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Chlorotrifluoromethylation of Terminal Olefins via Atom Transfer-Type Radical Reaction Catalyzed by Cobalt Complexes

Kazuki Maeda, Takuya Kurahashi,* and Seijiro Matsubara*

Dedicated to Professor Armin de Meijere on the occasion of his 80th birthday.

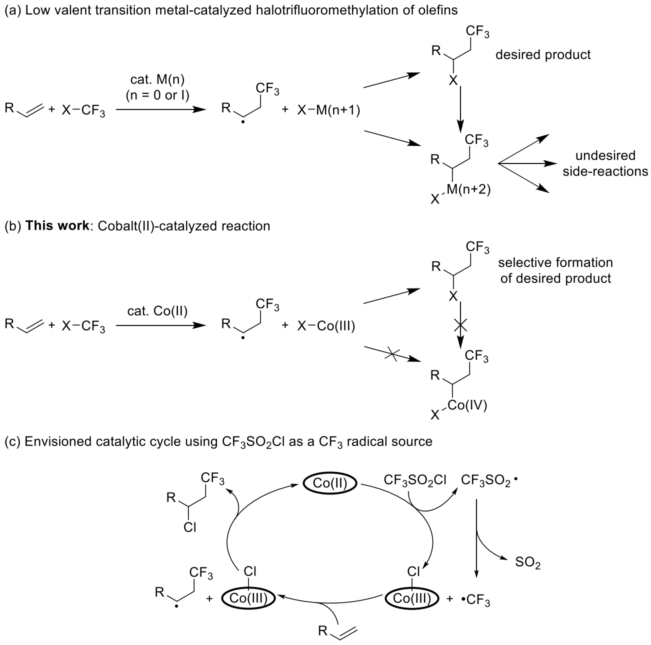
Abstract: A cobalt porphyrin-catalyzed chlorotrifluoromethylation reaction of olefins is described. The use of CF_3SO_2Cl as the CF_3 radical source and a cobalt catalyst enabled the selective addition of CF_3 radicals under thermal conditions. Various functional groups such as esters and Ar-X moieties, which can be reactive with low valent transition metal catalysts, were well-tolerated in this catalytic process. A highly functionalized alkaloid derivative was also tolerated as a substrate. As a demonstration of the bio-inspired catalytic system, catalytic usage of vitamin B_{12}, which is the commercially available form of the natural cobalt porphyrinoid, was employed, and diastereoselective chlorotrifluoromethylation of the alkaloid molecule was achieved.

Introduction

Trifluoromethyl (CF_3) groups are generally accepted as essential functionality in pharmaceutical chemistry because of their excellent anti-metabolic nature, electron negativity, membrane-permeability, and other expedient characteristics.[1] For these reasons, various methodologies which enable the introduction of CF_3 groups have been well established.[2] Among them, utilization of CF_3 radicals has been recognized as a powerful strategy for trifluoromethylation reactions. For example, MacMillan and co-workers demonstrated an elegant application of their photoredox technique in the electrophilic trifluoromethylation of electron-rich arenes.[3] After their pioneering results, photo-induced generation of the CF_3 free radical has become common methodology for mild and functional group-tolerant trifluoromethylative functionalization.[4]

In contrast, utilization of perfluoroalkyl radicals under thermal conditions using olefins and perfluoroalkyl halides is an old yet powerful methodology, and easier to apply in classical laboratory and industrial processes. Both early and late low valent transition metals are able to catalyze this type of perfluoroalkylation reaction, known as an atom transfer radical addition.[5] However, the low valent transition metal complexes are potentially reactive toward various functional groups, including the resulting carbon–halogen bond and the hydrogen atom at the β-position (Scheme 1(a)). This could result in a lack of chemoselectivity and could be problematic in the late stage trifluoromethylation reaction.

Considering the above issues, we supposed that some types of cobalt(II) complexes could be robust and selective catalysts for the thermal atom transfer radical trifluoromethylation reaction. Highly coordinated square-planar cobalt(II) complexes, such as cobalt(II) porphyrins or salens, are generally known to have unpaired electron in the $d_{z}2$ orbital. If the singly occupied orbital of the paramagnetic low-spin cobalt center can interact with the low-lying LUMO of the CF_3-containing substrate, selective generation of the CF_3 radical might be achieved (Scheme 1(b)).[6] Even more advantageously, such a cobalt catalyst does not possess reactive orbitals for side reactions, therefore, generation and addition of the CF_3 radical might proceed in a chemoselective manner.



Scheme 1. (a) Early transition metal-catalyzed atom transfer CF_3 radical addition, (b) Co(II) metalloradical for generation of CF_3 radicals, and (c) the envisaged catalytic cycle for the chlorotrifluoromethylation of olefins.

Results and Discussion

In the course of our trial, trifluoromethanesulfonyl chloride (CF_3SO_2Cl), which was previously used for the Ru(II) catalyzed chlorotrifluoromethylation of olefins,[7] was chosen as the highly electron-deficient CF_3 radical source. If the cobalt metalloradical can interact with the low-lying LUMO of CF_3SO_2Cl, homolytic abstraction of Cl might occur, and the CF_3 radical should be generated after the pyrolytic release of SO_2 gas (Scheme 1(c)). Pleasingly, when 5 mol % of cobalt(II) porphyrin, CoTPP (TPP: 5,10,15,20-tetraphenylporphyrinato), was used as the catalyst in the presence of olefin **1a** and CF_3SO_2Cl, the desired chlorotrifluoromethylated product **2a** was obtained in 77% yield (Table 1, entry 1). The use of the Jacobsen-type cobalt salen

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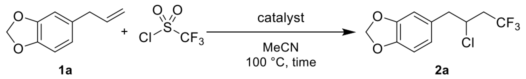
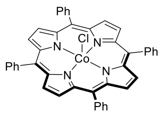
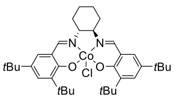


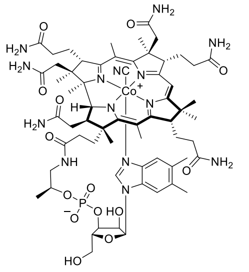
Table 1. Optimization of the chlorotrifluoromethylation of **1a**.[a]

entry	catalyst (loading)	time	conv.[b]	yield[b]
1	CoTPP (5 mol %)	4 h	95%	77%
2	(*R*,*R*)-Cosalen* (5 mol %)	4 h	64%	48%
3	Co(acac)$_2$ (5 mol %)	4 h	28%	21%
4	CoClTPP (5 mol %)[c]	4 h	90%	85%
5	(*R*,*R*)-CoClsalen* (5 mol %)[c]	4 h	66%	63%
6	Co(acac)$_3$ (5 mol %)[c]	4 h	22%	28%
7	CuI (5 mol %)[c]	4 h	69%	39%
8	[Cu(bathophen)$_2$]Cl (5 mol %)[c]	4 h	31%	28%
9	CuCl$_2$ (5 mol %)[c]	4 h	84%	48%
10	CuTPP (5 mol %)[c]	4 h	39%	31%
11	CoClTPP (1 mol %)[c]	12 h	>99%	92% (92%)
12	vitamin B$_{12}$ (5 mol %)[c]	4 h	80%	70%

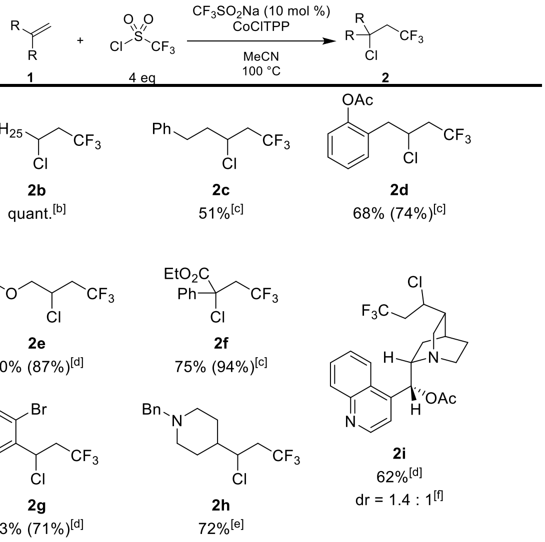
[a] The reactions were conducted with **1a** (0.1 mmol), CF_3SO_2Cl (0.4 mmol), CF_3SO_2Na (10 μmol), and catalyst (1 or 5 μmol) in MeCN (1 mL) at 100 °C for the indicated time under a N_2 gas atmosphere. [b] Determined by ^{1}H NMR using Bn_2O as an internal standard. Differences between the conversion and the yield might be due to an analytical error. The isolated yield is shown in parenthesis. [c] 10 μmol (10 mol % to **1a**) of CF_3SO_2Na was used as an additive. TPP = 5,10,15,20-tetraphenylporphyrinato, salen* = (1*R*,2*R*)-*N*,*N*-bis(3,5-di-*tert*-butylsalicylidene)cyclohexanediamine, acac = pentane-2,4-dionato, bathophen = 2,9-diphenyl-1,10-phenanthroline


CoClTPP


(*R*,*R*)-CoClsalen*


vitamin B$_{12}$

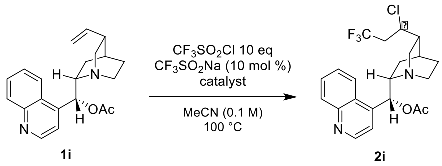
complex in place of the porphyrin also succeeded, though the yield was lower (48%, entry 2). The acetylacetonate salt of Co(II) and other cobalt salts failed to achieve good yields (entry 3; see Supporting Information for details). Further modification of the reaction conditions revealed that the combination of the Co(III) porphyrin, which can be easily prepared by air-oxidation of Co(II) complexes, and CF_3SO_2Na (Langlois' salts) as catalysts gave better yields (85%, entry 4).[8] Note these reactions proceeded well in the absence of light (see Supporting Information), indicating that the catalysis proceeds via a fully thermal reaction pathway. The Co(III) salen complex also gives the products in the presence of CF_3SO_2Na, though some decomposition of the Co salen complex under the reaction conditions diminished the yield (entry 5). This clearly reflects the importance of having a robust catalyst in this transformation. Co(acac)$_3$ was not effective for this reaction (entry 6). Some copper salts known to be important for atom transfer radical addition reactions[9] and other trifluoromethylative reactions[10] were also tested, however, none of these gave better results (entry 7-9). It is noteworthy that some by-products, likely derived from uncontrolled addition of the CF_3SO_2 radical intermediates, were detected in the reaction mixture of these copper-catalyzed reactions. This emphasizes the efficient catalytic ability of the Co porphyrin in controlling the generation and reactivity of the CF_3 radicals. The paramagnetic copper(II) porphyrin, CuTPP, afforded **2a** in only 31% yield (entry 10). This indicates the importance of the redox viability of the cobalt porphyrin catalyst in this reaction.[11] The combination of CoClTPP and CF_3SO_2Na was found to be a fairly effective catalytic system to furnish the product in 92% isolated yield even with only 1 mol % catalyst loading, although a somewhat longer reaction time was needed (entry 11). Thus, the combination of CoClTPP and CF_3SO_2Na was chosen as the best catalyst.Additionally, vitamin B$_{12}$ (commercially available cyanocobalamin form) was tested as a Co(III) porphyrinoid catalyst, and cleanly gave **2a** in 70% yield (entry 12). The catalytic use of cobalamin is well known in single-electron catalysis,[12] however, preactivation of the catalysts to the Co(I) species was commonly needed. In this transformation, no such highly reductive condition was required. Thus, this result might expand the utility of the cobalamins as environmentally friendly catalysts.



Scheme 2. Catalytic chlorotrifluoromethylation of terminal olefins catalyzed by Co(III) porphyrin.[a] [a] The reactions were conducted with **1a** (1 eq), CF_3SO_2Cl (4 eq), CF_3SO_2Na (10 mol %), and catalyst in MeCN (0.1 M) at 100 °C under a N_2 gas atmosphere. The isolated yield is shown. The NMR yield, determined by using Bn_2O as an internal standard, is shown in parentheses. [b] Catalyst (1 mol %), 12 h. [c] Catalyst (5 mol %), 6 h. [d] Catalyst (5 mol %), 24 h. [e] Catalyst (5 mol %), in 1,2-dichloroethane, 36 h [f] The diastereomeric ratio was determined by ^{19}F NMR.

To exemplify the usability of this cobalt-catalyzed protocol, functional group tolerance of the trifluoromethylation reaction was briefly tested (Scheme 2). A fully aliphatic olefin, **1b**, quantitatively gave product **2b**, and olefin **1c** was transformed to desired product **2c**.[13] A protected allyl phenol derivative, which is easily and readily accessible from substituted phenol, could also be used in the reaction, and **2d** was obtained in good yields. The reaction with protected allyl alcohol **1e** smoothly afforded **2e**. Despite the fact that this reaction might occur via electrophilic addition of the CF_3 radical equivalents to the olefins, electron deficient olefins and styrene type substrates **1f** and **1g** could be used in this transformation with extended reaction time (6-12 h). Importantly, no substitution product at the Ar–Br moiety, which could be produced in a reaction with the poorly coordinated low valent transition metal catalysts,[10] was observed in this cobalt porphyrin-catalyzed system with **1g**. A substrate which contains an amine moiety was pleasingly compatible and gave **2h** in 72% yield. As a demonstration of the utility of this catalysis, complex molecules directly relevant to bioactive compounds were also examined, and cinchona alkaloid-derived **1i** could be converted to **2i** in satisfying yields.

Table 2. Diastereoselective chlorotrifluoromethylation of **1i**.[a]



1i **2i**

entry	catalyst (loading)	time	dr[b]
1[c]	CoClTPP (5 mol %)	48 h	1.4:1
2	(*R*,*R*)-CoClsalen* (10 mol %)	24 h	1.8:1
3	(*S*,*S*)-CoClsalen* (10 mol %)	24 h	1.4:1
4	vitamin B_{12} (5 mol %)	48 h	6.4:1

[a] The reactions were conducted with **1h** (0.05 mmol), CF_3SO_2Cl (0.5 mmol), CF_3SO_2Na (5 μmol), and catalyst (5 μmol) in MeCN (0.5 mL) at 100 °C for the indicated time under a N_2 gas atmosphere. [b] Determined by NMR. [c] An identical result is shown in Table 1, entry 12.

Considering the result obtained with vitamin B_{12} catalysis (Table 1, entry 12), the possibility of stereoselective chloro-trifluoromethylation was examined (Table 2). Generally, dual functionalization of olefins by the atom transfer radical reaction have faced poor stereoselectivity because of the difficulty in controlling the reactivity around the catalytically active center.[14] Indeed, when **1i** was used as the substrate, both the Co(III) porphyrin and salen complexes resulted in low selectivity (entries 1-3). A greater selectivity, 6.4:1, was observed when vitamin B_{12} was used as the catalyst (entry 4). This sharp contrast clearly supports the possibility of the cobalt center contributing to C–Cl bond forming events and the existence of a secondary electrostatic interaction between the substrate and the outer sphere of the catalyst. This might open opportunities for establishing regio-, stereo-, and position-selective atom transfer-type transformations.

Conclusions

In summary, the cobalt porphyrin catalyst enabled chloro-trifluoromethylation of variously substituted olefins via a fully thermal process. This functional group-tolerant atom transfer radical reaction was achieved by use of a higher valent cobalt catalyst. Additionally, the preliminary trials suggest the possibility of stereoselective trifluoromethylation, which is especially essential for pharmaceutical applications. Development of other trifluoromethylative functionalization utilizing this catalytic system is ongoing in our laboratory.

Acknowledgements

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Keywords: atom transfer • cobalt catalysis • trifluoromethylation

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[12] Experimental values for the first oxidation potential of some types of the cobalt porphyrin and the copper porphyrin were 0.111 V and 0.463 V (vs ferrocene/ferrocenium redox potential), respectively, as determined by differential pulse voltammetry. Additionally, in the case of the cobalt porphyrins, oxidation occurs at the cobalt center (generating Co(III) porphyrin). The first oxidation of the copper porphyrin, in contrast, occurs at the porphyrin ligand.

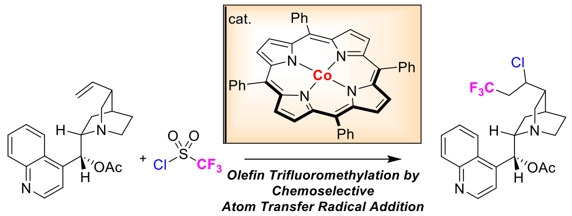
[13] For selected reviews on cobalamin catalysis, see: a) R. Scheffold, S. Abrecht, R. Orlinski, H.-R. Ruf, P. Stamouli, O. Tinembart, L. Walder, C. Weymuth, *Pure & Appl. Chem.* **1987**, *59*, 363–372; b) M. Giedyk, K. Goliszewska, D. Gryko, *Chem. Soc. Rev.*, **2015**, *44*, 3391–3404; c) H. Shimakoshi, Y. Hisaeda, *ChemPlusChem* **2017**, *82*, 18–29; d) K. Tahara, L. Pan, T. Ono, Y. Hisaeda, *Beilstein J. Org. Chem.* **2018,** *14,* 2553–2567. Very recently, cobalamin-mediated CF_3 radical transfer was also described: T. Ono, K. Wakiya, Md. J. Hossain, H. Shimakoshi, Y. Hisaeda. *Chem. Lett.* **2018**, *47*, 979–981.

[14] The yields determined from the amount of the isolated products were lower due to the high volatility of the products. Product **2c** in particular might be even evaporate during the work-up process.

[15] Recently, a report on highly stereoselective atom transfer-type functionalization of olefins has been published: B. Chen, C. Fang, P. Liu, J. M. Ready, *Angew. Chem. Int. Ed.* **2017**, *56*, 8780–8784; *Angew. Chem.* **2017**, *129*, 8906–8910. For pioneering examples of stereoselective reactions, see: a) S. Murai, R. Sugise, N. Sonoda, *Angew. Chem. Int. Ed.* **1981**, *20*, 475–476; *Angew. Chem.* **1981**, *93*, 481–482; b) M. Kameyama, N. Kamigata, M. Kobayashi, *J. Org. Chem.* **1987**, *52*, 3312–3316; c) Y. Iizuka, Z. Li, K. Satoh, M. Kamigaito, Y. Okamoto, J. Ito, H. Nishiyama, *Eur. J. Org. Chem.* **2007**, 782–791.

Entry for the Table of Contents

COMMUNICATION (Chlorotrifluoromethylation)



A cobalt porphyrin-catalyzed chlorotrifluoromethylation reaction of olefins is described. The use of CF_3SO_2Cl as the CF_3 radical source and a cobalt catalyst enabled the selective addition of CF_3 radicals under thermal conditions.

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