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Cinchona Alkaloid-Catalyzed Asymmetric Trifluoromethylation of Alkynyl Ketones with Trimethylsilyl Trifluoromethane

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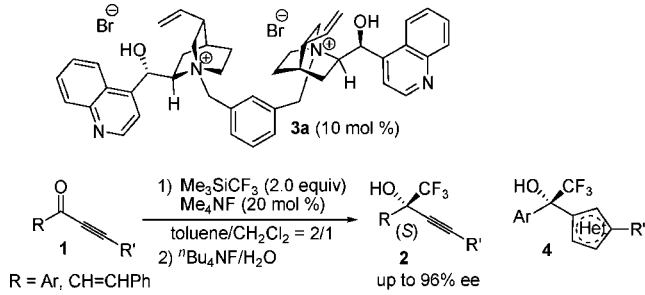
ABSTRACT



The first catalytic enantioselective trifluoromethylation of alkynyl ketones 1 with (trifluoromethyl)trimethylsilane is disclosed by an operationally simple procedure, based on the combination of ammonium bromide of bis-cinchona alkaloids with Me_4NF to afford trifluoromethyl-substituted tertiary propargyl alcohols (up to 96% ee), which are the important chiral building blocks for pharmaceuticals. Biologically attractive aryl heteroaryl trifluoromethyl carbinols were also synthesized.

Catalytic asymmetric synthesis of a tetrasubstituted chiral carbon center by carbon−carbon bond-forming reactions with ketones is a particularly demanding task in organic synthesis.[1] A number of methods have been developed to accomplish this task; however, catalytic enantioselective synthesis of trifluoromethyl-substituted tertiary propargyl alcohols is still a challenge,[2] despite their obvious importance as chiral building blocks for pharmaceuticals such as the anti-HIV drug Efavirenz and its related compounds,[3] which contain a trifluoromethyl group at the tetrasubstituted chiral center at a propargyl position. Two principal catalytic strategies are generally considered for the construction of the target structures: (1) the direct introduction of a trifluoromethyl group into aryl alkynyl ketones[4] and (2) a building block approach via the arylation of trifluoromethyl alkenyl ketones[5]

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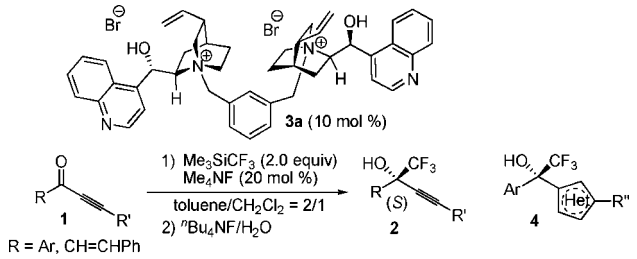
or the alkynylation of trifluoromethyl aryl ketones.[6] A couple of years ago, Shibasaki and Kanai et al. reported the copper(I) alkoxide-catalyzed enantioselective alkynylation of trifluoromethyl ketones to provide trifluoromethyl-substituted tertiary propargyl alcohol up to 52% ee.[6] Although the result of 52% ee is moderate, to our knowledge, this is the highest value for the catalytic enantioselective synthesis of pharmaceutically important aryl trifluoromethyl propargyl alcohols so far reported. We now report the first examples of the catalytic asymmetric direct trifluoromethylation of propargyl ketones **1** by trimethylsilyl trifluoromethane (Me_3SiCF_3) to produce desired trifluoromethyl-propargyl alcohols **2** with a quaternary carbon center up to 96% ee. The catalyst combination composed of cinchona alkaloid **3a** and tetramethyl ammonium fluoride (Me_4NF) was found to be very general for this transformation. The resulting trifluoromethyl-propargyl alcohols can be further transformed, yielding the biologically attractive aryl heteroaryl trifluoromethyl carbinols **4** (Scheme 1).

Scheme 1. Asymmetric Trifluoromethylation of Alkynyl Ketones and Its Application to Aryl Heteroaryl Trifluoromethyl Carbinols



In the 21st century, high enantioselectivity has been achieved consistently in the asymmetric addition to carbonyl compounds.[1] This is not the case for the addition of Me_3SiCF_3, in which selectivity is generally very low and substrates lack scope.[4,7] Since 2007, we disclosed enantioselective trifluoromethylation of aryl alkyl ketones, aryl aldehydes, and azomethine imines using Me_3SiCF_3 in the presence of a catalytic quantity of a chiral phase transfer catalyst to provide trifluoromethyl derivatives with a high degree of enantioselectivity.[8] Motivated by theses favorable outcomes, the application of these methodologies to previously unknown catalytic asymmetric trifluoromethylation processes of alkynyl aryl ketones to produce tertiary alcohols that contain a trifluoromethyl group at a propargyl position was of interest.[6] Our initial attempt at asymmetric trifluoromethylation of ethynyl phenyl ketone **1a** with Me_3SiCF_3 in the presence of catalytic amounts of *N*-3,5-bis(trifluoromethylbenzyl)cinchonium bromide **3b** and Me_4NF gave a disappointing result (Table 1, entry 1), presumably resulting from deprotonation of the alkynyl proton. Reaction of methylethenyl phenyl ketone **1b** with Me_3SiCF_3, under the same reaction conditions, also gave a complex mixture containing only a trace of the desired 1,2-addition product (entry 2). The unsuccessful results should be explained by the existence of a reactive hydrogen atom in the substrates **1**. Our strategy then turned to the trifluoromethylation of phenyl trimethylsilylethynyl ketone **1c**, which does not contain reactive hydrogen atoms. However, the attempt also led to a complex mixture of compounds (entry 3). In our fourth experiments using phenylethynyl phenyl ketone **1d**, we were able to obtain the desired product with an ee of 40% in 54% yield (entry 4). Changing the chiral catalyst **3b** for **3a** resulted in a good yield of **2d** with better enantioselectivity of 51% (entry 5). Gratifyingly, when the reaction was carried out using sterically demanding *tert*-butylethynyl phenyl ketone **1e**, the desired compound **2e** was obtained in 96% with 94% ee, although the loss of chemical yield was observed after the treatment with tetrabutylammonium fluoride ($^nBu_4NF$) (entry 6).

Encouraged by the result, the scope of this trifluoromethylation reaction was investigated with a range of alkynyl ketones (entries 7−22). The reaction is remarkably general. To allow for comparisons, all reactions were conducted with 10 mol % chiral catalyst on a 0.2 mmol scale and 2.0 equiv of the Me_3SiCF_3. Reactions were not individually optimized to establish the generality of the procedure. Most reactions were complete in 1−3 h at −60 °C to −50 °C. In all cases, the initial adduct was a trimethylsilyl-ether that was removed by treatment with $^nBu_4NF$ to provide the alcohol product **2**. All of the reactions proceeded in essentially quantitative yield as confirmed by TLC analysis, but the isolated yield of **2** was often lower due to loss of the product during the treatment with $^nBu_4NF$ to remove a trimethylsilyl group. High enantioselectivities were obtained for all cases up to 96% ee, with these being almost independent of the functional groups such as alkyl and sterically demanding alkyl, aryl, halogenyl, and methoxy moieties, as well as the positions of the aromatic ring (entries 8−16). For another aromatic analogue **1p** bearing a bulky naphthyl group, we also obtained the trifluoromethylated product **2p** in good yield with high enantioselectivity of 93% ee (entry 17). Cinnamyl-substituted alkynyl ketone **1q** is also a suitable substrate for **3a**/Me_4NF-catalyzed asymmetric trifluoromethylation with 83% ee (entry 18). A remarkable feature of this method is that the reaction is applicable not only for *tert*-butyl-substituted ethynyl ketones but also other sterically demanding ethynyl ketones. Namely, the aryl alkynyl ketones **1r**−**u** with sterically demanding hydroxypropyl tethers were nicely converted to the corresponding trifluoromethylated propargyl

(5) To our knowledge, enantioselective arylation of trifluoromethyl alkenyl ketones has not been reported. For a related reaction, see: (a) Tur, F.; Saá, J. M. *Org. Lett.* **2007**, *9*, 5079–5082. (b) Saá, J. M.; Tur, F.; González, J. *Chirality* **2009**, *21*, 836–842.

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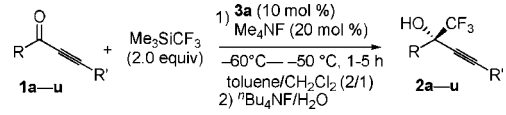
Table 1. Enantioselective Trifluoromethylation of **1** with Me_3SiCF_3 Catalyzed by **3a** and Me_4NF[a]

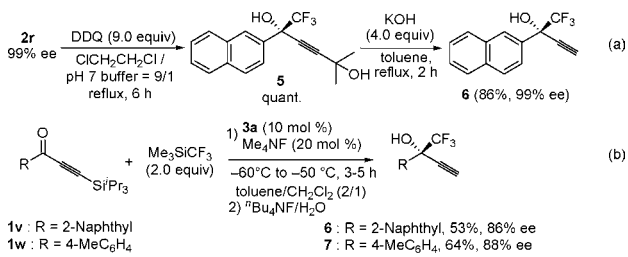


entry	1	R	R′	2	yield (%)	ee (%)
1[b]	**1a**	Ph	H	**2a**	cp	
2[b]	**1b**	Ph	Me	**2b**	cp	
3[b]	**1c**	Ph	$SiMe_3$	**2c**	cp	
4[b]	**1d**	Ph	Ph	**2d**	54	40
5	**1d**	Ph	Ph	**2d**	91	51
6	**1e**	Ph	^{t}Bu	**2e**	96[c]; 65[d]	94
7	**1f**	2-MeC_6H_4	^{t}Bu	**2f**	75	80
8	**1g**	3-MeC_6H_4	^{t}Bu	**2g**	81	92
9	**1h**	4-MeC_6H_4	^{t}Bu	**2h**	70	96
10	**1i**	3-$MeOC_6H_4$	^{t}Bu	**2i**	70	90
11	**1j**	4-$MeOC_6H_4$	^{t}Bu	**2j**	85	95
12	**1k**	3,4-$Me_2C_6H_3$	^{t}Bu	**2k**	87	92
13	**1l**	4-^{t}BuC_6H_4	^{t}Bu	**2l**	70	94
14	**1m**	4-PhC_6H_4	^{t}Bu	**2m**	88	91
15	**1n**	4-FC_6H_4	^{t}Bu	**2n**	81	86
16	**1o**	4-ClC_6H_4	^{t}Bu	**2o**	87	86
17	**1p**	2-naphthyl	^{t}Bu	**2p**	78	93
18	**1q**	PhCH=CH	^{t}Bu	**2q**	71	83
19	**1r**	2-naphthyl	$C(Me)_2OBn$	**2r**	93	83
20	**1s**	2-naphthyl	$C(Me)_2OCH_2$(*p*-BrC_6H_4)	**2s**	66	78
21	**1t**	2-naphthyl	$C(Me)_2OCHPh_2$	**2t**	99	83
22	**1u**	4-MeC_6H_4	$C(Me)_2OBn$	**2u**	90	91

[a] The reaction of **1** with Me_3SiCF_3 (2.0 equiv) was carried out in the presence of **3a** (10 mol %) and Me_4NF (20 mol %) in toluene/CH_2Cl_2 (2/1) at −60 °C to −50 °C, unless otherwise noted. All reactions proceeded in essentially quantitative yield as confirmed by TLC analysis. All yields are isolated yields of **2** unless otherwise stated; ee's were determined by Chiral HPLC; cp = complex. [b] *N*-3,5-Bis(trifluoromethylbenzyl)cinchonium bromide **3b** was used instead of **3a**. [c] Isolated yield as trimethylsilyl ether without treatment with ^{n}Bu$_4$NF. [d] Isolated yield after treatment with ^{n}Bu$_4$NF.

alcohols in high yields with high enantioselectivities up to 91% ee (entries 19−22). It should be noted that the hydroxypropyl tethers can be removed quantitatively in two steps. First, the benzyl protecting group of **2r** (99% ee after recrystallization) was removed through oxidative cleavage with DDQ in aqueous dichloroethene to provide diol **5** quantitatively. Next, exposure of the resulting diol **5** to KOH in toluene effected cleavage of the hydroxypropyl protecting group to yield propargyl alcohol **6** in quantitative amounts without any loss of enantiomeric purity of **2r** (Scheme 2a). The absolute stereochemistry of a newly generated stereocenter in **2s** was determined by X-ray crystallographic analysis, and the stereochemistry of another trifluoromethylated alcohol **2** was tentatively assumed by analogy.[9] To the best of our knowledge, these are the first examples of enantioselective trifluoromethylation of alkynyl ketones **1**. Importantly, (triisopropylsilyl)ethynyl aryl ketones **1v**−**w** were also found to provide trifluoromethylated adducts **6** and **7** in good yields with 86% and 88% ees, respectively. The triisopropylsilyl group at the ethynyl position and the *O*-trimethylsilyl group were simultaneously removed by ^{n}Bu$_4$NF treatment to generate nonsilylated propargyl alcohols in good yields (Scheme 2b).

Scheme 2. Syntheses of Propargyl Alcohols **6** and **7**



We were next interested in the synthesis of aryl heteroaryl trifluoromethyl carbinols. Enantioenriched aryl heteroarylmethanols are important intermediates and structural motifs in medicinal chemistry,[10] and therefore, trifluoromethylated analogues of aryl heteroarylmethanols are of pottential interest as building blocks for biologically active compounds.[11] The trifluoromethylated propargyl alcohols **2** obtained here would be particularly interesting substrates

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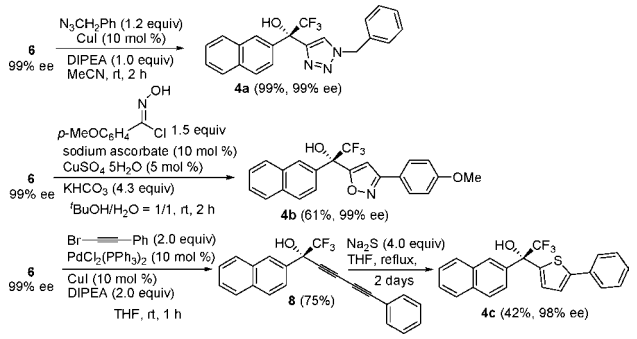
(9) The CCDC-782947 ((*S*)-**2s**) contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Scheme 3. Synthesis of Aryl Heteroaryl Trifluoromethyl Carbinols



since functionalization of the ethynyl moiety allows ready access to drug-like compounds mentioned above. First, the trifluoromethylated propargyl alcohol **6** was converted efficiently into medicinally attractive aryl 1,4-disubstituted 1,2,3-triazole trifluoromethyl carbinol **4a** in 99% under the click chemistry condition[12] using a catalytic amount of CuI in the presence of *N*,*N*-diisopropylethylamine (DIPEA) in MeCN at rt in 99% without any loss of enantiomeric purity (Scheme 3, top). Copper(I)-catalyzed transformation of **6** to 3,5-disubstituted isoxazole 2-naphtyl trifluoromethyl carbinol **4b** was successfully carried out by the catalyst prepared in situ by reduction of copper(II) sulfate (5 mol %) with ascorbate (10 mol %) in the presence of $KHCO_3$ in $^tBuOH/H_2O$[13] at rt for 2 h in 61% (Scheme 3, middle). Thiophenyl naphthyl trifluoromethyl carbinol **4c** was also successfully synthesized via tethered enediyne **8** prepared in good yield by the Sonogashira cross-coupling reaction[14] of **6** with phenylethynyl bromide catalyzed by $PdCl_2(PPh_3)_2$ (10 mol %) and CuI (10 mol %) in the presence of *N*,*N*-diisopropylethylamine (DIPEA) followed by the treatment with sodium sulphide in refluxing THF[15] in good overall yields (Scheme 3, bottom).

In summary, we have developed the first enantioselective trifluoromethylation of alkynyl ketones with Me_3SiCF_3. By employing ammonium salts of cinchona alkaloids and Me_4NF as catalysts, we have efficiently condensed a wide range of alkynyl ketones **1** and Me_3SiCF_3 to provide pharmaceutically important trifluoromethylated propargyl alcohols **2** having a quaternary carbon center in very good enantiomeric excess. The trifluoromethylated propargyl alcohols **2** were nicely transformed into biologically attractive aryl heteroaryl trifluoromethyl carbinols **4** without any loss of enantiomeric purity of **2**.

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Supporting Information Available: Experimental procedures, spectra data for all new compounds, X-ray crystallographic analysis of **2s** in CIF format, and HPLC charts. This material is available free of charge via the Internet at http://pubs.acs.org.

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