Copper-Catalyzed Intermolecular Trifluoromethylazidation of Alkenes: Convenient Access to CF₃-Containing Alkyl Azides**

Fei Wang, Xiaoxu Qi, Zhaoli Liang, Pinhong Chen, and Guosheng Liu*

Dedicated to Professor Huilin Chen on the occasion of his 75th birthday

Abstract: A novel copper-catalyzed intermolecular trifluoromethylazidation of alkenes has been developed under mild reaction conditions. A variety of CF_3 -containing organoazides were directly synthesized from a wide range of olefins, including activated and unactivated alkenes, and the resulting products can be easily transformed into the corresponding CF_3 -containing amine derivatives.

Orangoazides have been recognized as important organic compounds and are widely applied in organic synthesis as valuable intermediates and building blocks because of their versatile chemical reactivities and bioactivities.^[1] For instance, elegant methodologies have been developed for the transformation of organoazides into nitrogen-containing heterocycles which have extensively been used in pharmaceuticals and agricultral chemicals.^[1a,b,f] Its unique reactivity permits their use in bioconjugation with click chemistry.^[2] In addition, the azide moiety has been used to design lead compounds for drug discovery. Representative compounds (A-C) exhibited some bioactivity, such as enzyme inhibition or antiviral and disrafting activity (Figure 1).^[3] Therefore, the introduction of an azide group into organic molecules has attracted much attention.^[1a,b,4,5] As we know, the trifluoromethyl group is prevalent in pharmaceuticals and agrochemicals owing to its unique properties.^[6] We speculated that, if both CF₃ and azide



Figure 1. Representative bioactive organic azides.

[*] F. Wang, X. Qi, Z. Liang, Dr. P. Chen, Prof. Dr. G. Liu State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences 345 Lingling Road, Shanghai, 200032 (China) E-mail: gliu@mail.sioc.ac.cn

[**] We are grateful for financial support from the National Natural Science Foundation of China (21225210, 21121062, and 20923005), the National Basic Research Program of China (973-2011CB808700), the Science Technology Commission of the Shanghai Municipality (11JC1415000), and the CAS/SAFEA International Partnership Program for Creative Research Teams.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201309991.

groups can be simultaneously introduced into organic compounds, efficient synthesis of trifluoromethylated organoazides and related amine derivatives might be expected, and might provide an opportunity to introduce CF_3 into the original lead compounds or drugs to adjust their bioactivity. However, the efficient synthesis of CF_3 -containing organoazides is quite rare.^[7] Herein, we report a novel coppercatalyzed intermolecular trifluoromethylazidation of alkenes to deliver vicinal CF_3 -substituted alkyl azides in one step, where the less reactive Togni reagent II is employed as a CF_3 source (Scheme 1). Importantly, broad substrate scope with respect to the olefins was observed, and a wide range of functional groups were tolerated under these reaction conditions. These CF_3 -containing organoazides can be easily transformed into related amine derivatives.

Recently, the groups of Buchwald, Liu, Wang and, Sodeoka reported copper-catalyzed allylic trifluoromethylation.^[8] Meanwhile, our group reported the first difunctionalization of alkenes involving trifluoromethylation using a palladium catalyst.^[9] Since then, a variety of trifluoromethylation reactions of terminal alkenes have been published.^[10] Among these studies, most of reactions were focused on terminal electron-rich olefins with limited substrate scope, and employed the very reactive Togni Reagent I as a CF3+ source. In addition, a carbon radical or carbon cation intermediate was proposed to be involved in these reactions (Scheme 1). Thus, we envisioned that, if this intermediate could be trapped by an azide reagent, a highly efficient synthesis of CF₃-containing organoazides might be expected. To test the above hypothesis, initial studies were focused on the model reaction of styrene (1a) with azidotrimethylsilane (TMSN₃) and a trifluoromethylating reagent in the presence of a copper catalyst.

As shown in Table 1, screening for the CF_3 source implied that the combination of $PhI(OAc)_2$ with trimethyl(trifluoromethyl)silane (TMSCF₃) did not deliver the desired trifluor-



Scheme 1. Trifluoromethylazidation of alkenes.

Angew. Chem. Int. Ed. 2014, 53, 1881-1886

© 2014 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Table 1: Optimization of the reaction conditions.[a,b]



-			
1	$PhI(OAc)_2 + TMSCF_3$	TMSN₃	0
2	Umemoto reagent	TMSN₃	38
3	Togni reagent I	TMSN ₃	65
4	Togni reagent II	TMSN₃	88
5	Togni reagent II	TsN ₃	0
6	Togni reagent II	NaN ₃	0
7 ^[c]	Togni reagent II	TMSN₃	89
8 ^[d]	Togni reagent II	TMSN₃	77
9 ^[e]	Togni reagent II	TMSN ₃	0

[a] Reaction conditions: **1a** (0.1 mmol), Cu catalyst (10 mol%), [N₃] (0.2 mmol), [CF₃⁺] reagent (0.15 mmol) in *N*,*N*-dimethylacetamide (DMA, 0.5 mL) at room temperature. [b] Yield determined by ¹⁹F NMR spectroscopy. [c] Copper(I) catalyst (5 mol%). [d] Copper(I) catalyst (2 mol%). [e] Without copper catalyst. TMS = trimethylsilyl, TsN₃ = 4-methylbenzenesulfonyl azide.

omethylazidation product (entry 1).^[11] Gratifyingly, the commonly used CF_3^+ reagent, such as the Umemoto reagent and Togni reagent I, could be used to achieve the intermolecular trifluoromethylazidation of alkenes (entries 2 and 3). And the reaction did afford the desired product 2a in 65% yield in the presence of the Togni reagent I. Unfortunately, a significant amount of a trifluoromethyl esterification product was also obtained as a side product, wherein o-iodobenzoic acid, released from Togni reagent I, was involved in the reaction.^[10c] And this side reaction could not be suppressed by further optimization of the reaction conditions. To address this issue, the less reactive Togni reagent II was applied and the reaction afforded **2a** in excellent yield (88%, entry 4). Next, some azide reagents were investigated. Only TMSN₃ was proven to be an efficient nitrogen source, and other reagents, such as TsN₃ and NaN₃, were ineffective (entries 4-6). Finally, a survey on metal catalysts demonstrated that copper salts were active catalysts, and $[Cu(CH_3CN)_4]PF_6$ was the best one. There is no significant drop in the yield when the catalyst loading is lowered to 5 mol%, and good yield (77%) could be also obtained with only 2 mol% catalyst. No reaction occurred in the absence of a copper catalyst (entries 7–9).^[12]

With the optimized reaction conditions in hand, the substrate scope of the styrenes was examined in the presence of 5 mol% of the copper catalyst and the results are summarized in Table 2. Substrates **1a–q**, having various substituents (R) on the aromatic ring, including electron-donating and electron-withdrawing groups, were compatible with the current transformation. And a series of functional groups, such as halogen, ester, phenol, nitro, nitrile, carboxylic acid, aldehyde, were tolerated under the reaction conditions to give the desired products **2a–q** in good yields. In particular,

Table 2: Substrate scope of the styrenes.^[a,b]



[a] All the reactions were conducted in 0.2 mmol scale. [b] Yield of isolated product. [c] 3.0 mmol scale. [d] (*E*)- β -methyl styrene as substrate. [e] (*Z*)- β -methyl styrene. [f] d.r. = 8:1; [g] d.r. = 12:1.

the substrate 1n, bearing an o-carboxylic acid, delivered the product 2n in good yield without any of the cyclization product.^[13] In addition, 2-chloro-3-vinylquinoline (1r) was also suitable for this transformation, thus giving the product 2r in 65% yield. The substrate 1s, with a triazole group, provided the corresponding product 2s in 95% yield. For the 1,1-disubstituted substrate 1t, the reaction proceeded very well to give the β -CF₃-substituted tertiary alkyl azide 2t in 93% yield. Compared to terminal alkenes, internal alkenes exhibited slightly lower reactivity. For instance, reactions of both (E)-1u and (Z)-1u afforded 2u with the same diastereoisomeric ratio (8:1), but in low yield (40 and 33%, respectively). For the electron-deficient styrene tert-butyl cinnamate (1v), the reaction also provided the desired product 2v in moderate yield (45%) and good diastereoselectivity (12:1), and it can be further transformed into a CF₃substituted β -amino acid.

Inspired by the reaction of styrenes, we turned our attention to expanding the substrate scope to alkyl-substituted alkenes. First, 1,1-dialkyl substituted alkenes were surveyed under standard reaction conditions. As shown in Table 3, to our great delight, a range of 1,1-dialkyl-substituted alkenes (3a-h) were suitable for this trifluoromethylazidation reaction and gave the tertiary alkyl azides 4a-h in good yields. Similar to styrenes, a series of functional groups, such as ester, ether, imide, and good leaving groups (OTs), were tolerated under these reaction conditions. However, following a survey of monoalkyl-substituted alkenes, the desired product was obtained in low yield. After additional optimization of the reaction conditions, we were delighted to find that the reaction yield could be improved by switching the solvent from DMA to CH₃CN (see the Supporting Information). As shown in Table 3, a number of monoalkyl-substituted alkenes Table 3: Substrate scope for acyclic alkenes.^[a,b]



[a] All the reactions were conducted on a 0.2 mmol scale. [b] Yield of isolated product. [c] Ratio of regioisomer.

could be transformed into the desired products 4i-q in moderate to good yields. Again, good functional-group compatibility was also observed. Furthermore, we postulated that, if α , β -unsaturated carboxylates were good candidates for this transformation, a highly efficient method for the synthesis of CF₃-containing α -amino acids might be achieved because of the easy conversion of an organoazide into an amine. Thus, several α,β -unsaturated substrates were tested. As shown in Table 3, all of those substrates were well tolerated under the reaction conditions and gave the corresponding products 4r-v in satisfactory yields. Interestingly, the vinyl phosphonic ester 3w delivered the desired product 4w, albeit in aslightly lower yield (30%). Finally, two conjugated dienes, 3x and 3y, were treated under the standard reaction conditions, and the substrate-controlled regioselectivities were observed to provide either 1,2- or 1,4-addition products. For instance, the reaction of 3x, bearing an aryl-substituted diene, afforded the 1,2-addition product 4x as the major product in 52% yield with 7:1 regioselectivity. In contrast, the reaction of 3y with the alkyl-substituted diene delivered the 1,4-addition product Table 4: Substrate scope of the cyclic alkenes.^[a,b]



[a] All the reactions were conducted on a 0.2 mmol scale. [b] Yield of isolated product. [c] CH₃OH as solvent. [d] Yield determined by ¹⁹F NMR spectroscopy. [e] Yield of the isolated amine derivatives RNHCbz (one-pot reaction). [f] Yield of the isolated RNHCOC₆H₄NO₂-p (one-pot reaction).

4y as the major product in 62% yield and 10:1 regioselectivity.

As mentioned above, the acyclic internal alkenes exhibited slightly poor reactivity. Thus, we turned to cyclic alkenes. As shown in Table 4, the reactions of cyclic substrates from five- to eight-membered rings proceeded smoothly to produce the trifluoromethylated cyclic organoazides 6a-e in good yields. Importantly, most of these reactions (5a-d) exhibited excellent diastereoselectivity. In contrast, reaction of the eight-membered-ring substrate 5e had moderate diastereoselectivity (5:1). Notably, as a result of the highly volatile nature of 6a,b and 6d,e, these products were directly transformed in situ into their amine derivatives for characterization. The structure of 6c was determined by X-ray analysis. For the substrates 5f,g, the reactions led to the products 6f,gin moderate yields with excellent diastereomeric ratios (> 20:1).

Next, several complex molecules containing an alkenyl group were selected as candidates for this transformation. As listed in Table 5, the steroid substrates 7a and 7b, bearing a cyclic alkenyl group, were compatible under these reaction conditions and yielded the desired *trans*-products **8a** and **8b**, respectively, in satisfactory yields with excellent regio- and diastereoselectivity. The structure of 8a was confirmed by Xray analysis. The cinchonine derivatives 7c and 7d were also good candidates for this transformation, thus giving 8c and 8d, respectively, in 50-54% yield with good diastereoselectivity (10:1). However, detailed configurations for 8c and 8d have not yet been determined. Finally, the alkene substrate 7e with a sugar moiety and the estrone derivative 7 f afforded the corresponding organoazide products 8e and 8f in 45% and 81% yields, respectively, but with low diastereoselectivity (1:1). All those products could be potentially utilized in medicinal chemistry.

Sodeoka and co-workers have reported that the reaction of 9 could yield the CF₃-containing oxindole 11 in the



Table 5: Substrate scope with respect to complex molecules.^[a,b]



[a] All the reactions were conducted on a 0.2 mmol scale. [b] Yield of the isolated product. [c] TMSN₃ (4 equiv) and the Togni reagent II (4 equiv). [d] Yield based on recovery of **7b** and **7e**. [e] CH_3CN as solvent.

presence of the Togni reagent I [Eq. (1)]. However, no reaction occurred by replacing the Togni reagent I with the less reactive Togni reagent II. Interestingly, when 9 was treated under our reaction conditions, the reaction only afforded the product 10 in 74% yield. This observation suggested that the Togni reagent II might be activated by a TMS group, then reacted with copper(I) to give the CF₃ radical species for the subsequent step.^[14] In addition, the alkene substrate 1w, having a cyclopropyl group, also proceeded well to afford the ring-open product (E)-2w in good yield and excellent stereoselectivity [Eq. (2)]. For the alkene 3z, bearing a cyclobutane group, the reaction also afforded the ring-open product 4z in 71% yield [Eq. (3)]. These experiments also indicate the involvement of a radical species in the catalytic process. For the final C-N₃ bond formation, either a pathway involving a carbon radical species trapped by an azide radical or a carbon cation intermediate reacting with an azide anion, are possible, but it is hard to differentiate at the moment.

Then, α , β -unsaturated carboxylic acids were subjected to the standard reaction conditions for the efficient synthesis of CF₃-substituted amino acids. As shown in Equation (4), the acrylic acids **12a** and **12b** could be directly converted into the corresponding **13a** and **13b** in good yields, and they can be readily transformed into the CF₃-amino acids **14a** and **14b**,



respectively, by hydrogenation. To achieve the synthesis of chiral CF₃ amino acids, a chiral sulfonylamide (NR*) was introduced into the substrates. As shown in Equation (5), the reaction of **15a** afforded **16a** in 68% yield with a 4:1 diastereomeric ratio. In contrast, reaction of **15b** delivered **16b** in 59% yield with good diastereomeric ratio (9:1). After recystallization, the chiral products **16b** (d.r. = 13:1) were further transformed into the related chiral CF₃ amino acids **14b** in good yields.





Further transformation of the trifluoromethylazidation products was investigated. As shown in Scheme 2, both 2aand 4i reacted with phenyl acetylene by employing copper(I) as a catalyst to give the CF₃-containing triazoles 17a (75%) and 17i (84%), respectively. In addition, those CF₃-containing azides, such as 2a and 4b, could also be reduced and protected to deliver trifluoroethyl-substituted amine derivatives in excellent yields. Interestingly, 4p was directly converted into 5-trifluoroethyl-2-pyrrolidone (18c). Finally, the CF₃-substituted amine of 18d was also obtained from the reduction of 8b in 86% yield.

In summary, we have developed a novel copper-catalyzed intermolecular trifluoromethylazidation of alkenes, in which the less reactive Togni reagent II was employed as an oxidant



Scheme 2. Further transformation of CF₃-containing organoazides. Reaction conditions: 1) In/NH₄Cl (2 equiv), MeOH, reflux; 2) CbzCl (1.1 equiv), Na₂CO₃ (1.2 equiv), THF, RT; 3) Boc₂O (2 equiv), EtOAc. Boc = *tert*-butoxycarbonyl, Cbz = benzyloxycarbonyl, THF = tetrahydrofuran.

as well as a CF₃ source under mild reaction conditions. Both activated and unactivated alkenes were suitable for this transformation, and a wide range of functional groups were tolerated under the reaction conditions. Those CF₃-containing organoazides can be easily converted into the corresponding amine derivatives. In addition, this method provides an efficient way to synthesize CF₃ amino acids. Further application of this reaction is in progress.

Received: November 18, 2013 Published online: January 13, 2014

Keywords: alkenes · azides · copper · fluorine · synthetic methods

- a) D. M. Huryn, M. Okabe, Chem. Rev. 1992, 92, 1745; b) S. Bräse, C. Gil, K. Knepper, V. Zimmermann, Angew. Chem. 2005, 117, 5320; Angew. Chem. Int. Ed. 2005, 44, 5188; c) S. Bräse, K. Banert, Organic Azides, Wiley-VCH, Weinheim, 2010; d) W. Song, S. I. Kozhushkov, L. Ackermann, Angew. Chem. 2013, 125, 6706; Angew. Chem. Int. Ed. 2013, 52, 6576; e) N. Jung, S. Bräse, Angew. Chem. 2012, 124, 12335; Angew. Chem. Int. Ed. 2012, 51, 12169; f) E. T. Hennessy, T. A. Betley, Science 2013, 340, 591.
- [2] a) P. Wu, A. K. Feldman, A. K. Nugent, C. J. Hawker, A. Scheel, B. Voit, J. Pyun, J. M. J. Fréchet, K. B. Sharpless, V. V. Fokin, *Angew. Chem.* **2004**, *116*, 4018; *Angew. Chem. Int. Ed.* **2004**, *43*, 3928; b) L. Li, G. Zhang, A. Zhu, L. Zhang, J. Org. Chem. **2008**, *73*, 3630.
- [3] a) R. Kumar, L. I. Wiebe, E. E. Knaus, J. Med. Chem. 1993, 36, 2470; b) L. Chen, Y. Zhang, G. Ding, M. Ba, Y. Guo, Z. Zou, Molecules 2013, 18, 1477.
- [4] For some recent azidation reactions, see: a) M. V. Vita, J. Waser, Org. Lett. 2013, 15, 3246; b) Q.-H. Deng, T. Bleith, H. Wadepohl,

L. H. Gade, J. Am. Chem. Soc. 2013, 135, 5356; c) F. Xie, Z. Qi, X. Li, Angew. Chem. 2013, 125, 12042; Angew. Chem. Int. Ed. 2013, 52, 11862; d) C. Tang, N. Jiao, J. Am. Chem. Soc. 2012, 134, 18924; e) E. Nyfeler, P. Renaud, Org. Lett. 2008, 10, 985.

- [5] For the azidation of alkenes, see: a) J. Waser, H. Nambu, E. M. Carreira, J. Am. Chem. Soc. 2005, 127, 8294; b) J. Waser, B. Gaspar, H. Nambu, E. M. Carreira, J. Am. Chem. Soc. 2006, 128, 11693; c) K. Weidner, A. Giroult, P. Panchaud, P. Renaud, J. Am. Chem. Soc. 2010, 132, 17511; d) C. Ollivier, P. Renaud, J. Am. Chem. Soc. 2001, 123, 4717; e) A. Kapat, A. König, F. Montermini, P. Renaud, J. Am. Chem. Soc. 2011, 133, 13890; f) K. Matcha, R. Narayan, A. P. Antonchick, Angew. Chem. 2013, 125, 8143; Angew. Chem. Int. Ed. 2013, 52, 7985; g) Y. Yuan, T. Shen, K. Wang, N. Jiao, Chem. Asian J. 2013, 8, 2932; h) E. K. Leggans, T. J. Barker, K. K. Duncan, D. L. Boger, Org. Lett. 2012, 14, 1428; i) X. Wei, Y. Li, A. Zhou, T. Yang, S. Yang, Org. Lett. 2013, 15, 4158.
- [6] a) T. Hiyama, Organofluorine Compounds: Chemistry and Applications, Springer, Berlin, 2000, 137-177; b) I. Ojima, Fluorine in Medical Chemistry and Chemical Biology, Wiley-Blackwell, Chichester, UK, 2009; c) P. Jeschke, ChemBioChem 2004, 5, 570; d) K. Müller, C. Faeh, F. Diederich, Science 2007, 317, 1881.
- [7] Limited cases were reported for the multistep synthesis of vicinal CF₃-substituted alkyl azides. See: a) Z.-X. Jiang, X.-P. Liu, X.-L. Qiu, F.-L. Qing, J. Fluorine Chem. 2005, 126, 497; b) P. Wang, Y. Tang, D. A. Tirrell, J. Am. Chem. Soc. 2003, 125, 6900; c) A. Solladie-Cavallo, S. Quazzotti, J. Fischer, A. DeCian, J. Org. Chem. 1992, 57, 174.
- [8] For recent trifluoromethylation of alkenes, see: a) A. T. Parsons, S. L. Buchwald, Angew. Chem. 2011, 123, 9286; Angew. Chem. Int. Ed. 2011, 50, 9120; b) J. Xu, Y. Fu, D. Luo, Y. Jiang, B. Xiao, Z. Liu, T. Gong, L. Liu, J. Am. Chem. Soc. 2011, 133, 15300; c) X. Wang, Y. Ye, S. Zhang, J. Feng, Y. Xu, Y. Zhang, J. Wang, J. Am. Chem. Soc. 2011, 133, 16410; d) R. Shimizu, H. Egami, Y. Hamashima, M. Sodeoka, Angew. Chem. 2012, 124, 4655; Angew. Chem. Int. Ed. 2012, 51, 4577; e) L. Chu, F. Qing, Org. Lett. 2012, 14, 2106; f) S. Mizuta, O. Galicia-López, K. M. Engle, S. Verhoog, K. Wheelhouse, G. Rassias, V. Gouverneur, Chem. Eur. J. 2012, 18, 8583.
- [9] X. Mu, T. Wu, H.-Y. Wang, Y.-L. Guo, G. Liu, J. Am. Chem. Soc. 2012, 134, 878.
- [10] For recent reviews on trifluoromethylation of alkenes, see: a) A. Studer, Angew. Chem. 2012, 124, 9082; Angew. Chem. Int. Ed. 2012, 51, 8950; b) P. Chen, G. Liu, Synthesis 2013, 2919; for selective reactions, see: c) P. G. Janson, I. Ghoneim, N. O. IIchenko, K. J. Szabó, Org. Lett. 2012, 14, 2882; d) Y. Li, A. Studer, Angew. Chem. 2012, 124, 8345; Angew. Chem. Int. Ed. 2012, 51, 8221; e) Y. Yasu, T. Koike, M. Akita, Angew. Chem. 2012, 124, 9705; Angew. Chem. Int. Ed. 2012, 51, 9567; f) R. Zhu, S. L. Buchwald, J. Am. Chem. Soc. 2012, 134, 12462; g) C. Feng, T.-P. Loh, Chem. Sci. 2012, 3, 3458; h) S. Mizuta, S. Verhoog, K. M. Engle, T. Khotavivattana, M. O'Duill, K. Wheelhouse, G. Rassias, M. Médebielle, V. Gouverneur, J. Am. Chem. Soc. 2013, 135, 2505; i) X. Wu, L. Chu, F. Qing, Angew. Chem. 2013, 125, 2254; Angew. Chem. Int. Ed. 2013, 52, 2198; j) H. Egami, R. Shimizu, S. Kawamura, M. Sodeoka, Angew. Chem. 2013, 125, 4092; Angew. Chem. Int. Ed. 2013, 52, 4000; k) H. Egami, S. Kawamura, A. Miyazaki, M. Sodeoka, Angew. Chem. 2013, 125, 7995; Angew. Chem. Int. Ed. 2013, 52, 7841; 1) C. Feng, T.-P. Loh, Angew. Chem. 2013, 125, 12640; Angew. Chem. Int. Ed. 2013, 52, 12414; m) H. Egami, R. Shimizu, Y. Usui, M. Sodeoka, Chem. Commun. 2013, 49, 7346; n) H. Egami, R. Shimizua, M. Sodeoka, J. Fluorine Chem. 2013, 152, 51; o) X. Liu, F. Xiong, X. Huang, L. Xu, P. Li, X. Wu, Angew. Chem. 2013, 125, 7100; Angew. Chem. Int. Ed. 2013, 52, 6962; p) Z.-M. Chen, W. Bai, S.-



H. Wang, B.-M. Yang, Y.-Q. Tu, F.-M. Zhang, *Angew. Chem.* **2013**, *125*, 9963; *Angew. Chem. Int. Ed.* **2013**, *52*, 9781.

- [11] Combination of PhI(OAc)₂ and TMSCF₃ for trifluoromethylation. See Ref. [9] and: a) X. Mu, S. Chen, X. Zhen, G. Liu, *Chem. Eur. J.* 2011, *17*, 6039; b) L. Chu, F.-L. Qing, *J. Am. Chem. Soc.* 2012, *134*, 1298.
- [12] To identify whether this process was triggered by a Lewis acid, $[Cu(CH_3CN)_4]^+PF_6^-$ was replaced by Yb(OTf)₃ or In(OTf)₃, but

no reaction occurred. See the Supporting Information (Table S1).

- [13] For copper-catalyzed trifluoroesterification of **2n** to give the cyclization product, see Ref. [10f].
- [14] Addition of TEMPO could significantly inhibit this trifluoromethyl azidation reaction and a CF₃-TEMPO adduct was observed. For more details, see the Supporting Information.