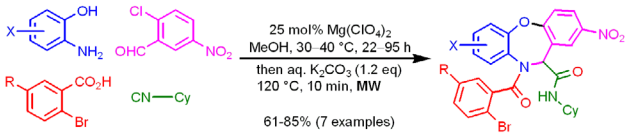
Research Article **Open Access**

Jialu Luo, Jinlong Wu, Wei-Min Dai*

One-Pot Synthesis of Dibenz[*b*,*f*][1,4]oxazepines via $Mg(ClO_4)_2$-Catalyzed Ugi Four-Component Reaction and Microwave-Assisted Intramolecular S_NAr

Abstract: A general one-pot synthesis of dibenz[*b*,*f*][1,4]oxazepine-11(10*H*)-carboxamides is described. The Ugi four-component reaction (U-4CR) of 2-aminophenols, cyclohexyl isocyanide, 2-chloro-5-nitrobenzaldehyde, and 2-bromobenzoic acids in MeOH in the presence of 25 mol% $Mg(ClO_4)_2$ at 30–40 ºC for 22–95 h gave the linear Ugi products. The latter were treated with aqueous K_2CO_3 in MeOH under microwave heating at 120 ºC for 10 min for promoting the intramolecular nucleophilic aromatic substitution (S_NAr), affording the 6/7/6-fused tricyclic heterocycles in 61–85% yields.



Keywords: dibenz[*b*,*f*][1,4]oxazepine, Lewis acid, microwave, multicomponent reactions, nucleophilic aromatic substitutions

Doi: 10.2478/dos-2014-0001
received May 17, 2014; accepted June 20, 2014

1 Introduction

Ugi four-component reaction (U-4CR) is the most valuable isocyanide-based multicomponent reaction (IMCR) for generating molecular diversity [1-3]. Manipulation with the acid, amine, isocyanide, and oxo inputs can provide numerous opportunities for accessing novel molecular entity [4]. Moreover, the linear Ugi products, α-acylaminoamides, can be converted into cyclic scaffolds through a variety of conventional and metal-catalyzed reactions [5-7]. These post-Ugi transformations have been developed as one-pot processes and tandem sequences for achieving high synthetic efficiency. In recent years controlled microwave heating has been established as an enabling technology for expanding the capability of chemical synthesis with remarkable efficiency [8-11]. Integration of microwave heating with U-4CR and post-Ugi transformations offers a promising strategy for generation of molecular diversity in a manner fulfilling the green chemistry principles [12].

In our previous work, we demonstrated that highly functionalized 3,4-dihydro-3-oxo-2*H*-1,4-benzoxazines (structure not shown) and dibenz[*b*,*f*][1,4]oxazepin-11(10*H*)-ones **1** could be synthesized by microwave-assisted one-pot U-4CR and intramolecular S_N2 and S_NAr processes, respectively (Figure 1) [13-16]. By incorporating additional functionalities within **1**, the novel 2-oxindole conjugates **2** were assembled by microwave-assisted Pd-catalyzed intramolecular amidation [15] while the 1,3-dihydro-2*H*-3-benzazepin-2-one conjugates **3** could be constructed by Pd-catalyzed intramolecular hydroamidation of alkynes [16]. We also found that the microwave-assisted U-4CR–S_NAr process starting 2-amino-4-methylphenol, 2-chloro-5-nitrobenzaldehyde, cyclohexyl isocyanide with benzoic and 2-halobenzoic acids afforded, in a pK_a-dependent manner, dibenz[*b*,*f*][1,4]oxazepine-11(10*H*)-carboxamides **4** in 17–49% yields [15]. The highest yield (49%) of **4** (X = Br) was obtained for 2-bromobenzoic acid. We report here on a comparative study on the U-4CR of substituted 2-aminophenols under microwave heating and Lewis acid catalysis. The latter has been incorporated with our microwave-assisted intramolecular S_NAr to provide a one-pot process for efficient synthesis of dibenz[*b*,*f*][1,4]oxazepine-11(10*H*)-carboxamides.

***Corresponding author: Wei-Min Dai:** Laboratory of Advanced Catalysis and Synthesis, Department of Chemistry, The Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong SAR, P. R. of China, Fax: +852-23581594;
E-mail: chdai@ust.hk
Jialu Luo, Jinlong Wu, Wei-Min Dai: Laboratory of Asymmetric Catalysis and Synthesis, Department of Chemistry, Zhejiang University, Hangzhou 310027, P. R. of China

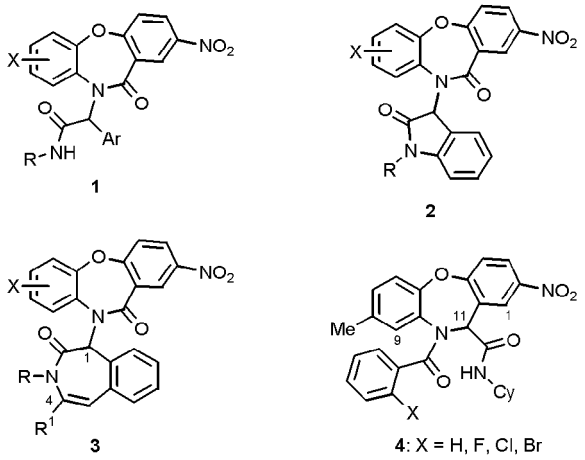
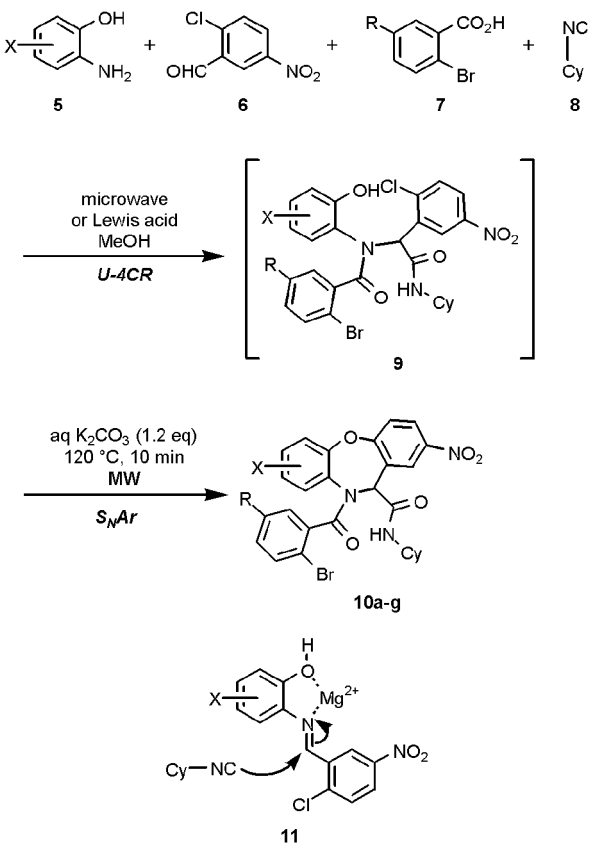


Figure 1. Structures of dibenz[*b*,*f*][1,4]oxazepines and the C–N bond-linked conjugates.



Scheme 1. Synthesis of dibenz[*b*,*f*][1,4]oxazepines **10a**–**g** via one-pot U-4CR and microwave-assisted intramolecular S_NAr.

2 Results and Discussion

We first examined the reactions of 2-aminophenols **5** with 2-chloro-5-nitrobenzaldehyde **6**, 2-bromobenzoic acid (**7**, R = H), and cyclohexyl isocyanide **8** *in the absence of a Lewis acid*. The U-4CR was heated with microwave irradiation at 60 ºC for 30 min followed by treating the Ugi product with aqueous K_2CO_3 under microwave heating at 120 ºC for 10 min to furnish the tricyclic products **10a**–**e** (Scheme 1). The results are summarized in Table 1 (entries 1–5).

Table 1. One-pot synthesis of dibenz[*b*,*f*][1,4]oxazepine-11(10*H*)-carboxamides **10** via microwave-assisted and Lewis acid-catalyzed U-4CR.

Entry	Product	R	X[a]	Microwave heating[b]	With $Mg(ClO_4)_2$[d]		mp (ºC)[e]
				Yield (%)	*t* (h)	Yield (%)	
1	**10a**	H	H	57	95	61	228–229
2	**10b**	H	8-Me	49	44	68	210–212
3	**10c**	H	8-Ph	36 (36[c])	95	69	269–270
4	**10d**	H	8-Cl	20 (33[c])	63	85	218–220
5	**10e**	H	6,8-Me_2	48 (41[c])	166[f]	67	230–232
6	**10f**	H	7-Me	–	44	80	214–215[g]
7	**10g**	OMe	8-Cl	–	22	66	235–236[g]

[a] The dibenz[*b*,*f*][1,4]oxazepine skeleton numbering is used.
[b] The U-4CR was carried out in MeOH (3 mL) at 60 ºC for 30 min under microwave heating. After adding 1.2 equiv of aq. K_2CO_3 (1 mL H_2O), the mixture was heating again at 120 ºC for 10 min under microwave irradiation.
[c] The U-4CR was carried out at 80 ºC for 30 min and other operation was the same as described in the footnote (b).
[d] The U-4CR was carried out in the presence of 25 mol% $Mg(ClO_4)_2$ in MeOH (3 mL) at 30–40 ºC for the indicated time in an oil bath. After adding 1.2 equiv of aq. K_2CO_3 (1 mL H_2O), the mixture was heating at 120 ºC for 10 min under microwave irradiation.
[e] Recrystallized from EtOAc–hexane.
[f] Without the Lewis acid.
[g] Recrystallized from CH_2Cl_2–hexane.

In general, the substituted 2-aminophenols **5** gave lower yields of 20–49% for **10b**–**e** as compared to 57% yield for **10a**. Increase of the Ugi reaction temperature to 80 ºC afforded mixed results with no significant improvement in the yields of **10c**–**e** (entries 3–5, Table 1). We attributed these poor results to the electron-deficient imines, formed between **5** and the nitrobenzaldehyde **6**, which was not readily activated through protonation toward the addition by an isocyanide [13]. Besides the use of stronger acid inputs as demonstrated in the formation of **4**, we envisaged that Lewis acids might offer an alternative activation method for the U-4CR involving electron-deficient imines [17-20].

We carried out the Ugi reaction of 2-bromo-5-methoxybenzoic acid (**7**, R = OMe) at 60 ºC in MeOH for screening Lewis acid catalysts. When a catalytic amount of $TiCl_4$ was applied [17,19,20], the target heterocycle **10g** was obtained in 33% yield (entry 1, Table 2). Activation of imines by rare earth metal triflates such as $Yb(OTf)_3$ in the aza-Diels–Alder reactions involving 2-aminophenols has been reported [21-23]. We employed 25 mol% of $Yb(OTf)_3$ in the same Ugi reaction at 60 ºC for 24 h, affording **10g** in 34% yield (entry 2, Table 2). In contrast, $In(OTf)_3$ and $Sn(OTf)_3$ were much less efficient as the catalysts (entries 3 and 4, Table 2). It was found that $Mg(ClO_4)_2$ [20,24,25] was the best catalyst among all tested Lewis acids and the product **10g** was produced in 45% yield (entry 5, Table 2). The latter could be further improved to 66% by conducting the Ugi reaction at 30–40 ºC for 22 h followed by the base treatment at 120 ºC for 10 min under microwave irradiation (entry 6, Table 2). It is considered that the Mg(II) complex **11** enhances the polarity of the imine moiety and it might be responsible for the observed higher reactivity of the imine formed from the electron-deficient aldehyde **6** [26].

Table 2. Effect of Lewis acid on U-4CR.

Entry	Lewis acid[a]	*t* (h)	10g: Yield (%)
1	$TiCl_4$[b]	42	33
2	$Yb(OTf)_3$	24	34
3	$In(OTf)_3$	24	12
4	$Sn(OTf)_3$	24	5
5	$Mg(ClO_4)_2$	24	45
6	$Mg(ClO_4)_2$	22[c]	66

[a] The U-4CR was carried out in the presence of 25 mol% of the Lewis acid in MeOH (3 mL) at 60 ºC for 24 h in an oil bath. The conditions for the following S_NAr were the same as given in the footnote (a) of Table 1.
[b] Two drops were added.
[c] The U-4CR was carried out at 30–40 ºC.

The $Mg(ClO_4)_2$-catalyzed U-4CR of **5**–**8** at 30–40 ºC in MeOH was confirmed to be general and the results are summarized in Table 1. By adjusting the Ugi reaction time between 22–95 h, the tricyclic products **10a**–**d**,**f**,**g** could be synthesized by the one-pot process in 61–85% yields (Table 1, entries 1–4, 6, and 7). In the case of **10e**, a comparable yield of 67% was obtained without use of the Lewis acid although much longer reaction time (166 h) was required for the Ugi reaction (Table 1, entry 5). Therefore, it is apparent that Lewis acids can significantly shorten the duration of the U-4CR involving electron-deficient imine species. It should be mentioned that the long reaction times required for the U-4CR originated from the electron-deficient imine species formed from aromatic amine and aromatic aldehyde inputs [13]. Higher reaction temperatures with or without microwave irradiation might shorten the reaction times with good yields [13,15] but the opposite was observed in the current study (entry 5 vs. entry 6, Table 2). Use of solvents other than MeOH might be considered. But, the same reaction in MeOH and MeCN might give different product distributions [20]. The non-conventional solvents such as trifluoroethanol [CF_3CH_2OH] might be used but its higher cost than MeOH is not suitable for general use and was not examined in this study. Activation of $Mg(ClO_4)_2$ on the intramolecular S_NAr might be possible by coordination with the nitro group. However, this scenario might be ruled out, or if any, minimum on the basis that the same intramolecular S_NAr could complete under the same microwave heating conditions in the absence of the Lewis acid [15].

3 Conclusion

We have studied the Ugi four-component reaction involving substituted 2-aminophenols and 2-chloro-5-nitrobenzaldehdye, as the amine and oxo inputs, under microwave heating and Lewis acid catalysis, respectively. We found that temperatures higher than 60 °C gave inferior results while a Lewis acid, such as $Mg(ClO_4)_2$, enables activation of the electron-deficient imine species, resulting in short reaction times and higher yields. By using the one-pot $Mg(ClO_4)_2$-catalyzed U-4CR and the microwave-assisted intramolecular S_NAr protocol, we have established a general and efficient synthesis of dibenz[*b,f*][1,4]oxazepine-11(10*H*)-carboxamides **10a**–**g**. Moreover, our results concur with the early observations on the Lewis acid-catalyzed isocyanide-based multicomponent reactions [17–20] which may offer alternative reaction pathways or end products.

4 Experimental Section

4.1 General Methods

Melting points are not corrected. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer (for ^{1}H or 100 MHz for ^{13}C) in $CDCl_3$ with residual $CHCl_3$ as the internal reference. IR spectra were taken on a FTIR spectrophotometer. Mass spectra (MS) were measured by the +ESI, +TOF, or +FAB method. Elemental analyses were performed by Zhejiang University. All microwave-assisted reactions were carried out in closed vials on a technical microwave reactor with the temperature measured by an IR sensor. The microwave-assisted reaction time is the hold time at the final temperature. Silica gel plates pre-coated on glass were used for thin-layer chromatography using UV light, or 7% ethanolic phosphomolybdic acid and heating as the visualizing methods. Silica gel and petroleum ether (PE; bp 60–90 ºC) were used for flash column chromatography. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials.

4.2 General Procedure for One-Pot Synthesis of 10a–g.

To a 10-mL pressurized process vial were added sequentially 2-aminophenol **5** (0.50 mmol), 2-chloro-5-nitrobenzaldehyde **6** (0.50 mmol), 2-bromobenzoic acid **7** (0.55 mmol), $Mg(ClO_4)_2$ (0.125 mmol), and MeOH (3 mL). To the resultant mixture, cyclohexyl isocyanide **8** (0.55 mmol) was then added. The vial was then sealed with a cap containing a silicon septum and heated at 30–40 ºC in an oil bath for 22–95 h. Then, an aqueous solution of K_2CO_3 (1.5 mL, 0.6 mmol) was added to the reaction vial through a syringe followed by heating at 120 ºC for 10 min in the cavity of microwave reactor. Water was added to the reaction mixture and the resultant mixture was extracted with EtOAc (10 mL × 3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and condensed under reduced pressure. The residue was purified by column chromatography on silica gel eluted with EtOAc–PE or CH_2Cl_2–PE to afford the U-4CR product **10**.

*Note: Due to rotation of the two amide moieties at C10 and C11, the compounds **10** exhibit atropisomerism in $CDCl_3$ so that one or two aromatic carbon signal(s) cannot be seen in the ^{13}C NMR spectra.* ***N*-Cyclohexyl 10-(2'-Bromobenzoyl)dibenz[*b*,*f*][1,4]oxazepine-11(10*H*)-carboxamide (10a).** A pale yellow solid; R_f = 0.20 (25% EtOAc in PE). IR (KBr): 3292, 2931, 2854, 1685, 1646, 1523, 1343, 1325, 1266 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19–8.16 (m, 1H), 8.16 (s, 1H), 7.52–7.50 (m, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.21–7.13 (m, 5H), 7.02 (d, *J* = 8.0 Hz, 1H), 6.91–6.89 (m, 1H), 6.86 (s, 1H), 6.23–6.21 (m, 1H, N*H*), 3.66–3.61 (m, 1H), 1.86–1.51 (m, 5H), 1.32–1.23 (m, 2H) , 1.18–1.11 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.0, 165.6, 158.5, 151.7, 142.9, 136.2, 132.9, 131.1, 130.0, 129.3 (br), 128.1 (br), 127.7, 127.2, 125.3 (br), 124.8, 123.5, 122.2, 121.5, 120.4 (br), 60.2, 49.0, 33.1, 32.9, 25.3, 24.7 (2×) (one aromatic carbon is not seen). MS (+ESI): *m/z* (%) = 574 (M+2+Na$^+$, 100), 572 (M+Na$^+$, 97), 552 (M+2+H$^+$, 64), 550 (M+H$^+$, 60). Anal. Calcd for $C_{27}H_{24}BrN_3O_5$: C, 58.92; H, 4.40; N, 7.63. Found: C, 58.95; H, 4.39; N, 7.71.

***N*-Cyclohexyl 10-(2'-Bromobenzoyl)-8-methyldibenz[*b*,*f*][1,4]oxazepine-11(10*H*)-carboxamide (10b).** A white solid; R_f = 0.41 (33% EtOAc in PE). IR (KBr): 3291, 2931, 2854, 1685, 1669 (br), 1583, 1523, 1506, 1344, 1326, 1267 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16–8.14 (m, 1H), 8.14 (s, 1H), 7.52–7.50 (m, 1H), 7.34 (d, *J* = 9.6 Hz, 1H), 7.24–7.07 (m, 3H), 7.06 (d, *J* = 8.4 Hz, 1H), 6.94 (d, *J* = 8.0 Hz, 1H), 6.86 (s, 1H), 6.85 (d, *J* = 6.8 Hz, 1H), 6.42 (d, *J* = 8.4 Hz, 1H, N*H*), 3.64–3.57 (m, 1H), 2.06 (s, 3H), 1.78–1.50 (m, 5H), 1.31–1.00 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.9, 165.6, 158.7, 149.5, 142.7, 136.4, 135.0 (br), 132.8, 131.0, 130.5, 129.6 (br), 128.0 (br), 127.6, 127.1, 124.6, 123.5, 122.1, 120.9, 120.2, 60.2, 48.8, 33.0, 32.7, 25.3, 24.7, 24.7, 20.3 (one aromatic carbon is not seen). MS (+ESI): *m/z* (%) = 588 (M+2+Na$^+$, 100), 586 (M+Na$^+$, 86), 566 (M+2+H$^+$, 42), 564 (M+H$^+$, 43). Anal. Calcd for $C_{28}H_{26}BrN_3O_5$: C, 59.58; H, 4.64; N, 7.44. Found: C, 59.57; H, 4.65; N, 7.45.

***N*-Cyclohexyl 10-(2'-Bromobenzoyl)-8-phenyldibenz[*b*,*f*][1,4]oxazepine-11(10*H*)-carboxamide (10c).** A white solid; R_f = 0.44 (33% EtOAc in PE). IR (KBr): 3292, 2931, 2853, 1685, 1654, 1518, 1485, 1343, 1329 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20 (s, 1H), 8.20–8.17 (m, 1H), 7.56 (br s, 1H), 7.46–7.10 (m, 12H), 6.92 (s, 1H), 6.48 (d, *J* = 6.8 Hz, 1H, N*H*), 3.60–3.50 (m, 1H), 1.80–1.40 (m, 5H), 1.28–0.88 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.9, 165.5, 158.5, 150.6, 142.7, 138.6, 138.0 (br), 136.5, 132.8, 131.1, 128.8 (3×), 128.2, 127.6, 127.4, 127.3, 126.5 (2×), 124.8, 123.6, 122.1, 121.6, 120.2 (br), 60.4 (br), 48.7, 32.9, 32.5, 25.2, 24.5, 24.4 (two aromatic carbons are not seen). MS (+ESI): *m/z* (%) = 650 (M+2+Na$^+$, 100), 648 (M+Na$^+$, 90), 628 (M+2+H$^+$, 62), 626 (M+H$^+$, 53). Anal. Calcd for $C_{33}H_{28}BrN_3O_5$: C, 63.27; H, 4.50; N, 6.71. Found: C, 63.19; H, 4.51; N, 6.73.

***N*-Cyclohexyl 10-(2'-Bromobenzoyl)-8-chlorodibenz[*b*,*f*][1,4]oxazepine-11(10*H*)-carboxamide (10d).** A yellow solid; R_f = 0.46 (33% EtOAc

in PE). IR (KBr): 3288, 2933, 2855, 1684, 1654, 1526, 1491, 1347, 1323, 1263 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.16 (d, *J* = 9.5 Hz, 1H), 8.14 (s, 1H), 7.54 (br s, 1H), 7.35 (d, *J* = 8.8 Hz, 1H), 7.25–7.09 (m, 5H), 7.03 (br s, 1H), 6.85 (s, 1H), 6.50 (d, *J* = 7.6 Hz, 1H, N*H*), 3.66–3.52 (m, 1H), 1.81–1.46 (m, 5H), 1.35–0.99 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.7, 165.3, 158.1, 150.2, 142.9, 135.9, 133.0, 131.4, 129.9, 129.8 (br), 129.3 (br), 128.0 (br), 127.4, 127.3, 124.8, 123.5, 122.4, 122.1, 120.0 (br), 60.2, 48.9, 33.0, 32.6, 25.2, 24.6 (2×) (one aromatic carbon is not seen). MS (+ESI): *m/z* (%) = 610 ($M+4+Na^+$, 23), 608 ($M+2+Na^+$, 85), 606 ($M+Na^+$, 59), 588 ($M+4+H^+$, 26), 586 ($M+2+H^+$, 100), 584 ($M+H^+$, 71). Anal. Calcd for $C_{27}H_{23}BrClN_3O_5$: C, 55.45; H, 3.96; N, 7.18. Found: C, 55.50; H, 4.23; N, 7.20.

***N*-Cyclohexyl 10-(2'-Bromobenzoyl)-6,8-dimethyldibenz[*b*,*f*][1,4]oxazepine-11(10*H*)-carboxamide (10e).** A white solid; R_f = 0.42 (33% EtOAc in PE). IR (KBr): 3287, 2931, 2855, 1691, 1669, 1632, 1523, 1480, 1343, 1249, 1232 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.17–8.13 (m, 2H), 7.55–7.52 (m, 1H), 7.39 (d, *J* = 8.8 Hz, 1H), 7.15–7.12 (m, 3H), 6.85 (s, 1H), 6.82 (s, 1H), 6.70 (s, 1H), 6.33 (d, *J* = 8.0 Hz, 1H, N*H*), 3.74–3.62 (m, 1H), 2.31 (s, 3H), 2.03 (s, 3H), 1.91–1.55 (m, 5H), 1.36–1.10 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.2, 165.9, 158.6, 148.3, 142.9, 136.4, 134.6, 132.8, 132.3, 131.0, 130.4, 130.1 (br), 128.0, 127.9 (br), 127.2, 126.8 (br), 124.5, 124.0, 122.0, 120.4, 59.8, 48.9, 33.2, 32.9, 25.3, 24.8 (2×), 20.4, 16.2. MS (+ESI): *m/z* (%) = 602 ($M+2+Na^+$, 98), 600 ($M+Na^+$, 100). Anal. Calcd for $C_{29}H_{28}BrN_3O_5$: C, 60.21; H, 4.88; N, 7.26. Found: C, 60.20; H, 4.94; N, 7.29.

***N*-Cyclohexyl 10-(2'-Bromobenzoyl)-7-methyldibenz[*b*,*f*][1,4]oxazepine-11(10*H*)-carboxamide (10f).** A white crystals; R_f =0.35 (33% EtOAc in hexane). IR (film): 3312, 2930, 2855, 1648 (br), 1523, 1513, 1343, 1325 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.18–8.14 (m, 1H), 8.14 (s, 1H), 7.53–7.49 (m, 1H), 7.35 (d, *J* = 8.7 Hz, 1H), 7.20–7.10 (m, 3H), 7.00 (s, 1H), 6.89 (d, *J* = 8.1 Hz, 1H), 6.84 (s, 1H), 6.68 (d, *J* = 8.1 Hz, 1H), 6.28 (d, *J* = 7.8 Hz, 1H, N*H*), 3.73–3.55 (m, 1H), 2.22 (s, 3H), 1.92–1.50 (m, 5H), 1.38–1.00 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.9, 165.6, 158.5, 151.2, 142.7, 140.5, 136.3, 132.8, 130.8, 128.6 (br), 128.0 (br), 127.6, 127.1, 126.0, 124.5, 123.5, 122.1, 121.8, 120.2 (br), 60.3, 49.0, 33.2, 33.0, 25.4, 24.8 (2×), 21.1 (one aromatic carbon is not seen). MS (+TOF): *m/z* (%) = 566 ($M+2+H^+$, 47), 564 ($M+H^+$, 44), 467 (M^++2–CyNH, 100), 465 (M^+–CyNH, 99). Anal. Calcd for $C_{28}H_{26}BrN_3O_5$: C, 59.58; H, 4.64; N, 7.44. Found: C, 59.86; H, 4.69; N, 7.41.

***N*-Cyclohexyl 10-(2'-Bromo-5'-methoxybenzoyl)-8-chlorodibenz[*b*,*f*][1,4]oxazepine-11(10*H*)-carboxamide (10g).** A white crystals; R_f =0.35 (33% EtOAc in hexane). IR (film): 3303, 2934, 2855, 1653 (br), 1525, 1480, 1345, 1322, 1290, 1263, 1235 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.20–8.13 (m, 2H), 7.41 (d, *J* = 8.7 Hz, 1H), 7.36 (d, *J* = 9.0 Hz, 1H), 7.20–7.11 (m, 2H), 7.05 (br s, 1H), 6.80 (s, 1H), 6.50–6.63 (m, 2H), 6.19 (d, *J* = 7.5 Hz, 1H, N*H*), 3.68 (s, 3H), 3.68–3.51 (m, 1H), 1.90–1.51 (m, 5H), 1.40–1.10 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.5, 165.3, 158.7, 158.1, 150.4, 143.1, 136.4, 133.9, 130.1 (br), 129.3 (br), 127.6, 124.9, 123.4, 122.4, 122.1, 117.5, 113.4 (br), 110.5, 60.2, 55.6, 49.0, 33.1, 32.8, 25.3, 24.7 (2×) (two aromatic carbons are not seen). MS (+FAB): *m/z* (%) = 618 ($M+4+H^+$, 20), 616 ($M+2+H^+$, 84), 614 ($M+H^+$, 100). Anal. Calcd for $C_{28}H_{25}BrClN_3O_6$: C, 54.69; H, 4.10; N, 6.83. Found: C, 54.75; H, 4.19; N, 6.51.

Supporting Information for this article is available online at http://http://www.degruyter.com/view/j/dos.2014.1.issue-1/dos-2014-0001/suppl/dos-2014-0001_sm.pdf. Included are the copies of ^1H and ^{13}C NMR spectra of the products **10a**–**g**.

Acknowledgment: The Laboratory of Asymmetric Catalysis and Synthesis is established under the Cheung Kong Scholars Program of The Ministry of Education of China. This work is supported in part by the research grants from The National Natural Science Foundation of China (Grant No. 20672092), Zhejiang University, and Zhejiang University Education Foundation.

References

[1] (a) Dömling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168–3210. (b) Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89.
[2] *Multicomponent Reactions*; Zhu, J.; Bienayme, H., Eds.; Wiley-VCH: Weinheim, **2005**.
[3] Sadjadi, S.; Heravi, M. M. *Tetrahedron* **2011**, *67*, 2707–2752.
[4] (a) El Kaïm, L.; Grimaud, L. *Tetrahedron* **2009**, *65*, 2153–2171. (b) van der Heijden, G.; Ruijter, E.; Orru, R. V. A. *Synlett* **2013**, *24*, 666–685.
[5] Akritopoulou-Zanze, I.; Djuric, S. W. *Heterocycles* **2007**, *73*, 125–147.
[6] (a) Sunderhaus, J. D.; Martin, S. F. *Chem. Eur. J.* **2009**, *15*, 1300–1308. (b) Banfi, L.; Riva, R.; Basso, A. *Synlett* **2010**, 23–41. (c) Koopmanschap, G.; Ruijter, E.; Orru, R. V. A. *Beilstein J. Org. Chem.* **2014**, *10*, 544–598.
[7] Dai, W.-M. *Diversity Oriented Synthesis* **2012**, *1*, 11–20.
[8] (a) Kappe, C. O. *Angew. Chem. Int. Ed.* **2004**, *43*, 6250–6284. (b) de la Hoz, A.; Díaz-Ortiz, Á, Moreno, A. *Chem. Soc. Rev.* **2005**, *34*, 164–178.
[9] (a) Dai, W.-M.; Shi, J. *Comb. Chem. High Throughput Screening* **2007**, *10*, 837–856. (b) Appukkuttan, P.; Van der Eycken, E. *Eur.*

J. Org. Chem. **2008**, 1133–1155. (c) Abid, M.; Török, B.; Huang, X. *Aust. J. Chem.* **2009**, *62*, 208–222.

[10] (a) Kappe, C. O.; Dallinger, D. *Mol. Divers.* **2009**, *13*, 71–193. (b) Hügel, H. M. *Mol. Divers.* **2009**, *14*, 4936–4972. (c) Caddick, S.; Fitzmaurice, R. *Tetrahedron* **2009**, *65*, 3325–3355. (d) Bassyouni, F. A.; Abu-Bakr, S. M.; Rehim, M. A. *Res. Chem. Intermed.* **2012**, *38*, 283–322.

[11] (a) Kappe, C. O; Damm, M. *Mol. Divers.* **2012**, *16*, 5–25. (b) Kappe, C. O.; Pieber, B.; Dallinger, D. *Angew. Chem. Int. Ed.* **2013**, *52*, 1088–1094. (c) Kappe, C. O. *Acc. Chem. Res.* **2013**, *46*, 1579–1587.

[12] Anstas, P. T.; Warner, J. C. Green Chemistry: Theory and Practice; Oxford University Press: New York, **1998**.

[13] Xing, X.; Wu, J.; Feng, G.; Dai, W.-M. *Tetrahedron* **2006**, *62*, 6774–6781.

[14] Feng, G.; Wu, J.; Dai, W.-M. *Tetrahedron Lett.* **2007**, *28*, 401–404.

[15] Xing, X.; Wu, J.; Luo, J.; Dai, W.-M. *Synlett* **2006**, 2099–2103.

[16] Wu, J.; Jiang, Y.; Dai, W.-M. *Synlett* **2009**, 1162–1166.

[17] Godet, T.; Bonvin, Y.; Vincent, G.; Merle, D.; Thozet, A. Ciufolini, M. A. *Org. Lett.* **2004**, *6*, 3281–3284.

[18] Okandeji, B. O.; Gordon, J. R.; Sello, J. K. *J. Org. Chem.* **2008**, *73*, 5595–5597.

[19] Kusebauch, U.; Beck, B.; Messer, K.; Herdtweck, E.; Dömling, A. *Org. Lett.* **2003**, *5*, 4021–4024.

[20] Dai, W.-M.; Li, H. *Tetrahedron* **2007**, *63*, 12866–12876.

[21] Ma, Y.; Qian, C.; Xie, M.; Sun, J. *J. Org. Chem.* **1999**, *64*, 6462–6467.

[22] Xing, X.; Wu, J.; Dai, W.-M. *Tetrahdron* **2006**, *62*, 11200–11206.

[23] For a review, see: Kouznetsov, V. V. *Tetrahedron* **2009**, *65*, 2721–2750.

[24] El Kaïm, L.; Grimaud, L.; Oble, J. *Angew. Chem. Int. Ed.* **2005**, *44*, 7961–7964.

[25] Wu, C.; Shen, R.; Chen, J.; Hu, C. *Bull. Korean Chem. Soc.* **2013**, *34*, 2431–2435.

[26.] (a) Shaabani, A.; Keshipour, S.; Shaabani, S.; Mahyari, M. *Tetrahedron Lett.* **2012**, *53*, 1641–1644. (b) Chéron, N.; Ramozzi, R.; El Kaïm, L.; Grimaud, L.; Fleurat-Lessard, P. *J. Org. Chem.* **2012**, *77*, 1361–1366.