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Diastereoselective synthesis of fused oxazolidines and highly substituted 1*H*-pyrrolo [2,1-*c*][1,4] oxazines *via* C–H functionalization†

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The first one pot protocol for the diastereoselective synthesis of oxazolo[2,3-*c*]isoquinoline was achieved by a metal-free, benzoic acid catalyzed reaction of 1,2,3,4-tetrahydroisoquinoline or trypoline with aldehydes under mild conditions *via* C–H, C–O bond functionalization. A new approach for the synthesis of highly substituted 1*H*-pyrrolo[2,1-*c*][1,4]oxazine was carried out.

Functionalization of C–H bonds into C–C and/or C–O bonds is an important area of organic synthesis for the construction of biologically active complex molecules.[1] [3 + 2]-Cycloadditions of azomethine ylides are the powerful tools to construct heterocyclic compounds from relatively simple precursors.[2] Many methods are available to generate nonstabilized azomethine ylides *in situ*, these dipolar species are most frequently prepared *via* decarboxylative condensation of aldehydes with amino acids such as proline and sarcosine.[3] Examples of azomethine ylide formation from simple, unfunctionalized cyclic amines and their subsequent dipolar cycloadditions remain rare as they require relatively high reaction temperatures even for the most activated amines such as 1,2,3,4-tetrahydroisoquinoline (THIQ). The domino reaction is one of the major strategies for the construction of novel heterocycles from easily available starting materials.[4] However, the utilities of redox-neutral domino reactions in stereo selective syntheses of bioactive molecules have not been extensively explored so far. Tetrahydrooxazolidines and pyrrolo[2,1-*c*][1,4]oxazine are the key intermediates in synthetic as well as in pharmaceutical chemistry and are important building blocks in the syntheses of various biologically active nitrogen containing heterocycles.[5,6] As a consequence, substantial attention has been paid to develop efficient methods for their syntheses.[7,8] Very recently, Hajra and co-workers[9] accomplished the diastereoselective synthesis of fused oxazolidines by aromatic aldehydes and pyrrolidine, using potassium acetate under microwave conditions but substrate scope was limited.

In continuation of our interest in *in situ* generated azomethine ylide followed by the intermolecular [3 + 2]-cycloaddition reaction[10] and synthesis of heterocyclic compounds[11] we explored a method to access intermolecular [3 + 2]-cycloadditions of azomethine ylides from simple THIQs and trypolines under mild conditions. To facilitate reaction development, we began our investigation with THIQ (1.0 equiv.) and 2-bromobenzaldehyde (2.0 equiv.) under reflux for 18 h in toluene. The expected product was formed in 36% yield (Table 1, entry 1) as a single diastereomer in which two phenyl groups are in trans arrangement and the structure of this diastereomer was confirmed by single X-ray crystal studies. As it has been shown that benzoic acid and molecular sieves facilitate amine α-functionalization *via* intermediate azomethine ylides,[12] we tested benzoic acid as an additive at 20 mol% loading which led to marked rate acceleration with the reaction being completed after 4 h (Table 1, entry 2) giving an increased yield of 45% (Table 1, entry 2). The mild acids like acetic acid and 2-ethyl hexanoic acid were quite less effective (Table 1, entries 17–18) and strong acids such as CF_3COOH and *p*-toluene sulfonoic acid were ineffective. The solvents screened included CH_3CN, THF, EtOAc, xylene, DMF and toluene among which CH_3CN was found to be the prefered solvent (Table 1, entries 9–13). A lower amount of the desired product was obtained at room temperature when it was stirred for 48 h (Table 1, entry 8). Remarkably, the reaction proceeded efficiently at 50 °C. In fact, the highest yield of **3j** (78%) was realized at this instance (Table 1, entry 9). No significant change in the yield was observed when benzoic acid was increased to 50 mol% (Table 1, entry 14). Reduction in the loading of benzoic acid to 10 mol% had negative effect on the yield of **3j** (Table 1, entry 15). The optimized reaction condition was 20 mol% benzoic acid in CH_3CN at 50 °C (Table 1, entry 9).

Having identified a useful set of reaction conditions, remarkable tolerance toward electronic demands of

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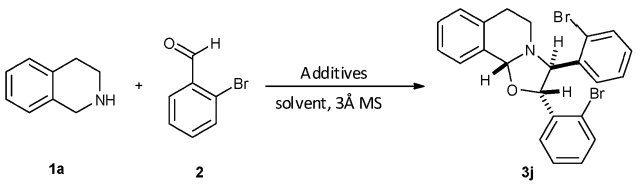
† Electronic supplementary information (ESI) available: CCDC **3j**-1061480, **3k**-1061453, **3n**-1061458, **5b**-1061457 and **7a**-1061479. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5ra10030e

Table 1 Reaction optimization for **3j**[a]



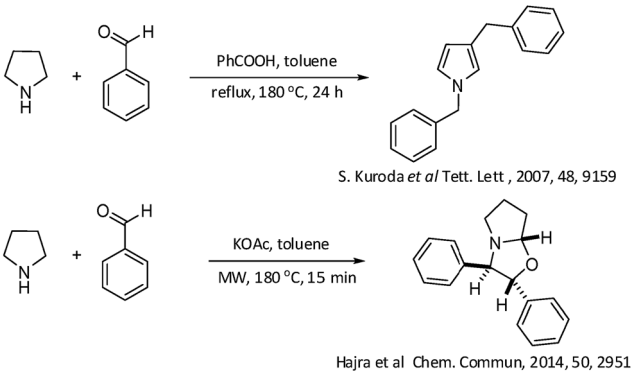
Entry	Additives (mol%)	Solvents	T [°C]	Time [h]	Yield[b] (%)
1	—	Toluene	Reflux	18	36
2	$PhCO_2H$(20)	Toluene	Reflux	4	45
3	$PhCO_2H$(20)	Toluene	100	5	48
4	$PhCO_2H$(20)	Toluene	80	7	51
5	$PhCO_2H$(20)	Toluene	60	18	62
6	$PhCO_2H$(20)	Toluene	50	18	65
7	$PhCO_2H$(20)	Toluene	40	24	58
8	$PhCO_2H$(20)	Toluene	rt	48	59
9	$PhCO_2H$(20)	CH_3CN	50	14	78
10	$PhCO_2H$(20)	Benzene	50	24	57
11	$PhCO_2H$(20)	Xylene	40	24	63
12	$PhCO_2H$(20)	EtOAc	50	24	NR
13	$PhCO_2H$(20)	THF	50	24	NR
14	$PhCO_2H$(50)	CH_3CN	50	12	74
15	$PhCO_2H$(10)	CH_3CN	50	12	57
16	CH_3CO_2H(20)	CH_3CN	50	24	61
17	EHA(20)	CH_3CN	50	24	63
18	CF_3CO_2H(20)	CH_3CN	50	24	NR
19	PTSA(20)	CH_3CN	50	24	NR

[a] Reactions were performed with 1.0 mmol of **2** and 1.2 mmol of THIQ **1a**. [b] Yields are of chromatographically isolated purified compounds.

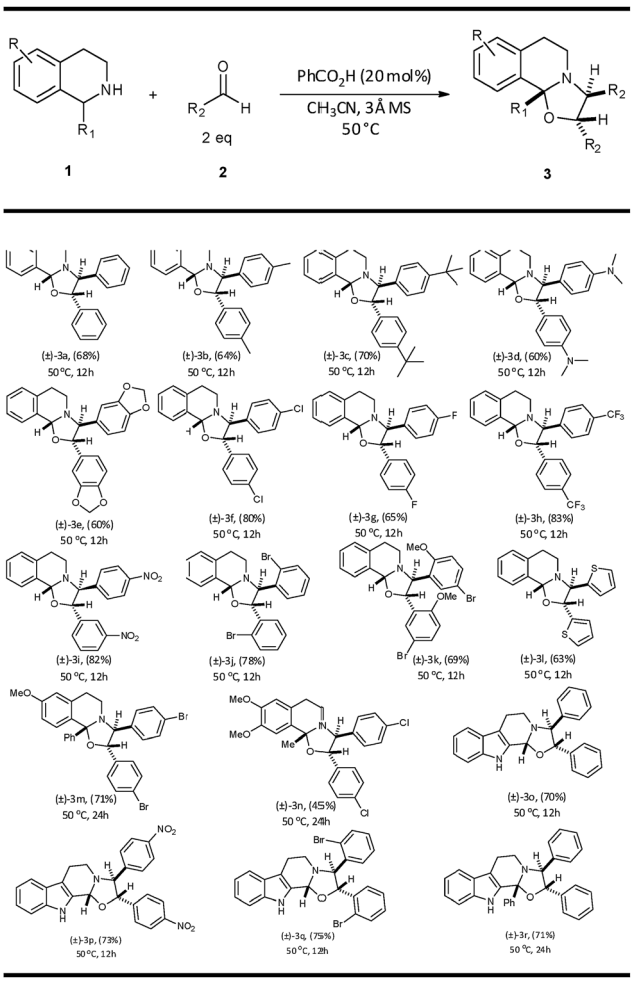
substituent's in the aldehyde precursors was shown (Scheme 2). The presence of electron-donating groups like –Me, *tert*-butyl and even $N(Me)_2$ delivered oxazolidine analogues in moderate yields (**3b–d**). Aldehydes bearing halogens such as –F, –Cl, –Br, CF_3 and a strong electron-withdrawing group like $–NO_2$ were underwent the title reaction to form desired products in good yields (**3f–j**). Even disubstituted aldehyde successfully formed the product without diminishing the yield **3k**. Piperonal and Hetero cyclic aldehyde like 2-thiophene carboxaldehyde also underwent the reaction to give the desired product **3e** and **3l** respectively in good yields. Moreover in each case, the formation of a single diastereomer was observed and the absolute stereochemistry was unambiguously determined by single X-ray crystallography for the compounds (**3j**, **3k** and **3o**). The scope of the reaction was successfully extended to other substrates such as trypoline and sterically demanding 1-alkyl THIQ, 1-aryl THIQ and 1-aryl-trypoline which also underwent the title reaction under equally mild conditions (**3m–r**).

The other high reactive amines like isoindoline failed to give the desired product but under similar reaction condition it ends up with an unusual product **5b** (Scheme 3) which was finally confirmed by single X-ray crystal studies.

With the interest of further enhancement of scope of the process the reaction was performed with challenging precursor like pyrrolidine. Examples of azomethine ylide formation from simple, unfunctionalized cyclic amines like pyrrolidine remain

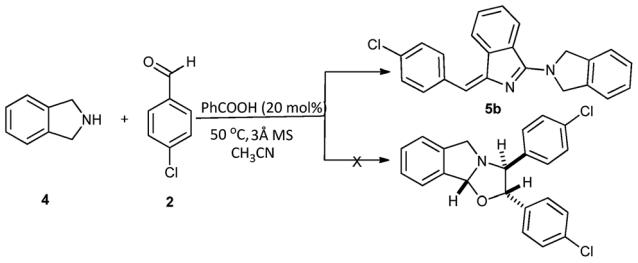


Scheme 1 Examples of the redox-neutral approach.

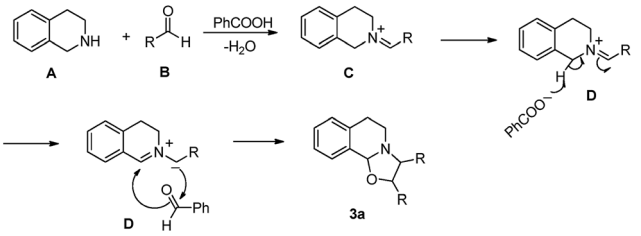


Scheme 2 Substrate scope for the [3 + 2]-cycloaddition with THIQs and trypoline.

rare as they require relatively high reaction temperatures.[10,12] The reaction up to difuctionalization and aromatization was reported under harsh and microwave condition (Scheme 1).[13] In this context, we were particularly delighted to discover a rare poly C–H bond functionalization *via* domino process which furnished the highly substituted 1*H*-pyrrolo[2,1-*c*][1,4]oxazines.



Scheme 3 Unusual product with isoindoline.



Scheme 5 Probable mechanism for the formation of oxazolo[2,3-*c*] isoquinoline.

We were surprised with the formation of 1*H*-pyrrolo[2,1-*c*][1,4] oxazine derivative as a major product with the yield of 40% with only 2 equivalence of aldehyde. Then with intent of increasing the yield of the product, the reaction was successfully carried out with 4 equivalence of aldehyde to yield upto 65% while the 5 equivalence of aldehyde had no further positive impact on the yield of the product. The structure of the compound **7a** was confirmed by single X-ray crystal (Fig 1).

There are very few methods available for the synthesis of substituted pyrrolo benzoxazines and oxazines which suffer from demerits like high cost, multistep and tedious process.[8]

To the best of our knowledge, this methodology represents the first one pot protocol for the synthesis of highly substituted fused 1*H*-pyrrolo[2,1-*c*][1,4]oxazine derivatives from readily available cost effective precursors (Scheme 4).

A probable mechanistic explanation for the formation of fused oxazolo[2,3-*a*]isoquinoline reaction is outlined in Scheme 5. The first step is the formation of the iminium ion **C** by the reaction between THIQ and aldehyde. Then iminium ion **C** transformed into azomethine ylide **D** *via* iminium α-deprotonation by the carboxylate anion.[5a] The intermolecular [3 + 2]-cycloaddition reaction between another equivalent of the aldehyde and the generated azomethine ylide **D** afforded the corresponding product **3a** in good yield.

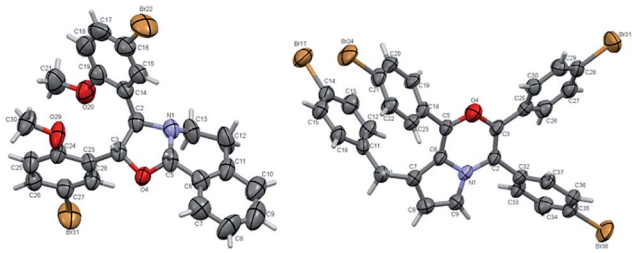
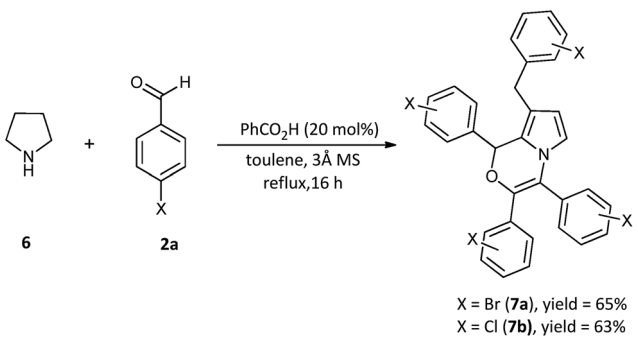


Fig. 1 ORTEP crystal structure of **3k** and **7a**.



Scheme 4 Synthesis of 1*H*-pyrrolo[2,1-*c*][1,4]oxazines.

Conclusion

In summary, we present a simple and versatile method for the diastereoselective synthesis of fused oxazolidine derivatives and 1*H*-pyrrolo[2,1-*c*][1,4]oxazine *via* amine C–H and aldehyde C–O bond funtionalization for the first time. All of the synthesized oxazolidine derivatives obtained as a single diastereomer. The less reactive substrate like pyrrolidine underwent redox neutral domino reaction to give highly substituted 1*H*-pyrrolo[2,1-*c*][1,4] oxazine derivatives. Efficient, One pot, mild, transition metal-free conditions, cost effective, readily accessible precursors and broad substrate scope are the attractive features of this protocol. The excellent levels in terms of constructing fused five membered and six membered hetero cycles suggest this strategy as a valuable candidate for the preparation of stereo chemically defined oxazolidine derivatives and highly substituted 1*H*-pyrrolo[2,1-*c*][1,4]oxazine. Further studies on this and related reactions are ongoing.

Experimental section

(±)-3*a*:(2*S*,3*S*,10*bR*)-2,3-Diphenyl-3,5,6,10*b*-tetrahydro-2*H*-oxazolo[2,3-*a*]isoquinoline

Colorless solid; yield 68%; (R_f = 0.8 in hexanes/EtOAc 95 : 05 v/v); MP 142–144 °C; IR (KBr): 3010, 2850, 1670, 1639, 1608, 1070 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.42 (dd, J = 1.6 Hz, 8.8 Hz, 1H), 7.27–7.23 (comp, 3H), 7.21–7.12 (comp, 9H), 7.11–7.08 (m, 1H), 5.72 (s, 1H), 4.77 (d, J = 8.0 Hz, 1H), 3.90 (d, J = 6.8 Hz, 1H), 3.06–2.97 (m, 2H), 2.85–2.82 (m, 1H), 2.76–2.71 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.5, 139.6, 135.6, 133.3, 128.8, 128.5, 128.3, 127.7, 127.46, 127.43, 126.9, 126.65, 126.60, 90.4, 87.1, 76.3, 46.7, 28.4; *m*/*z* (ESI-MS) $[M + H]^+$ calculated 328.1623 found 328.1688.

(±)-3*b*:(2*S*,3*S*,10*bR*)-2,3-Di-*p*-tolyl-3,5,6,10*b*-tetrahydro-2*H*-oxazolo[2,3-*a*]isoquinoline

Colorless solid; yield 64%; (R_f = 0.86 in hexanes/EtOAc 80 : 20 v/v); MP 138–140 °C; IR (KBr): 3018, 2915, 1670, 1629, 1599, 1050 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.49 (d, J = 5.2 Hz, 1H),

7.32–7.26 (m, 2H), 7.22–7.17 (comp, 2H), 7.15–7.10 (m, 5H), 7.06 (d, J = 5.2 Hz, 2H), 5.78 (s, 1H), 4.81 (d, J = 7.6 Hz, 1H), 3.92 (d, J = 7.2 Hz, 1H), 3.13–3.05 (m, 2H), 3.02–2.80 (m, 2H), 2.34 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.5, 137.4, 136.9, 136.6, 135.6, 133.5, 129.1, 129.0, 128.6, 127.9, 127.0, 126.7, 126.4, 126.1, 90.2, 87.2, 75.9, 46.5, 28.3, 21.0; m/z (ESI-MS) $[M + H]^+$ calculated 356.1936 found 356.1956.

(±)-3*c*:(2*S*,3*S*,10*bR*)-2,3-Bis(4-*tert*-butylphenyl)-3,5,6,10*b*tetrahydro-2*H*-oxazolo[2,3-*a*]isoquinoline

Colorless solid; yield 70%; (R_f = 0.88 in hexanes/EtOAc 80 : 20 v/v); MP 148–150 °C; IR (KBr): 3018, 2902, 2898, 2853, 1673, 1648, 1621, 1070 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.48 (m, 1H), 7.39–7.33 (m, 2H), 7.13 (d, J = 7.2 Hz, 4H), 7.28–7.23 (m, 4H), 7.20–7.16 (m, 1H), 5.76 (s, 1H), 4.86 (d, J = 7.6 Hz, 1H), 4.02 (d, J = 7.2 Hz, 1H), 3.22–3.17 (m, 1H), 3.09–2.95 (m, 2H), 2.87–2.80 (m, 1H), 1.32 (s, 9H), 1.29 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.6, 150.0, 138.3, 138.0, 136.8, 135.6, 133.2, 128.8, 127.9, 126.5, 126.3, 126.0, 125.4, 125.3, 90.3, 86.8, 75.8, 46.9, 31.3, 28.8; m/z (ESI-MS) $[M + H]^+$ calculated 440.2875 found 440.2897.

(±)-3*d*:4,4′-((2*S*,3*S*,10*bR*)-3,5,6,10*b*-Tetrahydro-2*H*-oxazolo[2,3-*a*]isoquinoline-2,3-diyl)bis(*N*,*N*-dimethylaniline)

Colorless solid yield 60%; (R_f = 0.65 in hexanes/EtOAc 80 : 20 v/v); MP 124–126 °C; IR (KBr): 3018, 2850, 1640, 1639, 1622, 1079 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (d, J = 8.0 Hz, 1H), 7.26–7.13 (comp, 6H), 7.07–7.05 (m, 2H), 6.79 (t, J = 6.8 Hz, 2H), 4.92 (s, 1H), 4.62 (d, J = 8.4 Hz, 1H), 3.88 (d, J = 8.0 Hz, 1H), 2.99 (s, 12H), 2.94–2.89 (m, 2H), 2.58–2.55 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.1, 130.0, 128.8, 128.5, 128.1, 127.8, 126.8, 126.3, 125.6, 125.0, 112.1, 90.3, 85.1, 70.07, 45.7, 41.8, 29.4; m/z (ESI-MS) $[M + H]^+$ calculated 401.2389 found 401.2381.

(±)-3*e*:(2*S*,3*S*,10*bR*)-2,3-Di(benzo[*d*][1,3]dioxol-5-yl)-3,5,6,10*b*tetrahydro-2*H*-oxazolo[2,3-*a*]isoquinoline

Colorless solid; yield 60%; (R_f = 0.55 in hexanes/EtOAc 85 : 15 v/v); MP 114–116 °C; IR (KBr): 3015, 2915, 1668, 1629, 1622, 107 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49 (t, J = 4.0 Hz, 1H), 7.35–7.29 (m, 2H), 7.25 (d, J = 8 Hz, 6H), 7.22–7.18 (m, 1H), 7.16 (d, J = 8 Hz, 1H), 5.8 (s, 1H), 4.76 (d, J = 7.6 Hz, 1H), 3.87 (d, J = 7.2 Hz, 1H), 3.10–3.04 (m, 2H), 2.93–2.81 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.9, 147.7, 147.2, 146.9, 135.4, 134.1, 133.5, 133.1, 128.6, 128.5, 128.2, 126.5, 122.1, 120.4, 109.4, 108.1, 107.3, 106.6, 101.0, 100.9, 90.0, 87.3, 75.6, 46.3, 29.0; m/z (ESI-MS) $[M + H]^+$ calculated 402.1263 found 402.1259.

(±)-3*f*:(2*S*,3*S*,10*bR*)-2,3-Bis(4-chlorophenyl)-3,5,6,10*b*-tetrahydro-2*H*-oxazolo[2,3-*a*]isoquinoline

Colorless solid; yield 80%; (R_f = 0.55 in hexanes/EtOAc 95 : 05 v/v); MP 140–142 °C; IR (KBr): 3012, 2852, 1667, 1648, 1633, 1079, 790 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.23 (m, 2H), 7.19–7.16 (m, 2H), 7.09 (s, 1H), 6.92 (s, 1H), 6.82–6.71 (comp, 3H); 6.68 (d, J = 3.2 Hz, 1H), 5.94 (s, 4H), 5.76 (s, 1H), 4.71 (d, J = 7.6 Hz, 1H), 3.82 (d, J = 7.6 Hz, 1H), 3.08 (t, J = 6.0, 1H), 2.89–2.84 (m, 2H), 2.74–2.73 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.4, 137.7, 135.4, 133.7, 133.3, 133.2, 128.9, 128.7, 128.6, 128.4, 128.1, 128.0, 127.4, 126.6, 90.4, 86.6, 75.6, 46.4, 28.0; m/z (ESI-MS) $[M + H]^+$ calculated 396.0844 found 396.0846.

(±)-3*g*:(2*S*,3*S*,10*bR*)-2,3-Bis(4-fluorophenyl)-3,5,6,10*b*-tetrahydro-2*H*-oxazolo[2,3-*a*]isoquinoline

Colorless solid; yield 65%; (R_f = 0.50 in hexanes/EtOAc 95 : 05 v/v); MP 132–134 °C; IR (KBr): 3012, 2895, 1680, 1619, 1611, 1110 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22 (dd, J = 0.8 Hz, 8.8 Hz, 2H), 7.22–7.18 (m, 4H), 7.12–6.98 (m, 3H), 6.95–6.86 (m, 4H), 5.73 (s, 1H), 4.65 (d, J = 7.6 Hz, 1H), 3.80 (d, J = 7.6 Hz, 1H), 3.02–2.99 (m, 2H), 2.82–2.73 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.6 (d, $J_{C\text{-}F}$ = 72.8 Hz, 1C), 161.1 (d, $J_{C\text{-}F}$ = 469.6 Hz, 1C), 135.5, 135.4, 134.8, 133.3, 128.8, 128.4, 128.4, 128.1, 128.09, 128.02, 115.6, 115.5, 115.38, 115.31, 90.3, 86.9, 75.5, 46.4, 27.9; m/z (ESI-MS) $[M + H]^+$ calculated 364.1935 found 364.1929.

(±)-3*h*: (3*S*,10*bR*)-2,3-Bis(4-(trifluoromethyl)phenyl)-3,5,6,10*b*tetrahydro-2*H*-oxazolo[2,3-*a*]isoquinoline

Colorless solid; yield 83%; (R_f = 0.68 in hexanes/EtOAc 90 : 10 v/v); MP 100–102 °C; IR (KBr): 3018, 2912, 1671, 1629, 1611, 1070, 990, 1118 cm^1; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, J = 8.0 Hz, 2H), 7.56 (d, J = 8.1 Hz, 2H), 7.51 (d, J = 4.4 Hz, 1H), 7.46 (d, J = 8.4 Hz, 2H), 7.37–7.31 (m, 4H), 7.24–7.21 (m, 1H), 5.84 (s, 1H), 4.87 (d, J = 7.2 Hz, 1H), 3.0 (d, J = 7.0 Hz, 1H), 3.12–3.09 (m, 2H), 3.00–2.92 (m, 1H), 2.88–2.83 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.0, 143.2, 135.3, 132.7, 130.4, 130.1, 128.5, 128.3, 128.1, 127.4, 126.9, 126.6, 126.2, 125.6, 125.5, 125.3, 122.7, 122.6, 90.7, 86.3, 76.0, 46.6, 28.1; m/z (ESI-MS) $[M + H]^+$ calculated 464.1371 found 464.1381.

(±)3*i*:(3*S*,10*bR*)-2,3-Bis(4-nitrophenyl)-3,5,6,10*b*-tetrahydro-2*H*oxazolo[2,3-*a*]isoquinoline

Colorless solid; yield 82%; (R_f = 0.58 in hexanes/EtOAc 85 : 15 v/v); MP 136–138 °C; IR (KBr): 3012, 2912, 1684, 1643, 1611, 1530, 1311, 1180 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22 (d, J = 8.4 Hz, 2H), 8.16 (d, J = 8.4 Hz, 2H), 7.50 (t, J = 7.6 Hz, 3H), 7.41 (d, J = 8.20 Hz, 2H), 7.33 (t, J = 4.4 Hz, 2H), 7.24–7.22 (m, 1H), 5.84 (s, 1H), 4.89 (d, J = 7.6 Hz, 1H), 4.04 (d, J = 6.8 Hz, 1H), 3.12–3.08 (m, 2H), 3.00–2.84 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.8, 147.7, 147.2, 146.3, 135.2, 132.3, 128.5, 128.4, 128.1, 127.90, 127.92, 127.4, 126.8, 124.0, 123.9, 91.0, 85.8, 76.0, 46.8, 28.2; m/z (ESI-MS) $[M + H]^+$ calculated 418.1325 found 418.1333.

(±)-3*j*:(2*S*,3*S*,10*bR*)-2,3-Bis(2-bromophenyl)-3,5,6,10*b*-tetrahydro-2*H*-oxazolo[2,3-*a*]isoquinoline

Colorless solid; yield 78%; (R_f = 0.85 in hexanes/EtOAc 95 : 05 v/v); MP 138–140 °C; IR (KBr) cm^{-1} 3014, 2910, 1658, 1612, 1112, 710, 738; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, J = 7.2 Hz, 1H), 7.55–7.51 (m, 3H), 7.44 (d, J = 8 Hz, 1H), 7.39 (t, J = 7.6 Hz, 1H), 7.33–7.28 (m, 2H), 7.26–7.18 (m, 2H), 7.14 (t, J = 7.6 Hz, 1H), 7.08 (t, J = 7.2 Hz, 1H), 5.92 (s, 1H), 5.45 (d, J = 6.4 Hz, 1H), 4.64

(d, J = 6.4 Hz, 1H), 3.19–3.07 (m, 1H), 2.91–2.87 (m, 1H), 2.83 (t, J = 3.2 Hz, 1H), 2.79 (t, J = 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.5, 135.4, 132.96, 132.90, 132.5, 129.0, 128.9, 128.8, 128.6, 128.4, 128.1, 128.0, 127.7, 127.6, 126.5, 124.8, 122.8, 90.5, 83.5, 74.9, 46.9, 28.6; m/z (ESI-MS) $[M + H]^+$ calculated 472.9735 found 472.9727.

(±)-3*k*:(2*S*,3*S*,10*bR*)-2,3-Bis(5-bromo-2-methoxyphenyl)-3,5,6,10*b*tetrahydro-2*H*-oxazolo[2,3-*a*]isoquinoline

Colorless solid; yield 69%; (R_f = 0.66 in hexanes/EtOAc 80 : 20 v/v); MP 134–136 °C; IR (KBr): 3018, 2902, 1658, 1659, 1090, 690 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (d, J = 2 Hz, 1H), 7.56 (d, J = 2.4 Hz, 1H), 7.48–7.46 (m, 1H), 7.33–7.25 (m, 4H), 7.21–7.19 (m, 1H), 6.66 (d, J = 8.4 Hz, 2H), 5.66 (s, 1H), 5.15 (d, J = 6.8 Hz, 1H), 4.36 (d, J = 7.2 Hz, 1H), 3.53 (s, 3H), 3.44 (s, 3H), 3.22–3.19 (m, 1H), 3.05–3.02 (m, 2H), 2.84–2.80 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.3, 156.2, 135.7, 132.3, 131.0, 130.6, 130.3, 130.2, 130.1, 128.9, 128.2, 128.0, 126.3, 112.99, 112.97, 111.8, 111.6, 90.1, 79.2, 70.5, 55.3, 54.9, 47.4, 29.6; m/z (ESI-MS) $[M + H]^+$ calculated 546.0024 found 546.0018.

(±)-3*l*:(2*R*,3*R*,10*bR*)-2,3-Di(thiophen-2-yl)-3,5,6,10*b*-tetrahydro-2*H*oxazolo[2,3-*a*]isoquinoline

Yellow solid; yield 63%; (R_f = 0.75 in hexanes/EtOAc 80 : 20 v/v); MP 120–122 °C; IR (KBr): 3014, 2912, 1668, 1638, 1612, 1080 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 (d, J = 8.8 Hz, 1H), 7.21–7.13 (m, 4H), 7.12–7.08 (m, 1H), 6.95 (d, J = 3.2 Hz, 1H), 6.90 (m, 1H), 6.85 (t, J = 4.8 Hz, 2H), 5.66 (s, 1H), 5.14 (d, J = 6.8 Hz, 1H), 4.30 (d, J = 6.4 Hz, 1H), 3.20–3.13 (m, 1H), 3.08–3.03 (m, 1H), 2.95–2.87 (m, 1H), 2.78–2.72 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.8, 135.5, 132.4, 128.9, 128.7, 128.1, 127.9, 127.3, 126.3, 125.7, 125.4, 124.6, 124.0, 123.9, 90.3, 83.0, 72.9, 47.0, 28.7; m/z (ESI-MS) $[M + H]^+$ calculated 340.0752 found 340.0750.

(±)-3*m*:(2*S*,3*S*,10*bR*)-2,3-Bis(4-bromophenyl)-8-methoxy-10*b*phenyl-3,5,6,10*b*-tetrahydro-2*H*-oxazolo[2,3-*a*] isoquinoline

Colorless solid; yield 71%; (R_f = 0.40 in hexanes/EtOAc 90 : 10 v/v); MP 162–164 °C; IR (KBr): 3021, 2918, 1670, 1648, 1621, 1070, 658, 748 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52–7.50 (m, 2H), 7.46–7.41 (m, 3H), 7.35–7.29 (m, 5H), 7.11 (d, J = 8.0 Hz, 2H), 6.90 (d, J = 6.4, 11.2 Hz, 1H), 6.82 (d, J = 8.4 Hz, 2H), 6.66 (d, J = 2.8 Hz, 1H), 4.99 (d, J = 8.8 Hz, 1H), 3.84 (dd, J = 8.1 Hz, 1H), 3.84 (s, 3H), 3.15–3.09 (m, 1H), 2.87–2.78 (m, 2H), 2.59–2.53 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.7, 146.0, 137.7, 136.3, 135.3, 131.7, 131.2, 130.4, 130.3, 130.2, 129.8, 129.0, 128.3, 127.8, 127.7, 121.9, 121.8, 113.3, 112.2, 112.1, 96.1, 87.0, 72.2, 55.2, 41.1, 29.6; m/z (ESI-MS) $[M + H]^+$ calculated 592.0232 found 592.0236.

(±)-3*n*:2,3-Bis-[4-chlorophenyl]-8,9-dimethoxy-10*b*-methyl-3,5,6,10*b*-tetrahydro-2*H*-oxazaolo[2,3-*a*]isoquinoline

Colorless solid; yield 45%; (R_f = 0.40 in hexanes/EtOAc 80 : 20 v/v); MP 104–106 °C; IR (KBr): 3394, 2998, 2934, 1685, 1604, 1054 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24–7.14 (m, 6H), 7.11–7.08 (m, 1H), 7.05 (d, J = 8.4 Hz, 1H), 6.96 (s, 1H), 6.84 (s, 1H), 4.85 (d, J = 12.4 Hz, 1H), 3.9 (d, J = 12, 1H), 3.84 (s, 3H), 3.76 (s, 3H), 3.05–3.0 (m, 2H), 2.94–2.84 (m, 2H), 1.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.6, 138.8, 136.4, 135.7, 134.4, 134.2, 127.9, 127.7, 127.6, 127.4, 127.1, 127.0, 126.4, 125.6, 90.4, 86.6, 75.6, 55.3, 46.9, 28.5, 21.2; m/z (ESI-MS) $[M + H]^+$ calculated 467.1420 found 468.1413.

(±)-3*o*:2,3-Diphenyl-2,3,4,5,10,10*b*-hexahydro-1-oxa-3*a*,10-diazacyclopenta[*a*]fluorine

Colorless solid; yield 65%; (R_f = 0.36 in hexanes/EtOAc 80 : 20 v/v); MP 144–146 °C; IR (KBr): 3358, 3018, 2912, 1660, 1638, 1621, 1078 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.53 (s, 1H), 7.58 (d, J = 7.6 Hz, 1H), 7.38–7.28 (m, 7H), 7.25–7.14 (m, 6H), 7.12–7.09 (m, 1H), 7.01 (dd, J = 2.0 Hz, 8 Hz, 1H), 6.22 (s, 1H), 5.01 (d, J = 7.6 Hz, 1H), 4.02 (d, J = 8.2 Hz, 1H), 3.24 (q, J = 4.4 Hz, 2H) 2.88–2.86 (m, 1H), 2.68–2.64 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.8, 137.9, 136.6, 131.9, 128.6, 128.3, 128.0, 127.9, 127.2, 127.1, 126.8, 126.6, 126.59, 126.54, 122.5, 119.6, 119.5, 118.9, 111.4, 109.8, 88.5, 86.8, 71.4, 43.9, 29.7; m/z (ESI-MS) $[M + H]^+$ calculated 367.1732 found 367.1748.

(±)-3*p*: 2,3-Bis-(4-nitro-phenyl)-2,3,4,5,10,10*b*-hexahydro-1-oxa-3*a*,10-diaza-cyclopenta[*a*]fluorine

Colorless solid; yield 73%; (R_f = 0.36 in hexanes/EtOAc 80 : 20 v/v); MP 154–156 °C; IR (KBr): 3348, 3010, 2914, 1674, 1645, 1621, 1514, 1318, 1079 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.36 (br, s, 1H), 8.22 (d, J = 8.8 Hz, 2H), 8.03 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 8.0 Hz, 1H), 7.48–7.39 (m, 3H), 7.29–7.24 (m, 1H), 7.16 (t, J = 8.0 Hz, 1H), 7.10 (d, J = 8.8 Hz, 1H), 4.99 (d, J = 7.6 Hz, 1H), 4.06 (d, J = 5.6 Hz, 1H), 3.28–3.23 (m, 1H), 3.16–3.13 (m, 1H), 2.88–2.80 (m, 1H), 2.72–2.68 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.0, 147.8, 145.5, 144.7, 136.8, 130.6, 128.7, 128.4, 128.2, 127.3, 126.5, 126.2, 124.1, 123.7, 123.2, 120.0, 119.1, 111.5, 86.9, 71.0, 44.13, 29.6; m/z (ESI-MS) $[M + H]^+$ calculated 406.1199 found 406.1191.

(±)3*q*:(2*S*,3*S*,11*bR*)-2,3-Bis(2-bromophenyl)-2,3,5,6,11,11*b*hexahydrooxazolo[3′,2′:1,2]pyrido[3,4-*b*]indole

Colorless solid; yield 74%; (R_f = 0.30 in hexanes/EtOAc 80 : 20 v/v); MP 152–154 °C; IR (KBr): 3340, 3014, 2914, 1659, 1657, 1622, 1110, 680, 710 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.36 (s 1H), 7.89 (d, J = 7.6 Hz, 1H), 7.59 (d, J = 8 Hz, 1H), 7.47 (d, J = 7.6 Hz, 1H), 7.43–7.37 (m, 3H), 7.26 (t, J = 10.4 Hz, 2H), 7.18–7.22 (m, 3H), 7.04 (t, J = 8.0 Hz, 1H), 6.23 (s, 1H), 5.52 (d, J = 7.2 Hz, 1H), 4.66 (d, J = 7.2 Hz, 1H), 3.25–3.21 (m, 1H), 3.15–3.12 (m, 1H), 2.93–2.86 (m, 1H), 2.70–2.69 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.1, 132.8, 132.4, 131.4, 129.4, 129.2, 128.9, 127.8, 127.7, 125.2, 122.9, 122.6, 119.6, 119.1, 111.4, 110.5, 86.8, 85.5, 69.3, 44.3, 29.6, 18.0; m/z (ESI-MS) $[M + H]^+$ calculated 524.9922 found 524.9914.

(±)3*r*:(2*S*,3*S*,11*bR*)-2,3,11*b*-Triphenyl-2,3,5,6,11,11*b*hexahydrooxazolo[3′,2′:1,2]pyrido[3,4-*b*]indole

Colorless solid; yield 71%; (R_f = 0.30 in hexanes/EtOAc 80 : 20 v/v); MP 168–170 °C; IR (KBr): 3336, 3010, 2898, 1678, 1635, 1608, 1079 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.14 (s, 1H), 8.01 (d, J = 8.0 Hz, 1H), 7.91 (comp, 1H), 7.55 (comp, 1H), 7.48 (comp, 2H), 7.37 (comp, 2H), 7.29–7.23 (m, 4H), 7.18 (d, J = 7.2 Hz, 5H), 6.75 (d, J = 6.4, 2H), 5.62 (d, J = 8.0 Hz, 1H), 4.52 (d, J = 8.0 Hz, 1H), 3.18–3.13 (m, 1H), 3.06–3.03 (m, 1H), 2.78–2.70 (m, 1H), 2.6–2.58 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.1, 139.2, 136.2, 135.4, 134.1, 132.3, 132.1, 131.5, 131.3, 131.2, 130.0, 129.8, 129.7, 129.0, 128.97, 128.94, 128.8, 128.6, 128.4, 127.56, 127.52, 127.3, 127.2, 123.7, 121.8, 119.5, 115.3, 90.2, 75.1, 36.9, 21.1; m/z (ESI-MS) $[M + H]^+$ calculated 443.2045 found 443.2051.

(*Z*)-3-Benzylidene-1′,3′-dihydro-3*H*-1,2′-biisoindole

Colorless solid; yield 60%; (R_f = 0.45 in hexanes/EtOAc 85 : 15 v/v); MP 98 °C; IR (KBr): 3019, 2912, 1859, 1651, 1639, 1612 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.23 (dd, J = 4.8 Hz, 8.8 Hz, 2H), 7.65 (dd, J = 9.2 Hz, 16.4 Hz, 2H), 7.45–7.34 (comp, 9H), 6.58 (S, 1H), 5.38–5.25 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.7, 148.6, 144.7, 136.4, 136.0, 132.1, 131.6, 128.6, 128.4, 127.1, 122.6, 122.0, 119.9, 111.99, 111.94, 29.6; m/z (ESI-MS) $[M + H]^+$ calculated 323.1470 found 323.1498.

(*Z*)-3-(4-Chlorobenzylidene)-1′,3′-dihydro-3*H*-1,2′-biisoindole

Colorless solid; yield 65%; (R_f = 0.60 in hexanes/EtOAc 8515 v/v); MP 104 °C; IR (KBr): 3010, 2912, 890, 1678, 1649, 1612, 768 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.22 (d, J = 8.8 Hz, 2H), 7.79 (dd, J = 7.6 22.8 Hz, 2H), 7.45–7.34 (comp, 8H), 6.57 (s, 1H), 5.34–5.28 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.7, 148.6, 144.7, 136.4, 136.0, 132.1, 131.6, 128.6, 128.4, 127.7, 127.1, 122.6, 122.0, 119.9, 111.99, 111.94, 29.6; m/z (ESI-MS) $[M + H]^+$ calculated 357.1080 found 357.1088.

8-(4-Bromobenzyl)-3-(3-bromophenyl)-1,4-bis(4-bromophenyl)-1*H*-pyrrolo[2,1-*c*][1,4]oxazine

Colorless solid; yield 65%; (R_f = 0.60 in hexanes/EtOAc 8515 v/v); MP 215 °C; IR (KBr): 3010, 2914, 1898, 1648, 1620, 1156, 748, 724, 688, 656 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, J = 8.0 Hz, 2H), 7.52 (d, J = 7.6 Hz, 2H), 7.38–7.36 (m, 2H), 7.31–7.27 (m, 6H), 7.19–7.16 (m, 4H), 6.69 (d, J = 8.0 Hz, 2H), 6.58 (d, J = 2.8, 1H), 3.71 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.9, 136.2, 135.4, 134.1, 133.1, 131.6, 130.4, 129.8, 129.6, 129.5, 129.4, 128.8, 128.2, 125.8, 121.1, 117.9, 112.4, 82.8, 35.2; m/z (ESI-MS) $[M + H]^+$ calculated 754.8316 found 754.8324.

8-(4-Chlorobenzyl)-3-(3-chlorophenyl)-1,4-bis(4-chlorophenyl)-1*H*pyrrolo[2,1-*c*][1,4]oxazine

Colorless solid; yield 63%; (R_f = 0.60 in hexanes/EtOAc 8515 v/v); MP 210 °C; IR (KBr): 3006, 2912, 2898, 1670, 1647, 1611, 1148, 828, 810, 784, 762 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.52 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.8 Hz, 2H), 7.38–7.36 (m, 2H), 7.31–7.26 (m, 7H), 7.18–7.15 (m, 3H), 6.66 (d, J = 6.4 Hz, 2H), 6.55 (d, J = 2.8 Hz, 1H), 3.67 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.0, 134.4, 133.2, 132.1, 130.549, 129.9, 129.0, 128.4, 128.2, 128.1, 128.0, 127.4, 127.0, 122.19, 122.18, 116.0, 111.2, 84.2, 33.2; m/z (ESI-MS) $[M + H]^+$ calculated 578.0348 found 578.0368.

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