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Catalytic Desymmetrizing Dehydrogenation of 4-Substituted Cyclohexanones through Enamine Oxidation

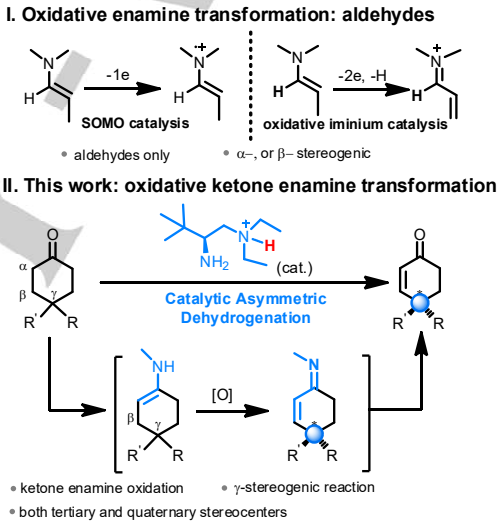
Lihui Zhu, Long Zhang and Sanzhong Luo*

Dedicated to Prof. Jin-Pei Cheng on the occasion of his 70's birthday

Abstract: A chiral primary amine catalyzed desymmetric dehydrogenation process is herein described. The reaction proceeds *via* ketone enamine oxidation by IBX and enables highly enantioselective desymmetrization of 4-substituted cyclohexanones, generating chiral 4-substituted cyclohexanones bearing remote γ-stereocenter.

As electron-rich species, enamine is inherently nucleophilic and redox-labile. These features, together with their readily accessibility and relative stability, make enamines versatile synthon and catalytic intermediates in carbonyl transformations.[1] Compared with the now well-received nucleophilic enamine catalysis, redox transformation of enamine remains less developed, particularly in a catalytic asymmetric manner. Single-electron transfer (SET) with enamine has been known to form an open shell radical cation, setting basis of SOMO catalysis that significantly expands the domain of enamine catalysis (Scheme 1).[2] On the other hand, nucleophilic enamine could be directly oxidized into electrophilic iminium ion in both stoichiometric and catalytic context (Scheme 1, I).[3] However, both SOMO catalysis and oxidative iminium catalysis have been limited to aldehydes, enantioselective oxidative enamine transformation with ketones has not been achieved.[4] Herein, we reported a chiral primary amine catalyzed ketone enamine oxidation process, resulting in a highly desymmetric dehydrogenation of 4-substituted cyclohexanones.

Direct dehydrogenation represents the most ideal and straightforward method to build an unsaturated bond from alkanes. Prominent advances have been made in synthetic methodology studies.[5, 6] Among these significant contributions, practical ketone dehydrogenation was mainly achieved through hypervalent iodine chemistry developed by Nicolaou[6a-6c] and Ishihara[6d], as well as Pd(II) species catalyzed aerobic Saegusa-type oxidation reported by Stahl[6e-6h]. Despite elegant procedures reported, no enantioselective processes have been reported for ketone dehydrogenation. As in the cases with 4-substituted cyclohexanones, direct dehydrogenation of these prochiral compounds would install unsaturation and meanwhile generate remote γ-stereocenters, an appealing yet unachieved process to access synthetically versatile 4-substituted cycohenxe-2-ones. A sequence of chiral enolate formation and oxidation was reported for the synthesis of 4-substituted cyclohenxe-2-ones from cyclohexanones, but the produce required stoichiometric amount of chiral amine under rather low temperature.[7] Though desymmetrization of 4-substituted cyclohexanones have been frequently explored,[8] an enantioselective direct dehydrogenation strategy remains to be developed.



Scheme 1. Oxidative enamine transformation with Cyclohexanones

We have tried to develop enamine ketone oxidative processes on the basis of our primary amine catalysis.[9] The desymmetric dehydrogenation of cyclohexanones was initially explored. The primary concern would be the oxidant tolerability of primary amine catalyst as well as the issues in attaining chemoselective ketone enamine oxidation in preference to amine oxidation. In addition, the targeted reaction also poses a daunting challenge in stereocontrol as the stereocenter is generated remote to the reaction center at γ-position, a feature departure from the typical α- or β- stereogenic aminocatalysis (Scheme 1, II). Ultimately, we accomplished a primary amine catalyzed desymmetrization of cyclohexanone utilizing commercially available IBX (2-iodoxybenzoic acid) as oxidant under mild conditions. IBX was known to be able to oxidize aldehyde and ketone to its unsaturated analogue.[6,10] Previous work by Wang have demonstrated that amine catalyst was compatible with IBX oxidation.[3a] Hence, the first difficulty in our case is to suppress uncontrolled reaction in order to ensure a completely catalyst controlled pathway.

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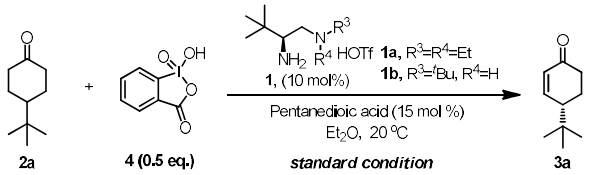
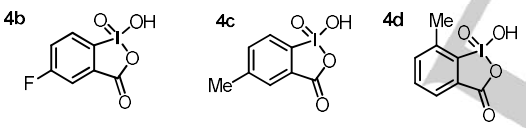
Table 1. Screening and Optimization[a]



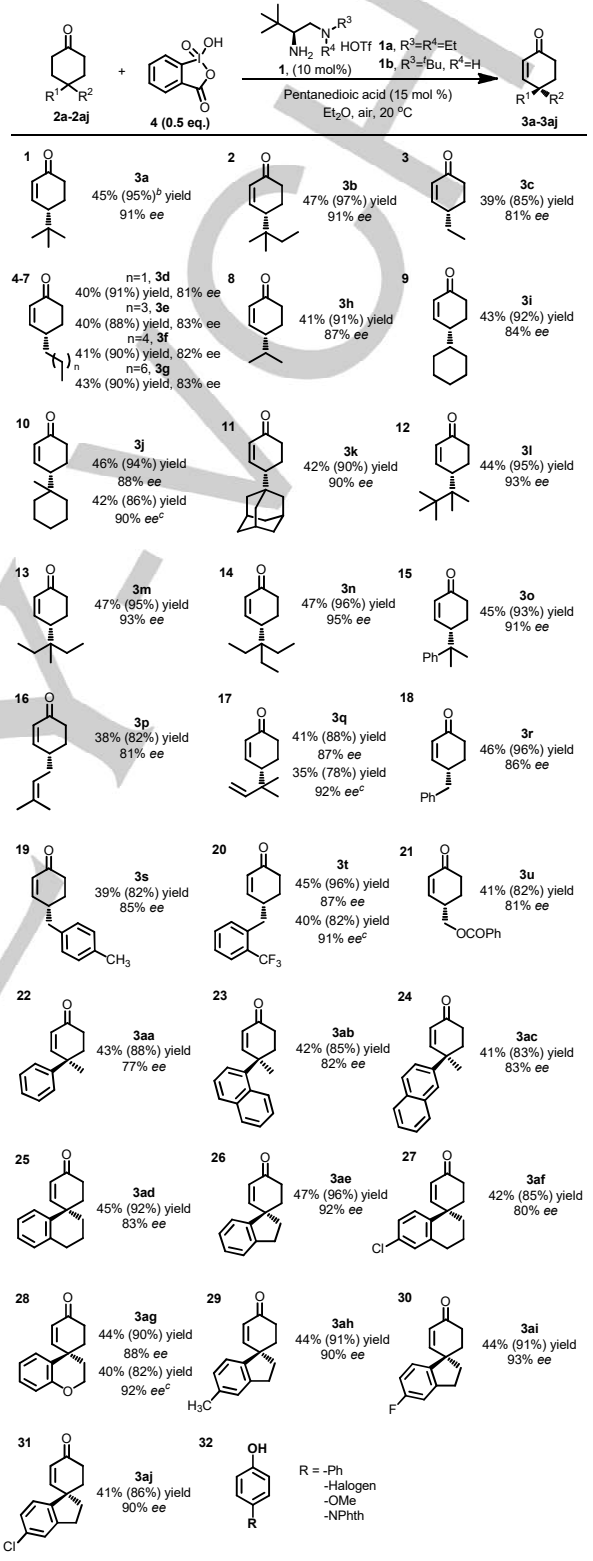
entry	variation from standard conditions	yield (%)[b]	*ee* (%)[c]
1	none	45 (95)[d]	91
2	DCM	22	56
3	Toluene	15	77
4	DMSO	35	racemic
5	Et_2O (0.5 M)	27	90
6	Et_2O (0.1 M)	13	87
7	**2a**:**4a** = 1:1	60	48
8	**2a**:**4a** = 3:1	29	90
9	without **1**	< 5	racemic
10	without pentanedioic acid	12	36
11	*m*-NO_2PhCO_2H	21	61
12	TsOH	< 5	< 20
13	$NaHCO_3$ (1 eq.)	no reaction	
14	Cat. **1b** instead of **1a**	39 (85)[d]	92
15	**4b** instead of **4a**	43	91
16	**4c** instead of **4a**	42	90
17	**4d** instead of **4a**	30	36



[a] Reactions were performed at room temperature in 0.1 mL of Et_2O with **2a** (0.2 mmol), **4a** (0.1 mmol), **1** (10 mol %) and pentanedioic acid (15 mol %) in air, 60 h. [b] ^1H NMR yield based on cyclohexanone with biphenyl as internal standard. Based on the loading of IBX, the maximum yield is 50%. [c] Determined by HPLC analysis. [d] Isolated yield based on recovered starting material.

In our standard conditions, we chose 4-*tert*-butyl cyclohexanone **2a** as the model substrate with IBX **4** as oxidant under the catalysis of **1**, generating the desired cyclohexanone **3a** in 45% yield based on ketone (95% isolated yield based on recovered starting material) and 91% *ee* at 20 °C (Table 1, entry 1). The use of concentrated ether suspension of IBX was critical for both the reactivity and stereoselectlvity, as the reaction in other solvents such as dichloromethane, toluene or DMSO led to lower enantioselectivity or even racemic product due to the background reaction (Table 1, entries 2-4). The use of high concentration led to a faster reaction (Table 1, entry 5 and 6). The ratio of **2a** and **4** also impacted both reactivity and enantioselectivity and a 2:1 ratio was identified to be optimal (Table 1, entry 1 *vs* entries 7 and 8). Presumably, the use of excess cyclohexanone would facilitate enamine formation, hence to suppress background reaction, to note that a 1:1 ratio resulted in serious reduction of enantioselectivity (entry 7). As the reaction was generally clean, the excess cyclohexanone

Table 2. Scopes of 4-Substituted Cyclohexanones[a]



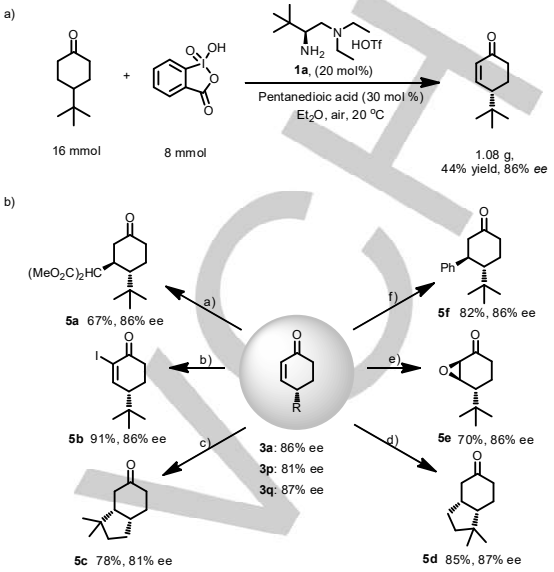
[a] Reactions were performed at room temperature in 0.1 mL of Et_2O with **2a** (0.2 mmol), **4** (0.1 mmol), **1a** (10 mol %) and pentanedioic acid (15 mol %) in air, 60 h. Isolated yield based on cyclohexanone. Enantiomeric excess was

determined by HPLC and GC analysis. [b] Yield based on recovered starting material was listed in parentheses. [c] Catalyst **1b** was employed instead of **1a**.

could be quantitatively recovered and this helps to increase the reaction economy. In addition, the absence of amine catalyst **1** led to trace product generation (Table 1, entry 9), pinpointing the critical role of amine catalyst in this reaction. The use of a weak acid additive such as pentanedioic acid was also essential for effective reaction. The replacement of pentanedioic acid with *m*-nitrobenzoic acid or *p*-toluenesulfonic acid gave inferior outcomes in terms of both activity and enantioselectivity (Table 1, entries 11 and 12). No reaction occurred with the addition of sodium bicarbonate (Table 1, entry 13). Mechanistically, weak acid plays a dual role to facilitate enamine formation as we previously reported, and to enhance the solubility of IBX in ether as known.[11] When catalyst **1b** was employed instead of **1a**, the enantioselectivity was raised slightly, albeit with a reduction in yield (Table 1, entry 14). Other substituted IBX have also been examined (Table 1, entries 15-17), both fluoro- and methyl-substituted IBX showed similar performance, indicating the absence of electronic effect in the oxidation. On the other hand, IBX bearing *ortho*-methyl group led to inferior activity and enantioselectivity, indicating a strong steric effect (Table 1, entry 17).

With the optimized conditions in hand, we then explored the scope of the substrates. The reactions worked well with cyclohexanones bearing different 4-alkyl group including those bulky groups such as ^{t}Bu, ^{t}Pent, ^{i}Pr and cycohexyl, giving the desired cyclohexen-2-ones with good *ee* (Table 2, entries 1-9). The bulky substitutes generally favors stereoselective control and 4-tertiary alkyl groups such as methylcyclohexyl, adamantyl, ^{t}Octyl, 3-methyl-3-pentyl, 3-ethyl-3-pentyl and cumyl group all led to > 90% *ee* with no decline in reactivity (Table 2, entries 10-15). Allylic substituted cyclohexanones also worked very well to deliver the desired cycohexen-2-ones (Table 2, entries 16 and 17) and those products can be readily utilized in the synthesis of terpenoid compounds.[12] 4-Benzyl substituted cyclohexanone could also be incorporated to give good yield and high enantioselectivity (Table 2, entry 18), and substituents on the benzene ring showed no obvious effect (Table 2, entry 19 and 20). A 4-ester moiety was also tolerated (Table 2, entry 21). In some cases, amine catalyst **1b** has been found to give slightly improved enantioselectivity but with a minor sacrifice of productivity (Table 2, entries 10, 17, 20, 27). Unfortunately, when hetero-atom or aryl group was introduced on the 4-position (R^2 = H), over-oxidation to phenols were obtained, without any cycohexenone observed (Table 2, entry 32).

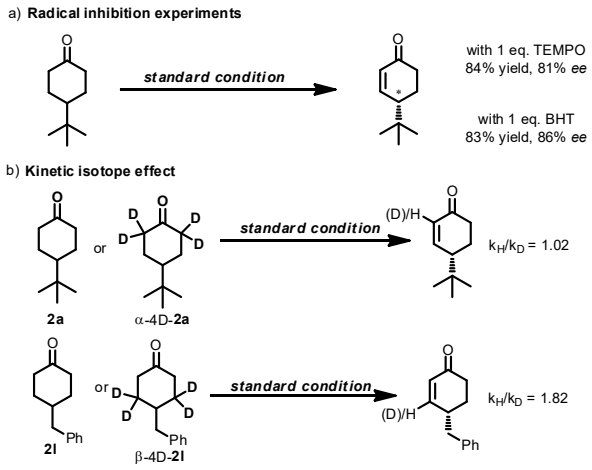
We then tested 4,4-disubstituted cyclohexanones, and in these cases, γ-quaternary stereocenters will be generated. We first examined the reactions with 4-aryl-4-methylcycohexanones and in these cases the desired cyclohexanones could be obtained in good yields and 77-83% *ee* (Table 2, entries 22-24). To further enhance synthetic applicability, we tested the reactions with cyclohexanones bearing spirocarbocyclic backbone, structural motif in many natural products. The reaction proceeded smoothly when five- or six- membered ring was introduced (Table 2, entries 25 and 26). In the meantime, the electronic nature on the benzene ring attached to spiro-compound showed neglectable effect on the reaction (Table 2, entries 27 and 31).



a) **3a**, $Zn(OTf)_2$, $CH_2(CO_2Me)_2$, THF, reflux, 24 h.; b) **3a**, I_2, Py, CCl_4, rt, 4h.; c) **3p**, $Fe(acac)_3$, $PhSiH_3$, EtOH, 60 °C, 12 h.; d) **3q**, $Fe(acac)_3$, $PhSiH_3$, EtOH, 60 °C, 12 h.; e) **3a**, H_2O_2(aq), $PhCOCF_3$, buffer in MeCN, rt, 3 h.; f) **3a**, $Pd(MeCN)_4OTf$, $NaNO_3$, $(PhBO)_3$, DCE, rt, 12 h.

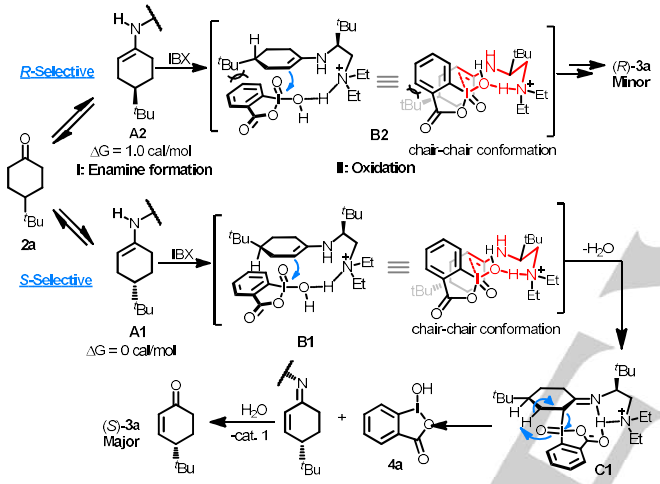
Scheme 2. Transformations and Scale-up Reactions

The reaction could be scaled up to gram scale with similar outcome and the excess cyclohexanone could be quantitatively recovered for further reactions, demonstrating the practicability. To demonstrate the synthetic utility, further derivatization were examined by transforming the enone moiety into different structural motif. In this regard, conjugate addition, aryl boric acid addition, α-iodination, radical reductive cyclization and epoxidation all worked smoothly to give the desired adduct with maintaining enantioselectivity as single diastereoisomers (Scheme 2).[13]



Scheme 3. Control Experiments

A number of control experiments were carried out to elucidate this oxidative desymmetrization process. The addition of typical radical scavenger such as butylated hydroxytoluene (BHT) or TEMPO showed on obvious inhibition effect (Scheme 3a). This observation together with the notable steric effect of IBX suggests that a SET initialized radical mechanism is unlikely operable in our case.[14, 3a] On this basis, a plausible substitution-elimination catalytic cycle, similar to the IBX-alcohol oxidation mechanism,[15] was proposed. This pathway involves enamine α-addition to IBX to form an α-iodic intermediate **C1/C2** (Scheme 4), which undergoes a concerted β-H abstraction-elimination to give the dehydrogenated adduct (Scheme 4). Coordination of enamine nitrogen or tertiary amine moiety to IBX is electronically feasible, however, this complex as an active intermediate was not considered due to its crowded coordination nature. On the other hand, the protonated tertiary amine moiety may direct the coupling of enamine and IBX *via* N-H-O hydrogen bonding in a chair-chair conformation (Scheme 4, B1 and B2).



Scheme 4. Proposed reaction sequence and stereocontrol mode

The intermolecular kinetic isotope effect of α-C-H and β-C-H bond was determined to be 1.02 and 1.82, respectively (Scheme 3b). This result suggested the rate-limiting step resides in the oxidation stage (Scheme 4, II), not in the enamine formation stage (Scheme 4, I) under the present conditions. The determined zero-order kinetics on cyclohexanone **2a** is consistent with this scenario (SI). The stereocontrol within this reaction sequence is another intriguing yet complicated issue. As different enamine conformers equilibrates under the present conditions (See SI for detailed analysis), both enamine formation and the oxidation steps could contribute in the stereocontrol. Shown in Scheme 4 are two equilibrated s-trans enamine **A1** and **A2** and the possible transition states **B1** and **B2** on reacting with IBX. DFT calculations indicated S-configured enamine **A1** is slightly favored over R-configured enamine **A2** by 1.0 Kcal/mol. In the following oxidation steps, steric effect of the 4-substituent (mono-substitution cases) may further reinforce the S-selective pathway (Scheme 4 and SI for detailed discussions).

In conclusion, we have developed the first catalytic desymmetric dehydrogenation of 4-substituted cyclohexanone *via* ketone enamine oxidation. The reaction proceed smoothly with both 4-mono- and 4,4-di-substituted cyclohexanone under mild conditions in high yield and good enantioselectivity. This unique desymmetrisation process is expected to achieve wide application in nature product synthesis and pharmaceutical industry. More cascade applications and mechanistic studies are underway in our laboratory.

Acknowledgements

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Keywords: enamine • desymmetrization • enantioselective dehydrogenation • ketone enamine oxidation • organocatalysis

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*Lihui Zhu, Long Zhang and Sanzhong Luo**

Page No. – Page No.

Catalytic Desymmetrizing Dehydrogenation of 4-Substituted Cyclohexanones through Enamine Oxidation

Desymmetric dehydrogenation: A chiral primary amine catalyzed desymmetric dehydrogenation process is herein described. The reaction proceeds via ketone enamine oxidation by IBX and enables highly enantioselective desymmetrization of 4-substituted cyclohexanones.