Annuloselectivity in Reactions of Diacyl Dichlorides and Imines: Combined Experimental and Theoretical Studies

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S Supporting Information

ABSTRACT: The annuloselectivity defined as the annulation selectivity between [2 + 2] and cascade annulations of diacyl dichlorides and imines in the presence of organic bases to afford bis- β -lactams and 2,3-dihydro-1,3-oxazin-4-ones has been studied extensively with a combination of experiments and density functional theory (DFT) calculations. The present results indicate that it is the preference of diacyl dichlorides in the formation of cyclic α -oxoketenes in the presence of organic



bases that controls the annuloselectivity. The cascade annulations of hexanedioyl and heptanedioyl dichlorides undergo the chloride-assisted cyclization of the corresponding ω -chlorocarbonylalkylketenes as the rate-determining step in the presence of triethylamine, rather than the generation of bisketenes followed by dimerization, affording five- and six-membered cyclic α -oxoketenes followed by the [4 + 2] annulations with imines to furnish 2,3-dihydro-1,3-oxazin-4-ones. This is an energetically competitive pathway to the normal Staudinger cycloaddition. Further decreasing (pentanedioyl dichloride) or increasing the linker length (octanedioyl and nonanedioyl dichlorides) results in the enhanced energetic barriers for the cyclization, which is less competitive to the direct Staudinger cycloaddition to afford bis*trans-\beta*-lactams as the sole products. The current results provide an insight into the annuloselective control in the reactions of diacyl dichlorides and imines.

■ INTRODUCTION

The $\begin{bmatrix} 2 + 2 \end{bmatrix}$ cycloaddition reaction of imines and ketenes, referred to as Staudinger reaction or Staudinger cycloaddition, has proven to be a powerful tool for the construction of β lactams, which serve as key structural figures in a series of antibiotics.² Though the numerous reports from our laboratory³ and others⁴ have focused on the synthetic methodologies and the diastereoselectivity of β -lactam formation in the Staudinger reaction, bisketenes are also found to be versatile intermediates that react with water, alcohols, amines, and even alkenes to afford anhydrides, esters, amides, and Diels-Alder cycloadducts, respectively.⁵ During the continuous exploration of the chemistry of bisketenes, a series of bisketenes has been successfully prepared; even the unstable ones have be detected and employed in organic synthesis.⁶ Among them, there are three representative methods to give rise to bisketenes: (a) elimination of HCl in diacyl dichlorides in the presence of base, (b) Wolff rearrangement of didiazomethyldiketones under photoirradiation or heating conditions, and (c) photolysis of cyclobutenediones.^{6b,7} With the development of the synthetic methods for bisketenes, their chemical properties and reactions have been widely investigated.8 Tidwell and co-workers have focused on this field for several decades and have provided systematic studies on the nature of bisketenes with a series of substitutents.⁹

Ketenes are widely used for construction of β -lactams with imines; however, bisketenes are relatively seldom reported to

react with imines, and the annuloselectivity of bisketenes with imines is still a contentious and unclear issue in the cycloadditions. Sudo and Endo reported that the reaction of dicarboxylic acid and an imine with pyridinium salt and triethylamine gives a bis- β -lactam (Scheme 1a).¹⁰ Dumas et al. also developed the synthesis of bis- β -lactams from transitionmetal carbene complexes with a cyclic imine (Scheme 1b).¹¹ In 2008, Allen et al. exploited the annulation of didiazomethyldiketones or diacyl dichlorides with N-benzylideneaniline to afford bis- β -lactams (Scheme 1c).¹² However, Jager achieved distinct results through the reaction of hexanedioyl dichloride with an imine to furnish an oxazinone (Scheme 1d).¹³ Presset et al. also obtained a similar oxazinone through Wolff rearrangement of α -diazo- β -diketone with an imine (Scheme 1e).¹⁴ Recently, we performed DFT calculations on the annulations of ketenes and imines, focusing on unraveling the mechanism of the two tandem reactions of $\begin{bmatrix} 2 + 2 + 2 \end{bmatrix}$ annulations and on in-depth comprehending the origin of the annuloselectivity in the Staudinger reactions (Scheme 2a).¹⁵ We also investigated the influence of base on the annuloselectivity and found base-switched annuloselectivity in the reactions of ethyl malonyl chloride and imines.¹⁶ However, to the best of our knowledge, there still lacks a clear mechanistic investigation on the annuloselectivity in reactions of bisketenes with imines. Herein, we report the combined

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Received: March 13, 2015
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Scheme 1. Previous Annulations of Bisketenes with Imines







experimental and computational studies on the origin of the annuloselectivity between [2 + 2] and tandem annulations in the reactions of diacyl dichlorides and imines in the presence of triethylamine, further unraveling the mechanism of the tandem annulations (Scheme 2b). We believe that it is critical not only to our mechanistic understanding of the tandem annulations and annuloselectivity but also to guiding the further control and application of the reactions between diacyl dichlorides and imines in organic synthesis.

RESULTS AND DISCUSSION

Initially, we employed hexanedioyl dichloride (adipoyl dichloride) (1) as a bisketene precursor to explore the annulation with a series of imines 2. As described in Table 1,

Table 1. Reaction of Adipoly Chloride (1) and Imines 2^{a}

CI CI		$R^2 \sim N^{-R^1} \frac{E}{tolu}$	t ₃ N iene 3 h	$ \begin{array}{c} $			
entry	\mathbb{R}^1	\mathbb{R}^2	3	yield ^{b} (%)			
1	Ph	Ph	3a	68			
2	Ph	$4-NO_2C_6H_4$	3b	99			
3	2,6-Me ₂ C ₆ H ₃	Ph	3c	32			
4	Bn	Ph	3d	72			
5	cHex	$4-NO_2C_6H_4$	3e	58			
6	allyl	Ph	3f	99			
7	iPr	Ph	3g	89			
8	iPr	4-MeOC ₆ H ₄	3h	87			
9	iPr	$4-MeC_6H_4$	3i	63			
10	iPr	$4-NO_2C_6H_4$	3j	42			
11	nPr	4-MeO-C ₆ H ₄	3k	92			
12	nPr	$4-NO_2C_6H_4$	31	73			
13	Me	Ph	3m	65			
14	Me	$4-NO_2C_6H_4$	3n	92			
³ Reaction conditions: 1 (1 mmol) 2 (2 mmol) Et.N (2 mmol) in							

"Reaction conditions: 1 (1 mmol), 2 (2 mmol), Et₃N (2 mmol) in toluene (5 mL) under N_2 at room temperature for 3 h. ^bIsolated yield.

most of the imines react well with 1 in the presence of triethylamine at room temperature to afford 2,3-dihydro-1,3-oxazin-4-one derivatives 3 as the sole products in good to excellent yields. Aryl-substituted imines with electron-with-drawing and electron-donating groups are fully compatible. Various aryl and alkyl substituents in imines are well tolerated, indicative of wide scope. No bis- β -lactam from [2 + 2] cycloaddition was observed in these cases.

By following the mild conditions, the scope of this reaction with heptanedioyl dichloride (pimeloyl chloride) (4) was next explored (Table 2). However, reactions of the substrate 4 were sluggish and afforded 2,3-dihydro-1,3-oxazin-4-one derivatives 5 in low yields under mild conditions. Further increasing the reaction temperature could improve the yields. Various aryl and alkyl substituents in imines are well tolerated, indicative of wide scope, though the yields are still moderate. After scrutiny of the reaction with 4 and 2a, 2,3-dihydro-1,3-oxazin-4-one 5a was formed in 27% yield, along with bis- β -lactam 6a in 6% yield (eq 1, Scheme 3). Reducing or increasing the tethered methylene groups in the diacyl dichlorides 7a-c could not provide 2,3dihydro-1,3-oxazin-4-one derivatives at room temperature, while under reflux conditions, only bis- β -lactams 8a-c were generated in about 12% yields (eq 2, Scheme 3). Diacyl

Table 2. Reaction of Pimeloyl Chloride (4) and Imines 2^{a}

cı	4	CI + R ² N ^{-R¹ - 2}	Et ₃ N toluene reflux, 3 h	
entry	R^1	\mathbb{R}^2	5	yield ^b (%)
1	Ph	Ph	5a	27
2	Ph	$4-NO_2C_6H_4$	5b	16
3	Bn	Ph	5d	16
4	cHex	$4-NO_2C_6H_4$	5e	13
5	allyl	Ph	5f	9
6	iPr	Ph	5g	19
7	iPr	4-MeOC ₆ H ₄	5h	8
8	iPr	$4-NO_2C_6H_4$	5j	25
9	nPr	4-MeOC ₆ H ₄	5k	14
10	nPr	$4-NO_2C_6H_4$	51	16
11	Me	Ph	5m	15
12	Me	$4-NO_2C_6H_4$	5n	14

"Reaction conditions: 4 (1 mmol), 2 (2 mmol), Et_3N (2 mmol) in toluene (5 mL) under N_2 at reflux conditions for 3 h. ^bIsolated yield.

dichlorides that tethered different numbers of the methylene group afford distinct annulation products, and the origin of annuloselectivity is still unclear.

The coupling constants (0-2.3 Hz) of the vicinal protons in bis- β -lactams **6a** and **8** indicate that all β -lactams possess trans configuration $(0-3 \text{ Hz} \text{ for } trans-\beta$ -lactams and $4-6 \text{ Hz} \text{ for } cis-\beta$ -lactams). Except for bis- β -lactam **8**c, duplicated peaks were observed in their ¹H NMR and ¹³C NMR spectra, indicating that diastereomeric bis- β -lactams, meso-bis- β -lactams and a pair of enantiomeric bis- β -lactams with double trans- β -lactams, exist in the products as in a previous observation.¹² Although no duplicated peak was observed in the ¹H NMR and ¹³C NMR spectra of bis- β -lactam **8**c, we believe that diastereomeric isomers still exist. The linker 1,5-pentylidene group is so long so that no difference appears in the NMR spectra for the different stereoisomers (eqs 1 and 2, Scheme 3). The diastereomeric bis- β -lactams cannot be separated in most cases because of similar polarity. Only *meso*-8a and (\pm)-8a were separated on silica gel column chromatography. We attempted to grow single crystals to distinguish their structures, and we failed. We assigned their stereostructures on the basis of their polarity. A less polar diastereomer is a pair of enantiomers (\pm)-8a, whereas a more polar one is *meso*-8a.

Computational Methods. All optimized geometries were calculated at the DFT M06-2X level¹⁷ with 6-311+G(d,p) basis set for all the atoms with the Gaussian 09 suite of programs.¹⁸ Frequency calculations at the M06-2X level at 298 K were performed to confirm each stationary point to be either a minimum or a transition structure. Solvation energies were evaluated by a self-consistent reaction field (SCRF) using the conductor-like polarizable continuum solvation (CPCM) model,¹⁹ where UFF radii were used. Solvation calculations were carried out at the M06-2X level on the optimized structures in solution. Unless specifically mentioned, all discussed relative energies in this paper are referred to $\Delta G_{sol298K}$. The structures in Figure 2 were prepared using CYLView.²⁰

DFT Studies on Annuloselectivity. To explore potential reaction pathways of the annulations, we conducted a density functional theory (DFT) calculation investigation into the annuloselectivity of the [2 + 2] cycloaddition (Pathway A) and cascade annulation (Pathway B) of adipoyl dichloride (1) and imine **2m** in the presence of trimethylamine as a model reaction. The potential energy profiles in Figure 1 for Pathway A show that the first step of the cascade process corresponds to elimination of HCl in **1** by trimethylamine with an activation free energy of 23.4 kcal/mol to afford monoketene **INT1**, which is slightly endergonic by 2.0 kcal/mol. Normally, the

Scheme 3. Annuloselectivity in Reactions of Different Diacyl Dichlorides with N-Benzylideneaniline





Figure 1. Calculated energy profiles for the [2 + 2] cycloaddition and cascade annulations of diacyl dichloride 1 with imine 2m at the M06-2X(CPCM)/6-311+G(d,p) levels of theory.

monoketene INT1 can be expected to undergo stepwise [2 + 2] Staudinger reaction directly with imine **2m** to give rise to the corresponding *cis-β*-lactam in which the first step is the generation of zwitterionic intermediate INT2-E via the transition-state **TS2-E** with an activation free energy of 17.5 kcal/mol, and the second step is the ring-closure to form the corresponding *cis-β*-lactam product INT3-*cis* through **TS3-E**. The second ring-closure step considered as the rate-determining step requires an activation free energy of 31.3 kcal/mol, which seems to be a little high under mild conditions. Alternatively, imine **2m** with (*E*)-configuration could undergo isomerization to **2m-Z** with (Z)-configuration via the **TS4-EZ** with an activation free energy of 29.9 kcal/mol. Then **2m-Z** attacks monoketene INT1 via **TS2-Z** with an activation free energy of 18.4 kcal/mol to generate zwitterionic intermediate

INT2-Z. The following ring-closure via **TS3-Z** to form the corresponding *trans-\beta*-lactam **INT3-***trans* requires an activation free energy of 26.6 kcal/mol, which is more favorable over **TS3-***E*. Besides, zwitterionic intermediate **INT2-***E* could convert to **INT2-***Z* via **TS5-***EZ*; however, it suffers from a high energetic barrier (44.3 kcal/mol).

In Pathway B, after elimination of HCl in 1, the generated monoketene INT1 could undergo cyclization to deliver α -oxoketene, followed by [4 + 2] annulation with imine **2m** to yield the 2,3-dihydro-1,3-oxazin-4-one derivative **3m**. Two pathways have been calculated to account for the cyclization of diacyl dichloride 1. In the previously proposed mechanism,¹⁵ monoketene INT1 was regarded to take part in the second elimination of HCl by trimethylamine via **TS6** with an activation free energy of 24.2 kcal/mol to provide diketene



Figure 2. Transition-state structures in the reaction of adipoyl dichloride (1) and imine 2m optimized at M06-2X(CPCM)/6-311+G(d,p) in the solution of toluene. The breaking or forming bonds are shown in the gray shaded lines, and the bond distances are shown in Å.

INT4. However, the subsequent dimerization of the diketene proceeds via TS7 with an activation free energy of 32.7 kcal/ mol to furnish the lactone INT5. This seems to suffer from a too high energetic barrier to allow the dimerization to proceed under the conditions used. Alternatively, monoketene INT1 directly undergoes cyclization through TS8 with the C-C bond formation, and the Cl atom shifts to produce cyclic acyl chloride INT6. This cyclization between acyl chloride and ketene readily proceeds with an activation free energy of only 22.3 kcal/mol. In transition-state TS8, the forming C-C bond distance is 1.91 Å and the breaking and forming C-Cl bond distances are 2.22 and 2.93 Å, respectively (Figure 2). The formed acyl chloride INT6 is removed hydrogen chloride by trimethylamine via TS9 readily to provide α -oxoketene INT7, which is exergonic by 6.2 kcal/mol. The subsequent step is the attack of imine 2m to α -oxoketene INT7 with an activation free energy of 13.5 kcal/mol. In TS10, the forming N-C bond distance is 2.15 Å. The generation of zwitterionic intermediate INT8 is slightly endergonic by 3.6 kcal/mol. Finally, the intermediate INT8 undergoes ring-closure via a six-membered ring transition state TS11, requiring a low activation free energy of 2.6 kcal/mol, to give rise to product 3m that is 34.6 kcal/mol more stable than the starting materials. The forming O-C bond distance in TS11 is 2.18 Å, which is not far from that in **INT8** (2.96 Å), making the pathway facile.

Reviewing the whole energy profile, we found that Pathway B is the most likely to take place to afford oxazinone 3m, and the annuloselectivity-determining step of this cascade annulation reaction is the cyclization between acyl chloride and ketene moieties, rather than the generation of bisketene followed by dimerization, which is very competitive to the direct Staudinger reaction (22.3 vs 29.9 kcal/mol). Moreover, our mechanistic understanding provides new insight into the formation of the dimerization products of diacyl dichlorides in the presence of organic bases. This is in accord with the previous experimental result²³ and is also supported by our experimental observation that the reaction of 1,6-diazo-2,5-hexanedione (9) as the bisketene precursor with imine 2a cannot afford oxazinone 3a (eq 3, Scheme 3), while adipoyl dichloride (1) can. These together provide a good proposal for the formation of the oxazinones as major products from adipoyl dichloride and imines.

Given the importance of cyclization between acyl chloride and ketene moieties as the annuloselectivity-determining step, we next explore the effect of the linker length of diacyl dichlorides on the cyclization (Table 3). When pentanedioyl dichloride (glutaroyl dichloride) (n = 3) is employed, the Gibbs



CI^		+Me ₃ N <u>-Me₃N•</u> CI			CI
entry	diacyl dichloride	n	$\Delta G^{\ddagger}(\mathrm{TS})$ (kcal/mol)	$\Delta H^{\ddagger}(\mathrm{TS}) \ (\mathrm{kcal}/\mathrm{mol})$	$-T\Delta S^{\ddagger}(\mathrm{TS})$ (kcal/mol)
1	7a	3	33.6	33.4	0.2
2	1	4	22.3	21.3	1.0
3	4	5	22.8	20.4	2.4
4	7b	6	29.1	26.2	2.9
5	7 c	7	33.8	30.7	3.1
6	EtCOCl	NA	30.9	19.8	11.1

free energy of the cyclization is high up to 33.6 kcal/mol with the four-membered ring strain (33.4 kcal/mol in activation enthalpy). For adipoyl dichloride (n = 4), the Gibbs free energy level at its lowest point (22.3 kcal/mol) makes the cyclization kinetically accessible, corresponding to our successful cascade annulation reactions in good yields. Heptanedioyl dichloride (n= 5) requires 22.8 kcal/mol in terms of the Gibbs free energy, slightly higher than adipoyl dichloride (22.3 kcal/mol), leading to a decrease in the yields, consistent with our experimentally observed results. Further increasing the linker length [octanedioyl dichloride (n = 6) and nonanedioyl dichloride (n = 7)] results in the enhanced energetic barriers (29.1 and 33.8 kcal/mol in free energy) for the cyclization, which is unfavorable in comparison with the direct Staudinger reaction (about 27 kcal/mol, TS3-Z), in good agreement with our experimental observation of bis- β -lactams as the sole products. Furthermore, two molecules of propionyl chloride considered as the simple model for the diacyl dichloride with the longer linker length undergo the cyclization (herein, dimerization) with 30.9 kcal/mol in terms of the Gibbs free energy, which is significantly contributed by the decrease of entropy $(-T\Delta S^{\ddagger} =$ 11.1 kcal/mol). This dimerization of propionyl chloride is also less competitive to the direct Staudinger reaction with imines, once again in accord with our previous experimental results.^{3c,24}

For aliphatic diacyl dichlorides, the elimination of HCl by trimethylamine requires an energetic barrier of about 23 kcal/mol, and it is slightly endergonic by about 2 kcal/mol. In addition, the reaction system of 2,2'-(1,2-phenylene)diacetyl dichloride from Allen et al.¹² is compared. It is found from the calculational results that the elimination of HCl in 2,2'-(1,2-phenylene)diacetyl dichloride is facile and exergonic by 2.5 kcal/mol to provide the corresponding bisketene possibly because of the existence of more acidic benzylic α -proton, in agreement with the experimental observation of bisketene.¹²

CONCLUSIONS

In summary, we have explored the annuloselectivity between [2 + 2] and cascade annulations of diacyl dichlorides and imines in the presence of triethylamine to afford bis- β -lactams and 2,3dihydro-1,3-oxazin-4-ones, respectively, and have provided mechanistic investigation with the aid of DFT calculations. The results indicate that the cascade annulations of hexanedioyl and heptanedioyl dichlorides with imines in the presence of organic bases undergo the chloride-assisted cyclization of the corresponding *w*-chlorocarbonylalkylketenes as the rate-determining step, rather than the generation of bisketenes and subsequent dimerization, to afford further cyclic α -oxoketenes followed by the [4 + 2] annulation with imines to furnish 1,3oxazin-4-ones. This reaction pathway is very competitive to the normal Staudinger reaction. Further decreasing (pentanedioyl dichloride) or increasing the linker length (octanedioyl and nonanedioyl dichlorides) between the two acyl chloride groups results in the enhanced energetic barriers for the cyclization, which is less competitive to the direct Staudinger reaction to afford bis- β -lactams as the sole products. The annuloselectivity between [2 + 2] and tandem annulations is controlled significantly by the linker length between the two acyl chloride groups. Actually, it is controlled by the preference in the formation of cyclic α -oxoketenes. Diacyl dichlorides show good preference in the formation of cyclic α -oxoketenes, generally five- and six-membered cyclic α -oxoketenes, in the presence of organic bases, favoring 1,3-oxazin-4-one products in the reactions with imines. Otherwise, diacyl dichlorides with poor preference in the formation of cyclic α -oxoketenes generate predominately bis-*trans*- β -lactams in the reactions with imines. The current combined experimental and DFT studies provide comprehensive understanding on the cascade reaction mechanism and the annuloselectivity and even guide the further application of diacyl dichlorides and imines in the design of new synthetic strategies for heterocyclic compounds.

EXPERIMENTAL SECTION

General Information. Melting points were obtained on a melting point apparatus and are uncorrected. ¹H NMR and ¹³C NMR spectra were recorded on a 300 or 400 MHz spectrometer with TMS as an internal standard in CDCl₃ solution. IR spectra were taken on an FT-IR spectrometer in KBr. HRMS data were obtained with an LC/MSD TOF mass spectrometer. Purification of reaction products was carried out by column chromatography using silica gel (200–300 mesh). TLC separations were performed on silica gel G plates with petroleum ether/ethyl acetate, and the plates were visualized with UV light.

General Procedure for the Reaction of Adipoyl Dichloride (1) and Imines 2. To a solution of imine 2 (2 mmol) and Et_3N (303 mg, 3 mmol) in dry toluene (5 mL)

under N₂ at room temperature was added adipoyl dichloride (1) (183 mg, 1 mmol) dropwise. The reaction mixture was stirred for 3 h at room temperature and was filtered. The filter cake was washed with dichloromethane. The combined filtrate was washed with water and brine and was dried over sodium sulfate. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel and was recrystallized from petroleum ether $(30-60 \ ^{\circ}C)/$ ethyl acetate (PE/EA = 8:1, v/v) to afford 3.

2,3,6,7-Tetrahydro-2,3-diphenylcyclopenta[e][1,3]oxazin-4(5H)-one (**3a**). White crystals, mp 97–100 °C (lit.¹³ 101–104 °C); 198 mg, yield 68%; ¹H NMR (400 MHz, CDCl₃) δ 7.52– 7.12 (m, 10H), 6.67 (s, 1H), 2.75–2.52 (m, 2H), 2.52–2.33 (m, 2H), 2.05–1.91 (m, 1H), 1.91–1.77 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 167.7, 161.9, 140.0, 137.3, 129.2, 128.9, 128.5, 127.1, 125.9, 125.4, 111.1, 91.5, 31.6, 25.9, 19.6.

2,3,6,7-Tetrahydro-2-(4-nitrophenyl)-3-phenylcyclopenta-[e][1,3]oxazin-4(5H)-one (**3b**). Orange crystals, mp 153–154 °C; 387 mg, yield 99%; ¹H NMR (400 MHz, CDCl₃) δ 8.24 (d, *J* = 8.7 Hz, 2H), 7.68 (d, *J* = 8.6 Hz, 2H), 7.39–7.30 (m, 2H), 7.28–7.17 (m, 3H), 6.74 (s, 1H), 2.74–2.58 (m, 2H), 2.51– 2.36 (m, 2H), 2.08–1.94 (m, 1H), 1.93–1.80 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 167.9, 161.3, 148.5, 144.6, 139.6, 129.2, 128.1, 126.4, 125.2, 123.8, 111.7, 90.4, 31.5, 25.9, 19.6; IR (cm⁻¹) 1667.8; EI-MS *m*/*z* = 336 [M⁺]; ESI-HRMS calcd for C₁₉H₁₇N₂O₄, *m*/*z* = 337.1183 [M + H]⁺; found, 337.1186.

3-(2,6-Dimethylphenyl)-2,3,6,7-tetrahydro-2-phenylcyclopenta[e][1,3]oxazin-4(5H)-one (**3**c). Brown crystals, mp 124–126 °C; 126 mg, yield 32%; ¹H NMR (400 MHz, CDCl₃) δ 7.38–7.32 (m, 2H), 7.27–7.15 (m, 3H), 6.97–6.82 (m, 3H), 6.45 (s, 1H), 2.82–2.62 (m, 4H), 2.24 (s, 3H), 2.11 (s, 3H), 2.13–2.01 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 169.8, 162.4, 137.7, 136.8, 136.7, 134.2, 129.6, 128.1, 128.0, 127.9, 127.7, 127.4, 110.8, 92.7, 31.3, 26.2, 20.0, 19.0, 18.9; IR (cm⁻¹) 1667.1; EI-MS m/z = 319 [M⁺]; ESI-HRMS calcd for C₂₁H₂₁NO₂, m/z = 320.1645 [M + H]⁺; found, 320.1650.

3-Benzyl-2,3,6,7-tetrahydro-2-phenylcyclopenta[e][1,3]oxazin-4(5H)-one (**3d**). Colorless oil; 222 mg, yield 72%; ¹H NMR (400 MHz, CDCl₃) δ 7.40–7.09 (m, 10H), 6.15 (s, 1H), 5.37 (d, *J* = 15.4 Hz, 1H), 3.82 (d, *J* = 15.4 Hz, 1H), 2.72–2.60 (m, 1H), 2.60–2.45 (m, 2H), 2.42–2.30 (m, 1H), 2.02–1.81 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 167.5, 163.0, 137.2, 135.9, 129.5, 128.5, 127.8, 127.4, 109.7, 89.4, 46.1, 31.5, 26.0, 19.7; IR (cm⁻¹) 1664.2; EI-MS *m*/*z* = 305 [M⁺]; ESI-HRMS calcd for C₂₀H₂₀NO₂, *m*/*z* = 306.1489 [M + H]⁺; found, 306.1494.

3-Cyclohexyl-2,3,6,7-tetrahydro-2-(4-nitrophenyl)cyclopenta[e][1,3]oxazin-4(5H)-one (**3e**). White crystals, mp 133–134.5 °C; 198 mg, yield 58%; ¹H NMR (400 MHz, CDCl₃) δ 8.21 (d, *J* = 8.7 Hz, 2H), 7.63 (d, *J* = 8.7 Hz, 2H), 6.43 (s, 1H), 4.60–4.48 (m, 1H), 2.66–2.56 (m, 1H), 2.54– 2.43 (m, 1H), 2.37–2.27 (m, 1H), 2.25–2.14 (m, 1H), 1.97– 1.70 (m, 7H), 1.52–1.39 (m, 3H), 1.12–0.93 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 166.3, 161.8, 148.3, 146.1, 128.0, 123.4, 111.8, 84.4, 51.9, 31.8, 31.5, 31.3, 25.8, 25.74, 25.69, 25.3, 19.4; IR (cm⁻¹) 1658.9; EI-MS *m*/*z* = 342 [M⁺]; ESI-HRMS calcd for C₁₉H₂₃N₂O₄, *m*/*z* = 343.1652 [M + H]⁺; found, 343.1655.

3-Allyl-2,3,6,7-tetrahydro-2-phenylcyclopenta[e][1,3]oxazin-4(5H)-one (**3f**). Colorless oil; 278 mg, yield 99%; ¹H NMR (400 MHz, CDCl₃) δ 7.40 (s, 5H), 6.22 (s, 1H), 5.76 (dddd, *J* = 17.2, 10.0, 7.2, 4.8 Hz, 1H), 5.15 (d, *J* = 17.2 Hz, 1H), 5.10 (d, *J* = 15.7 Hz, 1H), 4.65 (dd, *J* = 15.7, 4.8 Hz, 1H), 3.35 (dd, J = 15.7, 7.2 Hz, 1H), 2.67–2.57 (m, 1H), 2.55–2.44 (m, 2H), 2.42–2.31 (m, 1H), 2.01–1.80 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 167.4, 162.7, 136.2, 133.1, 129.5, 128.5, 127.3, 117.5, 109.9, 89.3, 45.3, 31.4, 25.9, 19.7; IR (cm⁻¹) 1662.4; EI-MS m/z = 255 [M⁺]; ESI-HRMS calcd for C₁₆H₁₈NO₂, m/z = 256.1332 [M + H]⁺; found, 256.1339.

2,3,6,7-Tetrahydro-3-isopropyl-2-phenylcyclopenta[e]-[1,3]oxazin-4(5H)-one (**3g**). White crystals, mp 125–127 °C; 228 mg, yield 89%; ¹H NMR (400 MHz, CDCl₃) δ 7.47–7.31 (m, 5H), 6.36 (s, 1H), 4.86 (hept, *J* = 6.9 Hz, 1H), 2.67–2.56 (m, 1H), 2.51–2.30 (m, 2H), 2.25–2.13 (m, 1H), 1.95–1.83 (m, 1H), 1.83–1.66 (m, 1H), 1.29 (d, *J* = 6.7 Hz, 3H), 1.05 (d, *J* = 6.9 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 165.9, 162.3, 138.6, 128.8, 128.2, 127.0, 111.1, 85.1, 43.9, 31.3, 25.8, 21.4, 20.6, 19.5; IR (cm⁻¹) 1658.6; EI-MS *m*/*z* = 257 [M⁺]; ESI-HRMS calcd for C₁₆H₂₀NO₂, *m*/*z* = 258.1489 [M + H]⁺; found, 258.1491.

2,3,6,7-Tetrahydro-3-isopropyl-2-(4-methoxylphenyl)cyclopenta[e][1,3]oxazin-4(5H)-one (**3h**). Brown crystals, mp 108–112 °C; 250 mg, yield 87%; ¹H NMR (400 MHz, CDCl₃) δ 7.34 (d, *J* = 8.0 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 6.32 (s, 1H), 4.83 (hept, *J* = 6.9 Hz, 1H), 3.81 (s, 3H), 2.67–2.56 (m, 1H), 2.50–2.32 (m, 2H), 2.24–2.13 (m, 1H), 1.95–1.81 (m, 1H), 1.81–1.68 (m, 1H), 1.27 (d, *J* = 6.7 Hz, 3H), 1.04 (d, *J* = 7.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 165.7, 162.3, 160.0, 130.6, 128.4, 113.5, 110.8, 85.0, 55.2, 43.8, 31.4, 25.9, 21.3, 20.6, 19.5; IR (cm⁻¹) 1658.6; EI-MS *m*/*z* = 287 [M⁺]; ESI-HRMS calcd for C₁₇H₂₂NO₃, *m*/*z* = 288.1594 [M + H]⁺; found, 288.1596.

2,3,6,7-Tetrahydro-3-isopropyl-2-(4-methylphenyl)cyclopenta[e][1,3]oxazin-4(5H)-one (**3i**). White crystals, mp 112–114 °C; 170 mg, yield 63%; ¹H NMR (400 MHz, CDCl₃) δ 7.32 (d, *J* = 8.0 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 6.34 (s, 1H), 4.86 (hept, *J* = 6.9 Hz, 1H), 2.68–2.58 (m, 1H), 2.54– 2.38 (m, 2H), 2.26–2.15 (m, 1H), 1.96–1.84 (m, 1H), 1.82– 1.69 (m, 1H), 2.37 (s, 3H), 1.29 (d, *J* = 6.8 Hz, 3H), 1.06 (d, *J* = 7.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 165.8, 162.4, 138.8, 135.7, 128.9, 127.0, 111.0, 85.2, 43.9, 31.4, 25.9, 21.4, 21.1, 20.6, 19.5; IR (cm⁻¹) 1659.3; EI-MS *m*/*z* = 271 [M⁺]; ESI-HRMS calcd for C₁₇H₂₂NO₂, *m*/*z* = 272.1645 [M + H]⁺; found, 272.1646.

2,3,6,7-Tetrahydro-3-isopropyl-2-(4-nitrophenyl)cyclopenta[e][1,3]oxazin-4(5H)-one (**3***j*). Yellow crystals, mp 156.5–158 °C; 127 mg, yield 42%; ¹H NMR (400 MHz, CDCl₃) δ 8.22 (d, *J* = 8.8 Hz, 2H), 7.64 (d, *J* = 8.6 Hz, 2H), 6.41 (s, 1H), 4.94 (hept, *J* = 6.9 Hz, 1H), 2.66–2.56 (m, 1H), 2.56–2.44 (m, 1H), 2.38–2.28 (m, 1H), 2.26–2.15 (m, 1H), 1.97–1.85 (m, 1H), 1.80–1.67 (m, 1H), 1.31 (d, *J* = 6.7 Hz, 3H), 1.09 (d, *J* = 7.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 166.4, 161.8, 148.3, 145.9, 128.0, 123.5, 111.8, 83.9, 44.1, 31.3, 25.8, 21.5, 20.7, 19.4; IR (cm⁻¹) 1659.1; EI-MS *m/z* = 302 [M⁺]; ESI-HRMS calcd for C₁₆H₁₉N₂O₄, *m/z* = 303.1339 [M + H]⁺; found, 303.1345.

2,3,6,7-Tetrahydro-2-(4-methoxylphenyl)-3-propylcyclopenta[e][1,3]oxazin-4(5H)-one (**3k**). Colorless oil; 263 mg, yield 92%; ¹H NMR (400 MHz, CDCl₃) δ 7.32 (d, *J* = 8.6 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 6.18 (s, 1H), 3.82 (s, 3H), 3.85– 3.73 (m, 1H), 2.78 (ddd, *J* = 14.4, 8.4, 6.0 Hz, 1H), 2.65–2.54 (m, 1H), 2.54–2.43 (m, 2H), 2.38–2.27 (m, 1H), 1.99–1.78 (m, 2H), 1.52 (ddt, *J* = 20.0, 13.6, 6.0 Hz, 2H), 0.85 (t, *J* = 7.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 166.8, 163.1, 160.3, 128.6, 113.8, 110.0, 89.9, 55.3, 45.1, 31.3, 25.9, 21.8, 19.7, 11.2; IR (cm⁻¹) 1663.5; EI-MS $m/z = 287 [M^+]$; ESI-HRMS calcd for C₁₇H₂₁NO₃, $m/z = 288.1594 [M + H]^+$; found, 288.1599. 2,3,6,7-Tetrahydro-2-(4-nitrophenyl)-3-propylcyclopenta-

2,3,6,7-1etranyaro-2-(4-nitrophenyi)-3-propylcyclopenta-[e][1,3]oxazin-4(5H)-one (**3**]). Brown crystals, mp 97–99 °C; 220 mg, yield 73%; ¹H NMR (400 MHz, CDCl₃) δ 8.24 (d, *J* = 8.4 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 2H), 6.30 (s, 1H), 4.04–3.93 (m, 1H), 2.91–2.81 (m, 1H), 2.66–2.48 (m, 2H), 2.44–2.25 (m, 2H), 2.00–1.87 (m, 1H), 1.87–1.75 (m, 1H), 1.61 (ddt, *J* = 20.0, 13.6, 6.0 Hz, 2H), 0.93 (t, *J* = 7.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 166.7, 162.2, 148.5, 144.4, 127.9, 123.7, 111.0, 88.5, 45.9, 31.4, 25.8, 22.0, 19.5, 11.2; IR (cm⁻¹) 1665.0; EI-MS *m*/*z* = 302 [M⁺]; ESI-HRMS calcd for C₁₆H₁₉N₂O₄, *m*/ *z* = 303.1339 [M + H]⁺; found, 303.1334.

2,3,6,7-Tetrahydro-3-methyl-2-phenylcyclopenta[e][1,3]oxazin-4(5H)-one (**3m**). Yellow crystals, mp 127–130.5 °C; 148 mg, yield 65%; ¹H NMR (400 MHz, CDCl₃) δ 7.42 (s, SH), 6.14 (s, 1H), 2.83 (s, 3H), 2.66–2.40 (m, 4H), 2.01–1.85 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 167.4, 163.7, 136.0, 129.7, 128.7, 127.3, 109.7, 91.6, 31.3, 30.5, 26.0, 19.8; IR (cm⁻¹) 1665.0; EI-MS *m*/*z* = 229 [M⁺]; ESI-HRMS calcd for C₁₄H₁₆NO₂, *m*/*z* = 230.1176 [M + H]⁺; found, 230.1177.

2,3,6,7-Tetrahydro-3-methyl-2-(4-nitrophenyl)cyclopenta-[e][1,3]oxazin-4(5H)-one (**3n**). Yellow crystals, mp 161–164 °C; 253 mg, yield 92%; ¹H NMR (400 MHz, CDCl₃) δ 8.27 (d, *J* = 8.7 Hz, 2H), 7.59 (d, *J* = 8.6 Hz, 2H), 6.26 (s, 1H), 2.97 (s, 3H), 2.68–2.51 (m, 2H), 2.51–2.45 (m, 1H), 2.42–2.32 (m, 1H), 2.02–1.80 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 167.1, 162.7, 148.6, 143.5, 128.0, 123.9, 110.4, 90.0, 31.3, 31.2, 25.9, 19.6; IR (cm⁻¹) 1665.4; EI-MS *m*/*z* = 274 [M⁺]; ESI-HRMS calcd for C₁₄H₁₄N₂NaO₄, *m*/*z* = 297.0846 [M + Na]⁺; found, 297.0850.

General Procedure for the Reaction of Heptanedioyl Dichloride (4) and Imines 2. To a solution of imine 2 (2 mmol) and Et_3N (303 mg, 3 mmol) in dry toluene (5 mL) under N₂ and reflux was added heptanedioyl dichloride (4) (197 mg, 1 mmol) dropwise. The reaction mixture was stirred for 3 h under reflux and was filtered. The residue was washed with dichloromethane. The combined organic phase was washed with water and brine and was dried over sodium sulfate. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel and was recrystallized from petroleum ether (30–60 °C)/ ethyl acetate (PE/EA = 8:1, v/v) to afford 5.

2,3,5,6,7,8-Hexahydro-2,3-diphenylbenzo[e][1,3]oxazin-4one (**5a**).²¹ Colorless oil; 82 mg, yield 27%; ¹H NMR (400 MHz, CDCl₃) δ 7.48–7.12 (m, 10H), 6.54 (s, 1H), 2.43–2.32 (m, 1H), 2.32–2.16 (m, 2H), 2.09–1.97 (m, 1H), 1.74–1.56 (m, 3H), 1.44–1.31 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 163.0, 160.9, 139.9, 137.4, 129.1, 128.8, 128.4, 127.1, 125.9, 125.1, 109.0, 89.0, 27.6, 21.84, 21.78, 21.3.

2,3,5,6,7,8-Hexahydro-2-(4-nitrophenyl)-3-phenylbenzo-[e][1,3]oxazin-4-one (**5b**). Yellow crystals, mp 192–193.5 °C; 57 mg, yield 16%; ¹H NMR (400 MHz, CDCl₃) δ 8.22 (d, *J* = 8.7 Hz, 2H), 7.65 (d, *J* = 8.7 Hz, 2H), 7.39–7.30 (m, 2H), 7.27–7.17 (m, 3H), 6.61 (s, 1H), 2.43–2.25 (m, 2H), 2.24– 2.13 (m, 1H), 2.10–1.97 (m, 1H), 1.77–1.58 (m, 3H), 1.43– 1.31 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 162.4, 161.2, 148.4, 144.7, 139.5, 129.1, 128.0, 126.4, 124.9, 123.7, 109.5, 87.9, 27.6, 21.71, 21.66, 21.2; IR (cm⁻¹) 1665.2; EI-MS *m*/*z* = 350 [M⁺]; ESI-HRMS calcd for C₂₀H₁₉N₂O₄, *m*/*z* = 351.1339 [M + H]⁺; found, 351.1342.

3-Benzyl-2,3,5,6,7,8-hexahydro-2-phenylbenzo[e][1,3]oxazin-4-one (5d). White crystals, mp 89–90.5 °C; 50 mg, yield 16%; ¹H NMR (400 MHz, CDCl₃) δ 7.40–7.30 (m, 3H), 7.30–7.20 (m, 5H), 7.14–7.09 (m, 2H), 6.02 (s, 1H), 5.29 (d, *J* = 15.4 Hz, 1H), 3.84 (d, *J* = 15.4 Hz, 1H), 2.43–2.25 (m, 2H), 2.23–2.12 (m, 1H), 2.04–1.91 (m, 1H), 1.67–1.60 (m, 3H), 1.57–1.46 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 164.2, 161.1, 137.2, 136.0, 129.4, 128.48, 128.47, 127.8, 127.4, 127.3, 107.7, 87.1, 46.5, 27.4, 22.0, 21.9, 21.4; IR (cm⁻¹) 1662.7; EI-MS *m*/*z* = 319 [M⁺]; ESI-HRMS calcd for C₂₁H₂₁NNaO₂, *m*/*z* = 342.1465 [M + Na]⁺; found, 342.1466.

3-Cyclohexyl-2,3,5,6,7,8-hexahydro-2-(4-nitrophenyl)benzo[e][1,3]oxazin-4-one (**5e**). White crystals, mp 171–173 °C; 47 mg, yield 13%; ¹H NMR (400 MHz, CDCl₃) δ 8.20 (d, J = 8.8 Hz, 2H), 7.60 (d, J = 8.6 Hz, 2H), 6.28 (s, 1H), 4.52 (tt, J = 12.1, 3.6 Hz, 1H), 2.39–2.28 (m, 1H), 2.19–2.01 (m, 2H), 1.96–1.89 (m, 1H), 1.86–1.70 (m, 4H), 1.69–1.61 (m, 3H), 1.56–1.34 (m, 4H), 1.25–1.13 (m, 1H), 1.11–0.93 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 162.4, 159.2, 148.2, 146.4, 127.9, 123.4, 109.9, 81.9, 52.1, 31.6, 31.1, 27.5, 25.71, 25.66, 25.3, 21.7, 21.6, 21.2; IR (cm⁻¹) 1660.2; MS *m*/*z* = 356 [M⁺]; HRMS calcd for C₂₀H₂₅N₂O₄, *m*/*z* = 357.1809 [M + H]⁺; found, 357.1809.

3-Allyl-2,3,5,6,7,8-hexahydro-2-phenylbenzo[e][1,3]oxazin-4-one (**5f**).¹⁴ Colorless oil; 23 mg, yield 9%; ¹H NMR (400 MHz, CDCl₃) δ 7.39 (s, 5H), 6.08 (s, 1H), 5.75 (dddd, J = 17.2, 10.0, 7.2, 4.8 Hz, 1H), 5.11 (d, J = 17.2 Hz, 1H), 5.07 (d, J = 15.7 Hz, 1H), 4.57 (dd, J = 15.7, 4.8 Hz, 1H), 3.35 (dd, J = 15.8, 7.2 Hz, 1H), 2.38–2.29 (m, 1H), 2.29–2.13 (m, 2H), 2.06–1.95 (m, 1H), 1.66–1.59 (m, 3H), 1.55–1.43 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 163.8, 160.9, 136.3, 133.0, 129.4, 128.5, 127.3, 117.4, 107.9, 87.0, 45.6, 27.3, 21.9, 21.8, 21.3.

2,3,5,6,7,8-Hexahydro-3-isopropyl-2-phenylbenzo[e][1,3]oxazin-4-one (**5g**). White crystals, mp 110–112 °C; 51 mg, yield 19%; ¹H NMR (400 MHz, CDCl₃) δ 7.47–7.30 (m, 5H), 6.21 (s, 1H), 4.80 (hept, *J* = 6.9 Hz, 1H), 2.40–2.29 (m, 1H), 2.16–2.05 (m, 2H), 1.85–1.73 (m, 1H), 1.69–1.56 (m, 2H), 1.54–1.43 (m, 1H), 1.27–1.20 (m, 1H), 1.30 (d, *J* = 6.7 Hz, 3H), 1.04 (d, *J* = 7.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 163.0, 158.9, 138.7, 128.7, 128.1, 127.0, 109.3, 82.7, 44.2, 27.4, 21.8, 21.7, 21.3, 21.2, 20.2; IR (cm⁻¹) 1661.2; EI-MS *m*/*z* = 271 [M⁺]; ESI-HRMS calcd for C₁₇H₂₂NO₂, *m*/*z* = 272.1645 [M + H]⁺; found, 272.1648.

2,3,5,6,7,8-Hexahydro-3-isopropyl-2-(4-methoxylphenyl)benzo[e][1,3]oxazin-4-one (5h). Yellow crystals, mp 122.5– 125 °C; 23 mg, yield 8%; ¹H NMR (400 MHz, CDCl₃) δ 7.31 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 6.17 (s, 1H), 4.77 (hept, *J* = 6.9 Hz, 1H), 3.81 (s, 3H), 2.39–2.29 (m, 1H), 2.16– 2.04 (m, 2H), 1.83–1.73 (m, 1H), 1.68–1.57 (m, 2H), 1.54– 1.44 (m, 1H), 1.33–1.21 (m, 1H), 1.29 (d, *J* = 6.8 Hz, 3H), 1.03 (d, *J* = 7.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 163.0, 159.9, 158.7, 130.7, 128.3, 113.4, 109.0, 82.6, 55.2, 44.2, 27.4, 21.9, 21.7, 21.3, 21.2, 20.2; IR (cm⁻¹) 1660.7; EI-MS *m/z* = 301 [M⁺]; ESI-HRMS calcd for C₁₈H₂₄NO₃, *m/z* = 302.1751 [M + H]⁺; found, 302.1754.

2,3,5,6,7,8-Hexahydro-3-isopropyl-2-(4-nitrophenyl)benzo[e][1,3]oxazin-4-one (5j). Yellow crystals, mp 147–148 °C; 79 mg, yield 25%; ¹H NMR (400 MHz, CDCl₃) δ 8.21 (d, J = 8.5 Hz, 2H), 7.60 (d, J = 8.7 Hz, 2H), 6.26 (s, 1H), 4.90 (hept, J = 6.9 Hz, 1H), 2.40–2.29 (m, 1H), 2.20–2.01 (m, 2H), 1.85–1.73 (m, 1H), 1.71–1.57 (m, 2H), 1.56–1.42 (m, 1H), 1.24–1.14 (m, 1H), 1.32 (d, J = 6.7 Hz, 3H), 1.07 (d, J = 7.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 162.5, 159.3, 148.2, 146.2, 127.9, 123.4, 109.9, 81.5, 44.3, 27.4, 21.7, 21.6, 21.4, 21.1, 20.3; IR (cm⁻¹) 1661.3; EI-MS $m/z = 316 [M^+]$; ESI-HRMS calcd for C₁₇H₂₁N₂O₄, $m/z = 317.1496 [M + H]^+$; found, 317.1499.

2,3,5,6,7,8-Hexahydro-2-(4-methoxylphenyl)-3-propylbenzo[e][1,3]oxazin-4-one (5k). Colorless oil; 42 mg, yield 14%; ¹H NMR (400 MHz, CDCl₃) δ 7.31 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.6 Hz, 2H), 6.03 (s, 1H), 3.82 (s, 3H), 3.71 (ddd, *J* = 14.4, 8.4, 6.0 Hz, 1H), 2.77 (ddd, *J* = 14.4, 8.4, 6.0 Hz, 1H), 2.37–2.22 (m, 2H), 2.22–2.10 (m, 1H), 2.02–1.91 (m, 1H), 1.67–1.57 (m, 3H), 1.56–1.43 (m, 3H), 0.83 (t, *J* = 7.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 164.2, 160.31, 160.28, 128.63, 128.58, 113.8, 107.9, 87.6, 55.3, 45.3, 27.3, 21.9, 21.8, 21.6, 21.3, 11.3; IR (cm⁻¹) 1664.3; EI-MS *m*/*z* = 301 [M⁺]; ESI-HRMS calcd for C₁₈H₂₄NO₃, *m*/*z* = 302.1751 [M + H]⁺; found, 302.1758.

2,3,5,6,7,8-Hexahydro-2-(4-nitrophenyl)-3-propylbenzo-[e][1,3]oxazin-4-one (**5**1). Colorless oil; 51 mg, yield 16%; ¹H NMR (400 MHz, CDCl₃) δ 8.24 (d, *J* = 8.3 Hz, 2H), 7.57 (d, *J* = 8.6 Hz, 2H), 6.17 (s, 1H), 4.00–3.88 (m, 1H), 2.83 (ddd, *J* = 14.4, 8.4, 6.0 Hz, 1H), 2.38–2.26 (m, 1H), 2.26–2.08 (m, 2H), 1.99–1.88 (m, 1H), 1.70–1.54 (m, 5H), 1.40–1.28, (m, 1H), 0.92 (t, *J* = 7.3 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 163.1, 160.1, 148.4, 144.6, 127.8, 123.7, 108.8, 86.1, 46.2, 27.3, 21.8, 21.7, 21.6, 21.1, 11.2; IR (cm⁻¹) 1665.1; EI-MS *m*/*z* = 316 [M⁺]; ESI-HRMS calcd for C₁₇H₂₁N₂O₄, *m*/*z* = 317.1496 [M + H]⁺; found, 317.1497.

2,3,5,6,7,8-Hexahydro-3-methyl-2-phenylbenzo[e][1,3]oxazin-4-one (**5***m*). Colorless oil; 37 mg, yield 15%; ¹H NMR (400 MHz, CDCl₃) δ 7.41 (s, 5H), 5.99 (s, 1H), 2.79 (s, 3H), 2.33–2.26 (m, 2H), 2.20–2.13 (m, 1H), 2.11–2.00 (m, 1H), 1.69–1.62 (m, 2H), 1.62–1.55 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 164.8, 161.1, 136.2, 129.6, 128.7, 127.3, 107.6, 89.2, 30.6, 27.2, 21.93, 21.87, 21.4; IR (cm⁻¹) 1665.6; EI-MS *m*/*z* = 243 [M⁺]; ESI-HRMS calcd for C₁₅H₁₈NO₂, *m*/*z* = 244.1332 [M + H]⁺; found, 244.1338.

2,3,5,6,7,8-Hexahydro-3-methyl-2-(4-nitrophenyl)benzo-[e][1,3]oxazin-4-one (**5***n*). Yellow crystals, mp 207.5–209 °C; 40 mg, yield 14%; ¹H NMR (400 MHz, CDCl₃) δ 8.20 (d, *J* = 8.7 Hz, 2H), 7.51 (d, *J* = 8.6 Hz, 2H), 6.04 (s, 1H), 2.86 (s, 3H), 2.30–2.20 (m, 1H), 2.19–2.07 (m, 2H), 1.98–1.87 (m, 1H), 1.60–1.50 (m, 3H), 1.45–1.34 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 163.8, 160.7, 148.6, 143.6, 128.1, 123.9, 108.2, 87.7, 31.3, 27.2, 21.8, 21.7, 21.2; IR (cm⁻¹) 1665.3; EI-MS *m*/*z* = 288 [M⁺]; ESI-HRMS calcd for C₁₃H₁₇N₂O₄, *m*/*z* = 289.1183 [M + H]⁺; found, 289.1185.

General Procedure for the Reaction of Diacyl Dichlorides and Imine 2a. To a solution of imine 2a (362 mg, 2 mmol) and Et₃N (303 mg, 3 mmol) in toluene (5 mL) under N₂ and reflux was added diacyl dichloride 4 or 7 (1 mmol) dropwise. The reaction mixture was stirred for 12 h under reflux and was filtered. The filter cake was washed with dichloromethane. The combined filtrate was washed with water and brine and was dried over sodium sulfate. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel and was recrystallized from petroleum ether (30–60 °C)/ethyl acetate (PE/EA = 8:1, v/v) to afford 6a or 8.

meso-3,3'-(1,3-Propylidene)bis(trans-1,4-diphenylazetidin-2-one) (meso-**6a**) and rel(3S,3'S,4R,4'R)-3,3'-(1,3propylidene)bis(1,4-diphenylazetidin-2-one) ((±)-**6a**). White crystals, mp 182–185 °C; 26 mg, yield 6%; ¹H NMR (400 MHz, CDCl₃) δ 7.45–7.17 (m, 20H), 4.64 (d, *J* = 2.3 Hz, 2H), 3.09 (ddd, *J* = 14.4, 6.4, 2.0 Hz, 2H), 2.03–1.84 (m, 4H), 1.84–1.70 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 167.5, 137.9, 137.7, 129.2, 129.0, 128.4, 125.8, 123.8, 116.9, 61.10/ 61.07, 60.21/60.13, 28.8/28.5, 24.9/24.6; IR (cm⁻¹) 1660.1; EI-MS *m*/*z* = 486 [M⁺]; ESI-HRMS calcd for C₃₃H₃₁N₂O₂, *m*/ *z* = 487.2380 [M + H]⁺; found, 487.2386.

rel(3*S*,3'*S*,4*R*,4'*R*)-3,3'-(*Methylene*)*bis*(1,4-*diphenylazetidin-2-one*) ((±)-**8***a*). White crystals, mp 197–199 °C; 28 mg, yield 6%; $R_f = 0.56$ (silica gel plate, PE/EA = 5:1, ν/ν). ¹H NMR (400 MHz, CDCl₃) δ 7.35–7.21 (m, 18H), 7.05–7.01 (m, 2H), 4.84 (d, *J* = 2.1 Hz, 2H), 3.21 (td, *J* = 7.7, 2.2 Hz, 2H), 2.49 (t, *J* = 7.8 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 166.6, 137.5, 137.3, 129.12, 129.06, 128.5, 125.8, 124.0, 117.0, 60.9, 58.8, 28.2. IR (cm⁻¹) 1660.2; EI-MS m/z = 458 [M⁺]; ESI-HRMS calcd for C₃₁H₂₇N₂O₂, m/z = 459.2067 [M + H]⁺; found, 459.2063.

meso-3,3'-(Methylene)bis(trans-1,4-diphenylazetidin-2one) (meso-**8***a*). White crystals, mp 262–264 °C; 24 mg, yield 5%; $R_f = 0.55$ (silica gel plate, PE/EA = 5:1, v/v). ¹H NMR (400 MHz, CDCl₃) δ 7.34–7.19 (m, 18H), 7.05–7.02 (m, 2H), 4.90 (d, J = 2.4 Hz, 2H), 3.38 (td, J = 7.7, 2.4 Hz, 2H), 2.52 (t, J = 7.8 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 166.5, 137.3, 137.2, 129.2, 129.02, 128.96, 125.5, 124.0, 117.1, 59.9, 57.6, 26.4. IR (cm⁻¹) 1660.3; EI-MS m/z = 458 [M⁺]; ESI-HRMS calcd for C₃₁H₂₇N₂O₂, m/z = 459.2067 [M + H]⁺; found, 459.2065.

meso-3,3'-(1,4-Butylidene)bis(trans-1,4-diphenylazetidin-2-one) (meso-**8b**) and rel(35,3'5,4R,4'R)-3,3'-(1,4-Butylidene)bis(1,4-diphenylazetidin-2-one) ((±)-**8b**). White crystals, mp 168–174 °C; 60 mg, yield 12%; ¹H NMR (400 MHz, CDCl₃) δ 7.42–7.17 (m, 18H), 7.08–6.96 (m, 2H), 4.60 (s, 2H), 3.07 (t, *J* = 6.8 Hz, 2H), 2.04–1.76 (m, 4H), 1.61–1.46 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 167.6, 138.1, 137.7, 129.2, 129.0, 128.4, 125.8, 123.7, 116.9, 61.1, 60.5, 28.6, 27.1. IR (cm⁻¹) 1659.7; EI-MS *m*/*z* = 500 [M⁺]; ESI-HRMS calcd for C₃₄H₃₃N₂O₂, *m*/*z* = 501.2537 [M + H]⁺; found, 501.2545.

meso-3,3'-(1,5-Pentylidene)bis(trans-1,4-diphenylazetidin-2-one) (meso-8c) and rel(35,3'5,4R,4'R)-3,3'-(1,5-Pentylidene)bis(1,4-diphenylazetidin-2-one) ((±)-8c). White crystals, mp 126–130 °C; 60 mg, yield 12%; ¹H NMR (400 MHz, CDCl₃) δ 7.49–7.19 (m, 18H), 7.10–6.96 (m, 2H), 4.64 (s, 2H), 3.06 (t, J = 6.5 Hz, 2H), 2.04–1.73 (m, 4H), 1.63– 1.44 (m, 4H), 1.42–1.29 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 167.8, 138.1, 137.7, 129.2, 129.0, 128.4, 125.8, 123.7, 116.9, 61.1, 60.5, 29.4, 28.7, 26.9. IR (cm⁻¹) 1661.9; EI-MS $m/z = 514 [M^+]$; ESI-HRMS calcd for C₃₅H₃₅N₂O₂, $m/z = 515.2693 [M + H]^+$; found, 515.2703.

Preparation of 1,6-Bis(diazo)-2,5-hexanedione (9). To a solution of diazomethane (approximate 25 mmol) in diethyl ether (50 mL) was added calcium oxide (1.23 g), and then a solution of succinic dichloride (1.54 g, 10 mmol) in dry diethyl ether (10 mL) at -40 °C was added. The resulting solution was stirred for 5 h and was allowed to warm to room temperature. Excess diazomethane was destroyed by addition of acetic acid. The mixture was concentrated under reduced pressure, and the residue was dissolved in diethyl ether. The organic phase was washed successively with saturated sodium bicarbonate solution, 10% aq citric acid, and brine and was dried over Na₂SO₄. After removal of solvent, the residue was purified on silica gel column with a mixture of petroleum ether (30–60 °C)/ethyl acetate (8:1, v/v) to afford brown crystals, mp 62– 63 °C (lit.²² mp 62–63 °C); 129 mg, yield 7.8%; ¹H NMR (400 MHz, CDCl₃) δ 5.34 (s, 2H), 2.69 (s, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 193.1, 54.7, 34.8.

ASSOCIATED CONTENT

Supporting Information

Copies of ¹H NMR and ¹³C NMR spectra of the products and computational details. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.Sb00573.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The project was supported by the National Basic Research Program of China (No. 2013CB328905), the National Natural Science Foundation of China (Nos. 21372025, 21172017, and 20772005), the specialized Research Fund for the Doctoral Program of Higher Education, Ministry of Education of China (No. 20110010110011), and "CHEMCLOUDCOMPUTING" of Beijing University of Chemical Technology.

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