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Catalytic Asymmetric Intermolecular Bromoesterification of Unfunctionalized Olefins

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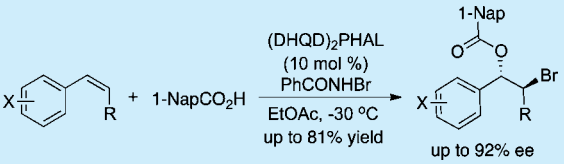
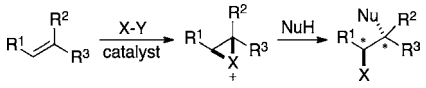
Supporting Information

ABSTRACT: An asymmetric intermolecular bromoesterification of unfunctionalized olefins catalyzed by $(DHQD)_2PHAL$ is described. Optically active bromoesters can be obtained with up to 92% ee.



Electrophilic addition to olefins via a halonium ion allows simultaneous introduction of two heteroatoms onto the C−C double bond and represents one of the most classic and important organic transformations.[1] An asymmetric version of such a transformation has great synthetic value and has been actively pursued. In recent years, significant progress has been made in asymmetric intramolecular halogenation of alkenes.[2,3] For the intermolecular processes,[4] a number of effective systems have also been developed including aminohalogenation of α,β-unsaturated carbonyl compounds by Feng;[5] dihalogenation of allylic alcohols by Nicolaou[6] and Burns;[7] bromoamination of enecarbamates by Masson;[8] oxyfluorination of enamides by Toste;[9] bromoesterification of allylic sulfonamides by Tang;[10] and bromohydroxylation of allylic alcohols by Ma.[11] However, catalytic asymmetric intermolecular halogenation of unfunctionalized olefins still presents a formidable challenge (Scheme 1).[12−15,10]

Scheme 1. Catalytic Asymmetric Halogenation of Olefins



In our ongoing studies on asymmetric electrophilic addition to olefins,[16,17] we have explored asymmetric halogenation of olefins containing no heteroatom directing groups with various catalytic systems (Figure 1) and found that up to 92% ee can be obtained with dimeric cinchona alkaloid $(DHQD)_2PHAL$[18,19] as catalyst. Herein we wish to report our preliminary studies on this subject.

Our initial studies were carried out with 1,2-dihydronaphthalene (**1a**) as test substrate, benzoic acid (**2a**) as nucleophile, and NBS (**4a**) as bromine source using various catalytic systems in EtOAc at 0 °C. No desired product was formed when chiral phosphoric acid **3a** was used as catalyst (Table 1, entry 1). A messy mixture was obtained with chiral phosphine−$Sc(OTf)_3$ complex **3b** as catalyst (Table 1, entry 2).[16b] Subsequently, chiral

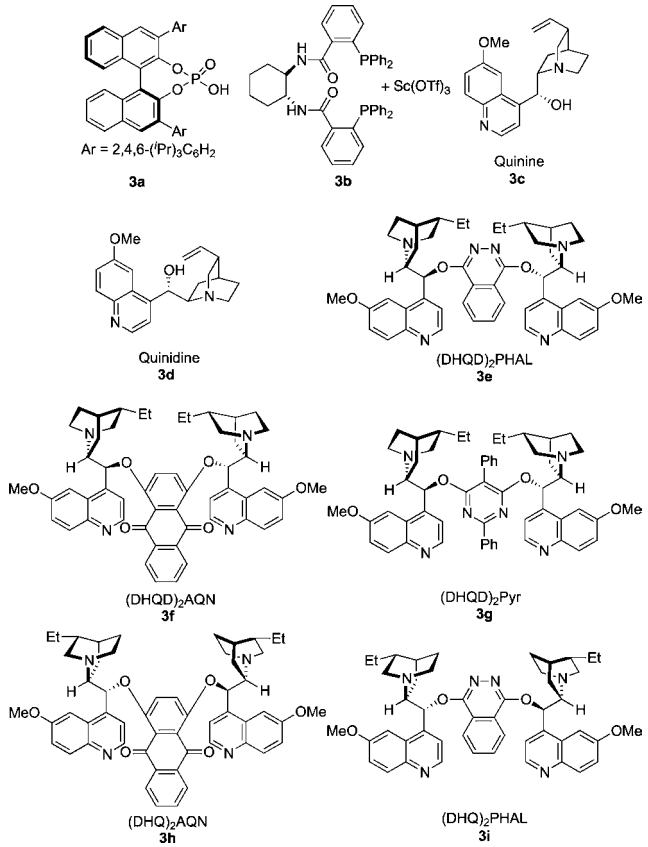


Figure 1. Selected examples of catalyst examined.

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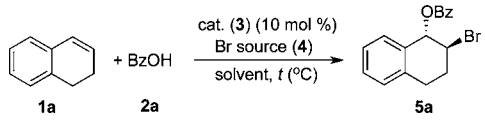
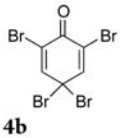
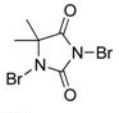
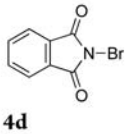
Table 1. Studies of the Reaction Conditions[a]

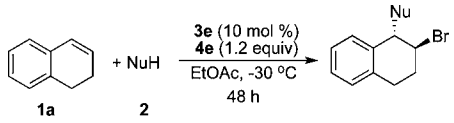


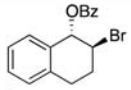
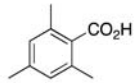
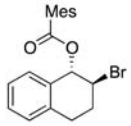
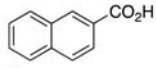
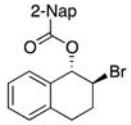
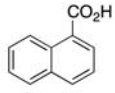
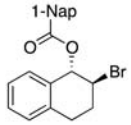
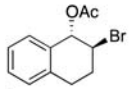
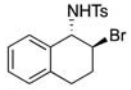
entry	cat.	Br source	solvent	yield (%)[d]	ee (%)[e]
1	**3a**	NBS (**4a**)	EtOAc	-	-
2	**3b**	NBS	EtOAc	mixture	-
3	**3c**	NBS	EtOAc	43	-4
4	**3d**	NBS	EtOAc	46	-3
5	**3e**	NBS	EtOAc	68	56
6	**3f**	NBS	EtOAc	47	-2
7	**3g**	NBS	EtOAc	46	1
8	**3h**	NBS	EtOAc	44	0
9	**3i**	NBS	EtOAc	63	-48
10	**3e**	 **4b**	EtOAc	mixture	-
11	**3e**	 **4c**	EtOAc	72	42
12	**3e**	 **4d**	EtOAc	77	54
13	**3e**	 **4e**	EtOAc	71	65
14	**3e**	**4e**	THF	mixture	-
15	**3e**	**4e**	CH_2Cl_2	49	17
16	**3e**	**4e**	$CHCl_3$	60	26
17	**3e**	**4e**	toluene	70	38
18[b]	**3e**	**4e**	EtOAc	72	75
19[c]	**3e**	**4e**	EtOAc	47	78

[a]Reactions were carried out with substrate **1a** (0.30 mmol), nucleophile **2a** (0.36 mmol), catalyst **3** (0.030 mmol), and Br source **4** (0.36 mmol) in solvent (3.0 mL) at 0 °C for 24 h unless otherwise noted. [b]At −30 °C for 48 h. [c]At −50 °C for 48 h. [d]Isolated yield. [e]Determined by chiral HPLC analysis.

cinchona alkaloid derivatives were investigated for the reaction. While bromoester **5a** was isolated in 43% and 46% yield with quinine (**3c**) and quinidine (**3d**), only 3−4% ee was obtained (Table 1, entries 3 and 4). Bromoester **5a** was formed in 68% yield and 56% ee with dimeric cinchona alkaloid $(DHQD)_2PHAL$ (**3e**) (Table 1, entry 5). Other dimeric cinchona alkaloid catalysts **3f−h** gave **5a** essentially as a racemate (Table 1, entries 6−8). The opposite enantiomer was obtained in 63% yield and 48% ee with $(DHQ)_2PHAL$ (**3i**) (Table 1, entry 9). Among the bromine sources examined (Table 1, entries 5, 10−13), *N*-bromobenzamide (**4e**) gave the highest enantioselectivity (65% ee) (Table 1, entry 13). EtOAc was found to be the solvent of choice (Table 1, entries 13−17). The ee increased to 75% as the reaction temperature was lowered to −30 °C (Table 1, entry 18). However, the yield was substantially reduced when the reaction was carried out at −50 °C (Table 1, entry 19). Other nucleophiles

Table 2. Studies of the Nucleophiles[a]



entry	NuH	product	yield (%)[b]	ee (%)[c]
1	BzOH **2a**	 **5a**	72	75
2	 **2b**	 **6a**	67	76
3	 **2c**	 **7a**	72	75
4	 **2d**	 **8a**	73	83
5	AcOH **2e**	 **9a**	61	67
6	$TsNH_2$ **2f**	 **10a**	17	0

[a]Reactions were carried out with substrate **1a** (0.30 mmol), nucleophile **2** (0.36 mmol), catalyst **3e** (0.030 mmol), and bromine source **4e** (0.36 mmol) in EtOAc (3.0 mL) at −30 °C for 48 h unless otherwise noted. [b]Isolated yield. [c]Determined by chiral HPLC analysis. Mes = 2,4,6-trimethylphenyl; Nap = naphthyl.

were subsequently investigated with 1,2-dihydronaphthalene (**1a**), catalyst **3e** (10 mol %), and *N*-bromobenzamide (**4e**) (1.2 equiv) in EtOAc at −30 °C (Table 2). The best ee was achieved with 1-naphthoic acid (**2d**), giving bromoester **8a** in 73% yield and 83% ee (Table 2, entry 4) (for the X-ray structure of **8a**, see Figure 2).

With the optimized reaction conditions in hand, the substrate scope was subsequently investigated. As shown in Table 3, the bromoesterification can be extended to 1,2-dihydronaphthalenes containing various substituents such as F, Cl, Br, CO_2Me, CHO, NO_2, Ph, OMe, and Me, giving the corresponding bromoesters in 47−81% yield with 74−92% ee (Table 3, entries 1−12). The enantioselectivity was influenced by the electronic property of the substituents. Generally, electron-withdrawing groups provided higher enantioselectivity (89−92%) (Table 3, entries 2−7, 11, and 12), while electron-donating groups gave lower ee's (Table 2, entries 9 and 10). 6,7-Dihydro-5*H*-benzocycloheptene (**1m**) and 1*H*-indene (**1n**) were also found to be suitable substrates for the reaction, producing the corresponding bromoesters in up to 82% ee (Table 3, entries 13 and 14). When terminal olefin **1o** was subjected to the reaction condition, bromoester **8o** was obtained in 69% ee (Table 3,

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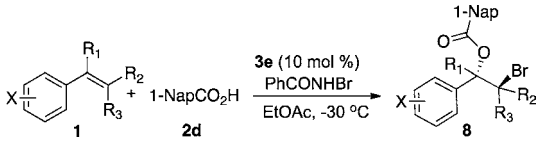
Table 3. Asymmetric Bromoesterification of Olefins[a]



entry	substrate	product[c]	yield (%)[d]	ee (%)[e]
1	X = H, **1a**	**8a**	81	83
2	X = F, **1b**	**8b**	72	91
3	X = Cl, **1c**	**8c**	72	92
4	X = Br, **1d**	**8d**	75	92
5	X = CO_2Me, **1e**	**8e**	78	91
6	X = CHO, **1f**	**8f**	71	90
7	X = NO_2, **1g**	**8g**	47	89
8	X = Ph, **1h**	**8h**	81	83
9	X = OMe, **1i**	**8i**	73	77
10	X = Me, **1j**	**8j**	70	74
11	X = Cl, **1k**	**8k**	78	89
12	X = Br, **1l**	**8l**	76	91
13	**1m**	**8m**	66	82
14	**1n**	**8n**	56	76
15[b]	**1o**	**8o**	44	69
16	**1p**	**8p**	35	59
17	**1q**	**8q**	48	41

[a]Reactions were carried out with substrate **1** (0.50 mmol), **2d** (0.60 mmol), **3e** (0.050 mmol), and **4e** (0.60 mmol) in EtOAc (5.0 mL) at −30 °C for 72 h unless otherwise noted. [b]With **4e** (1.00 mmol) for 5 days. [c]For entries 1 and 15, the absolute configurations were determined by comparing the optical rotations of the corresponding bromohydrins with the reported ones upon reduction with DIBAL-H. For entries 2−14, the absolute configurations were tentatively assigned by analogy. For entries 16 and 17, the stereochemistry indicated is relative stereochemistry. [d]Isolated yield. [e]Determined by chiral HPLC analysis.

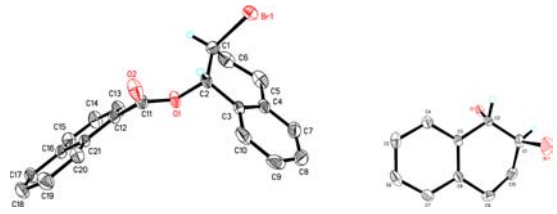
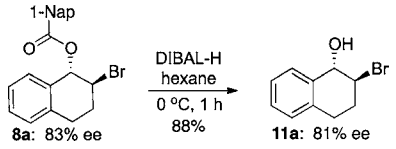


Figure 2. X-ray structures of compounds **8a** and **11a**.

Scheme 2



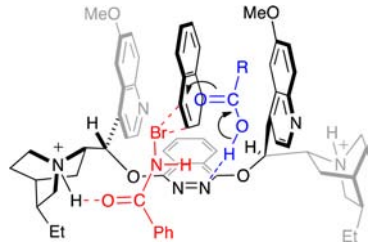


Figure 3. Proposed transition-state model for bromoesterification.

entry 15). Lower ee's were obtained for *trans*-β-methylstyrene and 1-phenylcyclohexhene (Table 3, entries 16 and 17). The absolute configurations of **8a** (Figure 2) and **8o** were determined by comparing the optical rotations of the corresponding bromohydrins[20] with the reported ones upon reduction with DIBAL-H (Scheme 2).

While a precise understanding of the origin of the enantioselectivity awaits further study, a plausible transition state model is proposed in Figure 3.[3b,r,w,x,6,10] The tertiary amines of the catalyst are likely to be protonated by acid nucleophile under the reaction conditions. The proton of the quaternary ammonium salt could form a hydrogen-bond with *N*-bromobenzamide (**4e**) to activate and direct it toward the double bond of the substrate, which is located in the chiral pocket via π,π-stack with the quinoline of the catalyst. The phthalazine nitrogen could also form a hydrogen bond with the acid to increase its nucleophilicity and direct its attack to the reacting site.

In summary, we have developed an efficient enantioselective intermolecular bromoesterification of unfunctionalized olefins with dimeric cinchona alkaloid $(DHQD)_2PHAL$ as catalyst, *N*-bromobenzamide as bromine source, and 1-naphthoic acid as nucleophile, giving the corresponding bromoesters in up to 92% ee. The current reaction process demonstrates the feasibility of achieving high enantioselectivity for intermolecular halogenation of unfunctionalized olefins, which has been extremely challenging. Further efforts will be devoted to understanding the mechanism, expanding the substrate scope, as well as developing more effective catalytic systems.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterizations, X-ray structures, data for determination of enantiomeric excess, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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