Fluorination

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Cinchona Alkaloid Catalyzed Enantioselective Fluorination of Allyl Silanes, Silyl Enol Ethers, and Oxindoles**

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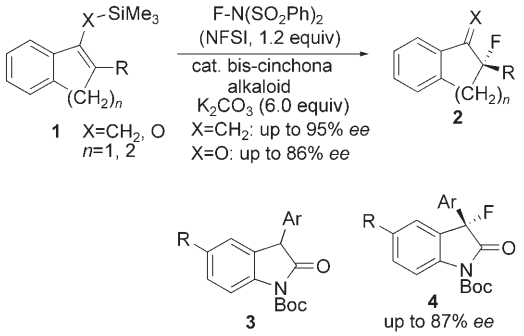
The enantioselective incorporation of fluorine into organic molecules has been extensively exploited because chiral functional groups with a C–F unit have attractive properties for pharmaceutical and materials applications.[1] The first results on catalytic enantioselective fluorination were reported by Togni et al. in 2000 for the reaction of β-keto esters using Ti^{IV}/TADDOL catalysts.[2a] Since then, several methods for the catalytic enantioselective fluorination of 1,3-dicarbonyl compounds and related substrates have been developed.[2,3] The enantioselective fluorination of aldehydes catalyzed by proline and its analogues is also a recent topic in this field.[4] However, a major limitation of this methodology is that ketones are poor substrates. Thus, the construction of compounds containing a chiral quaternary carbon center with a fluoro substituent remains problematic, with the exception of the examples reported by Jørgensen et al.[4e]

In 2000 we developed combinations of cinchona alkaloids and Selectfluor, that is, *N*-fluoroammonium salts of cinchona alkaloids, as enantioselective fluorinating reagents,[5a] and similar reagents were also independently reported by Cahard et al.[6a] The advantage of these reagents is that a wide range of substrates including silyl enol ethers, 1,3-dicarbonyl compounds, lactones, oxindoles, dipeptides, and allyl silanes can be effectively fluorinated in a highly enantioselective manner.[6] The asymmetric fluoro semipinacol rearrangement of allylic alcohols is also induced by this combination.[6i] However, this methodology requires a stoichiometric amount of the cinchona alkaloid, and the catalytic version of the reaction has not been very successful.[7] Herein we disclose the first successful catalytic enantioselective fluorination based on cinchona alkaloids (Scheme 1). Allyl silanes and silyl enol ethers undergo efficient enantioselective fluorodesilylation with *N*-fluorobenzenesulfonimide (NFSI) and a catalytic amount of a bis-cinchona alkaloid in the presence of excess base to provide the corresponding fluorinated compounds with a F-substituted quaternary carbon center with enantioselectivities up to 95% *ee*. Furthermore, we demonstrate that the methodology can be effectively extended to the catalytic enantioselective fluorination of oxindoles. The X-ray crystal structure of the bis-cinchona alkaloid dihydroquinine(2,5-diphenyl-4,6-pyrimidinediyl diether) ($(DHQ)_2PYR$) is also disclosed for the first time.



Scheme 1. Cinchona alkaloid catalyzed enantioselective fluorination. BOC = *tert*-butyloxycarbonyl.

We started by attempting a catalytic version of the stoichiometric enantioselective fluorodesilylation of allyl silane **1a** described by Gouverneur et al.[6h] (Table 1). Using a catalytic amount of $(DHQ)_2PYR$ and 1.2 equiv of Selectfluor as the fluorination reagent in CH_3CN at 0 °C, **1a** was converted to allylic fluoride **2a** in 46% yield as a racemate (entry 1, Table 1). We assume that an initial transfer fluorination from Selectfluor to $(DHQ)_2PYR$ did not proceed since Selectfluor reacts more readily with allyl silane **1a** than with the cinchona alkaloid. We next used NFSI as a fluorinating reagent. Although (*R*)-**2a** was produced in 62% yield, the enantioselectivity was only 19% *ee* (entry 2, Table 1). To our great delight, the addition of K_2CO_3 dramatically improved the enantioselectivity to 85% *ee* (entry 3, Table 1), and the enantioselectivity of **2a** was further enhanced to 91–94% ee by the use of a large excess of K_2CO_3 (entries 4–7, Table 1). Solvents also had a considerable effect on the enantioselectivity (entries 8–10, Table 1). The configuration of **2a** was determined to be *R* by comparing the optical rotation and HPLC data with the literature values.[6h] It should be mentioned that the same selectivity for (*R*)-**2a** was observed for the stoichiometric reaction reported by Gouverneur et al.[6h]

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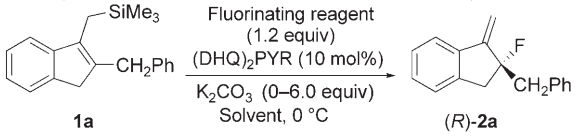
Table 1: Optimization of the enantioselective fluorodesilylation of **1a**.



1a (*R*)-**2a**

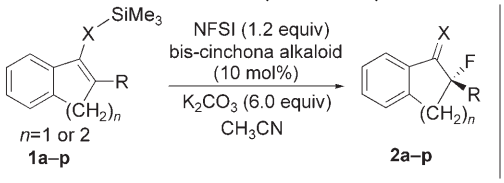
Entry	Fluorinating reagent	K_2CO_3 [equiv]	Solv.	*t* [h]	Yield [%]	*ee* [%]
1	Selectfluor	–	CH_3CN	10 min	46	0
2	NFSI	–	CH_3CN	46	62	19
3	NFSI	1.0	CH_3CN	4	61	85
4	NFSI	3.0	CH_3CN	2	68	90
5	NFSI	6.0	CH_3CN	2	79	91
6[a]	NFSI	6.0	CH_3CN	9	63	94
7[b]	NFSI	6.0	CH_3CN	72	75	94
8	NFSI	6.0	CH_2Cl_2	4	55	86
9	NFSI	6.0	THF	60	26	68
10	NFSI	6.0	toluene	60	11	50

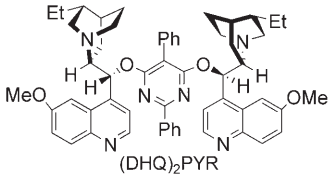
[a] Reaction was carried out at −20 °C. [b] Reaction was carried out at −40 °C.

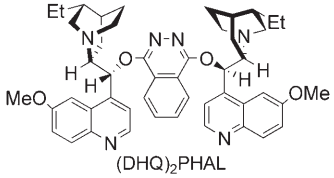
The scope of the allylic enantioselective fluorodesilylation of allyl silanes was investigated. As shown in Table 2, various allyl silanes were good substrates for this reaction, providing the desired allylic fluorides in good yields with good to high enantioselectivities in the presence of a catalytic amount of $(DHQ)_2PYR$ (entries 1–10, Table 2). Allyl silanes with dihydroindene (**1a–h**, $n=1$) as well as tetrahydronaphthalene (**1i**,**1j**, $n=2$) cores worked well to give the desired chiral fluorinated compounds with up to 95% *ee*. The size of the substituent at the C2 position of substrates **1** influenced the enantioselectivity slightly. The methyl-substituted and unsubstituted allyl silanes **1g** and **1h** were converted to the corresponding allylic fluorides **2g** and **2h** with 72% *ee* and 52% *ee*, respectively (entries 7 and 8, Table 2). The fluorodesilylation of **2a** in the presence of the hydroquinidine variant $(DHQD)_2PYR$ provided the opposite enantiomer, (*S*)-**2a**, in 76% *ee* (entry 11, Table 2).

Since bis-cinchona alkaloid/NFSI/K_2CO_3 proved to be an effective catalyst combination for the enantioselective fluorodesilylation of allyl silanes, we next extended the procedure to the catalytic enantioselective fluorodesilylation of silyl enol ethers, which was previously achieved by the stoichiometric reaction.[5a,b] While the catalyst $(DHQ)_2PYR$ was not suitable for the enantioselective fluorodesilylation of silyl enol ether **1k** (entry 12, Table 2), the desired α-fluoroketone **2k** was obtained in 90% yield with 71% *ee* using $(DHQ)_2PHAL$ as a catalyst (entry 13, Table 2). The *ee* value for the product was improved when the reaction was carried out at a lower temperature (76% *ee*, entry 14, Table 2). The best result was obtained using 20 mol% of the catalyst at −40 °C (82% *ee*, entry 15, Table 2). To probe the scope of the reaction, the enantioselective fluorodesilylation of silyl enol ethers **1k–o** with NFSI was undertaken using $(DHQ)_2PHAL$ to furnish

Table 2: Enantioselective fluorodesilylation of allyl silanes and silyl enol ethers catalyzed by bis-cinchona alkaloids.[a]





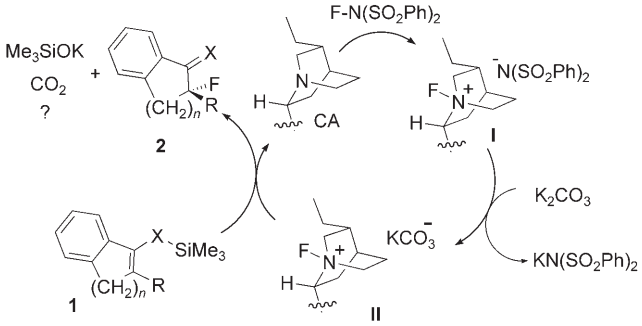


Entry	1	X	R	*n*	Bis-cinchona alkaloid	2	*T* [°C]	*t*	Yield [%]	*ee* [%]
1	**1a**	CH_2	$CH_2C_6H_5$	1	$(DHQ)_2PYR$	**2a**	−40	3 days	75	94
2	**1b**	CH_2	$CH_2C_6H_4$-*p*-Me	1	$(DHQ)_2PYR$	**2b**	−20	12 h	75	95
3	**1c**	CH_2	$CH_2C_6H_4$-*p*-Cl	1	$(DHQ)_2PYR$	**2c**	−20	18 h	81	94
4	**1d**	CH_2	$CH_2C_6H_4$-*p*-OMe	1	$(DHQ)_2PYR$	**2d**	−20	34 h	65	90
5	**1e**	CH_2	$CH_2C_6H_4$-*o*-OMe	1	$(DHQ)_2PYR$	**2e**	−20	9 h	58	93
6	**1f**	CH_2	2-naphthylmethyl	1	$(DHQ)_2PYR$	**2f**	−20	34 h	69	91
7	**1g**	CH_2	Me	1	$(DHQ)_2PYR$	**2g**	−40	24 h	73	72
8	**1h**	CH_2	H	1	$(DHQ)_2PYR$	**2h**	−20	5 days	58	51
9	**1i**	CH_2	$CH_2C_6H_5$	2	$(DHQ)_2PYR$[c]	**2i**	−20	4 days	74	81
10	**1j**	CH_2	$CH_2C_6H_4$-*p*-Me	2	$(DHQ)_2PYR$	**2j**	−20	36 h	71	81
11	**1a**	CH_2	$CH_2C_6H_5$	1	$(DHQD)_2PYR$	**2a**	0	2 h	59	76[b]
12	**1k**	O	$CH_2C_6H_5$	2	$(DHQ)_2PYR$	**2k**	0	16 h	96	31
13	**1k**	O	$CH_2C_6H_5$	2	$(DHQ)_2PHAL$	**2k**	0	12 h	90	71
14	**1k**	O	$CH_2C_6H_5$	2	$(DHQ)_2PHAL$	**2k**	−40	7 days	81	76
15	**1k**	O	$CH_2C_6H_5$	2	$(DHQ)_2PHAL$[c]	**2k**	−40	10 days	82	82
16	**1l**	O	$CH_2C_6H_4$-*p*-Me	2	$(DHQ)_2PHAL$[c]	**2l**	−40	8 days	79	86
17	**1m**	O	$CH_2C_6H_4$-*p*-Cl	2	$(DHQ)_2PHAL$[c]	**2m**	−40	8 days	74	86
18	**1n**	O	$CH_2C_6H_4$-*p*-OMe	2	$(DHQ)_2PHAL$[c]	**2n**	−40	6 days	84	85
19	**1o**	O	2-naphthylmethyl	2	$(DHQ)_2PHAL$[c]	**2o**	−40	6 days	88	84
20	**1p**	O	Et	2	$(DHQ)_2PHAL$[c]	**2p**	−40	7 days	95	67

[a] For detailed reaction conditions, see the Supporting Information. The absolute configurations of **2a**, **2i**, **2k**, and **2p** were determined by comparison with the optical rotations and HPLC analyses in literature.[6h,5b] The configurations of other compounds were tentatively assigned by comparing the signs of their optical rotations to those of **2a**, **2i**, **2k**, and **2p**. [b] (*S*)-**2a** was obtained. [c] 20 mol% of the cinchona alkaloid was used.

the desired α-fluorinated ketones **2k–o** in good yields and with high *ee* values (82–86% *ee*, entries 15–19, Table 2). A lower enantioselectivity of 67% *ee* was observed for the fluorodesilylation of ethyl-substituted silyl enol ether **1p** (entry 20, Table 2); this tendency is similar to that observed for the less bulky allyl silanes **1g** and **1h** (entries 7 and 8, Table 2). The requirement for a bulky substituent on the substrates is a major limitation on the enantioselectivity of this method.

The fact that the same enantioselectivity is observed both the catalytic and stoichiometric reactions suggests that the *N*-fluoroammonium salt of the cinchona alkaloid should be a species in the catalytic cycle (Scheme 2).[5a–d,6h] It has been reported previously that the cinchona alkaloid reacts with



Scheme 2. A plausible catalytic cycle for cinchona alkaloids (CAs)-catalyzed enantioselective fluorodesilylation of **1** to **2**.

NFSI to form a stable *N*-fluoroammonium salt by transfer fluorination,[6e] and we believe that this is an initial step in the reaction. However, in the absence of K_2CO_3, the reactivity of *N*-fluoroammonium salt **I** with the substrate is really poor (entry 2, Table 1). We therefore speculate that the *N*-fluoroammonium sulfonimide salt **I** could act as a phase-transfer catalyst to react with K_2CO_3 leading to the formation of the *N*-fluoroammonium KCO_3^- salt **II**. The fluorodesilylation of substrates **1** is then triggered by KCO_3^- followed by the enantioselective transfer fluorination from the *N*-fluoroammonium ion to the substrates to yield the fluorinated products **2** and regenerating the cinchona alkaloid. Although we have not isolated the intermediates, the observations in Table 1 are consistent with the catalytic cycle shown in Scheme 2.

Our X-ray crystal structure analysis of single crystals of $(DHQ)_2PYR$ indicated that the selectivity for (*R*)-**2a** should be induced in an enzyme-like cleft in $(DHQ)_2PYR$. The X-ray structure of $(DHQ)_2PYR$ and a proposed transition-state assembly for the enantioselective fluorodesilylation of **1a** to give **2a** are shown in Figure 1. As evident in the crystal structure, one of the two dihydroquinine moieties exists in a closed conformation (right half) and the other is in an open conformation (left half). In our previous report on enantioselctive fluorination using a stoichiometric amount of cinchona alkaloid/Selectfluor, we found that *N*-fluorinated quininium and *N*-fluorinated dihydoroquinidinium salts exist in the open conformations both in solid and solution states.[5b] Therefore, in the present case the dihydroquinine moiety with the open conformation might be responsible for

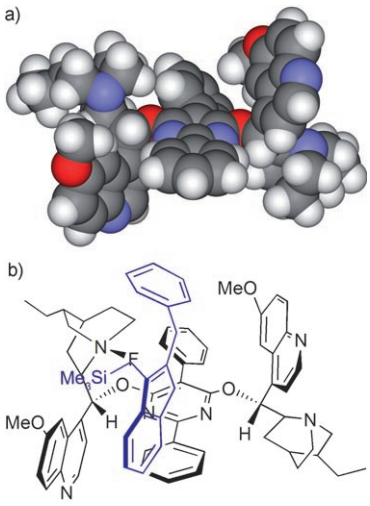
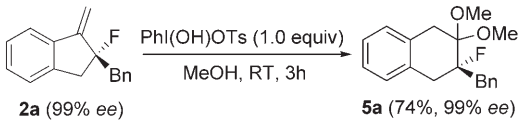


Figure 1. a) X-ray crystal structure of $(DHQ)_2PYR$. b) Proposed transition-state assembly for enantioselective fluorodesilylation of **1a** to give **2a**.

the enantioselective transfer fluorination, although further studies should be required to elucidate the mechanism (Figure 1).

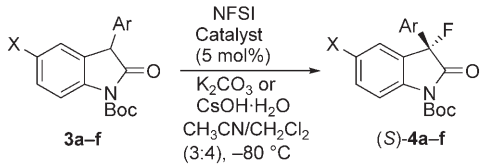
A transformation of **2a** was next demonstrated to show the utility of the fluorodesilylation products. The allyl fluoride **2a** (99% *ee* after recrystallization) was treated with hydroxy(tosyloxy)iodobenzene in anhydrous MeOH (the modified Koser's procedure[8]) to give the 2-tetralone derivative **5a** by means of a ring-expansion reaction in good yield without racemization (99% *ee*, Scheme 3).

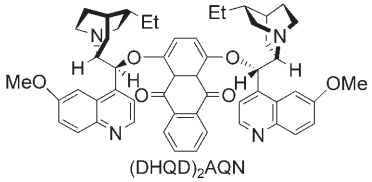


Scheme 3. Ring expansion of **2a** to **5a**.

To demonstrate the further synthetic utility of this catalytic approach, we finally investigated the catalytic enantioselective fluorination of oxindoles. Pharmaceutically important 3-aryl-3-fluoro-2-oxindoles were selected as the target molecules.[9] Enantioselective fluorination of oxindoles was previously examined by us[5b,c] and Cahard et al.[6f] using a stoichiometric amount of cinchona alkaloids/Selectfluor combinations. The Sodeoka group[2g] and Shibata et al.[3b] reported the catalytic enantioselective fluorination of oxindoles using metal/chiral ligand complexes. However, no enantioselective method for the reaction using organocatalysts has been described. Bis-cinchona alkaloids were screened for the reaction of *N*-*tert*-butoxycarbonyl-3-phenyl-2-oxindole (**3a**) with NFSI in CH_3CN in the presence of K_2CO_3 at room temperature (Table 3). $(DHQ)_2PYR$, $(DHQ)_2PHAL$, $(DHQ)_2AQN$, and $(DHQD)_2AQN$ showed nearly equal reactivity and enantioselectivity (entries 1–4, Table 3). The enantioselectivity was improved to 66% *ee* when the reaction was carried out in CH_3CN/CH_2Cl_2 (3:4) at −80 °C. Interest-

Table 3: Enantioselective fluorination of oxindoles **3**.[a]





$(DHQD)_2AQN$

Entry	3	Catalyst	Ar	X	*t* [days]	*ee* [%]/Yield [%]
1[b]	**3a**	$(DHQ)_2PYR$[c]	Ph	H	1 h	35[d]/99
2[b]	**3a**	$(DHQ)_2PHAL$[c]	Ph	H	1 h	32[d]/92
3[b]	**3a**	$(DHQ)_2AQN$[c]	Ph	H	1 h	35[d]/87
4[b]	**3a**	$(DHQD)_2AQN$[c]	Ph	H	1 h	37/98
5	**3a**	$(DHQD)_2AQN$[c]	Ph	H	2	66/92
6	**3a**	$(DHQD)_2AQN$	Ph	H	5	80/77
7	**3a**	$(DHQD)_2AQN$	Ph	H	5	87/87
8	**3b**	$(DHQD)_2AQN$	*p*-Tol	H	5	83/86
9	**3c**	$(DHQD)_2AQN$	*p*-Tol	Me	5.5	81/81
10	**3d**	$(DHQD)_2AQN$	Ph	OMe	5	84/92
11	**3e**	$(DHQD)_2AQN$	*p*-Tol	OMe	5	79/86
12	**3f**	$(DHQD)_2AQN$	pFC_6H_4	OMe	5	81/86
13	**3a**	$(DHQ)_2AQN$	Ph	H	5	85[d]/99
14	**3b**	$(DHQ)_2AQN$	*p*-Tol	H	5	86[d]/94
15	**3c**	$(DHQ)_2AQN$	*p*-Tol	Me	7	84[d]/86
16	**3e**	$(DHQ)_2AQN$	*p*-Tol	OMe	5	85[d]/99

[a] The reaction was carried out in the presence of cinchona alkaloid (5 mol%), $CsOH·H_2O$ (6.0 equiv) in CH_3CN/CH_2Cl_2 at −80°C, unless otherwise noted. The absolute configurations of **4** were determined by comparison with the optical rotations and HPLC data in the literature.[2g,3b] [b] Reactions were carried out in CH_3CN at room temperature. [c] 10 mol%of the cinchona alkaloid was used. [d] (*R*)-**4** was obtained.

ingly, the fluorination product was obtained in higher selectivity when less cinchona alkaloid was used (5 mol%; 80% *ee*, entry 6, Table 3). Furthermore, the *ee* value for **4a** was much higher with $CsOH·H_2O$ as a base (87% *ee*, entry 7, Table 3). The scope of the reaction under optimal conditions was evaluated with various substrates. The $(DHQD)_2AQN$/NFSI/$CsOH·H_2O$ system proved to be a suitable combination for the catalytic enantioselective fluorination of oxindoles with high enantiomeric excess (entries 8–12, Table 3). The absolute configurations of products **4** were determined by comparison with the optical rotations and HPLC data in the literature.[2g,3b] The quinine derivative $(DHQ)_2AQN$ showed reverse enantioselectivity for the fluorination of **3a**–**c**,**e** to afford (*R*)-**4a**–**c**,**e** in 86–99% yield with 84–86% *ee* (entries 13–16, Table 3).

In conclusion, we have developed the first catalytic enantioselective fluorodesilylation reaction of allyl silanes and silyl enol ethers using bis-cinchona alkaloids in the presence of excess base. The catalytic system was applied to the enantioselective fluorination of oxindoles. Despite a limited substrate scope, this unprecedented cinchona alkaloid mediated catalytic approach offers the advantage of substrate variation in the field of catalytic enantioselective fluorination reactions. The X-ray crystal structure of $(DHQ)_2PYR$ should also have strong impact on the field of asymmetric synthesis.

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Keywords: allyl silanes · asymmetric catalysis · cinchona alkaloids · fluorination · silyl enol ethers

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