base, to give trifluoromethyl spirobenzofuranone-lactam. If this approach is successful, it will give new insight into the convenient and step-economical synthesis of CF_3-containing spirobenzofuranone-lactam scaffold of armeniaspiroles as novel antibacterial lead structures.[1c−e] To our delight, treatment of **1h** with the one-pot process identical to those of the synthesis of **4** gave the expected product **5h** in 68% yield as a mixture of two diastereomers (1:1 dr) (Table 3). Under the optimal conditions, a range of substrates containing electron-donating or -withdrawing groups at the phenyl ring were also well tolerated to afford **5r**−**5v** in 63−74% yields. The structure of **5t** was confirmed by X-ray analysis.[16] The importance of the current one-pot protocol was further highlighted by the efficient synthesis of other novel azaspiro polycyclic molecules, as exemplified with **5w**, while changing the methyl ester to an acetyl group (**1w**) in the tether.

To further evaluate the practicality of this one-pot process, the reaction was carried out on a gram scale. There was almost

Scheme 3. Proposed Mechanism



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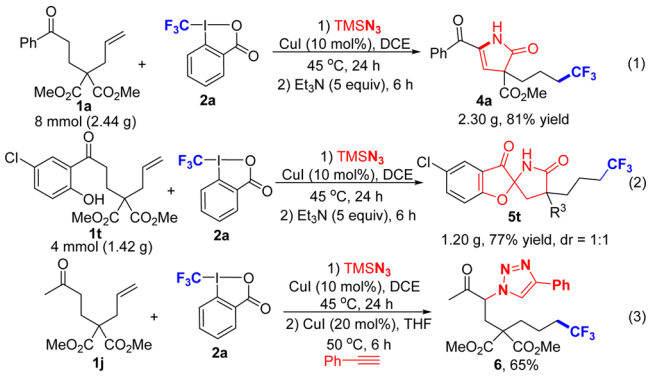
no influence on the chemical yield for the synthesis of **4a** (2.3 g, 81% yield) and **5t** (1.2 g, 77% yield), respectively, clearly demonstrating the robustness of this process (eqs 1 and 2). Meanwhile, to facilitate its potential transformation of CF_3-containing α-azido ketones, the one-pot process involving treatment of **1j** with $TMSN_3$ and **2a** and following direct reaction of phenyl acetylene was successfully realized to afford the desired CF_3-containing triazole **6** in 65% yield (eq 3).



Although further investigations are required, we propose the following reaction mechanism on the basis of the above results and by considering our previous mechanistic investigation (Scheme 3).[8] At the first step, the CF_3 radical, generated from reaction of **2a** with Cu(I), attacks alkene to produce the intermediate **A**, followed by translocation of a proximal hydrogen atom adjacent to the carbonyl group via a 1,5-H radical shift to generate radical **B**. The Cu(II)X intermediate, in situ-generated from ligand exchange of Cu(II)(X)(O_2CAr) species with $TMSN_3$, could then be oxidized by radical **B** to give a Cu(III) species **C** (path A),[10e,17] which leads to the final product **3**, through reductive elimination.[18] An alternative reaction pathway involving the formation of carbonyl cation **D**[19] through single-electron oxidation from Cu(II) species, followed by subsequent nucleophilic addition of $TMSN_3$, could not be excluded at the present stage (path B). Then, in the presence of base, the resultant base-sensitive α-azido ketone **3** could undergo base-promoted deprotonation and subsequent denitrogenation to give imino anion **F**.[20] Subsequent intramolecular nucleophilic trapping of this imino anion by ester affords cyclic intermediate **G**, followed by tautomerization to provide **4**. In the case of a substrate bearing a hydroxyl group, the intermediate **F** or **G** could further undergo intramolecular nucleophilic attack by its hydroxyl oxygen atom to furnish **5**.

In summary, we have successfully developed the first copper-catalyzed domino radical protocol for the concurrent incorporation of CF_3 and azide into alkene and remote carbonyl α-C–H position via carbonyl-stabilized radical intermediate triggered by trifluoromethylation of an alkene via a 1,5-H radical shift in a highly controlled site-selective manner. Most importantly, the newly developed one-pot domino protocol provides novel and rapid access to valuable diverse CF_3-containing γ-lactam and spirobenzofuranone-lactam scaffolds of antibacterial armeniaspirole, thus demonstrating great potential in synthetic and medicinal chemistry. Mechanistic studies, an asymmetric variant, and exploring the SAR are currently under investigation.

■ ASSOCIATED CONTENT

Supporting Information

The following files are available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.5b00311.

Experimental procedures, characterization of all new compounds (PDF)

X-ray data (cif files) of **3q** (CIF)

X-ray data (cif files) of **5t** (CIF)

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Notes

The authors declare no competing financial interest.

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(16) CCDC 1048188 (**3q**) and CCDC 1048187 (**5t**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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