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Developments in Meyers' Lactamization Methodology: En Route to Bi(hetero)aryl Structures with Defined Axial Chirality

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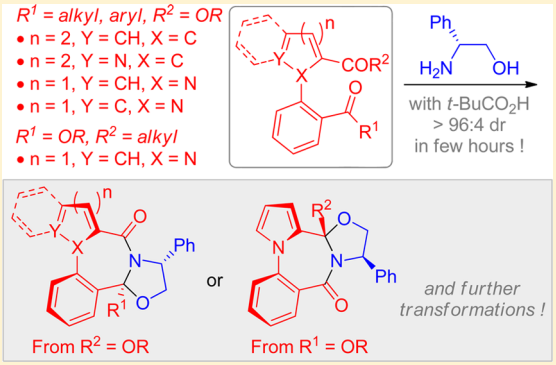
Supporting Information

ABSTRACT: Highly atroposelective Meyers' lactamization promoted by pivalic acid under microwave irradiation is reported which allows the construction of nonracemic substituted-dibenzo(di)azepine derivatives through a center to axial chirality transfer principle, controlling the otherwise configurationally labile biaryl axis. This approach provides a straightforward entry to enantioenriched analogues of biorelevant architectures.



Among the privileged biaryl architectures in pharmaceutical ingredients,[1] the dibenzazepine and dibenzodiazepine derivatives of type **1** occupy a significant place (Figure 1).

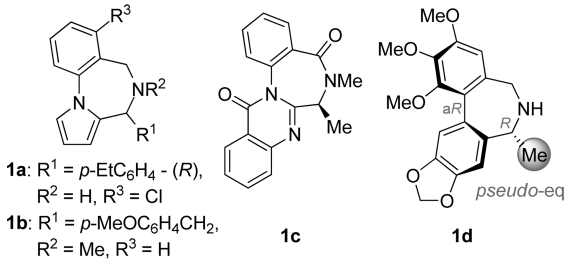


Figure 1. Dibenzo(di)azepine derivatives.

The −($CH_2NR^2CHR^1$−) bridge not only affords opportunities for structure/activity modulation but belongs to a seven-membered ring whose conformation dictates both the dihedral angle and the absolute configuration of the biaryl axis. Consequently, a substituent, either pseudoequatorial or pseudoaxial, at the α-position of the nitrogen atom may lead to a central/axial chirality communication establishing a well-defined 3D-topology (Figure 1),[2,3] a crucial feature for the design of either catalysts or atropoisomeric bioligands.[4] For instance, along with the large family of benzodiazepines as therapeutics targeting central nervous system disorders, the racemic phenyl-substituted pyrrolobenzodiazepine **1a** and benzyl-substituted homologue **1b** displayed promising anti-fungal and antinociceptive activities, respectively.[5−7] Circumdatin F (**1c**) and homologues belong to naturally occurring quinazolinone alkaloids with a large array of biological activities.[8] Their stereoselective construction is mainly based on amino acid precursors following a chiral pool strategy. On the other hand, Baudoin and co-workers described an original and enantioselective synthesis of a 5-methyl-6,7-dihydro-5*H*-dibenzo[*c*,*e*]azepine **1d**, analogue of allocolchicine, manifesting an *aR* chiral axis as a direct consequence of the C-5 pseudoequatorial position adopted by the methyl group connected to a *R* stereogenic center.[9,10] Actually, the synthesis of enantiopure dibenzo(dia)zepines of type **1** via diastereoselective or enantioselective methodologies is not common despite the benefit of such skeletons for the elaboration of axially chiral ligands or biorelevant compounds.[4] In that context, the pioneered development of nonracemic 5,7-dimethyl-6,7-dihydro-5*H*-dibenzo[*c*,*e*]azepine as a chiral lithium amide base precursor by Kündig is noteworthy.[11] Recently, a larger array of 5-substituted dibenzazepines was described by Page and co-workers through a chiral auxiliary-based approach. Thus, a diastereoselective addition reaction of Grignard reagents to an azepinium precursor was achieved.[12]

A few years ago, the team of Wallace[13] and our group[14] developed independently a Meyers' lactamization process leading to axially chiral 7,5-fused lactams **3** with high diastereomeric excesses from biaryl precursors **2** (Scheme 1).[15] This alternative strategy allowed us to master in a one-step

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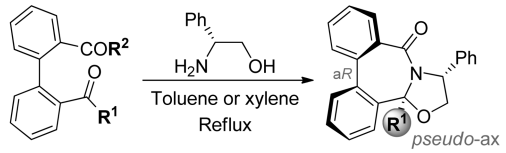
Scheme 1. Scope and Limitations in Atropoisomeric Meyers' Lactamization



2a R^1 = **H**, R^2 = **OMe**: 88%, 82% de (72 h)
2b R^1 = **Me**, R^2 = **OH**: 88%, 86% de (18h)
2c R^1 = **Me**, R^2 = **OEt**: 95%, > 95% de (138h)

3a R^1 = **H**
3b R^1 = **Me**

operation both the absolute configuration of the stereogenic center bearing the pseudoaxial R^1 substituent and the a*R* biaryl axis configuration derived thereof, central to axial chirality transfer in action indeed. Despite the promises of this approach to control an otherwise configurationally unstable biaryl axis, important bottlenecks remain: (1) limitation to R^1 = Me and few heterocyclic benzodiazepine derivatives probed besides biaryl compounds, and (2) better diastereoselectivities (>95% de) were usually obtained by means of keto-ester **2c** instead of aldehyde ester **2a** or keto-carboxylic acid **2b** (82−86% de) starting materials, but several days of reaction were required to reach completion.[13,14] Herewith, we are pleased to report a novel development of this original methodology allowing the construction of dibenzo(di)azepine architectures flanked by various R^1 substituents requiring only few hours of reaction upon the use of a suited coacid and microwave irradiation.

At the onset, we desired to take advantage of recent investigations demonstrating a significant acceleration of Meyers' lactamization reactions upon microwave irradiation (Table 1).[16] Unfortunately, no transformation of the model keto-ester **2c** in the presence of phenylglycinol was observed at 110 °C as representative temperature in either toluene or α,α,α-trifluorotoluene solutions (entry 1). Taking into account that keto-acid **2b** gave a faster reaction rate (Scheme 1, **2b** versus **2c**), we investigated the use of acid additives. Although 2 equivalents of *p*-toluenesulfonic acid turned out to be ineffective (entry 2), the lactamization process took place within 1 h by means of benzoic or acetic acids with 17 and 53% of conversion, respectively, together with more than 96:4 diastereomeric ratio (entries 3 and 4). Interestingly, the reaction efficacy increased as the pK_a of the acid additive increased to reach that of $MeCO_2H$ (entries 3 and 4), likely preventing a complete protonation of the phenylglycinol chiral auxiliary. Eventually, the best results were obtained with pivalic acid giving 76% of conversion (entry 5). Then, attempts to use pivalic acid catalytically resulted in a dramatic drop in the reaction conversion (entries 6 and 7), while no significant solvent effect was detected by using α,α,α-trifluorotoluene, nevertheless renowned for being more efficient under microwave activation (entry 6). However, 1.2 equiv of *t*-$BuCO_2H$ was enough to furnish product **3b** in 79% yield at higher temperature (150 °C) with a high diastereomeric ratio, as less than 4% of the minor isomer was detected in the ^{1}H NMR spectrum of the crude product (entry 8). This lack of dr erosion in the presence of acid additives is welcome for keto-ester **2c** considering that keto-acid **2b** affording **3b** in one day with significant lower diastereomeric excesses (see Scheme 1, **2b** versus **2c**). To our delight, more than 90% yield for **3b** was provided (entry 9) if the reaction was pursued during 2.5 h, which constitutes a great advance with respect to the previously required 5 days for the Dean−Stark reaction in refluxing toluene for keto-ester **2c**. This acid-promoted transformation could also be carried out without solvent (entry 10), but these reaction conditions were somewhat irreproducible with other substrates. Moreover, although comparable reaction conversions could be reached under a conventional preheated oil bath at 150 °C (into sealed-vessel microwave reactors), crude products could not be obtained as clean as with MW heating and made the purification somewhat tricky (entry 11).[17]

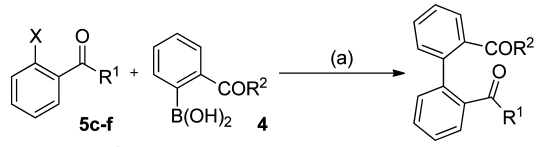
Next, we sought to apply these efficient atroposelective Meyers' lactamization conditions to the elaboration of various R^1 substituted analogues of **3b** and/or dibenzodiazepines possessing a heterocyclic backbone. A cross-coupling approach, between ketone- and ester-substituted (hetero)aromatics, appeared to be an appealing synthetic pathway in terms of convergence and structural diversity issues to access the required bi(hetero)aryl structures. Nevertheless, in our hands, known metal-catalyzed strategies were not easily extrapolated to yield the corresponding products **2** (Scheme 2)[14a,18] or **8** (Table 2)[19] from different electron-poor coupling partners **4**, **5**, and **7**. As far as the biaryl architectures **2** are concerned (Scheme 2), it was found that Fu's Suzuki-type coupling reaction employed efficient conditions for building methyl-, ethyl-, and phenyl-substituted compounds **2c−e**[20] from readily

Table 1. Optimization of Meyers' Lactamization under MW (2c to 3b)[a]

entry	acid (equiv)	temp (°C)	time (h)	conv[b,c] (%)	yield[d] (%)
1		110	1	0	
2	PTSA (2)	110	1	0	
3	$PhCO_2H$ (2)	110	1	17	
4	$MeCO_2H$ (2)	110	1	53	
5	*t*-$BuCO_2H$ (2)	110	1	76	
6	*t*-$BuCO_2H$ (1.2)	110	1	56 (58)[e]	
7	*t*-$BuCO_2H$ (0.3)	110	1	24	
8	*t*-$BuCO_2H$ (1.2)	150	1	91	79
9	*t*-$BuCO_2H$ (1.2)	150	2.5	99	92
10	*t*-$BuCO_2H$ (1.2)	150	2.5	93[f]	93
11	*t*-$BuCO_2H$ (1.2)	150[g]	2.5	91	88

[a]Ketoester **2c** (1 equiv, 0.5 M), phenylglycinol (1.2 equiv), acid (*x* equiv), and toluene in a sealed tube under microwave irradiation. [b]>96:4 ratio of diastereomers for **3b** measured by ^{1}H NMR of the crude product in all cases. [c]**2c**/**3b** ratio determined on the ^{1}H NMR of the crude product. [d]Isolated yield after silica gel column chromatography. [e]In $C_6H_5CF_3$ as solvent. [f]Without solvent. [g]In a sealed tube with a conventional oil bath heating.

Scheme 2. Suzuki Coupling Reaction toward Dibenzazepine Precursors[a]



5c X = Br, R^1 = Me (90% into **2c**)
5d X = Br, R^1 = Et (96% into **2d**)
5e X = Cl, R^1 = Ph (52% into **2e**)
5f X = Br, R^1 = Bn (36% conversion into **2f**)

(b) R^2 = OEt (**2c-e**), OMe (**2f**); R^1 = Ph, R^2 = OH (**6**)

(a) $Pd_2(dba)_3$ (1 mol%), $HP(tBu)_3{\cdot}BF_4$ (2.4 mol%), $KF{\cdot}2H_2O$ dioxane, 110°C, 18-24h. (b) NaOH, 88% yield from **2e**.

[a]Key: (a) $Pd_2(dba)_3$ (1 mol %), $HP(t\text{-}Bu)_3{\cdot}BF_4$(2.4 mol %), $KF{\cdot}2H_2O$ dioxane, 110 °C, 18−24 h; (b) NaOH, 88% yield from **2e**.

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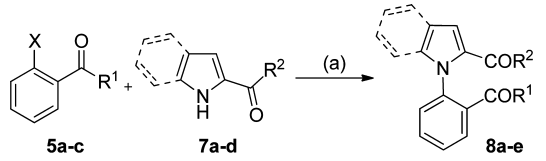
Table 2. Buchwald's Cross-Coupling Reaction toward Dibenzodiazepine Precursors



5a-c 7a-d 8a-e

entry	R^1	X	R^2	yield[b] (%)
1	Me	Br (**5a**)	OMe (pyrrole) (**7a**)	78 (**8a**)
2	Me	Br (**5a**)	OMe (indole) (**7b**)	80 (**8b**)
3	OEt	Br (**5b**)	Me (pyrrole) (**7c**)	0 (**8c**)
4	OMe	I (**5c**)	Me (pyrrole) (**7c**)	71 (**8d**)
5	OMe	I (**5c**)	Bn (pyrrole) (**7d**)	0 (**8e**)

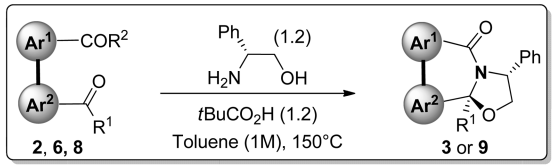
[a]Heterocycles (1 equiv), halogenated compound (2 equiv), CuI (5 mol %), *trans*-*N*,*N*′-Dimethylcyclohexane-1,2-diamine (20 mol %), K_2CO_3 (2.1 equiv), toluene, 110 °C. [b]Isolated yield after silica gel column chromatography.

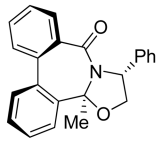
or commercially available *ortho*-halogenated ketone partners **5**,[21] even from chlorinated benzophenone **5e**. Unfortunately, ketone **5f** flanked by a benzyl moiety underwent the cross-coupling reaction with a modest 36% conversion into product **2f**, whose isolation by column chromatography turned out to be unsuccessful in our hands due to a complex crude mixture. Alternatively, compound **2f** was eventually synthesized upon the direct Claisen condensation−reaction of phenyl acetic acid to diphenic anhydride following an adapted Huang's procedure and the subsequent esterification reaction.[21b] In order to investigate further the reactivity of these new Meyers' lactam precursors (vide infra), the carboxylic acid **6** was also synthesized by a smooth saponification transformation.

Subsequently, an Ullman cross-coupling methodology was applied to construct heteroaryl−aryl architectures **8** through a C−N bond formation (Table 2). After slight modifications, the diamine-copper catalyzed Buchwald's conditions furnished the corresponding ester-functionalized **8a**, acetyl-functionalized pyrrole **8d** (entries 1 and 4), and indole **8b** (entry 2) derivatives.[19] Better results could be obtained in some cases with *ortho*-iodinated compounds instead of bromo analogues (entries 3 and 4). Once again, benzyl-functionalized ketone derivative **7d** did not furnish the corresponding product **8e** (entry 5), likely due to the sensitivity of the enolizable position. Eventually, pyrrole **8e** was synthesized from a commercially available *N*-phenylpyrrole precursor by means of a Friedel−Crafts reaction involving 2-phenylacetyl chloride, following a literature procedure (see the Experimental Section).[22]

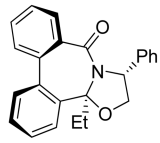
With these precursors in hands, we tackled the scope of pivalic acid promoted Meyers' lactamization reaction at 1 M concentration (Scheme 3). These reaction conditions allowed the straightforward formation of methyl (**3b**), ethyl (**3c**), and benzyl lactam (**3d**) derivatives with excellent diastereomeric ratios (>96:4). A complete conversion could be reached in more difficult cases by increasing the reaction time from 2.5 to 5 h (see product **3c** and **3d**). The limitation was met with the less reactive benzophenone **2e**. Pleasingly, a smooth transformation was achieved by means of the more reactive carboxylic acid **6** (see Scheme 1 for discussion), but once again, the presence of pivalic acid was also required. This outcome points out the usefulness of these new pivalic acid-promoted reaction conditions. In the heterocyclic series,

Scheme 3. Meyers' Lactamization toward Dibenzo(di)azepine Synthesis

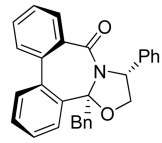




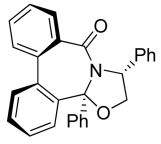
3b (92%, > 96:4 dr, 2.5 h)



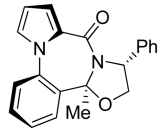
3c (90%, > 96:4 dr, 2.5 h)
3c (98%, > 96:4 dr, 5 h)



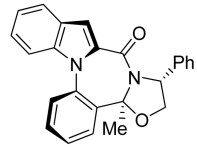
3d (86% conv., > 97:3 dr, 2.5 h)
3d (83%, > 97:3 dr, 5 h)
- with 2 equiv of pivalic acid -



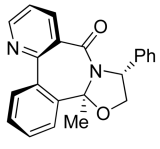
3e (0%, from **2e** - R^2 = OEt)
3e (64%, > 96:4 dr, from **6** - R^2 = OH, 2.5 h)
3e (75%, > 96:4 dr, from **6** - R^2 = OH, 5 h)



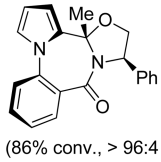
9a (93%, > 96:4 dr, 2.5 h)



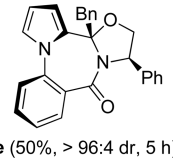
9b (93%, > 96:4 dr, 2.5 h)



9c (88%, > 96:4 dr, 2.5 h)



9d (86% conv., > 96:4 dr, 5 h)
9d (94%, > 96:4 dr, 5 h)
- with 2 equiv of pivalic acid -



9e (50%, > 96:4 dr, 5 h)
9e (72%, > 96:4 dr, 10 h)
- with 2 equiv of pivalic acid -

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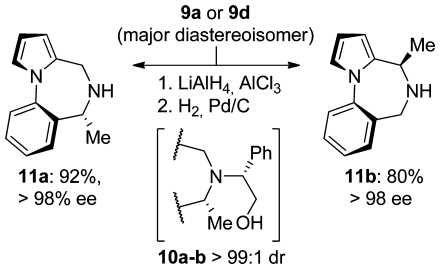
methyl-substituted pyrrole **9a**, trisubstituted indole **9b**, and pyridine **9c**[14a] were easily synthesized with excellent yields and diastereomeric ratios. On the other hand, the methyl- and benzylpyrrole homologues **9d−e** were obtained by starting from the corresponding keto-esters **8d,e** possessing ketone and ester substituents at reverse positions with regard to pyrrole **9a**. Interestingly, the initial 86% conversion of **8d** into **9d** observed after 5 h could be pushed up to completion by using 2 equivalents of pivalic acid. However, under the same conditions, pyrrole **9e** flanked by a benzyl moiety led to slow reaction rates with 78% of conversion even after 10 h at 150 °C. Eventually, the structures of compounds **9a**, **9b**, and **9d** were unequivocally proven by X-ray diffraction analyses.

In order to probe the usefulness of these new compounds (see Figure 1), we attempted the reductive cleavage of the chiral auxiliary moiety of pyrrole derivatives **9a** or **9d**. Interestingly, these precursors were obtained as a single diastereomer after a simple recrystallization (Scheme 4). In

Scheme 4. Alane Reduction



the past, Meyers demonstrated that alane reagents allowed highly stereoselective reduction of the oxazolidine ring, as nicely exemplified by Wallace on 5-methyl-6,7-dihydro-*SH*-dibenzo[*c*,*e*]azepine compound.[3b] In our hands, the alane reduction took place with high diastereoselectivity to give products **10a** and **10b** (the minor isomer was hardly seen by ^{1}H NMR), differing from each other by the position of the methyl substituents. Then, a simple palladium-catalyzed debenzylation furnished the corresponding pyrroles **11a** and **11b** with high yields over two steps. The pyrrole structures **11a,b** appeared as a single diastereomeric atropoisomer (with >99:1 ratio on the ^{1}H NMR spectra in $CDCl_3$) with likely pseudoequatorial methyl substitutent.[3b] This constitutes an unprecented access to enantioenriched dibenzodiazepines analogues incorporating a pyrrole subunit.

In conclusion, we have demonstrated the ability of metal-catalyzed cross-coupling processes followed by an original acid promoted highly atroposelective Meyers' lactamization to provide a straightforward and unprecedented entry to non-racemic substituted dibenzo(di)azepine derivatives, analogues of biorelevant architectures.

EXPERIMENTAL SECTION

Representative Procedure for Suzuki Coupling Reaction. Premixed catalyst $Pd_2(dba)_3$/$[HP(t\text{-}Bu)_3]BF_4$ (Pd/P(*t*-Bu)$_3$ = 1:1.2; 1 mol % of $Pd_2(dba)_3$), 2-(ethoxycarbonyl)phenylboronic acid (1.1 equiv), and KF·2H$_2$O (3.3 equiv) were added into a vial with a septum cap and flushed with argon for 3 min. Dry dioxane and the aryl halide (1.0 equiv, 0.5 M) were added, and the mixture was stirred at 110 °C (oil bath temperature) for 18 h. The reaction was cooled to room temperature, diluted with Et$_2$O, and filtered through a plug of Celite. The filtrate was concentrated under vacuum, and the residue was purified by flash chromatography on silica gel.

Ethyl 2′-Acetyl-1,1′-biphenyl-2-carboxylate (2c). 1-(2-Bromophenyl)ethanone (135 μL, 1 mmol), 2-(ethoxycarbonyl)-phenylboronic acid (213 mg, 1.1 mmol), $Pd_2(dba)_3$/$[HP(t\text{-}Bu)_3]BF_4$ (16.2 mg, 0.01 mmol of $Pd_2(dba)_3$), and KF·2H$_2$O (311 mg, 3.3 mmol) gave **2c** (petroleum ether/diethyl ether 4/1) as a colorless oil (240 mg, 90%). The analytical data match the previously reported NMR analysis.[14a]

Ethyl 2′-(1-Oxopropyl)[1,1′-biphenyl]-2-carboxylate (2d). 1-(2-Bromophenyl)propan-1-one (533 mg, 2.5 mmol), 2-(ethoxycarbonyl)phenylboronic acid (533 mg, 2.75 mmol), $Pd_2(dba)_3$/$[HP(t\text{-}Bu)_3]BF_4$ (20 mg, 0.025 mmol of $Pd_2(dba)_3$), and KF·2H$_2$O (776 mg, 8.25 mmol) gave **2d** (petroleum ether/diethyl ether 4/1; R_f = 0.22) as a colorless oil (675 mg, 96%): IR (ν_{max}/ cm^{-1}) 2980, 1715, 1688, 1595, 1439, 1365, 1247, 1128, 1086, 946, 752; ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.98 (1H, dd, J = 7.7 Hz, 1.4 Hz), 7.66−7.63 (1H, m), 7.54−7.39 (4H, m), 7.21−7.16 (2H, m), 4.07 (2H, q, J = 7.2 Hz), 2.55−2.45 (2H, m), 1.02 (3H, t, J = 7.1 Hz), 0.93 (3H, t, J = 7.3 Hz); ^{13}C NMR (75.4 MHz; $CDCl_3$) δ 205.5 (C), 167.4 (C), 142.4 (C), 140.7 (C), 139.2 (C), 131.5 (CH), 130.9 (CH), 130.38 (CH), 130.36 (CH), 130.28 (C), 130.23 (CH), 127.8 (CH), 127.7 (CH), 127.4 (CH), 60.9 (CH_2), 34.9 (CH_2), 13.8 (CH_3), 8.4 (CH_3); HRMS (ESI$^+$): calcd for $C_{18}H_{19}O_3$ [M + H$^+$] 283.1334, found 283.1331.

Ethyl 2′-Benzoyl[1,1′-biphenyl]-2-carboxylate (2e). (2-Chlorophenyl)(phenyl)methanone (217 mg, 1.0 mmol), 2-(ethoxycarbonyl)phenylboronic acid (213 mg, 1.1 mmol), $Pd_2(dba)_3$/$[HP(t\text{-}Bu)_3]BF_4$ (16 mg, 0.01 mmol of $Pd_2(dba)_3$), and KF·2H$_2$O (311 mg, 3.3 mmol) gave **2e** (petroleum ether/diethyl ether 3/2; R_f = 0.39) as a yellowish oil (170 mg, 52%). The analytical data match the previously reported NMR analysis.[23]

Methyl 2′-(Phenylacetyl)[1,1′-biphenyl]-2-carboxylate (2f). To a suspension of diphenic anhydride (1.12 g, 5.0 mmol) and 2-phenylacetic acid (681 mg, 5.0 mmol) in dry THF was added 2 M solution of NaHMDS in THF (10 mL, 20 mmol) at −78 °C under Ar atmosphere. The mixture was slowly warmed to 0 °C and stirred for 5 h. Then 10% HCl was added, and reaction mixture was stirred at room temperature for 1 h. The aqueous phase was extracted with ethyl acetate (3 × 50 mL), and the combined organic extracts were washed with saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under vacuum. The crude product was dissolved in MeOH (10 mL) and toluene (36 mL), and a 2 M solution of trimethylsilyldiazomethane in hexane (5 mL, 10 mmol) was added at room temperature. The resulting mixture was stirred for 2 h and concentrated under vacuum. The residue was purified by chromatography on silica gel (eluent: DCM; R_f = 0.68) to afford as colorless solid **2f** (130 mg, 13% over two steps): mp = 102−103 °C; IR (ν_{max}/ cm^{-1}) 1721, 1688, 1432, 1252, 1195, 1126,1086, 988, 750; ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.03−8.00 (1H, m), 7.68−7.65 (1H, m), 7.54−7.40 (4H, m), 7.27−7.14 (5H, m), 7.01−6.98 (2H, m), 3.91 (1H, d, J = 15.6 Hz), 3.73 (1H, d, J = 15.7 Hz), 3.68 (3H, s); ^{13}C NMR (75.4 MHz; $CDCl_3$) δ 202.2 (C), 167.7 (C), 142.3 (C), 140.6 (C), 139.0 (C), 134.4 (C), 131.8 (CH), 131.2 (CH), 130.6 (CH), 130.5 (CH), 130.2 (CH), 129.9 (C), 129.6 (CH), 128.5 (CH), 128.1 (CH), 127.8 (CH), 127.5 (CH), 126.8 (CH), 52.1 (CH_3), 48.4 (CH_2); HRMS (ESI$^+$) calcd for $C_{22}H_{19}O_3$ [M + H$^+$] 331.1334, found 331.1346.

2′-Benzoyl[1,1′-biphenyl]-2-carboxylic Acid (6).[24] NaOH (10 M aqueous solution, 2.3 mL) was added dropwise to a solution of ethyl 2′-benzoyl[1,1′-biphenyl]-2-carboxylate (**2e**) (770 mg, 2.33 mmol) in 12 mL of EtOH at 0 °C. The resulting mixture was stirred for an additional 18 h at rt. The solvent was evaporated under reduced pressure, and the residue was dissolved in 20 mL mixture of CH_2Cl_2/1 M HCl: 1/1. The water phase was extracted with CH_2Cl_2 (3 × 20 mL). Combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether/diethyl ether 1/1; R_f = 0.18) to afford the colorless solid **6** (618 mg, 88%): mp = 50−52 °C; IR (ν_{max}/ cm^{-1}) 1686, 1657, 1594, 1448, 1269, 1154, 929; ^{1}H NMR (300 MHz; $CDCl_3$) δ 10.51 (br, 1H), 7.85−7.83 (1 H, m), 7.78−7.75 (2H, m), 7.57−7.45 (4H, m), 7.43−7.32 (5H, m), 7.17−7.15 (1H, m); ^{13}C NMR (75.4 MHz; $CDCl_3$) δ 199.1 (C), 171.2 (C), 141.0 (C),

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140.8 (C), 137.8 (C), 137.0 (C), 133.6 (CH), 131.6 (CH), 130.9 (CH), 130.8 (CH), 130.7 (CH), 130.2 (CH), 129.1 (CH), 128.4 (CH), 127.9 (CH), 127.2 (CH) *two carbon signals are overlapped with other ones*; HRMS (ESI^-) calcd for $C_{20}H_{13}O_3$ [M − H^+] 301.0865, found 301.0860.

Representative Procedure for the Synthesis of Compounds 8 by *N*-Arylation of Heterocycles. CuI (5 mol %), the heterocycle (1.0 equiv), and base (2.1 equiv) were added into a reaction vessel fitted with a rubber septum. The vessel was evacuated and backfilled with argon. The aryl halide (2.0 equiv), *trans-N,N′*-dimethyl-1,2-cyclohexanediamine ligand (20 mol %), and toluene were then successively added under a stream of argon. The reaction tube was quickly sealed, and the contents were stirred while heating in an oil bath at 110 °C for 24−72 h. At ambient temperature, the mixture was diluted with ethyl acetate, filtered through a plug of silica gel, concentrated, and purified by column chromatography on silica gel.

Methyl 1-(2-Acetylphenyl)-1*H*-pyrrole-2-carboxylate (8a). Methyl 2-pyrrolecarboxylate (1.0 g, 7.90 mmol), 1-(2-bromophenyl)-1-ethanone (2.2 mL, 15.8 mmol), K_2CO_3 (2.2 g, 15.9 mmol), CuI (75 mg, 0.4 mmol), and ligand (255 μL, 1.58 mmol) in dry toluene (8 mL) gave **8a** (pentane/ethyl acetate: 3/1; R_f = 0.34) as a colorless viscous oil (1.5 g, 78%): IR (ν_{max}/ cm^{-1}) 2950, 1706, 1685, 1489, 1436, 1264, 1112, 1091; ^1H NMR (300 MHz; $CDCl_3$) δ 7.73 (1 H, dd, *J* = 1.8, 7.4 Hz), 7.55−7.43 (2 H, m), 7.27 (1 H, dd, *J* = 1.7, 7.7 Hz), 7.11 (1 H, dd, *J* = 1.8, 3.9 Hz), 6.86 (1 H, dd, *J* = 1.8, 2.6 Hz), 6.34 (1 H, dd, J = 2.6, 3.9 Hz), 3.69 (3 H, s), 1.99 (3 H, s); ^{13}C NMR (75 MHz; $CDCl_3$) δ 200.0 (C), 160.9 (C), 138.6 (C), 137.3 (C), 131.8 (CH), 130.2 (CH), 128.9 (CH), 128.7 (CH), 128.6 (CH), 124.1 (C), 118.9 (CH), 110.2 (CH), 51.4 (CH_3), 28.4 (CH_3); HRMS (ESI^+) calcd for $C_{14}H_{14}NO_3$ [M + H^+] 244.0974, found 244. 0969.

Methyl 1-(2-Acetylphenyl)-1*H*-indole-2-carboxylate (8b). Methyl 2-indolecarboxylate (25 mg, 0.14 mmol), 1-(2-iodophenyl)-1-ethanone (40 μL, 0.28 mmol), K_2CO_3 (43 mg, 0.29 mmol), CuI (3 mg, 0.014 mmol), and ligand (10 μL, 0.028 mmol) in dry toluene (0.56 mL) gave **8b** (pentane/ether: 7/3; R_f = 0.19) as a colorless viscous oil (33 mg, 80%): IR (ν_{max}/ cm^{-1}) 3059, 3002, 2952, 1712, 1684, 1453, 1260, 1216, 1181 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$) δ 7.91 (1 H, dd, *J* = 1.8, 7.3 Hz), 7.79−7.73 (1 H, m), 7.71−7.55 (2 H, m), 7.52 (1 H, d, *J* = 0.9 Hz), 7.35−7.15 (3 H, m), 6.95 (1 H, dd, *J* = 0.9, 8.3 Hz), 3.80 (3 H, s), 1.91 (3 H, s); ^{13}C NMR (75 MHz; $CDCl_3$) δ 199.6 (C), 161.7 (C), 140.7 (C), 138.1 (C), 136.8 (C), 132.5 (CH), 129.8 (CH), 129.6 (CH), 128.9 (CH), 126.3 (2C), 126.2 (CH), 122.7 (CH), 121.7 (CH), 112.1 (CH), 111.2 (CH), 51.9 (CH_3), 28.6 (CH_3); HRMS (ESI+) calcd for $C_{18}H_{16}NO_3$ [M + H^+] 294.1126, found 294. 1130.

Methyl 2-(2-Acetyl-1*H*-pyrrol-1-yl)benzoate (8d). 2-Acetylpyrrole (25 mg, 0.23 mmol), 1-(2-iodophenyl)-1-ethanone (70 μL, 0.46 mmol), K_2CO_3 (136 mg, 0.48 mmol), CuI (3 mg, 0.013 mmol), and ligand (8 μL, 0.093 mmol) in dry toluene (2 mL) gave **8d** (pentane/EtOAc 8/2; R_f = 0.28) as a colorless solid (40 mg, 71%): mp = 65−67 °C; IR (ν_{max}/ cm^{-1}) 3098, 2952, 1727, 1645, 1494, 1408, 1258, 1083; ^1H NMR (300 MHz; $CDCl_3$) δ 8.02 (1H, dd, *J* = 7.7, 1.6 Hz), 7.57 (1H, td, *J* = 7.6, 1.7 Hz), 7.48 (1H, td, *J* = 7.6, 1.4 Hz), 7.27 (1H, dd, *J* = 7.7, 1.3 Hz), 7.09 (1H, dd, *J* = 4.0, 1.7 Hz), 6.87 (1H, dd, *J* = 2.6, 1.7 Hz), 6.34 (1H, dd, *J* = 4.0, 2.6 Hz), 3.66 (3 H, s), 2.38 (3 H, s); ^{13}C NMR (75 MHz; $CDCl_3$) δ 187.2 (C), 165.3 (C), 141.1 (C), 132.4 (CH), 132.3 (C), 130.6 (CH), 130.5 (CH), 128.5 (CH), 128.1 (CH), 128.0 (C), 119.4 (CH), 109.2 (CH), 52.1 (CH_3), 26.6 (CH_3); HRMS (ESI^+) calcd for $C_{14}H_{14}NO_3$ [M + H^+] 244.0974, found 244.0964.

Methyl 2-(2-(2-Phenylacetyl)-1*H*-pyrrol-1-yl)benzoate (8e). To a solution of phenylacetyl chloride (8.7 mL, 66.0 mmol) and BF_3·OEt_2 (9 mL, 72.9 mmol) in 300 mL of dichloromethane under a nitrogen atmosphere was added methyl 2-(1*H*-pyrrol-1-yl)benzoate (3g, 14.9 mmol) at room temperature. The mixture was stirred for 20 h, quenched with ice/water solution, extracted with dichloromethane, and evaporated. The two 3- and 5-regioisomers (3 g, 63%, ratio 1:1 by NMR of the crude product) was separated by column chromatography on silica gel (pentane/EtOAc 8/2; R_f = 0.24), and the title compound was obtained after washing with ethanol as a pure white solid (1.5 g, 32%): mp = 78−80 °C ; IR (ν_{max}/ cm^{-1}) 3137, 2946, 1728, 1663, 1493, 1406, 1260, 1082; ^1H NMR (300 MHz; $CDCl_3$) δ 7.98 (1H, dd, *J* = 7.6, 1.5 Hz), 7.55 (1H, td, *J* = 7.6, 1.7 Hz), 7.45 (1H, td, *J* = 7.6, 1.4 Hz), 7.30−7.20 (7H, m), 6.89 (1H, dd, *J* = 2.6, 1.7 Hz), 6.36 (1H, dd, *J* = 4.0, 2.6 Hz), 4.07 (1H, d, *J* = 14.6 Hz), 4.00 (1H, d, *J* = 14.6 Hz), 3.51 (3H, s); ^{13}C NMR (75 MHz; $CDCl_3$) δ 187.0 (C), 165.4 (C), 141.0 (C), 135.4 (C), 132.5 (CH), 131.9 (C), 131.1 (CH), 130.8 (CH), 129.4 (2CH), 128.7 (CH), 128.5 (2CH), 128.1 (CH), 128 (C), 126.6 (CH), 119.7 (CH), 109.4 (CH), 52 (CH_3), 45.69 (CH_2); HRMS (ESI^+) calcd for $C_{20}H_{18}NO_3$ [M + H^+] 320.1287, found 320.1288.

Representative Procedure for Meyers' Lactamization. A solution of keto-ester **5** (1.0 equiv, 1 M), (*R*)-2-amino-2-phenylethanol (1.2 equiv), and pivalic acid (1.2 equiv) in toluene was placed in a sealed microwave tube under argon and heated in a microwave at 150 °C for 2.5 to 5 h (80 W). The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel. In all cases, >96:4 diastereomeric ratios were measured on ^1H NMR spectra of the crude products.

(4b*S*,7*R*)-4b-Methyl-7-phenyl-6,7-dihydrodibenzo[*c*,*e*][1,3]-oxazolo[3,2-*a*]azepin-9(4b*H*)-one 3b. Ethyl 2′-acetyl-1,1′-biphenyl-2-carboxylate (**2c**) (114 mg, 0.42 mmol), (*R*)-2-amino-2-phenylethanol (70 mg, 0.51 mmol), and pivalic acid (52 mg, 0.51 mmol) gave **3b** (petroleum ether/diethyl ether 3/2; R_f = 0.43) after 2.5 h as a white solid (138 mg, 95%, diastereomeric mixture of lactams **3c**). The pure major diastereomer could be isolated by column chromatography (134 mg, 92%). The analytical data match the previously reported NMR analysis.[14a]

(4b*S*,7*R*)-4b-Ethyl-7-phenyl-6,7-dihydrodibenzo[*c*,*e*][1,3]-oxazolo[3,2-*a*]azepin-9(4b*H*)-one (3c). Ethyl 2′-(1-oxopropyl)-[1,1′-biphenyl]-2-carboxylate (**2d**) (482 mg, 1.7 mmol), (*R*)-2-amino-2-phenylethanol (281 mg, 2.05 mmol), and pivalic acid (209 mg, 2.05 mmol) gave **3c** (petroleum ether/diethyl ether: 3/2; R_f = 0.18) after 5 h as a white solid (548 mg, 90%, diastereomeric mixture of lactams **3c**). The pure major diastereomer could be isolated by column chromatography (492 mg, 81%): white solid; mp = 102−104 °C; IR (ν_{max}/ cm^{-1}) 2877, 1632, 1446, 1396, 1290, 1174, 1082, 1041; ^1H NMR (300 MHz; $CDCl_3$) δ 7.86 (1H, dd, *J* = 7.7 Hz, 1.0 Hz,), 7.65−7.27 (12H, m), 5.47 (1H, d, *J* = 6.3 Hz), 4.40 (1H, dd, *J* = 8.7 Hz, 6.3 Hz), 4.30 (1H, dd, *J* = 8.7 Hz, 1.3 Hz), 1.84−1.71 (m, 2H), 0.64 (3H, t, *J* = 7.4 Hz); ^{13}C NMR (75 MHz, CDCl3) δ 165.0 (C), 140.8 (C), 140.1 (C), 137.2 (C), 136.0 (C), 133.6 (C), 131.3 (CH), 130.9 (CH), 130.3 (CH), 128.83 (CH), 128.82 (CH), 128.6 (CH), 128.08 (CH), 128.06 (CH), 127.6 (CH), 127.3 (CH), 124.1 (CH), 96.6 (C), 70.8 (CH_2), 61.6 (CH), 30.6 (CH_2), 9.1 (CH_3); HRMS (ESI^+) calcd for $C_{24}H_{21}NO_2$ [M + H^+] 356.1651, found 356.1649. Characteristic peaks of the minor diastereomer: ^1H NMR spectrum of a 1/4 minor/major mixture of lactams **6b** (300 MHz; $CDCl_3$) δ 5.68 (1H, m), 4.89 (1H, dd, *J* = 8.8 Hz, 7.1 Hz), 4.37 (1H, dd, *J* = 8.8 Hz, 6.2 Hz), 1.07 (3H, t, *J* = 7.3 Hz).

(4b*S*,7*R*)-4b-Benzyl-7-phenyl-6,7-dihydrodibenzo[*c*,*e*][1,3]-oxazolo[3,2-*a*]azepin-9(4b*H*)-one (3d). Methyl 2′-(phenylacetyl)-[1,1′-biphenyl]-2-carboxylate (**2f**) (165 mg, 0.5 mmol), (*R*)-2-amino-2-phenylethanol (82 mg, 0.6 mmol), and pivalic acid (102 mg, 1 mmol) gave **3d** (petroleum ether/diethyl ether 3/2; R_f = 0.38) after 5 h as a white solid (173 mg, 83%, major diastereomer): mp =72−74 °C; IR (ν_{max}/ cm^{-1}) 2246, 1629, 1495, 1447, 1396, 1162, 1036, 905; ^1H NMR (300 MHz; $CDCl_3$) δ 8.00 (1H, m), 7.67−7.64 (3H, m), 7.62−7.51 (1H, m), 7.47−7.37 (2H, m), 7.34−7.29 (6H, m), 7.16−7.06 (3H, m), 6.83−6.80 (2H, m), 5.45 (1H, dd, *J* = 6.4, 1.1 Hz), 4.42 (1H, dd, *J* = 8.7, 6.6 Hz), 4.30 (1H, dd, *J* = 8.7, 1.3 Hz), 3.07 (2H, s); ^{13}C NMR (75 MHz, CDCl3) δ 165.1 (C), 140.6 (C), 140.3 (C), 137.3 (C), 135.8 (C), 135.2 (C),133.9 (C), 131.6 (CH), 130.7 (CH), 130.6 (CH), 130.4 (CH), 128.9 (CH), 128.8 (CH), 128.5 (CH), 128.3 (CH), 128.1 (CH), 127.8 (CH), 127.3 (CH), 127.0 (CH), 126.7 (CH), 123.9 (CH), 96.1 (C), 70.8 (CH_2), 61.7 (CH), 43.0 (CH_2); HRMS (ESI^+) calcd for $C_{29}H_{24}NO_2$ [M + H^+] 418.1807, found 418.1802.

(4b*S*,7*R*)-4b,7-Diphenyl-6,7-dihydrodibenzo[*c*,*e*][1,3]-oxazolo[3,2-*a*]azepin-9(4b*H*)-one (3e). 2′-Benzoyl[1,1′-biphenyl]-

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2-carboxylic acid (**6**) (101 mg, 0.33 mmol), (*R*)-2-amino-2-phenylethanol (55 mg, 0.4 mmol), and pivalic acid (41 mg, 0.4 mmol) gave **3e** (petroleum ether/ethyl acetate 4/1; R_f = 0.26) after 5 h as a white solid (101 mg, 75%, diastereomeric mixture of lactams **3e**). The main diastereomer was isolated by column chromatography. Major diastereomer (96 mg, 71%): white solid; mp =255−257 °C; IR (ν_{max}/ cm^{-1}) 2117, 1634, 1493, 1444, 1385, 1280, 1210, 1136, 1082, 1066; ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.99−7.96 (1H, m), 7.75−7.73 (2H, m), 7.63−7.51 (4H, m), 7.44−7.33 (3H, m), 7.22−7.12 (2H, m), 7.10−6.89 (6H, m), 5.61 (1H, d, *J* = 5.6 Hz), 4.66 (1H, dd, *J* = 8.6 Hz, 6.5 Hz), 4.50 (1H, d, *J* = 8.8 Hz); ^{13}C NMR (75.4 MHz; $CDCl_3$) δ 165.7 (C), 141.1 (C), 140.2 (C), 138.8 (C), 137.2 (C), 136.6 (C), 134.5 (C), 131.0 (CH), 130,7 (CH), 129.3 (CH), 129.2 (CH), 129.0 (CH), 128.6 (CH), 128.4 (CH), 128.3 (CH), 128.1 (CH), 127.8 (CH), 127.6 (CH), 127.5 (CH), 127.4 (CH), 123.7 (CH), 97.0 (C), 72.1 (CH_2), 61.7 (CH); HRMS (ESI$^+$) calcd for $C_{28}H_{22}NO_2$ [M + H$^+$] 404.1651, found 404.1642.

(a*R*,4b*S*,7*R*)-4b-Methyl-7-phenyl-6,7-dihydrobenzo[*f*]-oxazolo[3,2-*d*]pyrrolo[1,2-*a*][1,4]diazepin-9(4b*H*)-one (9a). Methyl-1-(2-acetylphenyl)-1*H*-pyrrole-2-carboxylate (**8a**) (300 mg, 1.22 mmol), (*R*)-2-phenylglycinol (190 g, 1.46 mmol), and pivalic acid (150 mg, 1.47 mmol) gave **9a** (pentane/EtOAc 7/3; R_f = 0.24) after 2.5 h as a colorless oil (370 mg, 93%, diastereomeric mixture of lactams **9a**). The pure major diastereomer could be isolated by recrystallization from absolute ethanol (240 mg, 59%): white solid; mp = 137−139 °C; IR (ν_{max}/ cm^{-1}) 3029, 2935, 2891, 1625, 1487, 1388, 1029; ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.69 (1 H, m), 7.54 (2 H, m), 7.48 − 7.26 (6 H, m), 7.15 (1 H, dd, *J* = 2.8, 1.8 Hz), 7.03 (1 H, dd, *J* = 3.8, 1.8 Hz), 6.41 (1 H, dd, *J* = 3.8, 2.8 Hz), 5.32 (1 H, *p*d, *J* = 5.4 Hz), 4.39 (1 H, dd, *J* = 8.7, 5.7 Hz), 4.33 (1 H, dd, *J* = 8.7, 1.2 Hz), 1.56 (3 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.5 (C), 140.7 (C), 136.6 (C), 135.4 (C), 129.7 (CH), 128.6 (2CH), 127.8 (C), 127.6 (CH), 127.1 (2CH), 127.0 (CH), 124.2 (CH), 123.7 (2CH), 117.6 (CH), 111.0 (CH), 92.8 (C), 71.6 (CH_2), 61.5 (CH), 25.7 (CH_3); HRMS (ESI$^+$) calcd for $C_{21}H_{19}N_2O_2$ [M + H$^+$] 331.1447, found 331.1457. Characteristic peaks of the minor diastereomer: ^{1}H NMR spectrum of a 15/85 minor/major mixture of lactams (300 MHz; $CDCl_3$) δ 5.46 (1 H, dd, *J* = 6.7, 4.3 Hz), 4.58 (1 H, dd, *J* = 8.9, 6.7 Hz), 4.15 (1 H, dd, *J* = 8.9, 4.3 Hz), 1.48 (3H, s).

(a*R*,4b*S*,7*R*)-4b-Methyl-7-phenyl-6,7-dihydrobenzo[6,7]-oxazolo[3′,2′:4,5][1,4]diazepino[1,2-*a*]indol-9(4b*H*)-one (9b). Methyl 1-(2-acetylphenyl)-1*H*-indole-2-carboxylate (**8b**) (250 mg, 0.85 mmol), (*R*)-2-phenylglycinol (230 mg, 1.63 mmol), and pivalic acid (166 mg, 1.63 mmol) gave **9b** (pentane/EtOAc: 9/1; R_f = 0.27) after 2.5 h as a colorless oil (300 mg, 93%, diastereomeric mixture of lactams **9b**). The pure major diastereomer could be isolated by recrystallization from absolute ethanol (266 mg, 82%): colorless solid; mp = 178−180 °C; IR (ν_{max}/ cm^{-1}) 2982, 2950, 2901, 1624, 1450, 1325, 1242, 1036; ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.90−7.70 (4 H, m), 7.65−720 (10 H, m), 5.45 (1 H, *p*d, *J* = 5.4 Hz), 4.47 (1 H, dd, *J* = 8.7, 5.9 Hz), 4.40 (1 H, dd, *J* = 8.7, 1.2 Hz), 1.57 (3 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9 (C), 140.4 (C), 136.8 (C), 136.7 (C), 135.0 (C), 133 (C), 129.2 (CH), 128.7 (2CH), 127.7 (CH), 127.6 (C), 127.1 (2CH), 126.7 (CH), 125.5 (CH), 124.9 (CH), 124.0 (CH), 122.6 (CH), 122.1 (CH), 112.2 (CH), 110.4 (CH), 93.2 (C), 71.5 (CH_2), 61.4 (CH), 25.4 (CH_3); HRMS (ESI$^+$) calcd for $C_{25}H_{21}N_2O_2$ [M + H$^+$] 381.1603, found 381.1596. Characteristic peaks of the minor diastereomer: ^{1}H NMR spectrum of a 40/60 minor/major mixture of lactams (300 MHz; $CDCl_3$) δ 5.48 (1 H, dd, *J* = 6.6, 3.5 Hz), 4.6 (1 H, dd, *J* = 8.9, 6.7 Hz), 4.21 (1 H, m), 1.5 (3H, s).

(a*R*,4b*S*,7*R*)-4b-Methyl-7-phenyl-6,7-dihydrobenzo[*c*]-oxazolo[3,2-*a*]pyrido[2,3-*e*]azepin-9(4b*H*)-one (9c). The methyl keto-ester pyridine[14a] (25 mg, 0.09 mmol), (*R*)-2-amino-2-phenylethanol (16 mg, 0.12 mmol), and pivalic acid (12 mg, 0.12 mmol) gave **9c** (petroleum ether/AcOEt 6/4; R_f = 0.5) after 2.5 h as a white solid (29 mg, 88%, pure major diastereomer **9c**). The analytical data match the previously reported NMR analysis.[14a]

(a*R*,3b*R*,6*R*)-3b-Methyl-6-phenyl-5,6-dihydrobenzo[*e*]-oxazolo[3,2-*a*]pyrrolo[2,1-*c*][1,4]diazepin-8(3b*H*)-one (9d). Methyl 2-(2-acetyl-1*H*-pyrrol-1-yl)benzoate (**8d**) (25 mg, 0.1 mmol), (*R*)-2-phenylglycinol (17 mg, 0.12 mmol) and pivalic acid (21 mg, 0.2 mmol) gave **9d** (pentane/EtOAc 7/3; R_f = 0.29) after 5 h as a colorless oil (34 mg, 92%, diastereomeric mixture of lactams **9d**). The pure major diastereomer could be isolated by recrystallization from absolute ethanol (24 mg, 72%): white solid; mp = 189−191 °C; IR (ν_{max}/ cm^{-1}) 3109, 3036, 2895, 1630, 1490, 1373, 1213, 1036; ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.80 (1 H, dd, *J* = 7.8, 1.5 Hz,), 7.54 (2 H, m), 7.50 − 7.26 (8 H, m), 6.95 (1 H, dd, *J* = 2.9, 1.9 Hz), 6.26 - 6.15 (2 H, m), 5.38 (1 H, *p*d, *J* = 6 Hz), 4.50 (1 H, dd, *J* = 8.7, 6.2 Hz), 4.25 (1 H, dd, *J* = 8.7, 1.0 Hz), 1.52 (3 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.2 (C), 140.5 (C), 136.6 (C), 135.8 (C), 132.6 (CH), 132.0 (CH), 128.7 (2CH), 127.7 (2CH), 127.0 (2CH), 126.1 (CH), 122 (CH), 121.2 (CH), 110.1 (CH), 104.9 (CH), 91.1 (C), 71.8 (CH_2), 61.7 (CH), 26.6 (CH_3); HRMS (ESI$^+$) calcd for $C_{21}H_{19}N_2O_2$ [M + H$^+$] 331.1447, found 331.1439.

(a*R*,3b*R*,6*R*)-3b-Benzyl-6-phenyl-6,6a-dihydro-3b*H*-benzo-[*f*]furo[2,3-*c*]pyrrolo[1,2-*a*]azepin-7(5*H*)-one (9e). Methyl 2-(2-(2-phenylacetyl)-1*H*-pyrrol-1-yl)benzoate (**8e**) (65 mg, 0.19 mmol), (*R*)-2-phenylglycinol (33 mg, 0.24 mmol), and pivalic acid (39 mg, 0.38 mmol) gave **9e** (pentane/EtOAc: 8/2; R_f = 0.15) after 10 h as a colorless oil (58 mg, 72%, diastereomeric mixture of lactams **9d**, conversion of 78%). The pure major diastereomer could be isolated by recrystallization from absolute ethanol (45 mg, 54%): white solid; mp =69−71 °C; IR (ν_{max}/ cm^{-1}) 3029, 2884, 1726, 1634, 1494, 1391, 1256, 1153; ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.90 (1H, dd, *J* = 7.8, 1.5 Hz), 7.56 (1H, ddd, *J* = 8.1, 7.3, 1.5 Hz), 7.42 (1H, dd, *J* = 8.1, 0.9 Hz), 7.37−7.30 (1H, m), 7.28−7.19 (5H, m), 7.15−7.0 (3H, m), 6.99 (1H, dd, *J* = 2.9, 1.8 Hz), 6.72 (2H, dd, *J* = 7.6, 1.8 Hz), 6.17 (1H, dd, *J* = 3.5, 2.9 Hz), 5.98 (1H, dd, *J* = 3.5, 1.8 Hz), 5.41 (1H, dd, *J* = 6.5, 1.4 Hz), 4.51 (1H, dd, *J* = 8.7, 6.5 Hz), 4.28 (1H, dd, *J* = 8.7, 1.4 Hz), 3.05 (1H, d, *J* = 14.0 Hz), 2.99 (1H, d, *J* = 14.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8 (C), 140.2 (C), 136.8 (C), 134.9 (C), 133.7 (C), 132.9 (CH), 132.1 (CH), 130.5 (2CH), 128.6 (2CH), 128.1 (C), 127.9 (2CH), 127.5 (CH), 127.1 (2CH), 127.0 (CH), 126.3 (CH), 121.9 (CH), 120.9 (CH), 110.3 (CH), 107.4 (CH), 93.6 (C), 71.7 (CH_2), 61.64 (CH), 44.4 (CH_2); HRMS (ESI$^+$) calcd for $C_{27}H_{23}N_2O_2$ [M + H$^+$] 407.1760, found 407.1764.

Representative Procedure A for Lactam Reduction. A portion of aluminum chloride (1.2 equiv) was slowly diluted in THF (0.1 M) under nitrogen at 0 °C. After the mixture was stirred for 5 min, a solution of $LiAlH_4$ (1 M in THF, 3.5 equiv) was slowly added at 0 °C and the mixture was then stirred for 20 min at room temperature. The solution was then cooled to 0 °C and treated with a precooled (0 °C) solution of the lactam **9** (1 equiv) in dry THF (0.1 M) and stirred at 0 °C for 1 h and at room temperature for 3 h. The reaction was quenched by the cautious addition of 1 M aq HCl. Water was then added, and the aqueous layer was extracted with EtOAc. The combined organic extract was washed with 2 M aq NaOH, dried over $MgSO_4$, and evaporated under reduced pressure, giving the intermediate compound **10** (dr >99:1 by ^{1}H NMR spectroscopy) as a waxy solid which was used without further purification.

(*R*)-2-((*R*)-6-Methyl-4*H*-benzo[*f*]pyrrolo[1,2-*a*][1,4]diazepin-5(6*H*)-yl)-2-phenylethanol (10a): ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.27−7.10 (7H, m), 7.01 (1H, br s), 6.85 (1H, br s), 6.19 (1H, br s), 6.04 (1H, br s), 4.09 (1H, q, *J* = 7.1 Hz), 4.03−3.91 (2H, m), 3.72 (1H, m), 3.62 (1H, d, *J* = 12.7 Hz), 3.19 (1H, s), 3.09 (1H, d, *J* = 12.7 Hz), 0.83 (3H, d, *J* = 7.1 Hz).

(*R*)-2-((*R*)-4-Methyl-4*H*-benzo[*f*]pyrrolo[1,2-*a*][1,4]diazepin-5(6*H*)-yl)-2-phenylethanol (10b): ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.30−7.20 (7H, m), 7.1−6.9 (1H, d, *J* = 4.0 Hz), 6.85 (1H, d, *J* = 7.4 Hz), 6.81 (1H, dd, *J* = 2.9, 1.7 Hz), 6.17−6.13 (1H, m), 6.01 (1H, dd, *J* = 3.4, 1.7 Hz), 4.22 (1H, q, *J* = 6.9 Hz), 4.11- 3.95 (2H, m), 3.79-3.72 (1H, m), 3.47 (1H, d, *J* = 12.5 Hz), 3.34 (1H, d, *J* = 12.5 Hz), 3.06 (1H, s), 1.18 (3H, d, *J* = 6.9 Hz).

Representative Procedure B for Debenzylation. To a solution of **10** (1 equiv) in absolute ethanol (0.1 M) was added 10% Pd/C (10 mol %). The flask was fitted with a balloon containing hydrogen and stirred at room temperature for 16 h. The reaction mixture was filtered through Celite and the pad was rinsed with EtOAc. The solvents were

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evaporated under reduced pressure, and the residue was purified by chromatography over silica gel (packed with hexane plus a few drops of Et_3N, eluted with EtOAc, then EtOAc/MeOH/Et_3N 18:2:1, R_f = 0.32).

(*R*)-6-Methyl-5,6-dihydro-4*H*-benzo[*f*]pyrrolo[1,2-*a*][1,4]-diazepine (11a). Compound **9a** (73 mg, 0.22 mmol) gave a waxy solid (40 mg, 92% **11a**): $[\alpha]^{25}_D$ −54.8 ± 1 (*c* 1.9, $CHCl_3$); IR (ν_{max}/cm^{-1}) 2963, 1604, 1492, 1325, 1174, 888; ^1H NMR (300 MHz; $CDCl_3$) δ 7.60 (4H, m), 6.97 (1H, dd, *J* = 2.8, 1.7 Hz), 6.29 (1H, m), 6.26−6.17 (m, 1H), 4.02−3.87 (2H, m), 3.62 (1H, d, *J* = 14.1 Hz), 3.25 (1H, s), 1.47 (3H, d, *J* = 6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.2 (C), 134.1 (C), 131.4 (C), 128.7 (CH), 127.0 (CH), 126.8 (CH), 122.3 (CH), 120.1 (CH), 109.2 (CH), 107.4 (CH), 50.5 (CH), 41.6 (CH_2), 19.1 (CH_3); HRMS (ESI^+) calcd for $C_{13}H_{15}N_2$ [M + H^+] 199.1235, found 199.1241.

(*R*)-4-Methyl-5,6-dihydro-4*H*-benzo[*f*]pyrrolo[1,2-*a*][1,4]-diazepine (11b). Compound **9d** (58 mg, 0.17 mmol) gave a waxy solid (27 mg, 80% **11b**): $[\alpha]^{25}_D$ −35.5 ± 1 (*c* 1.9, $CHCl_3$); IR (ν_{max}/cm^{-1}) 2966, 1603, 1493, 1327, 1167, 1117; ^1H NMR (300 MHz; $CDCl_3$) δ 7.48- 7.21 (4H, m), 6.99 (1H, dd, *J* = 2.8, 1.7 Hz), 6.37−6.28 (1H, m), 6.20 (1H, m), 3.78 (3H, m), 2.46 (1H, s), 1.48 (1H, d, *J* = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.5 (C), 135.5 (C), 132.0 (C), 130.0 (CH), 129.0 (CH), 126.7 (CH), 121.9 (CH), 120.1 (CH), 108.9 (CH), 105.7 (CH), 48.7 (CH_2), 46.5 (CH), 19.1 (CH_3); HRMS (ESI^+) calcd for $C_{13}H_{15}N_2$ [M + H^+] 199.1235, found 199.1245.

■ ASSOCIATED CONTENT

Supporting Information

General experimental information, copies of NMR spectra for all newly formed products, and X-ray crystal data for compounds **9a**, **9b**, and **9d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Horton, D. A.; Bourne, G. T.; Smyte, M. L. *Chem. Rev.* **2003**, *103*, 893.

(2) For early examples of racemic series, see: (a) Tichý, M.; Buděšínský, M.; Günterová, J.; Závada, J.; Podlaha, J.; Císařová, I. *Tetrahedron* **1999**, *55*, 7893. (b) Hilt, G.; Galbiati, F.; Harms, K. *Synthesis* **2006**, 3575.

(3) For discussions of nonracemic series, see: (a) Vasse, J.-L.; Levacher, V.; Bourguignon, J.; Dupas, G. *Chem. Commun.* **2002**, 2256. (b) Pira, S. L.; Wallace, T. W.; Graham, J. P. *Org. Lett.* **2009**, *11*, 1663.

(4) For reviews on atropoisomers, see: (a) Wallace, T. W. *Org. Biomol. Chem.* **2006**, *4*, 3197. (b) Clayden, J.; Moran, W. J.; Edwards, P. J.; LaPlante, S. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 6398. (c) Anna, I. *Tetrahedron: Asymmetry* **2010**, *21*, 1943. (d) Bringmann, G.; Gulder, T.; Gulder, T. A. M.; Breuning, M. *Chem. Rev.* **2011**, *111*, 563. (e) LaPlante, S. R.; D. Fader, L.; Fandrick, K. R.; Fandrick, D. R.; Hucke, O.; Kemper, R.; Miller, S. P. F.; Edwards, P. J. *J. Med. Chem.* **2011**, *54*, 7005. (f) Aikawa, K.; Mikami, K. *Chem. Commun.* **2012**, *48*, 11050.

(5) Meerpoel, L.; Gestel, J. V.; Gerven, F. V.; Woestenborghs, F.; Marichal, P.; Sipido, V.; Terence, G.; Nash, R.; Corens, D.; Richards, R. D. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3453.

(6) Mai, A.; Di Santo, R.; Massa, S.; Artico, M.; Pantaleoni, G. C.; Giorgi, R.; Coppolino, M. F.; Barracchini, A. *Eur. J. Med. Chem.* **1995**, *30*, 593.

(7) For other examples in indole and imidazole series, see: (a) Ilyn, A. P.; Trifilenkov, A. S.; Kuzovkova, J. A.; Kutepov, S. A.; Nikitin, A. V.; Ivachtchenko, A. V. *J. Org. Chem.* **2005**, *70*, 1478. (b) Ohta, Y.; Chiba, H.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2008**, *10*, 3535. (c) Glass, L. S.; Bapat, A.; Kelley, M. R.; Georgiadis, M. M.; Long, E. C. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1685. (d) Wang, H.-J.; Wang, Y.; Camara, F.; Paquette, W. D.; Csakai, A. J.; Mangette, J. E. *Tetrahedron Lett.* **2011**, *52*, 541.

(8) For recent selected examples, see: (a) Tseng, M.-C.; Yang, H.-Y.; Chu, Y.-H. *Org. Biomol. Chem.* **2010**, *8*, 419. (b) Sorra, K.; Mukkanti, K.; Pusuluri, S. *Tetrahedron* **2012**, *68*, 2001 and references cited therein.

(9) Joncour, A.; Décor, A.; Liu, J.-M.; Tran Huu Dau, M.-E.; Baudoin, O. *Chem.—Eur. J.* **2007**, *13*, 5450.

(10) For other dibenzo[*c*,*e*]azepinones of this type, see: Mehta, V. P.; Modha, S. G.; Ruijter, E.; Van Hecke, K.; Van Meervelt, L.; Pannecouque, C.; Balzarini, J.; Orru, R. V. A.; Van der Eycken, E. *J. Org. Chem.* **2011**, *76*, 2828.

(11) Saudan, L. A.; Bernardinelli, G.; Kündig, E. P. *Synlett* **2000**, *2000*, 483.

(12) Bulman Page, P. C.; Bartlett, C. J.; Chan, Y.; Day, D.; Parker, P.; Buckley, B. R.; Rassias, G. A.; Slawin, A. M. Z.; Allin, S. M.; Lacour, J.; Pinto, A. *J. Org. Chem.* **2012**, *77*, 6128.

(13) (a) Edwards, D. J.; Pritchard, R. G.; Wallace, T. W. *Tetrahedron Lett.* **2003**, *44*, 4665. (b) Edwards, D. J.; House, D.; Sheldrake, H. M.; Stone, S. J.; Wallace, T. W. *Org. Biomol. Chem.* **2007**, *5*, 2658.

(14) (a) Penhoat, M.; Levacher, V.; Dupas, G. *J. Org. Chem.* **2003**, *68*, 9517. (b) Penhoat, M.; Bohn, P.; Dupas, G.; Papamicaël, C.; Marsais, F.; Levacher, V. *Tetrahedron: Asymmetry* **2006**, *17*, 281. (c) Bouet, A.; Heller, B.; Papamicael, C.; Dupas, G.; Oudeyer, S.; Marsais, F.; Levacher, V. *Org. Biomol. Chem.* **2007**, *5*, 1397.

(15) For reviews on Meyers' lactamization, see: (a) Groaning, M. D.; Meyers, A. I. *Tetrahedron* **2000**, *56*, 9843. (b) Amat, M.; Pérez, M.; Bosch, J. *Synlett* **2011**, 143.

(16) (a) Jida, M.; Deprez-Poulain, R.; Malaquin, S.; Roussel, P.; Agbossou-Niedercorn, F.; Deprez, B.; Laconde, G. *Green Chem.* **2010**, *12*, 961. (b) Sarkar, S.; Husain, S. M.; Schepmann, D.; Fröhlich, R.; Wünsch, B. *Tetrahedron* **2012**, *68*, 2687.

(17) For discussion on microwave effect vs standard heating method, see: Kappe, C. O.; Pieber, B.; Dallinger, D. *Angew. Chem., Int. Ed.* **2013**, *52*, 1088.

(18) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461.

(19) Antilla, J. C.; Baskin, J. M.; Barder, T. E.; Buchwald, S. L. *J. Org. Chem.* **2004**, *69*, 5578.

(20) Lou, S.; Fu, G. C. *Adv. Synth. Catal.* **2010**, *352*, 2081.

(21) (a) Matsuda, T.; Shigeno, M.; Makino, M.; Murakami, M. *Org. Lett.* **2006**, *8*, 3379. (b) Wu, G.; Yin, W.; Shen, H. C.; Huang, Y. *Green Chem.* **2012**, *14*, 580.

(22) Chatzopoulou, M.; Mamadou, E.; Juskova, M.; Koukoulitsa, C.; Nicolaou, I.; Stefek, M.; Demopoulos, V. J. *Bioorg. Med. Chem.* **2011**, *19*, 1426.

(23) Sapountzis, I.; Lin, W.; Kofink, C. C.; Despotopoulou, C.; Knochel, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 1654.

(24) Shriner, R. L.; Geipel, L. *J. Am. Chem. Soc.* **1957**, *79*, 227.