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Carbene-Catalyzed Dynamic Kinetic Resolution and Asymmetric Acylation of Hydroxyphthalides and Related Natural Products

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Abstract: A catalytic dynamic kinetic resolution and asymmetric acylation reaction of hydroxyphthalides is developed. The reaction involves formation of a carbene catalyst-derived chiral acyl azolium intermediate that effectively differentiates the two enantiomers of racemic hydroxyphthalides. Our method allows for quick access to enantiomerically enriched phthalidyl esters with proven applications in medicines. It also enables asymmetric modification of natural products and other functional molecules that contain acetal/ketal groups, such as Corollosporine and Fimbricalyx lactone C.

Phthalides are core structures of diverse natural products found in plants and fungal genera.^[1] Many of these phthalide-containing molecules exhibit a broad spectrum of biological activities^[2] with proven applications such as for the treatments of circulatory and heart diseases.^[3] Hydroxyphthalides, with a hydroxyl group attached to the anomeric carbon to form a ketal/acetal moiety, are a subgroup of phthalides with wide natural occurrence and significant utilities (Figure 1a).^[4] For example, talosolate was marked to treat inflammation and pain.^[5] Luteorosin was found in *chromodoris luteorosa* and exhibit ichthyotoxic activities.^[6] Corollosporine is an antibacterial metabolite of marine fungus *corollospora maritima*.^[7] Fimbricalyx lactone B & C were isolated from *Strophoblachia fimbricalyx* which is used as folk medicine to treat migraine, fever, and cancer^[4b]. Acylated hydroxyphthalides (such as talniflumate^[8], talampicillin^[9] and talmecatin^[10]) have also been used as prodrugs of carboxylic acids. The acetal/ketal moiety in hydroxyphthalides and their derivatives contains a labile chiral center. Therefore, it remains difficult to prepare hydroxyphthalide-containing molecules in enantiomerically pure forms. Indeed, enantioselective access to acetals/ketals is a general challenge in organic synthesis.^[11] List showed that with confined chiral phosphoric acids based on a C₂-symmetric imidodiphosphoric acid motif as organic catalysts^[12], an

enantioselective approach for spiroacetalization was developed in high yield and excellent e.r. value. In the area of N-heterocyclic carbene (NHC) organic catalysis, studies by Wang and co-workers showed 6-hydroxypyranones could be esterified asymmetrically with enals or alkynals through dynamic kinetic resolution pattern to form chiral acetal units.^[13] Tang and coworkers reported the dynamic kinetic diastereoselective acylation of lactols through chiral isothiourea catalytic reactions.^[14] We recently disclosed a carbene-catalyzed enantioselective modification of carboxylic acids for asymmetric access to optically enriched acetal products (Figure 1b).^[15]

a) Examples of hydroxyphthalide-containing drugs and natural products

b) NHC-catalyzed enantioselective synthesis of phthalidyl esters (our previous work)

c) Carbene-catalyzed dynamic kinetic resolution of hydroxyphthalides (this work)

Figure 1. Hydroxyphthalides and their enantioselective acylation via carbene-catalyzed dynamic kinetic resolution

Here we disclose a new approach for enantiomeric access to acylated hydroxyphthalides via a carbene-catalyzed dynamic kinetic resolution (DKR) process (Figure 1b). The o-acetylbenzoic (or formylbenzoic) acid substrate (**1**) undergoes an equilibrium with the corresponding racemic hydroxyphthalide (predominant in most solvents).^[16] The aldehyde substrate (**2**) reacts with an NHC catalyst in the presence of an oxidant to

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form a chiral acyl azolium intermediate (**I**).^[17] Similar acyl azolium intermediates can also be formed using enals as the aldehyde substrates without the need of oxidants. Selective acylation of hydroxyphthalide by acyl azolium intermediate **I** via a dynamic kinetic resolution process led to chiral acylal (**3**) with high e.r. values. Our method works well for diverse substrates and allows for enantioselective access to commercially used pharmaceuticals such as talosolate with 1:99 e.r. value. We have also shown that with our method hydroxyphthalide-containing natural products such as corollosporine^[7] and fimbriallyxlactone **C**^[4b] can be kinetically resolved and acylated to form optically enriched ester products.

Table 1. Condition optimization^[a]

Entry	NHC	Base	Solvent	Yield (%)	e.r.
1	A	Cs ₂ CO ₃	THF	48	52:48
2	B	Cs ₂ CO ₃	THF	24	32:68
3	C	Cs ₂ CO ₃	THF	59	6:94
4	D	Cs ₂ CO ₃	THF	80	95:5
5	D	DIEA	THF	81	98:2
6	D	DIEA	EtOAc	96	98:2
7	D ^[b]	DIEA	EtOAc	87	98:2
8	D ^[c]	DIEA	EtOAc	76	99:1

[a] Reaction condition: **1a** (0.12 mmol), **2a** (0.1 mmol), NHC pre-cat. (0.02 mmol), Base (0.1 mmol), **DQ** (0.12 mmol) = 3,3',5,5'-tetra-tert-butylidiphenylquinone, solvent (2 mL), DIEA = *N,N*-Diisopropylethylamine, EtOAc = ethyl acetate. Yields were determined by isolation. The e.r. was determined via chiral-phase HPLC analysis. [b] 10 mol% **D** was used. [c] 5 mol% **D** was used.

We started by using *o*-carboxybenzaldehyde (**1a**) and methyl 4-formylbenzoate (**2a**) as the model substrates to search for suitable catalysts and conditions. Key results from condition optimizations (see the Supporting Information) are shown in Table 1. The reaction was first performed in THF as a solvent with triazolium salt **A**^[18] as a NHC pre-catalyst in presence of Cs₂CO₃ as a base. Product **3a** was obtained in a moderate yield but a very low e.r. value (entry 1, 51% yield, 52:48). When we replaced NHC precursor **A** with chiral morpholine-derived NHC pre-catalyst **B**^[19], encouraging e.r. value was obtained but the yield was frustrating (entry 2, 24% yield, 32:68). Replacing it with aminoindanol-derived pre-catalyst **C**^[20], **D**^[21] led to the satisfactory yield and e.r. values. Between them, the electron-rich pre-catalyst **D** could produce **3a** with the best yield and e.r. (entry 5). Additional studies on the effect of bases and solvents (entries 4-6) eventually revealed that DIEA was an optimal base

with ethyl acetate as an excellent solvent (entry 6). Decreasing the catalyst loading resulted in low yields, although the e.r. of the product was not affected (entries 7-8).

Table 2 Examples of the aldehyde substrates^[a]

Product	Yield (%)	e.r.
3a	96%	98:2 e.r.
3b	61%	98:2 e.r.
3c	87%	97:3 e.r.
3d	93%	93:7 e.r.
3e	79%	98:2 e.r.
3f	61%	98:2 e.r.
3g	67%	97:3 e.r.
3h	85%	94:6 e.r.
3i	95%	94:6 e.r.
3j	95%	92:8 e.r.
3k	53%	6:94 e.r. ^[b]
3l	54%	1:99 e.r. ^[b]
3m	61%	95:5 e.r.
3n	67%	92:8 e.r.
3o	95%	84:16 e.r.
3p	83%	98:2 e.r.
3q	83%	97:3 e.r.
3r	74%	83:17 e.r.
3s	35%	94:6 e.r.
3t	37%	93:7 e.r.

[a] Reaction condition: **1a** (0.12 mmol), RCHO (0.1 mmol), NHC **D** (0.02 mmol), **DQ** (0.12 mmol) = 3,3',5,5'-tetra-tert-butylidiphenylquinone, DIEA (0.1 mmol), EtOAc (2 mL), 12 h. [b] carried out using **C** as the NHC pre-catalyst. Yields were determined by isolation. The e.r. was determined via chiral-phase HPLC analysis. **DQ** = 3,3',5,5'-tetra-tert-butylidiphenylquinone, DIEA = *N,N*-Diisopropylethylamine, EtOAc = ethyl acetate. e.r. = enantiomeric ratio. X-ray crystal information of **3o** is available under CCDC number 1914214.

With a few acceptable conditions in hand, we moved to explore the substrate scope (Table 2) with both aryl aldehydes and aliphatic aldehydes as the formal acylating agents. Benzaldehyde derivatives containing various substituents [such as halogen, nitro (-NO₂), methylcarbonyl (-COOCH₃) and acetoxyl (-OAc) groups] were all tolerated to give the desired products with excellent yields and e.r. values (**3a-l**). In most of the cases, the substitution patterns on the benzene ring have little influence on the reaction enantioselectivities and yields (**3a-j**). When iodine or acetoxyl group were installed at the *ortho*-

position of the benzene, relatively lower yields and e.r. values were obtained under the standard condition (with NHC precursor **D**, **3k**, 26% 93:7 e.r.; **3l**, 22%, 86:14 e.r.). We then found that when **D** was replaced by **C** as the NHC pre-catalyst, much-improved yields and e.r. values were obtained for **3k** (53%, 6:94 e.r.) and **3l** (54% yield, 1:99 e.r.). It's worth to note that talosalate (**3l**) is a drug marketed in the racemic form. With our method, talosalate could be prepared in essentially an optically pure form (1:99 e.r.). Replacing the phenyl unit of the aryl aldehyde substrate with a bromonaphthalene substituent was also tolerated (**3m**). A diverse set of heteroaryl aldehydes (such as those containing pyridine, furan, or thiofurans) also reacted effectively to afford the products (**3n-q**) with good to excellent yields and excellent e.r. values. The absolute configuration of **3o** was confirmed via single crystal X-ray analysis. Using aliphatic aldehydes as the substrates, the high e.r. values of the products remained, while the reaction yields dropped significantly (**3s-t**) under the standard and a few other conditions (see the Supporting Information).

Table 3. Example of the acetylbenzoic and formylbenzoic acid substrates [a]

[a] Reaction condition: **4a-g** (0.12 mmol), RCHO (0.1 mmol), **2a** or **2c** (0.12 mmol), NHC precursor **D** (0.02 mmol), **DQ** (0.12 mmol) = 3,3',5,5'-tetra-tert-butylidiphenylquinone, DIEA (0.1 mmol), EtOAc (2 mL), 12 h. [b] carried out by NHC **D**. Yields were determined by isolation. The e.r. was determined via chiral-phase HPLC analysis. **DQ** = 3,3',5,5'-tetra-tert-butylidiphenylquinone, DIEA = N, N-Diisopropylethylamine, EtOAc = ethyl acetate. e.r. = enantiomeric ratio.

We next examined the scope of the acetylbenzoic and formylbenzoic acid substrates. (Table 3). Placing substituents to the benzene ring of the formylbenzoic acid substrates led to a slight loss on product e.r. values under current conditions (**5a-b**). We were then delighted to find that when the aldehyde moiety in the benzoic acid was replaced with a ketone group, our dynamic kinetic resolution process still worked effectively to deliver the acylated hydroxyphthalide products with excellent yields (**5c-g**). The e.r. values of these products (**5c-g**) varied from 28:72 to 92:8 depending on both the benzoic acid and the aryl aldehyde substrates. It appears the steric hindrance introduced by the ketone moiety has an influence on the selective acylation step of the reaction.

The NHC catalyst-derived acyl azolium intermediate for the acylation reaction could also be prepared by using enals as the substrates^[22] (Table 4). Without the need of external oxidants, through an internal redox process enals can be converted to acyl azolium intermediate for efficient and enantioselective acylation reactions (**7a-c**).

Table 4. Use of enals as acylation reagents without the need of external oxidants [a].

[a] Reaction condition: **1a** (0.1 mmol.), **6a-c** (0.15 mmol.), NHC **D** (0.02 mmol), DIEA (0.1 mmol), EtOAc (2 mL), 12 h. Yields were determined by isolation. The e.r. was determined via chiral-phase HPLC analysis. DIEA = N,N-Diisopropylethylamine, EtOAc = ethyl acetate. e.r. = enantiomeric ratio.

At last, we applied our method for asymmetric acylation of two natural products (Corollosporine and Fimbricalyxactone C) containing a hydroxyphthalide moiety (Scheme 2). Corollosporine, prepared in one step using reported protocols^[23](see the Supporting Information), could be asymmetrically acylated under our standard condition to form product **8** with 75% yield and 83:17 e.r. We then developed a route for total synthesis of fimbricalyxactone C by starting from 1,6-dimethoxynaphthalene (Scheme 2b). The synthesis took 8 steps to afford fimbricalyxactone C in 44% overall yield(see the Supporting Information). Treatment of fimbricalyxactone C under our standard catalytic reaction condition could afford acylated product **10** with 80% yield and 82:18 e.r.

Scheme 2. Modification of natural products

In summary, we have developed a carbene-catalyzed dynamic kinetic resolution and asymmetric acylation reaction of 3-hydroxyphthalide for quick access to optically enriched phthalidyl esters. Our reaction also offers a convenient approach for asymmetric modification of natural products and other functional molecules bearing labile acetal moieties that are

difficult to be fixed stereo-selectively. We also expect our method to find unique application for saccharide molecules containing many hydroxyl groups with minute reactivity differences.

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Keywords: Dynamic kinetic resolution • Phthalidyl esters • N-heterocyclic carbene • Natural product synthesis • Chiral prodrug synthesis.

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Layout 2:

COMMUNICATION

Dynamic kinetic process: a carbene-catalyzed dynamic kinetic resolution process is developed for asymmetric acylation and modification of medicines and natural products that bear hydroxyphthalide and acetal/ketal moieties.

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