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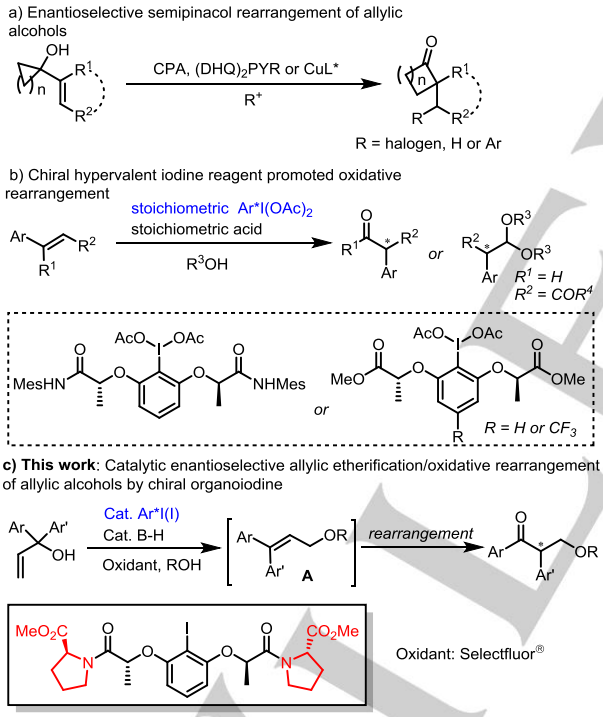
Organoiodine-Catalyzed Enantioselective Tandem Alkoxylation/ Oxidative Rearrangement of Allylic Alcohols

Dong-Yang Zhang, Ying Zhang, Hua Wu, and Liu-Zhu Gong*

Abstract: An enantioselective catalytic alkoxylation/oxidative rearrangement of allylic alcohols has been established by sequential promotion of the Brønsted acid and chiral organoiodine. The presence of 20 mol% of (*S*)-proline-derived C2-symmetric chiral iodine enabled the reaction to give enantioenriched α-arylated-β-alkoxylated ketones in good yields and with high levels of enantioselectivity (84%-94% ee).

The enantioselective rearrangement of allylic alcohols, represented by semipinacol rearrangement, has been identified as a powerful and valuable platform for the construction of α-substituted enantioenriched ketones, which are widely presented in a series of natural products and bioactive molecules.[1] In most cases, the reactions are usually initiated by the protonation, halogenation, expoxidation or arylation of the double bond and further driven by a ring-strain-releasing process, and therefore represent unconventional strategies for the difunctionalization of alkenes. Over the last decade, the enantioselective rearrangement of allylic alcohols has been extensively investigated benefiting from the rapid growth of asymmetric catalysis (Scheme 1a).[2-5] Among them, chiral phosphoric acids and bis-quinine derivatives such as $(DHQ)_2PYR$ are privileged chiral catalysts for the asymmetric semipinacol rearrangement.[2] In sharp contrast, to the best of our knowledge, chiral organoiodine-catalyzed enantioselective rearrangement of allylic alcohols remains underdeveloped.[6,7]



Scheme 1. Enantioselective rearrangement of allylic alcohols.

Recently, Wirth and coworkers reported the first example of chiral hypervalent iodine(III) reagent-promoted asymmetric oxidative rearrangement of chalcones to α-aryl acetals.[8] Subsequently, the same group developed an elegant enantioselective oxidative rearrangement of 1,1-disubstituted alkenes by using another chiral hypervalent iodine reagent.[9] In both cases, stoichiometric chiral hypervalent iodine reagents were required to ensure the smooth occurrence of these reactions and high levels of enantioselectivity (Scheme 1b).[10] Despite these notable advances, on the other hand, catalytic enantioselective rearrangement reactions enabled by chiral iodines have rarely been achieved. We have long been interested in chiral iodine-catalyzed enantioselective carbon-carbon formation reactions and developed an enantioselective catalytic direct C-H/C-H oxidative coupling reaction[11] and a dearomatizative spirocyclization.[12] Herein, we will report a highly enantioselective tandem allylic alkoxylation/oxidative rearrangement of allylic alochols catalyzed by a (*S*)-proline-derived *C2*-symmetric chiral iodine (Scheme 1c).

We envisaged that the allylic alcohol is principally able to participate in an alkoxylation reaction with another alcohol to afford a diarysubstituted alkene intermediate **A** under the catalysis of a Brønsted acid. The intermediate **A** might further undergo an oxidative rearrangement process, involving an enantioselective semipinacol-type 1,2-carbon shift catalyzed by an *in situ* formed hypervalent iodine(III) species (Scheme 1c). Readily available 1,1-diphenylprop-2-en-1-ol (**1a**) was chosen as a model substrate. The desired reaction of **1a** indeed proceeded in MeCN/BnOH and in the presence of iodobenzene (0.2 equiv), Selectfluor® (1.5 equiv) and $TsOH{\cdot}H_2O$ (0.5 equiv) at room temperature, but furnished a racemic rearranged product **2a** in only 10% yield (entry 1, Table 1). A variety of structurally diverse chiral *C2*-symmetric iodoarenes[13] were next evaluated to identify the best catalyst (entries 2-8, Table 1). Although chiral organoiodines (**3a** and **3b**) have successfully been applied to a series of enantioselective transformations,[12-14] they failed to give the product **2a** (entries 2-3, Table 1). To our delight, good yields and high enantioselectivities were observed for the rearranged product **2a** when chiral organoiodines containing tertiary amides were used as catalysts (entries 4-8, Table 1). In particular, (*S*)-proline-derived chiral organoiodine **3f**, which has been successfully used in the enantioselective catalytic C-C and C-O oxidative coupling reactions,[11,15] delivered the best results in terms of both the yield and enantiomeric excess (73% yield, 94%

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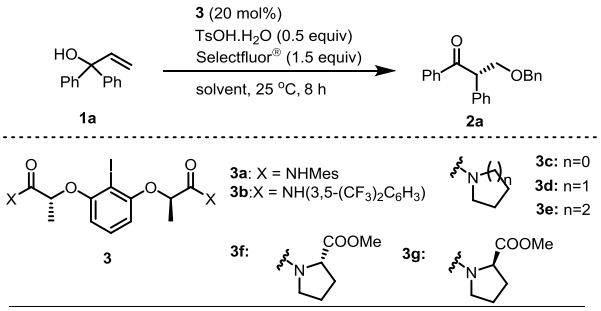
ee, entry 7). Using **3f** as the optimal catalyst, the impact of other reaction parameters, including co-solvents and temperature, on the reaction performance was investigated (entries 9-12). The polarity of the co-solvent exerted great effect on the reaction. Highly polar solvents such as MeCN and $MeNO_2$ allowed reaction to occur while no desired product was observed in the presence of CH_2Cl_2 co-solvent (entries 7 and 9-10). Varying the ratio of co-solvent, lowering the reaction temperature or the amount of catalyst did not affect the enantioselectivity, but eroded the yield (entries 11-14).

Table 1. Optimization of the reaction conditions.[a]

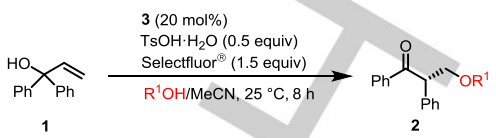


Entry	3	Solvent	Yield[%][b]	*ee*[%][c]
1	**PhI**	MeCN:BnOH(1:1)	10	-
2	**3a**	MeCN:BnOH(1:1)	trace	-
3	**3b**	MeCN:BnOH(1:1)	trace	-
4	**3c**	MeCN:BnOH(1:1)	61	92
5	**3d**	MeCN:BnOH(1:1)	55	78
6	**3e**	MeCN:BnOH(1:1)	46	91
7	**3f**	MeCN:BnOH(1:1)	73	94
8	**3g**	MeCN:BnOH(1:1)	68	92
9	**3f**	$MeNO_2$:BnOH(1:1)	28	93
10	**3f**	DCM:BnOH(1:1)	-[d]	-
11	**3f**	MeCN[e]	56	93
12[f]	**3f**	MeCN:BnOH(1:1)	57	94
13[g]	**3f**	MeCN:BnOH(1:1)	42	92
14[h]	**3f**	MeCN:BnOH(1:1)	57	93

[a] Unless indicated otherwise, the reaction was carried out on 0.1 mmol scale of **1a** at room temperature for 8 h. [b] Yield of isolated product. [c] The *ee* value was determined by HPLC analysis. [d] No desired product. **2a**. [e] 10 equivalents of BnOH added. [f] At 0 °C for 48h. [g] 5 mol% **3f** was used. [h] 10 mol% **3f** was used.

With the optimized conditions in hand, the scope of the enantioselective alkoxylation/oxidative rearrangement cascade reaction for alcohols was then explored (Table 2). Either primary or tertiary alcohols were able to smoothly undergo the rearrangement process to furnish the desired products in high levels of enantiopurity (entries 1-4). 2,2,2-Trifluoroethan-1-ol was also a good substrate and provided a chiral ketone **2f** in 72% yield and with 84% *ee* (entry 5). Moreover, variation of the substituent from eletron-neutral and -withdrawing to eletron-donating ones with different substution patterns on benzylic alcohols was always allowed, but did not excert apparant effect on the stereochemical control, and thus the corresponding tandem alkoxylation/oxidative rearrangement process proceeded nicely to generate chiral (benzyloxy)methaneketone derivatives in excellent enantioselectivities (entries 6-12). The absolute configuration of **2e** was determined by X-ray crystallography (see Supporting Information) and the configurations of other ketones were assigned by anology.[16]

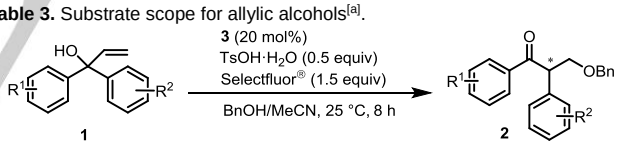
Table 2. Substrate scope for alcohols.[a]



Entry	2	R^1	Yield[%][b]	*ee*[%][c]
1	**2b**	Me	72	85
2	**2c**	Et	68	86
3	**2d**	n-Bu	71	90
4	**2e**	*t*-Bu	73	92
5	**2f**	CH_2CF_3	72	84
6	**2g**	$CH_2(4\text{-}FC_6H_4)$	66	92
7	**2h**	$CH_2(4\text{-}ClC_6H_4)$	70	91
8	**2i**	$CH_2(4\text{-}BrC_6H_4)$	72	90
9	**2j**	$CH_2(4\text{-}CF_3C_6H_4)$	58	89
10	**2k**	$CH_2(4\text{-}MeC_6H_4)$	78	92
11	**2l**	$CH_2(3\text{-}MeC_6H_4)$	77	92
12	**2m**	$CH_2(2\text{-}MeC_6H_4)$	75	92

[a] Unless indicated otherwise, the reaction was carried out on a 0.1 mmol scale of **1a** at room temperature for 8 h. [b] Yield of isolated product. [c] The *ee* value was determined by HPLC analysis.

Table 3. Substrate scope for allylic alcohols[a].



Entry	2	R^1	R^2	yield [%][b]	*ee* [%][c]	rr[d]
1	**2n**	4-F	4-F	71	91	-
2	**2o**	4-Cl	4-Cl	75	91	-
3	**2p**	4-Br	4-Br	78	91	-
4	**2q**	4-Me	4-Me	70	90	-
5	**2r**	3-Me	3-Me	71	91	-
6	**2s**	3-Me	-	68	92/93	1.5:1
7	**2t**	3,5-Me	-	70	88/92	2.4:1
8	**2u**	-	4-Me	68	90/88	2.3:1

[a] Reaction conditions: **1** (0.10 mmol), Selectfluor® (0.15 mmol), $TsOH{\cdot}H_2O$ (0.05 mmol), **3f** (20 mol%), co-solvent BnOH/MeCN (1mL). [b] Isolated yield. [c] The *ee* values were determined by HPLC. [d] Determined by ^1H NMR spectroscopy.

The final investigation of the substrate scope was focused on allylic alcohols (Table 3). The introduction of either an eletron-donating or -withdrawing substituent such as methyl, fluoro,

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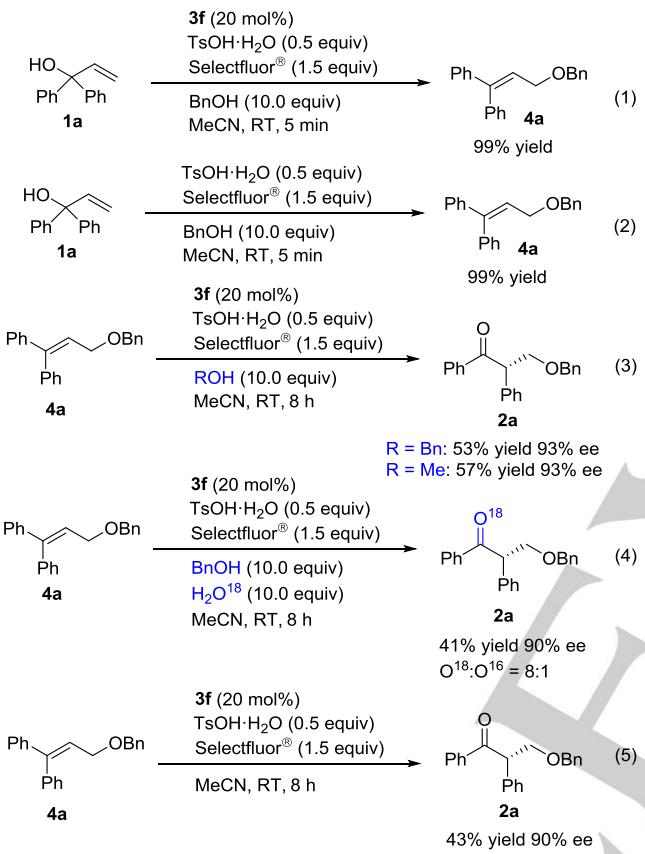
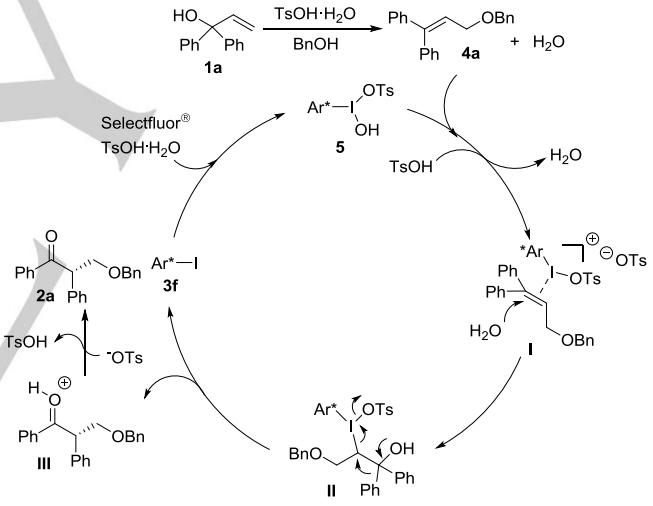
chloro and bromo at *para* or *meta* position of the benzene ring on gem-phenyl allylic alcohols was accomodated to provide the desired products in good yields and with excellent enantioselectivities (entries 1-5). Notably, racemic allylic alcohols poccessing two different aryl groups still participated in the enantioselective alkoxylation/oxidative rearrangement cascade to produce ketones **2s-2u** in good combined yields with moderate regioselectivity, but with high enantioselectivities for both regiomers, and the electron-rich aromatics have higher activity for 1,2-migration (entries 6-8).



Scheme 2. Experiments to understand mechanism.

To understand the reaction mechanism, a series of control experiments were carried out (Scheme 2). The exposure of 1,1-diphenyl 2-propenol (**1a**) to the standard reaction conditions for 5 minutes afforded a diphenyl substituted alkene intermediate **4a** in almost quantitative yield (eq. 1). In the absence of chiral organoiodine **3f**, the same alkene intermediate **4a** was also rapidly generated in a perfect yield under the otherwise identical conditions, indicating that the alkoxylation process was actually triggered by TsOH·H_2O (eq. 2). Interestingly, the treatment of the intermediate **4a** with the standard reactions in the presence of 10 equivalents of BnOH or methanol successfully delivered the rearrangement product **2a** with similar enantiomeric excess and yield (53% yield, 93% ee *vs* 56% yield, 93% ee in Table 1, entry 11), which verified that the oxidative rearrangement step was enabled by chiral organoiodine catalysis. Notably, no product **2b** was detected, even if large excess amounts of methanol presented in the reaction mixture, instead, **2a** was isolated in a comparable yield, implying that the external alcohol might not be involved in the rearrangent process (eq. 3). The reaction of **4a** in the presence of 10 equivalents of BnOH and heavy-oxygen water led to the formation of **2a** in a moderate yield and high enantiomeric excess (41% yield, 90% ee), interestingly, with an 8/1 ratio of O^{18} to O^{16} in **2a** (eq. 4), indicating that the water participated in the reaction in an intermolecular fasion rather than an intramolecular migration. Interestingly, the deisred product **2a** was obtained in 43% yield and 90% ee in the absence of BnOH, under the otherwise identical conditions, again suggesting that small amounts of water in the system got involved in the rearrangement step (eq. 5).

Based on the the experimental results, a plausible reaction mechamism was proposed (Scheme 3). Initially, the allylic alcohol **1a** reacts with phenylmethanol to generate the alkoxylated product **4a**. Subsequently, an active chiral organoiodine (III) **5** is formed from the oxidation of the catalyst **3f** with Selectfluor®.[17] Then, the hypervalent organoiodine **5** would react with the diphenyl alkene **4a** and TsOH, leading to an iodine(III)-substrate complex **I**.[18] Subsequently, the regioselective and enantioselective attack of water on the carbon-carbon double bond of the complex **I** generates a crucial intermediate **II**, which then undergoes a semipinacol-type rearrangement to generate an intermediate **III** with concurrent regeneration of the chiral organoiodine **3f**.[9] The deprotonation of the intermediate **III** leads to the product **2a** (Scheme 3).



Scheme 3. Plausible reaction mechanism.

In summary, we have developed a highly enantioselective tandem alkoxylation/oxidative rearrangement of allylic alcohols under the sequential promotion of the Brønsted acid and chiral organoiodine. In this process, the Brønsted acid drives the conversion of the allylic alcohol and benzylic alcohols to the benzylic allyl ether, which then undergoes the asymmetric rearrangement catalyzed by chiral organoiodine. The combination of (*S*)-proline-derived *C2*-symmetric organoiodine and Brønsted acid rendered the reaction to give chiral (benzyloxy)methaneketone derivatives in good yields and excellent enantioselectivities.

Acknowledgements

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Keywords: chiral organoiodine • cascade reaction • asymmetric rearrangement • alkoxylation • organocatalysis

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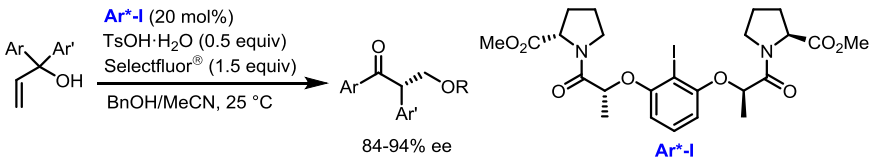

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Asymmetric catalytic alkoxylation/oxidative rearrangement of allylic alcohols enabled by sequential promotion of Brønsted acid and chiral organoiodine led to optically active α-arylated β- etherized ketones in good yields and excellent stereoselectivity.