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Dynamic kinetic asymmetric transformations of β-halo-α-keto esters by *N,N′*-dioxide/Ni(II)-catalyzed carbonyl-ene reaction

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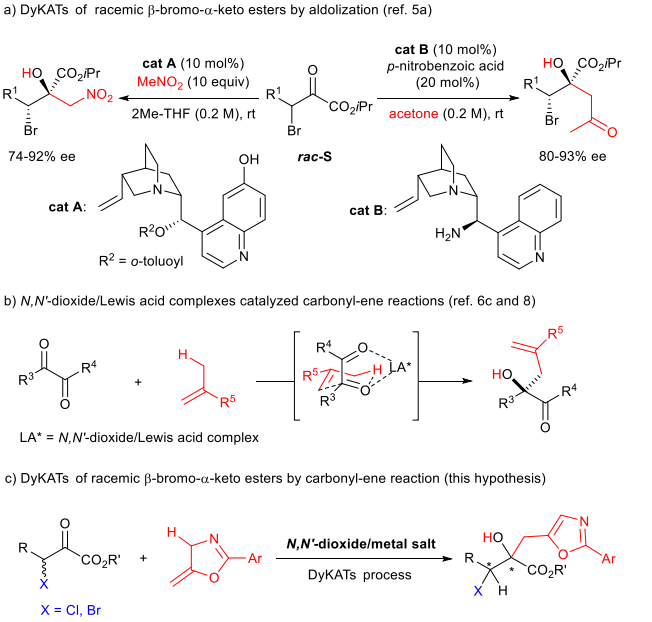
Dynamic kinetic asymmetric transformations of racemic β-halo-α-keto esters through carbonyl-ene reaction were realized by using a chiral *N,N′*-dioxide-nickel(II) complex, giving the corresponding β-halo-α-hydroxy esters containing two vicinal chiral tri- and tetrasubstituted carbon centers in good yields and dr with excellent ee values without the use of extra bases. Meanwhile, a proposed reaction mechanism was presented according to the configuration of the product.

Dynamic kinetic asymmetric transformations (DyKATs), which overcome the drawback of the theoretical maximum 50% yield in classical resolutions, are potent methods for the synthesis of enantioenriched molecules from racemic starting materials.[1] DyKATs conceptually refer to a process involving a chiral catalyst-mediated racemization of substrate enantiomers, and subsequent kinetic resolution leading to an enantioenriched product. Enantioconversion of racemic β-stereogenic α-keto esters is a prevalent protocol accessing to highly functionalized β-substituted glycolates containing two vicinal stereocenters,[2-5] generally including asymmetric transfer hydrogenation[2] and direct addition to the ketone carbonyl.[3-5] Calter's group reported the "interrupted" Feist-Bénary reactions of racemic β-stereogenic α-keto esters catalyzed by cinchona alkaloid catalysts.[3] Wang's group developed a dynamic kinetic resolution (DKR) of these typological substrates through cooperative catalysis.[4] Johnson's group made a great progress by developing diverse asymmetric reactions in this regard, such as annulation, arylation and so on.[2, 5] To the best of our knowledge, most of these cases focused on DKR by introducing extra bases to assist the racemization of β-stereogenic α-keto esters. Only one example through the way of DyKATs was realized, chiral quinidine derivatives were used to engage in the initial racemization of β-bromo-α-keto esters which subsequently occurred direct aldolization with nitromethane or acetone to give the corresponding products (Scheme 1a).[5a]



Scheme 1 Background and proposal

Carbonyl-ene reaction is one of the most powerful tools for the atom-economical formation of the C–C bond. A lot of enantioselective carbonyl-ene reactions were documented with the development of asymmetric catalysis over the past decades.[6] In recent years, our group developed a type of C_2 symmetric chiral *N,N′*-dioxide ligands, which could combine with various metal salts,[7] and the formed Lewis acid complexes have been successfully applied in the catalytic asymmetric carbonyl-ene reactions. The 1,2-dicarbonyl compounds could be activated by the Lewis acid catalyst in a stable five-membered ring fashion, giving the corresponding α-hydroxy carbonyl compounds (Scheme 1b).[8] Therefore, we conceive that

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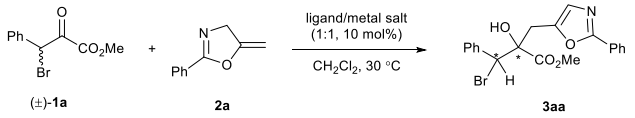
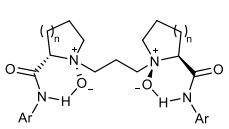
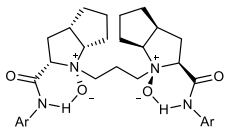
†Electronic Supplementary Information (ESI) available. CCDC 1561469. For ESI and crystallographic data in CIF or other electronic format see DOI:10.1039/x0xx00000x

Table 1 Optimization of the reaction conditions[a]





L-PrPr$_2$: Ar = 2,6-*i*Pr$_2$C$_6$H$_3$, n = 1
L-PiPr$_2$: Ar = 2,6-*i*Pr$_2$C$_6$H$_3$, n = 2



L-RaPr$_2$: Ar = 2,6-*i*Pr$_2$C$_6$H$_3$
L-RaEt$_2$: Ar = 2,6-Et$_2$C$_6$H$_3$
L-RaMe$_2$: Ar = 2,6-Me$_2$C$_6$H$_3$
L-RaPh: Ar = Phenyl

Entry	Metal salt	Ligand	Yield (%)[b]	dr[c]	ee (%)[d]
1	$Fe(ClO_4)_2·6H_2O$	**L-PiPr$_2$**	NR	-	-
2	$Co(ClO_4)_2·6H_2O$	**L-PiPr$_2$**	75	86:14	99
3	$Ni(ClO_4)_2·6H_2O$	**L-PiPr$_2$**	78	87:13	99
4	$Ni(ClO_4)_2·6H_2O$	**L-PrPr$_2$**	69	86:14	99
5	$Ni(ClO_4)_2·6H_2O$	**L-RaPr$_2$**	84	89:11	99
6	$Ni(ClO_4)_2·6H_2O$	**L-RaEt$_2$**	89	93:7	99
7	$Ni(ClO_4)_2·6H_2O$	**L-RaMe$_2$**	77	88:12	99
8	$Ni(ClO_4)_2·6H_2O$	**L-RaPh**	51	85:15	92

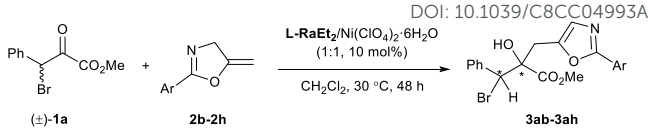
[a] Unless otherwise stated, all reactions were performed with **1a** (0.1 mmol), **2a** (0.2 mmol), and ligand/metal salt (1:1, 10 mol%) in CH_2Cl_2 (1.0 mL) at 30 °C for 48 h. [b] Yield of the isolated product. [c] Determined by ^{1}H NMR of the crude product. [d] Determined by HPLC analysis on a chiral stationary phase.

the DyKATs of racemic β-halo-α-keto esters can be achieved by an *N*,*N*′-dioxide/metal salt-catalyzed carbonyl-ene reaction (Scheme 1c).

In our preliminary investigation, β-bromo-α-keto ester **1a** and 5-methylene-2-phenyl-4,5-dihydrooxazole **2a** were selected as the model substrates to explore the DyKATs. Initially, various metal salts were screened to coordinate with (*S*)-pipecolic acid-derived chiral *N*,*N*′-dioxide **L-PiPr$_2$** in CH_2Cl_2 at 30 °C (Table 1, entries 1–3). No desired product was observed when **L-PiPr$_2$**/$Fe(ClO_4)_2·6H_2O$ was applied in the reaction. To our delight, the carbonyl-ene product β-bromo-α-hydroxy ester **3aa** could be smoothly obtained in high yields and dr with uniformly excellent ee values by the use of $Co(ClO_4)_2·6H_2O$ and $Ni(ClO_4)_2·6H_2O$, which demonstrated that our hypothesis of the DyKATs of racemic β-stereogenic α-keto esters was feasible in the presence of Lewis acid catalyst. The chiral backbone of the *N*,*N*′-dioxide ligands had a slight effect on the reaction. L-ramipril derived **L-RaPr$_2$** is more competent than **L-PrPr$_2$** derived from L-proline and **L-PiPr$_2$** in terms of dr and yield (Table 1, entry 5 vs entries 3 and 4). The investigation of the steric hindrance of the amide moiety showed that **L-RaEt$_2$**/$Ni(ClO_4)_2·6H_2O$ gave the best result (entries 5–8).

With the optimized reaction conditions in hand, a series of 5-methyleneoxazoline derivatives were probed to react with **1a**, giving the corresponding β-bromo-α-hydroxy esters in high yields and dr with excellent ee values (Table 2). The substituents on

Table 2 Substrate scope of 5-methyleneoxazoline derivatives[a]



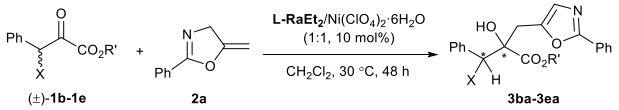
Entry	Ar	3	Yield (%)[b]	dr[c]	ee (%)[d]
1	C_6H_5	**3aa**	89	93:7	99
2	4-BrC_6H_4	**3ab**	82	94:6	99
3	4-MeC_6H_4	**3ac**	77	94:6	99
4	4-PhC_6H_4	**3ad**	64	94:6	99
5	3-ClC_6H_4	**3ae**	98	92:8	99
6	3-MeOC_6H_4	**3af**	81	94:6	99
7	3,5-Me$_2$C$_6$H$_3$	**3ag**	94	93:7	99
8	2-Naphthyl	**3ah**	82	93:7	99 (*S*,*S*)

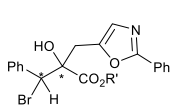
[a] Unless otherwise stated, all reactions were performed with **1a** (0.1 mmol), **2** (0.2 mmol), and **L-RaEt$_2$**/$Ni(ClO_4)_2·6H_2O$ (1:1, 10 mol%) in CH_2Cl_2 (1.0 mL) at 30 °C for 48 h. [b] Yield of the isolated product. [c] Determined by ^{1}H NMR of the crude mixture. [d] Determined by HPLC analysis on a chiral stationary phase.

the phenyl group had little effect on the diastereo- and enantioselectivities compared to the model reaction. A lower yield was observed with the substrate **3d** containing a phenyl substituent at the *para*-position of the aromatic ring (Table 2, entry 4). The dimethyl-substituted **2g** and naphthyl-substituted **2h** could be also tolerated in this reaction and gave good results (Table 2, entries 7 and 8). The absolute configuration of **3ah** was determined to be (*S,S*) by X-ray diffraction crystal analysis.[9]

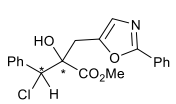
Subsequently, we turned our attention to broadening the substrate scope of the β-halo-α-keto esters (Table 3). The effect of the ester groups was evaluated firstly. The yields and dr decreased slightly when more sterically hindered ester groups were applied to this carbonyl-ene reaction. Chlorine-substituted α-keto ester **2e** could also transform into the corresponding product **3ea** in moderate yield and dr. It was noteworthy that the products could be formed with 99% ee in

Table 3 Effects of the ester group and halogen substituents[a]





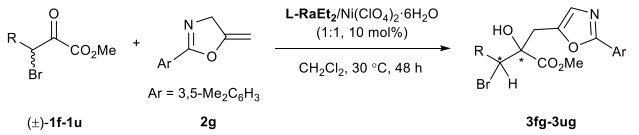
3ba, R' = Et, 69% yield, 92:8 dr, 99% ee
3ca, R' = *i*Pr, 83% yield, 92:8 dr, 99% ee
3da, R' = *n*Bu, 78% yield, 93:7 dr, 99% ee



3ea, 66% yield, 75:25 dr, 99% ee

[a] Unless otherwise stated, all reactions were performed with **1** (0.1 mmol), **2a** (0.2 mmol), and **L-RaEt$_2$**/$Ni(ClO_4)_2·6H_2O$ (1:1, 10 mol%) in CH_2Cl_2 (1.0 mL) at 30 °C for 48 h. Yield of the isolated product. Dr was determined by ^{1}H NMR of the crude mixture. Ee was determined by HPLC analysis on a chiral stationary phase.

Table 4 Substrate scope of the β-halo-α-keto esters[a]

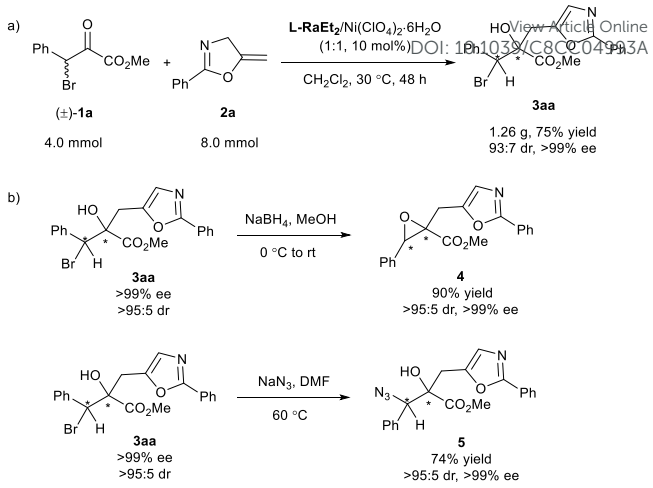


Entry	R	3	Yield (%)[b]	dr[c]	ee (%)[d]
1	2-MeC_6H_4	**3fg**	84	90:10	99
2	2-$MeOC_6H_4$	**3gg**	77	94:6	99
3	2-ClC_6H_4	**3hg**	78	90:10	99
4	3-$MeOC_6H_4$	**3ig**	89	>95:5	99
5	3-$BnOC_6H_4$	**3jg**	93	94:6	99
6	3-FC_6H_4	**3kg**	83	94:6	99
7	4-MeC_6H_4	**3lg**	96	94:6	99
8	4-*i*PrC_6H_4	**3mg**	95	93:7	99
9	4-$F_3CC_6H_4$	**3ng**	90	82:18	99
10	4-FC_6H_4	**3og**	84	89:11	99
11	4-ClC_6H_4	**3pg**	91	89:11	99
12	4-BrC_6H_4	**3qg**	81	88:12	99
13	3,4-$Me_2C_6H_3$	**3rg**	96	>95:5	99
14	2-Naphthyl	**3sg**	91	>95:5	99
15	1-Naphthyl	**3tg**	92	86:14	99
16[e]	Bn	**3ug**	76	67:33	99

[a] Unless otherwise stated, all reactions were performed with **1** (0.1 mmol), **2g** (0.2 mmol), and **L-RaEt₂**/Ni(ClO₄)₂·6H₂O (1:1, 10 mol%) in CH_2Cl_2 (1.0 mL) at 30 °C for 48 h. [b] Yield of the isolated product. [c] Determined by 1H NMR of the crude mixture. [d] Determined by HPLC analysis on a chiral stationary phase. [e] Using **L-PiPr₂**/Mg(OTf)₂ (1:1, 10 mol%) as the catalyst.

all the cases (**3ba**–**3ea**).

Next, the influence of R group of the β-bromo-α-keto esters **1** was investigated. The carbonyl-ene reaction between the structurally diverse **1** and 5-methyleneoxazoline derivative **2g** could smoothly proceed under the optimized reaction conditions (Table 4). Generally, the electronic nature and position of substituents on the phenyl group had no effect on the enantioselectivity of the carbonyl-ene reaction, and the desired products could be obtained in high yields and dr (Table 3, entries 1 – 12). Decreased diastereoselectivities were observed with the electron withdrawing substituents installing on the *para*-position of the phenyl group (Table 3, entries 9–12). Disubstituted and 2-naphthyl-substituted β-halo-α-keto esters **1r** and **1s** worked well to provide the corresponding products in 96% and 91% yields with excellent dr and ee values (Table 4, entries 13 and 14, >95:5 dr, 99% ee). The replacement of 2-naphthyl by 1-naphthyl (**3tg**) led to a decrease of dr without loss of yield and ee value (Table 4, entry 15). Moreover, the β-bromo-α-keto ester **1u** bearing a benzyl group at the β-position was suitable to provide the product **3ug** in 76% yield with 99% ee and 67:33

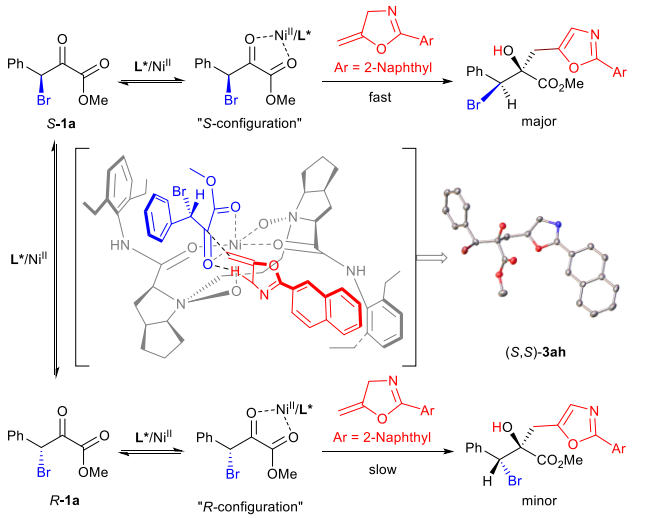


Scheme 2 (a) The gram-scale reaction (b) synthetic utility

dr by using a **L-PiPr₂**/Mg(OTf)₂ complex as the catalyst (Table 4, entry 16).

To show the synthetic utility of this reaction, a gram-scale version was conducted as shown in Scheme 2. **1a** (4.0 mmol) reacted with **2a** (8.0 mmol) under the optimized reaction conditions, providing the corresponding carbonyl-ene reaction product **3aa** in 75% yield (1.26 g), 93:7 dr and 99% ee. Intramolecular SN_2 substitution reaction of β-bromo alcohols is a straightforward way to achieve epoxides. After screening the reaction conditions, we found that the desired epoxide **4** could be obtained in high yield by manipulating **3aa** with $NaBH_4$ in MeOH. The C-Br bond of **3aa** routinely broke and a new C-N bond formed in the presence of NaN_3, affording the β-azido-α-hydroxy ester **5** without any erosion of the stereoselectivity.

According to the absolute configuration of product **3ah**,[9] a postulated reaction mechanism for this reaction was briefly illustrated in Scheme 3. The electron withdrawing carbonyl group and bromine atom allowed the rapid transformation between two configurationally labile β-bromo-α-keto ester in the presence of the chiral **L-RaEt₂**/Ni(ClO₄)₂·6H₂O complex. The *S*-configuration at β-position of **3ah** (*S*,*S*) indicated that the *S*-β-



Scheme 3 Proposed reaction mechanism and the absolute configuration of 3ah

bromo-α-keto ester reacts with 5-methyleneoxazoline derivative **2h** much faster than its enantiomer in the carbonyl-ene reaction. In addition, based on X-ray crystal structure of the *N*,*N*′-dioxide/Ni(II) complex,[10] a possible activation model was proposed. The two carbonyl groups of β-bromo-α-keto ester tended to coordinate with the Ni(II) in a bidentate fashion, forming a stable five-membered ring transition state, and the *Si* face was masked by the neighboring 2,6-diethylphenyl group of the ligand. The nucleophile **2h** attacked from the *Re* face predominantly to give **3ah** with *S*,*S*-configuration.

In summary, we have developed an *N*,*N*′-dioxide/Ni(II) catalytic system to promote the dynamic kinetic asymmetric transformations of racemic β-halo-α-keto esters by an enantioselective carbonyl-ene reaction. A series of corresponding β-halo-α-hydroxy esters with two vicinal chiral tri- and tetrasubstituted carbon centers could be smoothly obtained in good to high dr and excellent ee values under very mild reaction conditions without the use of bases. A possible reaction mechanism was proposed that the *N*,*N*′-dioxide/Ni(II) catalyst accelerated the racemization of β-halo-α-keto esters and subsequently catalyzed the carbonyl-ene in a resolution fashion.

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Conflicts of interest

There are no conflicts to declare.

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