Asymmetric Catalysis

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Cinchona-Alkaloid-Catalyzed Enantioselective Direct Aldol-Type Reaction of Oxindoles with Ethyl Trifluoropyruvate**

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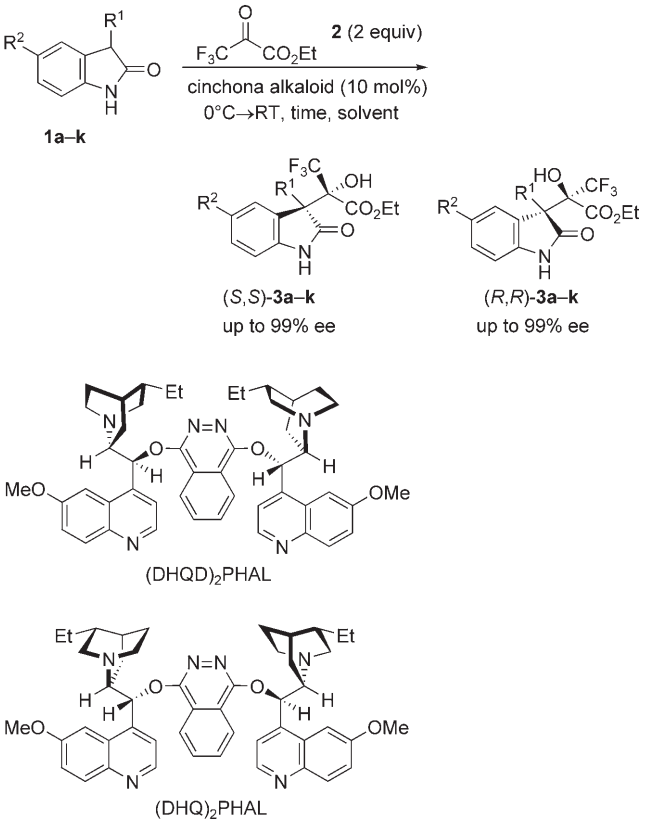
In memory of Yoshihiko Ito

Heterocycles that contain a trifluoromethyl group are important compounds in agricultural and medicinal chemistry. Therefore, the development of a simple and flexible method for the generation of trifluoromethylated heterocyclic systems has received much attention.[1] We believed that the incorporation of a tertiary α-trifluoromethyl alcohol stereocenter ($CF_3C^*(OH)R^1R^2$) into heterocycles could provide novel drug candidates with unusual biological activities as a result of the unique properties of the tertiary α-trifluoromethyl alcohol functionality.[2] We first became interested in the development of general methods for the synthesis of oxindoles with a tertiary α-trifluoromethyl alcohol moiety in a chiral environment. Oxindoles with a quaternary stereogenic center, especially spirooxindoles, are of potential medicinal interest owing to the unique biological activities of natural products and man-made compounds that contain such systems.[3] As part of our ongoing studies in medicinal fluorine chemistry,[4] we describe herein the highly enantioselective synthesis of oxindoles **3** with two contiguous asymmetric quaternary carbon atoms, including a tertiary α-trifluoromethyl alcohol center,[5] by an asymmetric direct aldol-type condensation of oxindoles with ethyl 3,3,3-trifluoropyruvate (**2**) under the catalysis of cinchona alkaloids.[6] The two enantiomeric products (*S*,*S*)-**3** and (*R*,*R*)-**3** are accessible selectively in high yields with up to 99% *ee* with pseudo-enantiomeric cinchona alkaloids (Scheme 1).

Trifluoropyruvate is one of the most versatile building blocks for the synthesis of chiral trifluoromethylated compounds. Examples of enantioselective nucleophilic addition to trifluoropyruvate in the Friedel–Crafts reaction, the aldol reaction, the Henry reaction, and the carbonyl-ene reaction under the catalysis of chiral Lewis acids, cinchona alkaloids, or proline derivatives have been reported.[7] However, there is no information available on the use of oxindoles as nucleophiles in the corresponding asymmetric addition reactions. We first attempted the enantioselective aldol-type reaction of 3-methyl-2-oxindole (**1a**; $R^1 = Me$, $R^2 = H$; Scheme 1) with **2** in the presence of cinchonidine as a catalyst.

Cinchonidine was found to be an effective catalyst for the enantioselective Friedel–Crafts reaction of indoles reported by Prakash and co-workers;[7e] however, in the direct aldol-type reaction of **1a** with **2**, the adduct **3a** was obtained in 67% yield with poor diastereoselectivity and 50% *ee* (Table 1, entry 1). At best only a slight improvement in the diastereomeric ratio and enantioselectivity was observed with other



Scheme 1. Aldol-type reaction of oxindoles **1** with ethyl trifluoropyruvate (**2**) under the catalysis of cinchona alkaloids.

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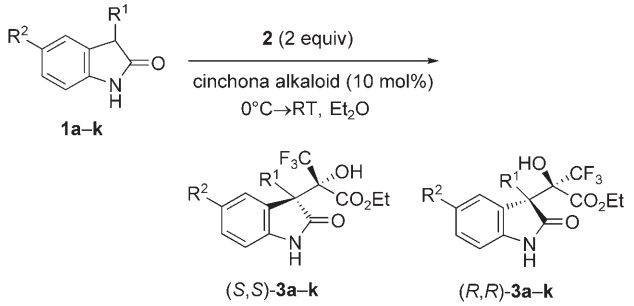
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

Table 1: Direct aldol-type reaction of **1a** (R^1 = Me, R^2 = H) with **2** under the catalysis of cinchona alkaloids.[a]

Entry	Cinchona alkaloid[b]	Solvent	*t* [h]	Yield [%]	d.r.[c]	*ee* [%][d]
1	cinchonidine	Et_2O	6	67	63:37	50[f]
2	cinchonine	Et_2O	28	61	80:20	66[e]
3	quinine	Et_2O	20	95	79:21	14[f]
4	quinidine	Et_2O	20	92	81:19	39[e]
5	$(DHQD)_2AQN$	Et_2O	4	93	82:18	84[e]
6	$(DHQD)_2PYR$	Et_2O	15	93	85:15	80[e]
7	$(DHQD)_2PHAL$	Et_2O	16	99	90:10	95[e]
8	$(DHQD)_2PHAL$	CH_2Cl_2	10	96	86:14	93[e]
9	$(DHQD)_2PHAL$	THF	18	99	86:14	96[e]
10	$(DHQD)_2PHAL$	MeCN	2	99	71:29	47[e]
11	$(DHQD)_2PHAL$	DMF	4	98	71:29	5[e]
12	$(DHQ)_2PHAL$	Et_2O	19	99	88:12	94[f]
13	QN-1-naphthoate	Et_2O	20	99	89:11	97[f]
14	QD-1-naphthoate	Et_2O	49	55	82:18	65[e]
15[g]	$(DHQD)_2PHAL$	Et_2O	22	23	95:5	17

[a] Reaction conditions (unless otherwise noted): **1a** (30 mg), **2** (2 equiv), solvent (1.0 mL), catalyst (10 mol%), 0°C→RT. [b] See the Supporting Information for the structure of the catalysts. $(DHQD)_2AQN$ = hydroquinidine anthraquinone-1,4-diyl diether, $(DHQD)_2PYR$ = hydroquinidine 2,5-diphenyl-4,6-pyrimidinediyl diether, QN = quinine, QD = quinidine. [c] The diastereomeric ratio was determined by ^{19}F NMR spectroscopic analysis of crude **3a**, as it changed only slightly upon purification by silica-gel chromatography and/or recrystallization. [d] The *ee* value of the major isomer is given, as determined by HPLC analysis. [e] Major isomer: (*S*,*S*)-**3a**. [f] Major isomer: (*R*,*R*)-**3a**. [g] Ethyl pyruvate was used instead of **2**; the corresponding nonfluorinated analogue of **3a** was obtained. DMF = *N*,*N*-dimethylformamide.

Table 2: Direct aldol-type reaction of **1a–k** with **2** under the catalysis of cinchona alkaloids.[a]



Entry	**1**	R^1	R^2	*t* [h]	Yield [%]	d.r.[b]	*ee* [%][c]
1[d]	**1a**	Me	H	16	99	90:10	95[e]
2[d]	**1b**	Et	H	18	90	94:6	95[e]
3[d]	**1c**	Bn	H	9	97	89:11	96[e]
4[d]	**1d**	4-$BrC_6H_4CH_2$	H	21	93	86:14	92[e]
5[d]	**1e**	4-$ClC_6H_4CH_2$	H	8	99	90:10	98[e]
6[d]	**1f**	4-$MeOC_6H_4CH_2$	H	12	89	89:11	99[e]
7[d]	**1g**	Et	Me	32	94	92:8	95[e]
8[d]	**1h**	Bn	Me	3	75	85:15	95[e]
9[f]	**1a**	Me	H	19	99	88:12	94[g]
10[f]	**1b**	Et	H	23	99	88:12	99[g]
11[f]	**1c**	Bn	H	3	95	95:5	98[g]
12[f]	**1d**	4-$BrC_6H_4CH_2$	H	10	90	97:3	98[g]
13[f]	**1e**	4-$ClC_6H_4CH_2$	H	3	99	94:6	99[g]
14[f]	**1f**	4-$MeOC_6H_4CH_2$	H	3	81	94:6	97[g]
15[f]	**1g**	Et	Me	23	97	95:5	90[g]
16[f]	**1h**	Bn	Me	3	78	92:8	95[g]
17[f,h]	**1a**	Me	H	26	98	92:8	88[g]
18[i]	**1a**	Me	H	20	99	89:11	97[g]
19[i]	**1b**	Et	H	55	37	89:11	89[g]
20[i]	**1c**	Bn	H	20	99	93:7	92[g]
21[i]	**1d**	4-$BrC_6H_4CH_2$	H	17	82	92:8	92[g]
22[i]	**1e**	4-$ClC_6H_4CH_2$	H	16	99	92:8	92[g]
23[i]	**1h**	Bn	Me	16	61	91:9	86[g]
24[d]	**1i**	$BocNHCH_2CH_2$	H	22	99	88:12	79[e]
25[d]	**1j**	$CbzNHCH_2CH_2$	H	23	91	90:10	83[e]
26[d]	**1k**	$BnNHCH_2CH_2$	H	72	41[j]	70:30	0
27[f]	**1i**	$BocNHCH_2CH_2$	H	26	82	90:10	79[g]
28[f]	**1j**	$CbzNHCH_2CH_2$	H	23	83	91:9	84[g]
29[f]	**1k**	$BnNHCH_2CH_2$	H	49	27[j]	71:29	1

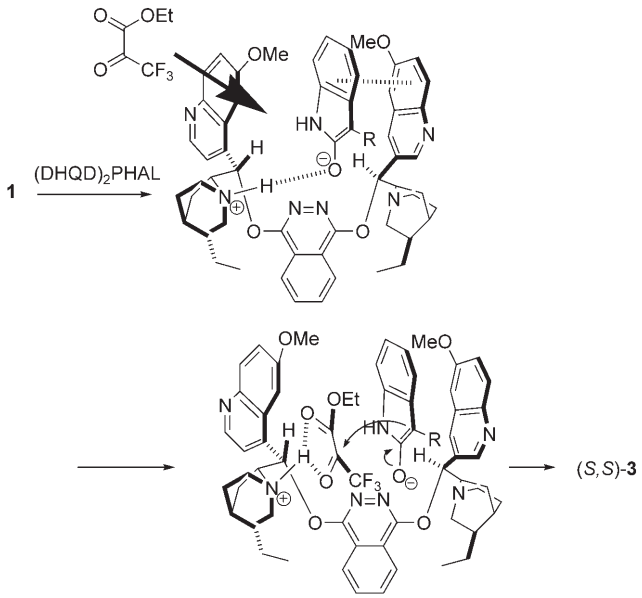
[a] Reaction conditions (unless otherwise noted): **1** (30 mg), **2** (2 equiv), Et_2O (1.0 mL), catalyst (10 mol%), 0°C→RT. [b] The diastereomeric ratio was determined by ^{19}F NMR spectroscopic analysis of crude **3**, as it changed only slightly upon purification by silica-gel chromatography and/or recrystallization. [c] The *ee* value of the major isomer is given, as determined by HPLC analysis. [d] $(DHQD)_2PHAL$ was used as the catalyst. [e] Major isomer: (*S*,*S*)-**3**. [f] $(DHQ)_2PHAL$ was used as the catalyst. [g] Major isomer: (*R*,*R*)-**3**. [h] $(DHQ)_2PHAL$: 5 mol%. [i] QN-1-naphthoate was used as the catalyst. [j] The spirooxindole **4k** was isolated instead of **3k** as a result of the spontaneous cyclization of **3k**. Bn = benzyl, Boc = *tert*-butoxycarbonyl, Cbz = carbobenzyloxy.

natural cinchona alkaloids (Table 1, entries 2–4). We tested commercially available biscinchona alkaloids as catalysts and found that the aldol-type reaction of the oxindole proceeded smoothly to yield the desired adduct (*S*,*S*)-**3a** in excellent yield with high diastereoselectivity and very high enantioselectivity in the presence of $(DHQD)_2PHAL$ (Table 1, entry 7).[8] The use of different solvents under similar conditions did not improve the result (Table 1, entries 8–11). In the presence of pseudoenantiomeric $(DHQ)_2PHAL$, the reaction gave the opposite enantiomer of the aldol product, (*R*,*R*)-**3a** (Table 1, entry 12). Sterically demanding QN-1-naphthoate also showed high enantioselectivity for (*R*,*R*)-**3a**, whereas QD-1-naphthoate was an inefficient catalyst (Table 1, entries 13 and 14). The CF_3 group on the pyruvate reagent plays an important role in the reactivity and selectivity of the reaction. Low conversion and low enantioselectivity were observed in the direct aldol-type reaction of **1a** with ethyl pyruvate (Table 1, entry 15).

This methodology served as a facile approach to the preparation of a range of trifluoromethylated oxindoles containing two stereogenic centers with excellent enantioselectivities (up to 99% *ee*) and high diastereoselectivities (d.r. up to 97:3; Table 2, entries 1–23). Both enantiomers of the products were synthesized in high yields with high enantioselectivities upon the selection of the appropriate cinchona alkaloid ($(DHQD)_2PHAL$ for (*S*,*S*)-**3**, $(DHQ)_2PHAL$ or QN-1-naphthoate for (*R*,*R*)-**3**).[8] When the amount of the catalyst was decreased to 5 mol%, slightly lower enantioselectivity was observed (Table 2, entry 17). The relative and absolute configuration of (*R*,*R*)-**3d**, the diastereomers of which were separated by recrystallization, was determined by X-ray crystallographic analysis. The configuration of the other oxindoles **3** was assigned tentatively by analogy.

Although the number of possible conformations of cinchona alkaloids in the solution state makes it difficult to analyze the transition-state structure of the substrate–catalyst

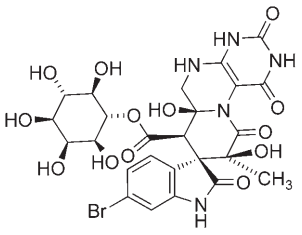
complexes, the reaction intermediate for the *S*,*S*-selective formation of oxindoles under the catalysis of $(DHQD)_2PHAL$ is presumably an open conformation similar to that described by Corey and Noe for osmium-catalyzed asymmetric dihydroxylation (Scheme 2).[9] With



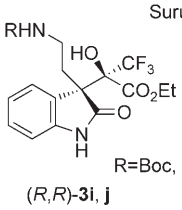
Scheme 2. Conformation of the $(DHQD)_2PHAL$ catalyst and proposed approximate structure of the substrate–catalyst complex for the *S*,*S*-selective formation of adducts **3** in the aldol-type condensation of oxindoles **1** with **2**.

$(DHQD)_2PHAL$ in the open conformation, the deprotonation of the oxindole is induced by the quinuclidine nitrogen atom, and the resulting enoates might be stabilized in part through hydrogen bonding and p stacking in the U-shaped cleft of $(DHQD)_2PHAL$. The *Si* face of the oxindole is covered so effectively by the quinoline ring that trifluoropyruvate approaches the *Re* face and is captured by the hydrogen-bonding network through the quinuclidine nitrogen atom. Consequently, the *S*,*S* isomers **3** are produced predominantly. The cinchona alkaloid may act as the catalytic base in the first step of the mechanism, the deprotonation step, and as the catalytic acid in the second step, the aldol reaction. Further studies are required to fully elucidate the mechanistic details of this direct aldol-type reaction of oxindoles (Scheme 2).

As a preliminary investigation into the application of this methodology to the preparation of biologically active molecules, we examined the asymmetric direct aldol-type reaction of substrates **1i**–**k** with 3-aminoethyl substituents (Table 2, entries 24–29) to form a core component of the trifluoromethyl analogue of surugatoxin. Surugatoxin[10] is a biologically active natural product isolated from the toxic Japanese ivory shell, *Babylonia japonica*. It depresses orthodromic transmission reversibly and antagonizes the depolarizing action of carbachol on isolated rat superior cervical ganglia. A total synthesis of racemic surugatoxin has been reported;[10b] however, neither an asymmetric total synthesis nor

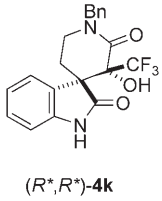


Surugatoxin



R=Boc, Cbz

(*R*,*R*)-**3i**, **j**



(*R**,*R**)-**4k**

the synthesis of biologically interesting analogues of surugatoxin has been attempted. We confirmed that **1i** and **1j** could be converted smoothly into the corresponding oxindole aldol adducts **3i** and **3j**, respectively, under the optimized reaction conditions (Table 2, entries 24, 25, 27, and 28). Unfortunately, however, the spirooxindole (*R**,*R**)-**4k** produced spontaneously in acceptable yields in the reaction of **1k** with ethyl trifluoropyruvate was obtained as a racemate as a result of a retro-aldol reaction of the intermediate **3k** caused by the basicity of the benzylamino moiety (Table 2, entries 26 and 29).

In conclusion, we have developed an organocatalytic enantioselective direct aldol-type reaction of oxindoles with trifluoropyruvate. By employing suitable pseudoenantiomeric cinchona alkaloids as catalysts, both enantiomers of the trifluoromethylated oxindole products with two contiguous asymmetric quaternary carbon centers can be obtained selectively in one step. The CF_3 group of the pyruvate is essential to the success of the oxindole-aldol reaction. Although the absolute configuration of the tertiary alcohol center in (*R*,*R*)-**3** is opposite to that of the equivalent center in natural surugatoxin, we are confident that the total synthesis of trifluoro-substituted surugatoxin will be possible by using this strategy, as methodology for the inversion of tertiary alcohols has been developed by Mukaiyama and co-workers.[11] Studies toward the total synthesis of the trifluoromethyl analogue of surugatoxin and epimeric compounds are ongoing.

Experimental Section

3a:**2** (54.0 μL, 0.40 mmol) was added slowly to a stirred mixture of **1a** (30.0 mg, 0.20 mmol) and $(DHQD)_2PHAL$ (15.8 mg, 0.020 mmol) in Et_2O (1.0 mL) at 0 °C. The resulting mixture was allowed to warm to room temperature over 5 h, and was stirred at room temperature for 11 h. The Et_2O solvent was then removed under reduced pressure, and the residue was purified by column chromatography on silica gel (AcOEt/*n*-hexane 1:4) to give (2*S*,3*S*)-**3a** (64.2 mg, 99%, d.r. 90:10, 95% *ee*) as a white solid. The minor diastereomer was obtained with 74% *ee*.

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