Synthetic Methodology

DOI: 10.1002/ange.201209355

Enantioselective Synthesis of Epoxides Having a Tetrasubstituted Trifluoromethylated Carbon Center: Methylhydrazine-Induced Aerobic Epoxidation of β,β-Disubstituted Enones**

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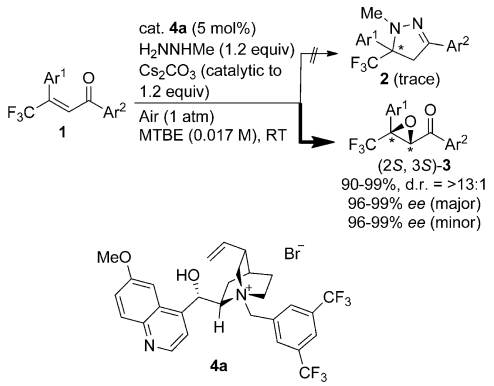
Ever since the milestone of asymmetric epoxidation of allylic alcohols in the early 1980s by Katsuki and Sharpless,[1] the catalytic asymmetric epoxidation of olefins has become one of the most powerful, well-explored, and reliable transformations in organic synthesis for providing enantiomerically enriched epoxides, which are versatile building blocks for the synthesis of biologically active molecules and advanced materials.[2] A large number of catalytic systems for asymmetric epoxidation have been devised over three decades and can be categorized into three classes according to the combination of catalysts and oxidants: a) metal complex/active oxidant,[1,3] b) metal complex/molecular oxygen,[4] and c) organocatalyst/active oxidant.[5] Despite tremendous efforts by many groups, the catalytic asymmetric epoxidation of acyclic β,β-disubstituted enones is still a challenge,[6] particularly for β,β-disubstituted enones bearing a trifluoromethyl group at the β-position. In 2011, Yamamoto and co-workers provided a very nice solution to the catalytic asymmetric epoxidation of acyclic β,β-disubstituted enones with an iron complex consisting of $Fe(OTf)_2$ and a carefully designed phenanthroline ligand.[6b] This chiral iron phenanthroline system is effective for the asymmetric epoxidation of a variety of acyclic β,β-disubstituted enones, however, no example was shown for the asymmetric epoxidation of β,β-disubstituted enones having a β-trifluoromethyl group. In 2012, Feng and co-workers investigated chiral N,N′-dioxide-metal complexes for the epoxidation of β-monosubstituted enones including a β-trifluoromethyl group using hydrogen peroxide and found that optically active epoxides could be obtained with excellent enantioselectivities, but method was not be applicable for β,β-disubstituted enones.[7] We disclose herein the first asymmetric epoxidation of β,β-disubstituted enones **1**, having a β-trifluoromethyl group, by the serendipitous discovery of an aerobic organocatalytic system consisting of methylhydrazine (H_2NNHMe), a base, and a cinchona alkaloid phase-transfer catalyst (Scheme 1). Enantiomerically enriched trifluoromethylated epoxides with a tetrasubstituted carbon centers (**3**) were obtained for the first time, instead of the pyrazolines **2**, in excellent yields, excellent diastereoselectivities, and enantioselectivities (96–99 % *ee*).



Scheme 1. Asymmetric aerobic epoxidation of β-trifluoromethyl-β,β-disubstituted enones **1** by a methylhydrazine/base/cinchona alkaloid system. MTBE = methyl *tert*-butyl ether.

Trifluoromethylated organic chemicals are finding increased utility in various fields including medicinal, biological, agricultural, and material chemistry. The trifluoromethyl group has a bigger van der Waals radius than a methyl group, the same electronegativity as oxygen an atom, and high lipophilicity, which often alters the physical, chemical, and physiological properties of the parent molecules when it is attached.[8] Our group has been engaged in the development of the efficient synthesis of trifluoromethyl-containing organic molecules for more than a decade.[9] During our recent research program directed at the catalytic asymmetric synthesis of biologically important isoxazolines, pyrrolines, and pyrazolines bearing a trifluoromethyl group at a chiral carbon center,[10] we discovered an unprecedented asymmetric epoxidation of the β,β-disubstituted enones **3**, a reaction which could be a solution for a long-standing synthetic problem. Namely, when we attempted to synthesize trifluoro-

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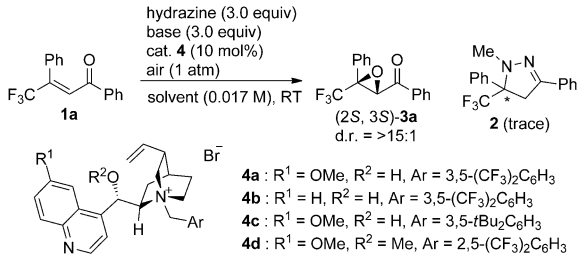
[**] This study was financially supported in part by Grants-in-Aid for Scientific Research from the MEXT (Ministry of Education, Culture, Sports, Science and Technology) (24105513, Project No. 2304: Advanced Molecular Transformation by Organocatalysts). We thank the Asahi Glass Foundation for partial support. E.T. acknowledges Grants-in-Aid for Scientific Research for financial support (24915016). We also thank INSA de Rouen, France for providing an internship for Z.Y.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201209355.

methylated pyrazoline **2** by the treatment of (*E*)-4,4,4-trifluoro-1,3-diphenylbut-2-en-1-one (**1a**) with methylhydrazine (H_2NNHMe, 3.0 equiv) in the presence of the cinchona alkaloid **4a** (10 mol%) and Cs_2CO_3 (3.0 equiv) in iPr_2O (0.017 M) at ambient temperature, the enantioenriched epoxide (2*S*,3*S*)-**3a** with a trifluoromethylated quaternary carbon center was obtained, instead of **2**, in a 99% yield with excellent diastereoselectivity (>15:1) and excellent enantioselectivity of 98% *ee* (Table 1, entry 1). This exciting result spurred us to investigate the detail of this unpredictable epoxidation reaction. No reaction took place in the absence of methylhydrazine (entry 2) or Cs_2CO_3 (entry 3). Low yields (5–7%) were obtained when other hydrazines such as H_2NNH_2, H_2NNHPh, and H_2NNHAc were used instead of H_2NNHMe (entries 4–6). Moreover, no reaction occurred when using dimethylhydrazine (H_2NNMe_2; entry 7). The choice of base was crucial to obtaining good reaction yields (entries 8–12), whereas the choice of solvent did not have significant effects (entries 13–17). This optimization resulted in the use of Cs_2CO_3 and MTBE as choice conditions with regard to both enantioselectivity and yield (entry 15). Other cinchona alkaloids (**4b**, **c**) were also effective for this transformation (entries 18 and 19) but the nature of the O protection had a clear influence only on the enantioselectivity (entry 20). The effect of the catalyst loading was further examined (entries 21–23). It should be noted that 1 mol% of **4a** gave a comparable result (96% *ee*; entry 22) to 5 mol% of **4a**. A catalyst loading of 5 mol% was chosen for the remaining experiments given the shorter reaction time and good enantioselectivity (entry 21). The amounts of H_2NNHMe and Cs_2CO_3 could be reduced to 1.2 equivalents without any sacrifice in yield of the isolated product, diastereo- and enantioselectivities (entry 23). Thus, the optimum reaction conditions required the use of 5 mol% of **4a**, 1.2 equivalents each of H_2NNHMe and Cs_2CO_3 in MTBE at ambient temperature under air. Interestingly, the catalytic amount of Cs_2CO_3 is enough for this transformation without any loss of the enantiomeric excess of **3a**, even though the chemical yield of **3a** is slightly lower (81% versus 91%) and a longer reaction time (21 h versus 6 h) is required under the catalytic conditions (entries 23 versus 24).

Table 1: Hydrazine-induced aerobic asymmetric epoxidation of **1a**: Optimization of reaction conditions.[a]



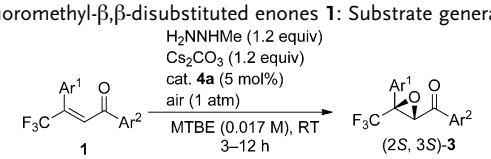
Entry	Hydrazine	4	Base	Solvent	*t* [h]	Yield [%][b]	*ee* [%][c] Major	Minor
1	H_2NNHMe	**4a**	Cs_2CO_3	iPr_2O	5	99	99	98
2	none	**4a**	Cs_2CO_3	iPr_2O	24	NR	–	–
3	H_2NNHMe	**4a**	none	iPr_2O	24	NR	–	–
4	H_2NNH_2	**4a**	Cs_2CO_3	iPr_2O	20	5	n.d.	n.d.
5	H_2NNHPh	**4a**	Cs_2CO_3	iPr_2O	20	7	n.d.	n.d.
6	H_2NNHAc	**4a**	Cs_2CO_3	iPr_2O	20	7	n.d.	n.d.
7	H_2NNMe_2	**4a**	Cs_2CO_3	iPr_2O	20	NR	–	–
8	H_2NNHMe	**4a**	Na_2CO_3	iPr_2O	20	trace	n.d.	n.d.
9	H_2NNHMe	**4a**	K_2CO_3	iPr_2O	24	70	96	98
10	H_2NNHMe	**4a**	KOH	iPr_2O	3	93	97	97
11	H_2NNHMe	**4a**	KOAc	iPr_2O	20	trace	n.d.	n.d.
12	H_2NNHMe	**4a**	*t*BuOK	iPr_2O	20	CP	n.d.	n.d.
13	H_2NNHMe	**4a**	Cs_2CO_3	Et_2O	20	95	97	98
14	H_2NNHMe	**4a**	Cs_2CO_3	THF	1	99	97	97
15	H_2NNHMe	**4a**	Cs_2CO_3	MTBE	2	97	98	99
16	H_2NNHMe	**4a**	Cs_2CO_3	toluene	3	96	96	97
17	H_2NNHMe	**4a**	Cs_2CO_3	CH_2Cl_2	24	96	87	91
18	H_2NNHMe	**4b**	Cs_2CO_3	iPr_2O	7	89	88	92
19	H_2NNHMe	**4c**	Cs_2CO_3	iPr_2O	4	90	96	98
20	H_2NNHMe	**4d**	Cs_2CO_3	iPr_2O	16	94	−45	−26
21[d]	H_2NNHMe	**4a**	Cs_2CO_3	MTBE	2	92	98	98
22[e]	H_2NNHMe	**4a**	Cs_2CO_3	MTBE	5	99	96	96
23[f]	H_2NNHMe	**4a**	Cs_2CO_3	MTBE	6	91	99	98
24[g]	H_2NNHMe	**4a**	Cs_2CO_3	MTBE	21	81	98	99

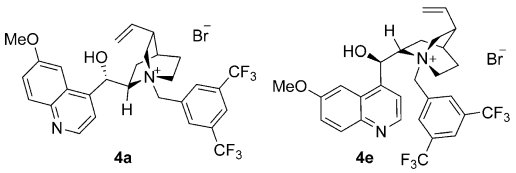
[a] The reaction of **1a** with hydrazine (3.0 equiv) was carried out in the presence of **4** (10 mol%) and base (3.0 equiv) in solvent (0.017 M) under air atmosphere at room temperature, unless otherwise noted. [b] Yield of isolated product. [c] Determined by HPLC using a chiral stationary phase. [d] Used 5 mol% of **4a**. [e] Used 1 mol% of **4a**. [f] Used 1.2 equiv of H_2NNHMe and Cs_2CO_3, 5 mol% of **4a**. [g] Used 1.2 equiv of H_2NNHMe, 0.3 equiv of Cs_2CO_3, 5 mol% of **4a**. THF = tetrahydrofuran.

With optimal reaction conditions in hand (entry 23, Table 1), the scope of the H_2NNHMe-mediated aerobic asymmetric epoxidation of the β-trifluoromethyl-disubstituted enones **1** was explored (Table 2). A series of trifluoromethylated enone derivatives (**1a–f**, **h–n**) having a variety of substituents, such as methyl, methoxy, chloro, bromo and nitro groups, on the aromatic rings were nicely converted into the corresponding products **3a–f**, **h–n** in excellent yields with 96–99% *ee* (entries 3–7 and 9–15). The sterically demanding naphthyl-substituted enones **1g** and **1o** were also compatible with the same reaction conditions, thus affording products **3g** and **3o** in excellent yields with 99 and 98% *ee*, respectively (entries 8 and 16). The absolute stereochemistry of **3a** was clearly determined to be 2*S*,3*S* by X-ray analysis of the *O*-3,5-dichlorobenzoyl oxime derivative of **3a** (see Figure S1 in the Supporting Information), and all the other products were tentatively assigned by analogy with **3a**. The analogous ammonium bromide **4e** derived from quinine showed similar excellent enantioselectivity for **3a** with the opposite stereochemistry (2*R*,3*R*; 99%, 97% *ee*, entry 2).

Next we used ^{18}O-labeling experiments to elucidate the mechanism of this unprecedented epoxidation reaction. In particular, one task was to determine the origin of oxygen atom of the epoxide, that is, whether it came from molecular oxygen (air) or from water (moisture; Table 3). Epoxidation did not occur under an argon atmosphere without exposure to oxygen (entry 2), even in the presence of $H_2{}^{18}O$ (entry 3). In contrast, the epoxidation of **1a** under an $^{18}O_2$ atmosphere quantitatively afforded the epoxide **3a** where ^{18}O incorporation into **3a** was 90% (entry 4). These results clearly indicate that the epoxide's oxygen atom originates from molecular oxygen in air, but not from trace amounts of water (i.e., moisture). Our next interest was the identification of an

Table 2: Methylhydrazine-induced aerobic asymmetric epoxidation of β-trifluoromethyl-β,β-disubstituted enones **1**: Substrate generality.[a]

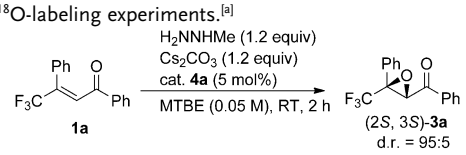




Entry	**1**	Ar^1	Ar^2	Yield [%][b]	d.r.[c]	*ee* [%][d] Major	Minor
1	**1a**	Ph	Ph	91	95:5	99	98
2[e]	**1a**	Ph	Ph	99	95:5	−97 (2*R*,3*R*)	−98
3	**1b**	3-MeC_6H_4	Ph	95	93:7	99	99
4	**1c**	4-MeC_6H_4	Ph	92	94:6	99	98
5	**1d**	4-$MeOC_6H_4$	Ph	91	94:6	98	99
6	**1e**	4-ClC_6H_4	Ph	90	95:5	98	99
7	**1f**	4-BrC_6H_4	Ph	97	95:5	98	97
8	**1g**	2-naphthyl	Ph	99	96:4	99	99
9	**1h**	Ph	2-MeC_6H_4	99	96:4	96	96
10	**1i**	Ph	3-MeC_6H_4	99	93:7	98	98
11	**1j**	Ph	4-MeC_6H_4	91	93:7	98	98
12	**1k**	Ph	4-$MeOC_6H_4$	98	93:7	98	98
13	**1l**	Ph	4-ClC_6H_4	92	93:7	98	99
14	**1m**	Ph	4-BrC_6H_4	91	93:7	97	98
15	**1n**	Ph	4-$NO_2C_6H_4$	98	94:6	96	97
16	**1o**	Ph	2-naphthyl	99	94:6	98	98

[a] The reaction of **1** with H_2NNHMe (1.2 equiv) was carried out in the presence of **4a** (5 mol%) and Cs_2CO_3 (1.2 equiv) in MTBE (0.017 M) under air atmosphere at room temperature. [b] Yield of isolated product. [c] Determined by ^{19}F NMR spectroscopy. [d] Determined by HPLC using a chiral stationary phase. [e] Used **4e** was instead of **4a**.

Table 3: ^{18}O-labeling experiments.[a]

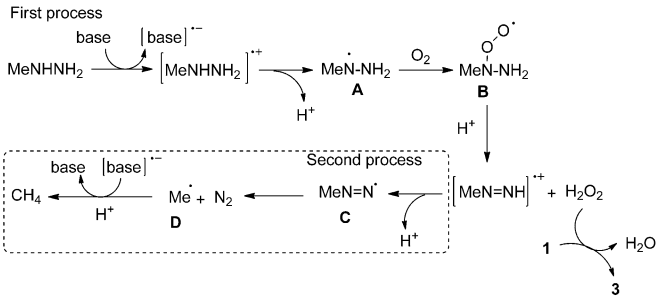


Entry	Conditions	Yield [%][b]	^{18}O Content[c]	*ee* [%][d] Major	Minor
1	air	90	–	97	98
2	argon	<3	–	n.d.	n.d.
3	$^{18}O_2$	95	90	97	98
4	argon + 10 equiv of $H_2{}^{18}O$	<2	–	n.d.	n.d.
5[e]	50% H_2O_2 (1.2 equiv)	66	–	97	98
6[e]	cumene hydrogen peroxide (1.2 equiv)	24	–	59	63

[a] The reaction of **1a** with H_2NNHMe (1.2 equiv) was carried out in the presence of **4a** (5 mol%) and Cs_2CO_3 (1.2 equiv) in MTBE (2.0 mL, 0.05 M) at room temperature. [b] Yield of isolated product. [c] Determined by EI mass analysis (average of three times) [d] Determined by HPLC using a chiral stationary phase. [e] The reaction was carried out in the absence of H_2NNHMe under nitrogen atmosphere.

actual oxidant generated from H_2NNHMe and molecular oxygen under the reaction conditions. It is reported that radical species are generated from hydrazine compounds through the formation of diazenes in the presence of oxidants.[11,12] This reaction also involves the formation of hydrogen peroxide through a radical process.[11,12] Thus, it appears that H_2NNHMe is oxidized by oxygen in the presence of a base, probably by a single-electron transfer.[11d,13] To see the in situ generation of hydrogen peroxide, we examined the reaction using 50% hydrogen peroxide under a nitrogen atmosphere instead of the H_2NNHMe/air system (entry 5). Interestingly, the reaction proceeded to provide **3a** with the same enantioselectivity, although the chemical yield was slightly decreased (66%). It would be interesting to know if any other oxidizing agents have been applied in this reaction. When cumene hydrogen peroxide was used, a lower yield and lower enantioselectivity were observed (entry 6).

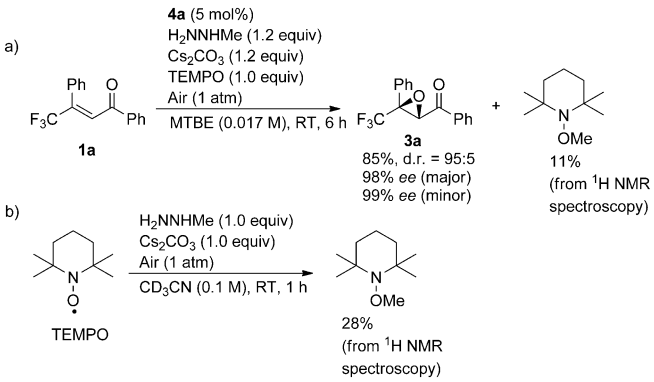
Based on these results, we propose the reaction mechanism to proceed as shown in Scheme 2.[12] First, the oxidation of H_2NNHMe with molecular oxygen is initiated by a single-electron transfer between H_2NNHMe and the base[11,13,14] to provide the methyldiazenyl radical **A** with loss of H^+. The



Scheme 2. A proposed reaction mechanism consisting of two processes.

radical **A** reacts with oxygen to give the radical peroxide **B**, which transforms into the cation radical of methyldiazene, $[MeN{=}NH]^{\bullet+}$, and hydrogen peroxide. This first process could be supported by the fact that the generation of hydrogen peroxide by oxidation of hydrazines with molecular oxygen is reported, although the reported process is generally catalyzed by transition metals such as $CoCl_2$.[11b,13] Thus the hydrogen peroxide generated in the first process oxidizes the β,β-disubstituted enone **1** to afford the epoxide **3** with the loss of a water. The lower chemical yield of **3a** when using 50% H_2O_2 instead of the H_2NNHMe/air system (entry 5, Table 3) might be explained by the purity of H_2O_2, since our H_2NNHMe/air system generates highly reactive and pure H_2O_2 in situ. In the second process (Scheme 2), the $[MeN{=}NH]^{\bullet+}$ is simultaneously converted into a methyl radical and nitrogen via the methyldiazenyl radical **C** ($MeN{=}N^{\bullet}$). Then the reaction sequence ends with the formation of methane and regeneration of the base.[14] The second process is supported by the fact that the formation of alkanes through oxidation of hydrazines, by way of the alkyl radicals formed by oxidation of the monosubstituted diazenes, is reported.[11c] Although the poor reactivity of hydrazine derivatives such as H_2NNH_2, H_2NNHPh, and H_2NNHAc (entries 4–6, Table 1) is not clear, it could be explained by the lack of stability of the corresponding amino radical intermediates compared to the

radical **A** derived from H_2NNHMe, thus causing the first step of peroxide generation to be slow. Besides, H_2NNHMe should be oxidized easier than other hydrazine derivatives because of the electron-rich nitrogen atom. The reason why there was no reaction using H_2NNMe_2 (entry 7, Table 1) is that H_2NNMe_2 cannot furnish the radical intermediate **A** because of the lack of hydrogen on the corresponding nitrogen atom. The radical process was finally confirmed by the experiments using TEMPO for the scavenger of generated methyl radical (Scheme 3a). Moreover, to ascertain whether Cs_2CO_3 is truly capable of catalysis for oxidation of H_2NNHMe with oxygen, a process which is usually catalyzed by transition metals,[11] the experiment as shown in Scheme 3b was carried out. Indeed, the formation of methylated TEMPO was observed.



Scheme 3. Experiments for the identification of methyl radical generated by the use of TEMPO.

In conclusion, we have discovered an unprecedented, asymmetric aerobic epoxidation induced by H_2NNHMe. The aerobic epoxidation of β-trifluoromethyl-β,β-disubstituted enones catalyzed by cinchona alkaloids under air in the presence of a base and H_2NNHMe provides enantiomerically enriched trifluoromethyl-substituted epoxides in excellent yields and enantioselectivities (96–99% *ee*). These epoxides can serve as potential building blocks in the field of medicinal, agrochemical, and material chemistry. The key for this success was the unique behavior of H_2NNHMe in the presence of oxygen with a base for the generation of pure hydrogen peroxide. Methylhydrazine is indispensable for aerobic epoxidation and this phenomenon would not have been discovered had used other hydrazine derivatives. Non-transition-metal activation of molecular oxygen is unique and, to the best of our knowledge, the aerobic system does not fall into the reported category of catalytic epoxidation. Further work on the application of this methylhydrazine-induced asymmetric aerobic epoxidation is in progress.[15]

Received: November 22, 2012
Revised: December 23, 2012
Published online: January 21, 2013

Keywords: epoxidation · organocatalyst · oxygen · reaction mechanisms · synthetic methodology

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[12] We sincerely acknowledge one of the reviewers on our manuscript for his/her smart suggestion concerning mechanism of our oxidation system.

[13] The base is indispensable for this oxidation since no reaction was observed in the absence of base (entry 3, Table 1).

[14] Although a catalytic amount of base is enough for this oxidation (entry 24, Table 1), we used a stoichiometric amount of base because of the shorter reaction time and higher chemical yields. This could be explained by a poor solubility of base in organic solvent.

[15] It should be noted that this hydrazine-induced aerobic epoxidation is not only applicable to trifluoromethyl-disubstituted enones, but also to nonfluorinated disubstituted enones, that is, aerobic epoxidation of the nonfluorinated analogue of **1a**, (*Z*)-1,3-diphenylbut-2-en-1-one, in the presence of **4a** (5 mol%), H_2NNHMe (3.0 equiv), and Cs_2CO_3 (3.0 equiv) in MTBE gave the nonfluorinated analogue of **3a**, ((2*S*,3*R*)-3-methyl-3-phenyloxiran-2-yl)(phenyl)methanone, in 71% yield as a major isomer (d.r. = 73:27), though no enantioselectivity was observed (6% *ee*).

