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Organocatalytic Asymmetric Halogenation/Semipinacol Rearrangement: Highly Efficient Synthesis of Chiral α-Oxa-Quaternary β-Haloketones

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Supporting Information

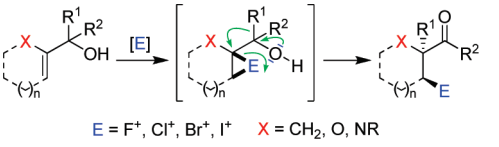
ABSTRACT: A novel asymmetric halogenation/semipinacol rearrangement reaction catalyzed by cinchona alkaloid derivatives was developed. Two types of β-haloketones (X = Br, Cl) were obtained with up to 95% yield and 99% enantiomeric excess. The desired (+) and (−) enantiomers of the β-haloketones were readily obtained.

Chiral organohalo compounds are a very important class of synthetic intermediates that are useful for many transformations in synthetic organic chemistry. There is much interest in development of synthetic methodologies in this area. Numerous asymmetric halogenating methods have been developed with different types of substrates and halogenating reagents.[1] Among them, a number of efforts to develop catalytic asymmetric halolactonization reactions and some related halocyclizations have been made,[2,3] and some halolactonization processes have been achieved in high enantioselectivity with organocatalysts recently.[4] Compared with enantioselective halolactonization reactions, the catalytic asymmetric halogenation/semipinacol rearrangement reactions are challenging and have attracted less attention. The halogenation/semipinacol rearrangement of allylic alcohols is a straightforward and commonly applied strategy for preparation of β-halocarbonyls, which are versatile intermediates with a broad range of potential applications in synthesis.[5] This tandem reaction simultaneously forms two adjacent stereocenters, one of which is quaternary, when starting from simple allylic alcohols (Scheme 1). Despite these important features, a suitable catalytic system has not been developed for catalytic asymmetric halogenation/semipinacol rearrangement reactions.

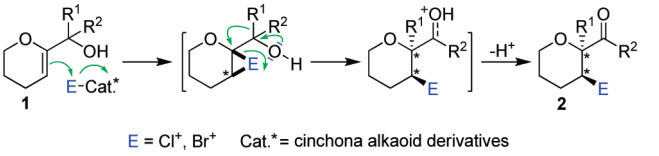
Recently, cinchona alkaloid derivatives have emerged as versatile enantioselective catalysts, and their use in a variety of enantioselective procedures has been widely reported.[6] They have been successfully employed in catalytic enantioselective halolactonizations.[4a,b] Inspired by the successful employment of these catalysts, and combined with our long-standing interest in semipinacol rearrangement reactions,[7] we envisioned synthesis of chiral β-halocarbonyls **2** by a cinchona alkaloid-catalyzed halogenation/semipinacol rearrangement of 2-oxa allylic alcohols **1** (Scheme 2). Herein, we report preliminary results for the halogenation/semipinacol rearrangement reaction catalyzed by cinchona alkaloid derivatives.

In our initial study, 2-oxa allylic alcohol **1a** was used as a model substrate, which was prepared according to literature procedures.[7f] As indicated in Table 1, some commercially

Scheme 1. Halogenation/Semipinacol Rearrangement in the Synthesis of β-Halocarbonyls



Scheme 2. Design for the Catalytic Enantioselective Halogenation/Semipinacol Rearrangement



available cinchona alkaloids (**3a**−**c**) were screened with *N*-bromosuccinimide (NBS) as the bromine source. Among them, a catalytic amount of hydroquinidine-2,5-diphenyl-4,6-pyrimidinediyl diether ((DHQD)$_2$PYR) (**3c**) and 1.1 equiv of NBS in CCl_4 at room temperature gave the best results and produced **2a** in 40% yield and 26% enantiomeric excess (ee) (entries 1−3). After **3c** was identified as a suitable catalyst, optimization of the reaction was investigated by varying the halogen source. The halogen source played a key role in the enantioselectivity of this reaction. When *N*-chlorosuccinimide (NCS) was used instead of NBS the ee decreased, whereas $CH_3CONHBr$ increased the enantioselectivity to 78% ee (entries 4−7). To further improve the yield and enantioselectivity, various solvents such as Et_2O, CH_2Cl_2, and toluene were investigated, wherein toluene was an effective solvent similar to CCl_4 in enantioselectivity (entries 8−10). By contrast with CCl_4, toluene is an inexpensive and environmentally benign solvent, so further investigation based on toluene is promising. *N*-Boc-L-phenylglycine (NBLP) was investigated as an additive instead of 4-methoxybenzoic acid and increased the enantioselectivity (entries 11 and 12). Remarkably, when the reaction temperature was lowered to −20 °C, the enantioselectivity was notably improved to 94% ee (entry 13). The addition of molecular sieves (MS; 5 Å) also greatly improved the yield to 92% (entry 14). In addition, *N*-Boc-D-phenylglycine

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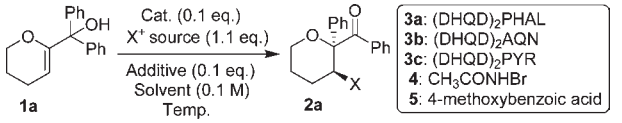
Table 1. Optimization of the Asymmetric Reaction[a]



entry	cat.	X^+ source	solvent	additive	yield (%)[b]	ee (%)[c]
1	**3a**	NBS	CCl_4	**5**	35	8
2	**3b**	NBS	CCl_4	**5**	20	5
3	**3c**	NBS	CCl_4	**5**	40	26
4	**3c**	NCS	CCl_4	**5**	25	11
5	**3c**	DBDMH	CCl_4	**5**	35	32
6	**3c**	DCDMH	CCl_4	**5**	30	54
7	**3c**	**4**	CCl_4	**5**	65	78
8	**3c**	**4**	Et_2O	**5**	–	–
9	**3c**	**4**	toluene	**5**	55	76
10	**3c**	**4**	CH_2Cl_2	**5**	–	–
11	**3c**	**4**	CCl_4	NBLP	50	84
12	**3c**	**4**	toluene	NBLP	53	88
13[d]	**3c**	**4**	toluene	NBLP	74	94
14[d,e]	**3c**	**4**	**toluene**	**NBLP**	**92**	**98**
15[d,e]	**3c**	**4**	toluene	NBDP	89	97

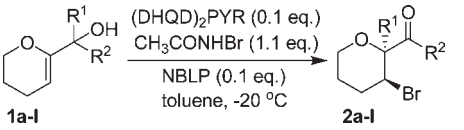
[a] All reactions were performed with 0.1 mmol of **1a** in 1 mL of solvent at room temperature. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] The reaction was carried out at −20 °C. [e] 5 Å MS (40 mg) were added.

(NBDP) was also examined as an additive, but with it the yield and enantioselectivity were slightly reduced (entry 15).

With the optimal conditions established above, the scope of this reaction was investigated with various 2-oxa allylic alcohols (**1b**−**l**). All substrates gave the desired chiral α-oxa-quaternary *β*-bromoketone derivatives in moderate to good yields with high to excellent enantioselectivities (Table 2).[8] Compared with the model substrate **1a**, electron-donating groups or electron-withdrawing groups at the *para* position of the phenyl moiety evidently did not change the enantioselectivity but did alter the yield. Generally, electron-withdrawing aryl substituents gave lower yields (48−86%, entries 3−5), while electron-donating aryl substituents gave higher yields (95%, entry 6). Meanwhile, the position of substituents influenced the enantioselectivity slightly and decreased the yield (entries 7 and 8). Furthermore, multiple substituents on the phenyl group had little influence on the enantioselectivity (entries 9 and 10). Notably, 2-naphthyl-substituted and heteroaromatic-substituted substrates were also amenable to the catalytic asymmetric protocol (entries 11 and 12). The absolute configuration of the product **2l** was unambiguously assigned by X-ray crystallography.[9]

It is well known that (+) and (−) enantiomers commonly have very different biological activities. Convenient access to both enantiomers is of great importance in asymmetric catalysis. To our delight, the reaction of **1a** with 10% hydroquinine 2,5-diphenyl-4,6-pyrimidinediyl diether ((DHQ)$_2$PYR) (**3d**) and $CH_3CONHBr$ in the presence of NBLP in toluene at −20 °C produced **2a′** in 76% yield with 95% ee (Table 3, entry 1). The reaction was also examined with NBDP, and the enantioselectivity was improved to 96% ee (entry 2). Accordingly, NBDP was chosen as an alternative additive. Next, the same substrate scope was explored under the optimized conditions, and the opposite

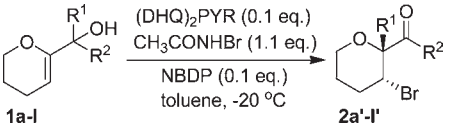
Table 2. Asymmetric Bromination Reaction Using Catalyst (DHQD)$_2$PYR[a]



entry	substrate	yield (%)[b]	ee (%)[c]
1	**1a**: $R^1 = R^2 = C_6H_5$	92	98
2	**1b**: $R^1 = R^2 = 4\text{-}CH_3\text{-}C_6H_4$	92	97
3	**1c**: $R^1 = R^2 = 4\text{-}F\text{-}C_6H_4$	86	94
4	**1d**: $R^1 = R^2 = 4\text{-}Cl\text{-}C_6H_4$	78	91
5	**1e**: $R^1 = R^2 = 4\text{-}CF_3\text{-}C_6H_4$	48	91
6[d]	**1f**: $R^1 = R^2 = 4\text{-}OMe\text{-}C_6H_4$	95	91
7	**1g**: $R^1 = R^2 = 2\text{-}F\text{-}C_6H_4$	61	99
8	**1h**: $R^1 = R^2 = 3\text{-}F\text{-}C_6H_4$	51	94
9	**1i**: $R^1 = R^2 = 3,5\text{-}(CH_3)_2\text{-}C_6H_3$	72	95
10[d]	**1j**:$R^1 = R^2$ = (3,4-methylenedioxy)phenyl	91	95
11	**1k**: $R^1 = R^2$ = 2-naphthyl	88	95
12[d]	**1l**: $R^1 = R^2$ = 2-thienyl	94	92

[a] Catalyst (DHQD)$_2$PYR (0.01 mmol) was dissolved in 0.5 mL of toluene followed by addition of $CH_3CONHBr$ (0.11 mmol), NBLP (0.01 mmol), and 5 Å MS (40 mg). After 10−30 min, **1a**−**l** (0.1 mmol) in 0.5 mL of toluene was added. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] The reaction proceeded at −40 °C.

Table 3. Asymmetric Bromination Reaction Using Catalyst (DHQ)$_2$PYR[a]



entry	substrate	yield (%)[b]	ee (%)[c]
1[d]	**1a**: $R^1 = R^2 = C_6H_5$	76	95
2	**1a**: $R^1 = R^2 = C_6H_5$	74	96
3	**1b**: $R^1 = R^2 = 4\text{-}CH_3\text{-}C_6H_4$	86	95
4	**1c**: $R^1 = R^2 = 4\text{-}F\text{-}C_6H_4$	72	82
5[e]	**1d**: $R^1 = R^2 = 4\text{-}Cl\text{-}C_6H_4$	63	82
6[e]	**1e**: $R^1 = R^2 = 4\text{-}CF_3\text{-}C_6H_4$	31	87
7[f]	**1f**: $R^1 = R^2 = 4\text{-}OMe\text{-}C_6H_4$	91	81
8	**1g**: $R^1 = R^2 = 2\text{-}F\text{-}C_6H_4$	40	98
9[e]	**1h**: $R^1 = R^2 = 3\text{-}F\text{-}C_6H_4$	43	88
10	**1i**: $R^1 = R^2 = 3,5\text{-}(CH_3)_2\text{-}C_6H_3$	78	96
11[f]	**1j**: $R^1 = R^2$ = (3,4-methylenedioxy)phenyl	69	89
12	**1k**: $R^1 = R^2$ = 2-naphthyl	66	97
13	**1l**: $R^1 = R^2$ = 2-thienyl	86	93

[a] Catalyst (DHQ)$_2$PYR (0.01 mmol) was dissolved in 0.5 mL of toluene, followed by addition of $CH_3CONHBr$ (0.11 mmol), NBDP (0.01 mmol), and 5 Å MS (40 mg). After 10−30 min, **1a**−**l** (0.1 mmol) in 0.5 mL of toluene was added. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] The additive was NBLP. [e] The reaction proceeded at −10 °C. [f] The reaction proceeded at −30 °C.

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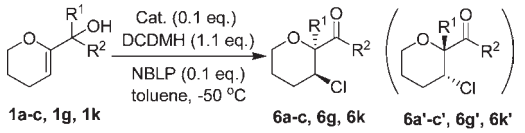
Table 4. Asymmetric Chlorination Reaction[a]



entry	substrate	cat.	product	yield (%)[b]	ee (%)[c]
1	**1a**	**3c**	**6a**	67	96[d]
2	**1a**	**3d**	**6a′**	49	94
3	**1b**	**3c**	**6b**	69	94
4[e]	**1b**	**3d**	**6b′**	42	74
5	**1c**	**3c**	**6c**	76	91
6[e]	**1c**	**3d**	**6c′**	40	76
7	**1g**	**3c**	**6g**	54	99
8[e]	**1g**	**3d**	**6g′**	41	95
9[f]	**1k**	**3c**	**6k**	66	86
10[e,f]	**1k**	**3d**	**6k′**	48	86

[a] Catalyst **3c** or **3d** (0.01 mmol) was dissolved in 0.5 mL of toluene, followed by addition of DCDMH (0.11 mmol), NBLP (0.01 mmol), and 5 Å MS (40 mg). After 10−30 min, **1a**−**c**, **1g**, and **1k** (0.1 mmol) in 0.5 mL of toluene were added. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Absolute configuration was determined by X-ray crystallography of **6a** (see Supporting Information). [e] DCDPH was added instead of DCDMH. [f] The reaction proceeded at −70 °C.

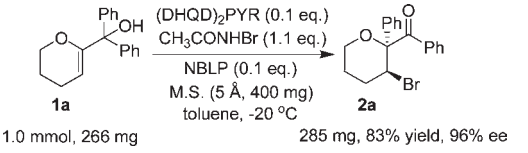
enantiomers of the products (**2a′**−**l′**) were obtained with moderate to excellent ee in moderate to good yields. By contrast to the products **2a**−**l**, the products **2a′**−**l′** were obtained in relatively low yields (31−91%). In some cases, the electronic nature of the substituents on the phenyl group appeared to negatively affect the ee (entries 4−7).

It is noteworthy that β-chloroketones also have important synthetic utility and bioactivity.[10] However, there are very few reports on enantioselective synthesis of β-chloroketones.[11] Consequently, we began investigating development of a catalytic asymmetric synthesis for chiral β-chloroketones. The good results for asymmetric bromination indicated that chiral β-chloroketone synthesis might be achieved with an appropriate chlorine source. NCS, 1,3-dichloro-5,5-dimethylhydantoin (DCDMH),[12] and 1,3-dichloro-5,5-diphenylhydantoin (DCDPH)[12] were screened as chlorine sources in the model reaction at −50 °C. When DCDMH or DCDPH was used as the chlorine source, the corresponding products were produced with moderate to high enantioselectivities for both diastereomers and moderate yields (Table 4). It should be noted that we also examined the effect of NBDP as an additive in our initial studies and found that it decreased the yield and enantioselectivity.[13]

To evaluate the synthetic utility of the catalyst system, a 1 mmol scale rearrangement of substrate **1a** was performed under the standard reaction conditions. As shown in Scheme 3, the desired product **2a** was obtained in 83% yield with 96% ee.

In conclusion, we have developed a novel asymmetric halogenation/semipinacol rearrangement reaction catalyzed by cinchona alkaloid derivatives. This reaction is valuable and versatile since two adjacent stereocenters, one of which is the chiral oxa-quaternary carbon, were constructed effectively and two types of β-haloketo compounds (X = Br, Cl) were readily obtained. Moreover, the desired (+) and (−) enantiomers of the products were obtained with moderate to good yields and high to excellent ee. Further studies are underway to determine the mechanism and investigate applications for related reactions, and those will be reported in due course.

Scheme 3. Asymmetric Bromination Reaction on a 1 mmol Scale



■ ASSOCIATED CONTENT

Supporting Information. Experimental details, compound characterization, and X-ray crystallographic data (CIF) for **2l** and **6a**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

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(8) We also examined CCl_4 as the solvent in our reaction system and found that two types of β-haloketo compounds (X = Br, Cl) were also obtained with moderate to good yields and high to excellent ee. For details, see Supporting Information.

(9) For details, see Supporting Information.

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(13) The reaction of **1a** with **3c** (0.1 equiv) and DCDMH (1.1 equiv) in the presence of NBDP (0.1 equiv) in toluene at −50 °C produced **6a** in 54% yield with 95% ee. Likewise, the reaction of **1a** with **3d** (0.1 equiv) and DCDMH (1.1 equiv) in the presence of NBDP (0.1 equiv) in toluene at −50 °C produced **6a′** in 45% yield with 93% ee.

■ NOTE ADDED AFTER ASAP PUBLICATION

Two references were omitted from the version of this Communication published ASAP May 11, 2011. New refs 6a,b were added in the version posted May 20, 2011.