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Enantiodivergent Steglich Rearrangement of *O*-Carboxylazlactones Catalyzed by a Chirality Switchable Helicene Containing a 4-Aminopyridine Unit

Chien-Tien Chen,* Cheng-Che Tsai, Pei-Kang Tsou, Gou-Tao Huang, and Chin-Hui Yu*

A pseudo-enantiomeric pair of optically switchable helicenes containing a catalytic 4-*N*-methylaminopyridine (MAP) bottom unit and a C_2 -symmetric, (10*R*,11*R*)-dimethoxymethyl-dibenzosuberane top template was synthesized. They underwent complementary photoswitching at 290 nm (*P*/*M'*, <1/>99) and 340 nm (*P*/*M'*, 91/9) and unidirectional, thermo-rotation at 130 °C (*P*/*M'*, >99/<1). They were utilized to catalyze enantiodivergent Steglich rearrangement of *O*- to *C*-carboxylazlactones, with formation of either enantiomers with up to 91% ee (*R*) and 94% ee (*S*), respectively.

The development of enantiodivergent catalysts has garnered significant interests in recent years, because it allows for the production of either enantiomerically enriched compounds based on a single chiral catalyst.¹ To date, several enantiodivergent catalytic systems under various conditions have been reported, in which the chiral environment of the complementary transition states can be tuned. For instance, reaction temperatures,² solvent effects,³ achiral co-catalysts,⁴ structural modifications of functional substrates,⁵ and different coordinating metal ions⁶ were found to facilitate enantiodivergent catalyses with good to high enantioselectivities (89-97 % ee). Nevertheless, such specific conditions may not be suitable for all desired transformations and substrate scopes. In marked contrast, enantiodivergent catalyses using pseudoenantiomers that can be interconverted by an external stimulus constitutes a more practical approach. For example, the enantiodivergent hydrosilylation of styrenes was first accomplished by Suginome and co-workers by using a polymer-based chiral catalyst, whose helical chirality depended on solvent polarity and attributes.7 Moreover, Canary and co-workers demonstrated an enantiodivergent, conjugate addition of diethyl malonates to nitrostyrene [up to 70% ee (R) and 72% ee (S)] by using redoxreconfigurable copper(I/II) complexes.⁸ In addition, Feringa and coworkers described a temperature-modulated, light-triggered enantiodivergent Michael addition [up to 54% ee (R) and 50% ee (S)], Henry reaction [up to 72% ee (R) and 42% ee (S)], and Pdcatalyzed allylic desymmetrization [up to 88% ee (S.R) and 86% ee (R,S)], utilizing a thiourea/DMAP hybrid organocatalyst or biphosphine ligand employing helically chiral molecular motor

scaffold.⁹ Photoswitchable catalysts that are capable of modulating reaction enantioselectivity [from 50% ee (S,S) to 5% ee (S,S)] have been established.¹⁰ However, as compared to enantiodivergent catalyses, the catalytic processes based on light- or heat-modulated, pseudo-enantiomeric catalysts remain challenging. Towards this end, herein we report a highly selective, enantiodivergent Steglich rearrangement of *O*-carboxylazlactones by using a nucleophilic helical catalyst with an embedded MAP unit, whose chirality can be switched.

Asymmetric Steglich rearrangement, an enantioselective O- to Ccarboxyl group transfer reaction, is a reliable method for the construction of a quaternary stereogenic center. Until now, a variety of chiral nucleophilic catalysts for asymmetric Steglich rearrangements have been developed with remarkable successes. For and central-chiral derivatives of 4example. planardimethylaminopyridine (i.e. DMAP) were first introduced by Fu,11 Richards,¹² and Vedejs.¹³ Recently, easily accessible, C-3 functionalized DAMPs were described by Poisson,14 Mandai and Suga.¹⁵ In addition, chiral tetrahydropyrimidine-based isothioureas and chiral N-heterocyclic carbenes (i.e. NHC) utilized by Smith,16 chiral ammonium betaines employed by Ooi,17 and chiral bicyclic imidazoles designed by Zhang¹⁸ were developed with better enantiocontol or broader substrate scope. In these distinguished works, however, only one of two possible enantiomers in the products could be obtained, except in Smith's work using pseudoenantiomeric isothioureas prepared from different chiral sources. With respect to the requirement of pharmacological study, a feasible access to both enantiomeric C-carboxyazlactones should be developed. In this study, we describe an enantiodivergent approach to obtain both enantiomeric C-carboxylazlactones by using a chirality switchable nucleophilic helicene containing a 4aminopyridine unit.

As part of our on-going researches on the C_2 -symmetric dibenzosuberane (DBS)-based helicenes as conformationally

Department of Chemistry, National Tsing Hua University, No. 101, Section 2, Kuang-Fu Road, Hsinchu 30013, Taiwan.

E-mail: ctchen@mx.nthu.edu.tw; chyu@mx.nthu.edu.tw

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flipable, chirochromic optical switches in liquid crystal materials and supramolecular organogels,¹⁹ we evaluated the feasibility of their uses in enantiodivergent catalysis. In this study, we synthesized a new photo-switchable and unidirectional thermo-rotable helicene **1**, whose catalytic activity was originated from 4-*N*-methylaminopyridine (i.e., MAP).^{20,21} Notably, the proximity of the catalytic site (i.e., N7⁹) to the upper chiral DBS template facilitates the asymmetric discrimination in the pyridine-centered activation event (Scheme. 1).



Scheme 1. Molecular design of chirality-switchable, helicene-based, 4-*N*-methylaminopyridine (MAP) as an organocatalyst.

The key synthetic steps towards the pyridine-incorporated helicene (10R,11R,P)-1 (i.e., (P)-1) is shown in Scheme 2 (see SI for details). Hydrazone 5, prepared from t-butyl-1,2,3,4-tetrahydro-1,6naphthyridine-1-carboxylate in 3 steps, was converted to the corresponding diazo compound by treatment with PhI(OCOCH₃)₂ at -20 °C in a 1/1 mixture of DMF/CH₂Cl₂. Subsequent reaction of the diazo compound with freshly prepared thicketone 4 afforded (10R,11R,1'S)-MOM-DBS-based episulfide 3 in 48% isolated yield as a single diastereomer. Support for the (S)-absolute configuration at C1' in 3 was obtained by circular dichroism (CD) analysis and comparing its sign of specific optical rotation and exciton chirality with those of analogous episulfides previously reported by us.^{19a,c} Stereospecific, reductive desulfurization of episulfide 3 with HMPT at 0 °C gave helicene (P)-2 in 76 % isolated yield. Finally, reductive methylation of N-Boc (P)-2 with DIBAL in THF at 50 °C furnished the desired N-methyl (P)-1 in 80% yield without epimerization of the helicene, as evidenced by HPLC analysis. The (P)-form helical chirality of 1 was confirmed by observing a negative exciton chirality at 221 nm by CD analysis (see Fig. 1c).²²



Scheme 2. Synthesis of (10*R*,11*R*,*P*)-helicene, (*P*)-**1**, bearing catalytic 4-*N*-methylaminopyridine (MAP) lower template. HMPT stands for hexamethylphosphorous triamide. DIBAL stands for diisobutylaluminum hydride.

In order to identify two distinctive irradiation wavelengths to induce photochemical switching between the two pseudoenantiomeric helicenes [i.e, (P)-1 and (M')-1], their individual UV/Vis and difference spectra with complementary changes in the extinction coefficient ($\Delta \varepsilon$) at two given wavelengths should be identified. This information provides their relative abundance and thus the composition of the photostationary state (i.e., pss) at a given irradiation wavelength to be assessed. The diastereomeric (i.e., pseudo-enantiomeric) excess of the pss from irradiation at a given wavelength (i.e., [de]_{pss})²³ can often be directly determined by the extinction coefficient difference under the conditions where the photoisomerization quantum yields $(\Phi_{M' \to P} \text{ and } \Phi_{P \to M'})$ for the both processes are similar. Therefore, to induce efficient switching in a highly diastereoselective (pseudo-eantiomeric in this system) manner, irradiation should be targeted at regions with significant and complementary differences in the extinction coefficients.



Fig. 1 Control and monitor of helical chirality. (a) Complementary photoisomerization of helicenes (*P*)-**1** and (*M*)-**1'** in degassed CH_2Cl_2 (1×10^{-4} M) and unidirectional, thermorotation of (*M*)-**1'** in xylene at 130 °C. (b) UV-Vis and difference spectra of (*P*)-**1** and (*M*)-**1'** in degassed CH_2Cl_2 (1×10^{-4} M). (c) Dynamic trace experiments with CD stacked plots before and after irradiation of (*P*)-**1** at 290 nm in degassed CH_2Cl_2 (1.0×10^{-4} M).

The photochemical switching experiments were carried out by irradiating individual (*P*)-1 and (*M*)-1²⁴ in degassed CH₂Cl₂ under a monochromator light source (Fig. 1a). The irradiation wavelengths were set at the wavelengths of 290 nm and 340 nm with the largest and complementary differences in the extinction coefficients which were determined by using the UV-vis difference spectrum between (*P*)-1 and (*M*)-1' (Fig. 1b). Photochemical switching of (*P*)-1 was first performed at 290 nm, which led to the exclusive formation of (*M*)-1' [(*P*)-1/(*M*)-1', <1/>99)]. The relative composition of the reaction mixture was monitored by HPLC on a Chiralcel AD column until the pss was reached (see Fig. S1-S3 in SI) with the detection wavelength set at the isosbestic point (i.e., 310 nm) of (*P*)-1 and (*M*)-1'. Photoisomerization of pure (*M*)-1 was then performed at 340 nm, which led to the predominant enrichment of (*P*)-1 [(*P*)-1:(*M*)-1', 91:9]. The diastereomerically pure (*P*)-1 can be regenerated either by

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Having established the complementary, photo-switching profiles of pseudo-enantiomeric helicenes (*P*)-1 and (*M*)-1', we investigated their individual performance as chiral organocatalysts in the Steglich rearrangement of *O*-carboxylazlactone (Table 1). Both (*P*)-1 and (*M*)-1' in the catalytic reaction are used in diastereomerically pure form. In an initial study, *O*-1,1,1-trichloro-*tert*-butoxycarbonyl (Cl₃*t*-Boc) derivative **6a** was treated with 5 mol% of (*P*)-1 in CH₂Cl₂ at ambient temperature, resulting in *C*-carboxylated product **7a** in modest yield of 57% with only 10% ee (entry 1). Replacement of the migrating Cl₃-*t*-Boc group with benzoxycarbonyl [BnOC(O)] and phenoxycarbonyl [PhOC(O)] led to a significant improvement in the enantioselectivities (41% and 63% ee; entries 2 and 3).²⁵





entry	R	solvent	catalyst	time(h)	yield(%) ^b	$ee (\%)^c$ $(config)^d$
1 ^e	CM ₂₂ GCl ₃	CH_2Cl_2	(P)- 1	48	57	10 (R)
2	Bn (6b)	CH_2Cl_2	(P)- 1	6	85	41 (R)
3	Ph (6c)	CH_2Cl_2	(P)- 1	6	90	63 (R)
4	Ph (6c)	toluene	(P)- 1	6	67	80 (R)
5	Ph (6c)	Et ₂ O	(P)- 1	48	78	79 (R)
6	Ph (6c)	THF	(P)- 1	12	80	72 (R)
7	Ph (6c)	DME	(P)- 1	6	82	80 (R)
8	Ph (6c)	DME/tAA (1/1)	(P)- 1	24	84	87 (<i>R</i>)
9	Ph (6c)	DME/tAA (1/1)	(M)-1'	24	81	91 (<i>S</i>)

^{*a*} The reactions were carried out in the presence of 5 mol% of (*P*)-1 at -40 °C under nitrogen atmosphere. ^{*b*} Isolated yield. ^{*c*} The enantiomeric purity of 7 was determined by using a chiral column (DAICEL Chiralcel OD-H) with hexane/propan-2-ol as eluents. ^{*d*} The absolute configuration of **7a-c** were determined by comparison of the HPLC retention time with those reported in reference 11a, 12, and 13. ^{*e*} The reaction was carried out at ambient temperature.

Further improvement in the enantioselectivity to around 80% ee was achieved by changing the solvent to toluene, ether, or 1,2dimethoxyethane (entries 4–7), suggesting that ionic pair intermediates may be solvated in polar solvents or stabilized by aromatic solvents through cation- π interaction.²⁶ Final optimization by using 1/1 mixture of 1,2-dimethoxyethane (DME)/*t*-amyl alcohol (tAA) led to the best results, giving (*R*)-**7**c in 84% yield with 87% ee (entry 8).²⁷ Conversely, the reaction of *O*-carboxylazlactone **6**c promoted by the pseudo-enantiomeric catalyst (*M*)-**1**' gave enantiomeric (*S*)-**7**c in 81% yield with 91% ee (entry 9). The switch of enantiocontrol indicated a complementary helical asymmetric environment in the pseudo-enantiomeric catalyst (M)-1'.

With the optimal reaction conditions in hands, the enantiodivergent Steglich rearrangements of various 0carboxylazlactones, 6d-6k, with pseudo-enantiomeric catalysts (P)-1 and (M)-1' were further examined (Table 2). It was found that rearrangements of 4-ethyl- and 4-i-butyl-1,3-oxazolyl phenyl carbonates (R' = Et and *i*-Bu) catalyzed by either (P)-1 or (M)-1' proceeded with excellent and complementary enantioselectivities (87-88% ee and 90-91% ee, respectively). Both products 7d,e were delivered in 80-85% yields (entries 1-4). Reaction of substrate 6f bearing 4-*i*-propyl-substituent with (P)-1 or (M)-1' gave the corresponding products in 71 and 70% yield with complementary enantiomeric excess of 69 and 72% (entries 5,6). These poorer yields were due to partial hydrolysis of carbonate group in the resulting products, consistent with the works of Smith^{16a,c} and Zhang.¹⁸ Substrates 6f-k bearing 4-allyl (entries 7,8), 4-(2-methylthio)ethyl (entries 9,10), 4-benzyl (entries 11,12), 4-(4-benzyloxy)benzyl (entries 13,14), and 4-(4-phenoxycarbonyloxy)benzyl (entries 15,16) groups were efficiently transformed into the corresponding products 7f-k in 81-86% yields with similarly excellent and complementary enantioselectivities (87-91% ee and 91-94% ee, respectively).

 Table 2
 Asymmetric
 Steglich
 rearrangement
 of
 various
 Ocarboxylazlactones
 catalyzed
 by (P)-1
 or
 (M)-1'.



^{*a*} The reaction was carried out in the presence of 5 mol% of (*P*)-1 or (*M*)-1' in 1,2dimethoxyethane/*tert*-amyl alcohol (v/v 1:1) at -40 °C under nitrogen atmosphere. ^{*b*} Isolated yields. ^{*c*} The enantiomeric purity of 7 was determined by using a chiral column (DAICEL Chiralcel OD-H or AD-H) with hexane/propan-2-ol as eluents ^{*d*} The absolute configuration of 7d and 7f-h were determined by comparison of the HPLC retention time with those reported in reference 16a.

In order to gain insight into the mechanism of Steglich rearrangement catalyzed by (P)-1 or (M)-1', the reversibility of O- to C-carboxyl group transfer process was investigated through some control experiments (Scheme 3). Initial crossover study was carried out by treatment of a 50:50 mixture of O-carboxylazlactones 6c and 61 with 5 mol% of catalyst (P)-1 at -40 °C in DME/tAA (1/1) mixed solvents. After 24 hours and reaction completion, a 22:27:23:28 mixture of four C-carboxylated products 7c, 7l, 7h, and 7i was observed (see Fig. S11,12 in SI). Further control experiment was performed by reaction of a mixture of C-carboxyl 7c and O-carboxyl 61 under the same reaction condition, giving C-carboxyl 7c and 7l, exclusively (see Fig. S13 in SI). These results indicated that Ccarboxylated products are configurationally stable under reaction conditions and that rapid crossover only occurs in O-carboxylation stage, which is consistent with those reported by Fu using planar chiral DAMPs^{11a} and by Smith using chiral isothioureas or chiral NHCs.16b,c Moreover, the complete crossover caused by rapid transcarboxylation between two different O-carboxyl azalctones indicated that ion pair intermediates are fully stabilized in the DME/tAA (1/1) mixed solvents.



Scheme 3. Crossover experiments of *O*-carboxylazlactones 6c and 6l under optimal reaction conditions.

Based on the control experiments, it was proposed that the catalytic process may proceed through an initial and reversible nucleophilic carboxyl substitution of the substrate carbonate moiety by catalyst (*P*)-1, resulting in the formation of a stabilized ion pair between enolate anion-I and pyridinium-cation II (Scheme 4).^{11b} The carbonyl group in the phenoxycarbonyl moiety in II is anti with respect to the 3-chloro appendage in the top template, thus avoiding stereoelectronic repulsion between the lone pairs of chlorine and the carbonyl oxygen. Subsequently, an irreversible *C*-carboxylation of enolate anion-I takes place with pyridinium-cation II in high enantiocontrol, giving the *C*-carboxylazlactone in *R* configuration.



Scheme 4. Proposed mechanism for the Steglich rearrangement of Ocarboxylazlactone catalyzed by (P)-1.

To gain further insight into the origin of enantiocontrol in the asymmetric catalytic process, molecular simulations of the transition state assemblies in the ion pair were performed by DFT calculations.²⁸ The preferred transition state assembly, **A**-syn, with *Re*-face attack leading to (*R*)-**7** is shown in Fig. 2b.

Presumably, the synclinal approach in A-syn assembly is more favored than the corresponding antiperiplanar approach in A-anti assembly in view of the advantageous donor-acceptor type, π - π interaction in A-syn and the unfavorable steric repulsion between the 4-methoxyphenyl group and the C11-methoxymethyl group in A-anti.

In transition state assembly **B**-anti with antiperiplanar approach and *Si*-face attack leading to (*S*)-7 (Fig. 2c), calculations show that the barrier for the *Si*-face attack is 1.19 kcal mol⁻¹ higher than that for the *Re*-face attack (see Fig. S8-S10 in SI). A greater overlap between HOMO and LUMO is observed for the *Re*-face attack based on the frontier molecular orbital analysis; therefore, the preference of the *Re*-face attack is rationalized. In addition, the stereoelectronic repulsions between the enolate oxygen lone pairs and the C11methoxymethyl group as well as between 4-methoxyphenyl and the *N*-methyl groups in the bottom template also contribute to a higher Gibbs free energy mentioned above.

(a) A-syn and A-anti transition state assemblies



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(b) **B**-anti transition state assembly



Fig. 2 Plausible transition state assemblies of Steglich rearrangement by using (*P*)-**1**. (a) **A**-syn and **A**-anti transition state assemblies using GaussView (side view) and ChemDraw (side and bottom views) presentations. (b) **B**-anti transition state assembly using ChemDraw (bottom view) presentation.

Conclusions

In summary, we have documented a pseudo-enantiomeric pair of optically switchable helicene catalysts (10R,11R,P)-1 and (10R,11R,M)-1', which contain a 4-N-methylaminopyridine (MAP) moiety. The helicene pair underwent complementary, photoswitching profiles at 290 nm (1/1', <1/>>99) and 340 nm (1/1', 91/9) and unidirectional thermo-rotation (1/1', >99/<1), as evidenced by UV-Vis difference, CD, and HPLC analyses. They can efficiently catalyze enantiodivergent Steglich rearrangements of O- to Ccarboxyazlactones at -40 °C in DME/tAA mixed solvents, resulting in the formation of either enantiomeric products of bio-medicinal importance²⁹ in up to 91% (R) and 94% (S) ee, respectively. Control experiments were performed to understand that the catalytic process may proceed through a reversible O-carboxylation and a subsequent irreversible C-carboxylation, Molecular simulations of the transition state assemblies of the incipient ion pairs indicate that synclinal Reface attack is favored in catalyst (P)-1 due to greater HOMO-LUMO interactions with minimal stereoelectronic repulsions. To our knowledge, this system provides the best complementary enantioselectivities among several light- or heat-controlled enantiodivergent catalytic reactions. Investigations toward examining other substrate classes, as well as applications to other organo-catalytic systems are underway.

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- 22 The negative exciton chirality is attributed to the electric transition dipole moment change from the bottom template to the top right.
- 23 The diastereomeric excess (de) of the pss at a given irradiation wavelength is given by $[de]_{pss} = (P-M')/(P+M') = [(\varepsilon_M \Phi_{M' \to P} - \varepsilon_P \Phi_{P \to M'})/[(\varepsilon_M \Phi_{M' \to P} + \varepsilon_P \Phi_{P \to M'})].$
- 24 (*M*)-1' is unavailable by chemical synthesis but subsequently obtained by photoisomerization of (*P*)-1 at 290 nm in CH_2Cl_2 for 1 hour.
- 25 The ee values of the resulting products were improved by about 10%, when the reaction temperature was lowered from 0 to -40 $^\circ$ C.
- 26 The calculated energy differences between the transition states in various solvents are less than 0.5 kcal mol⁻¹; therefore, the similar enantioselectivities in toluene, Et₂O, and DME are rationalized.
- 27 The control experiments in this work indicated the formation of a solvent-separated ion pair in the DME/tAA (1/1) mixed solvents, suggesting that the enolate anion in the ion-pair intermediate may be further stabilized by the additional tAA through partial hydrogen-bonding interaction.
- 28 Four transition states derived from (*P*)-1 or (*M*)-1' along with two possibilities of facial selectivity of enolate anion-I are shown in Gaussview presentation (Fig. S5) as well as in Chem 3D and Chem Draw presentations (see Fig. S6,7 in SI).
- 29 For a review of significance of α,α-disubstituted azlactones, see: (a) R. A. Mosey, J. S. Fisk and J. J. Tepe, *Tetrahedron: Asymmetry*, 2008, **19**, 2755-2762. For a representative example of bio-medicinal importance of α,α-disubstituted azlactones, see : (b) T. Zhou, R. C. Hider, P. Jenner, B. Campbell, C. J. Hobbs, S. Rose, M. Jairaj, K. A. Tayayrani-Binazir and A. Syme. *Bioorg. Med. Chem. Lett.*, 2013, **23**, 5279-5282.

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