A Highly Stereocontrolled, One-Pot Approach towards Pyrrolobenzoxazinones and Pyrroloquinazolinones through a Lewis Acid-Catalyzed [3+2]-Cycloannulation Process

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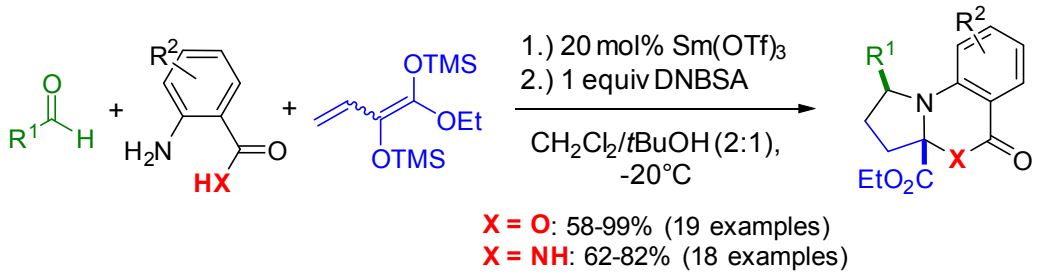


ABSTRACT: We report herein a stereocontrolled [3+2]-cycloheteroannulation of *bis*-silyl dienediolate **1** with 2-aminobenzoic acid- and 2-aminobenzamide-derived imines to furnish highly substituted pyrrolo[1,2-*a*]benzoxazinones **3** and pyrrolo[1,2-*a*]quinazolinones **4**, respectively, in good overall yields. This one-pot process rapidly generates molecular complexity and comprises a Lewis acid-catalyzed, vinylogous Mannich reaction of **1** followed by an intramolecular *N,O*-acetal- and *N,N*-aminal formation, respectively, which proceeds with good to excellent stereocontrol.

INTRODUCTION

The rapid and stereocontrolled synthesis of novel heterocyclic scaffolds which are relevant for biological studies and pharmaceutical applications is currently among the prime objectives in synthetic organic chemistry.[1] In the pursuit of this goal domino and sequential reactions that lead to multiple bond forming events in a one-pot operation are particularly attractive processes as they feature operational simplicity, flexibility, and efficiency.[2] In addition, such processes typically give rise to new reactive functional groups and stereogenic centers which are ideally established with high stereoselectivity.

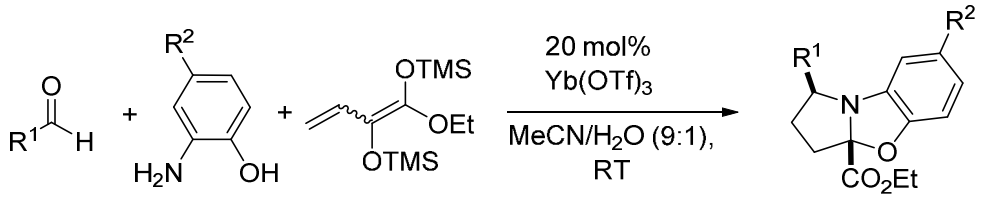
The benzoxazinone and dihydroquinazolinone motifs range prominent among nitrogen-containing heterocycles due to their occurrence in a broad range of biologically active natural products, pharmaceuticals, and agrochemicals.[3] Pharmaceutical activities associated with them include antimalarial,[4] antidiabetic,[5] anticancer,[6] antibacterial,[7] and antihypertensive properties.[8] Moreover, these structures are occasionally fused with other heterocycles and the corresponding pyrrolobenzoxazinones and pyrroloquinazolinones stand as two representative examples.[9]

The classical approach of synthesizing both the benzoxazinone and quinazolinone skeletons is based on the acid-catalyzed condensation of 2-aminobenzoic acid and 2-aminobenzamide, respectively, with carbonyl compounds furnishing directly the desired target molecules.[10] Moreover, the groups of List[11] and Rueping[12] have developed Brønsted acid-catalyzed protocols to execute these reactions in a highly enantioselective fashion and access optically highly enriched quinazolinones. In addition, copper-catalyzed protocols for the synthesis of 2-aryl quinazolinones have been reported that comprise Ullman-type couplings of amines and *ortho*-halogen-substituted benzamides and subsequent CH-amidation to effect the cyclization.[13] Very recently, gold-catalyzed hydroamination-cyclization processes have been added to the arsenal of synthetic chemists as well to prepare fused pyrrolobenzoxazinones and pyrroloquinazolinones.[14]

We have recently described a novel three-component, one-pot [3+2]-cycloannulation process that furnished a broad range of tetrahydropyrrolo[2,1-*b*]benzoxazoles **2** in good yields thereby establishing

four new σ-bonds and two new stereogenic centers with excellent diastereoselectivity in a domino-type fashion (Scheme 1).[15a] Mechanistically, this transformation was initiated by a Lewis acid-catalyzed, vinylogous Mannich reaction of the new *bis*-silyl dienediolate **1** with *ortho*-hydroxy aniline-derived imines followed by hydrolysis of the silyl enol ether moiety formed as an intermediate and finally *N,O*-acetalization of the in situ formed α-keto ester moiety that closed the pyrrolidine ring.

Scheme 1. The [3+2]-Cycloannulation Process towards Tetrahydropyrrolo[2,1-*b*]benzoxazoles 2



1 **2**, max. 87%, single diastereomers

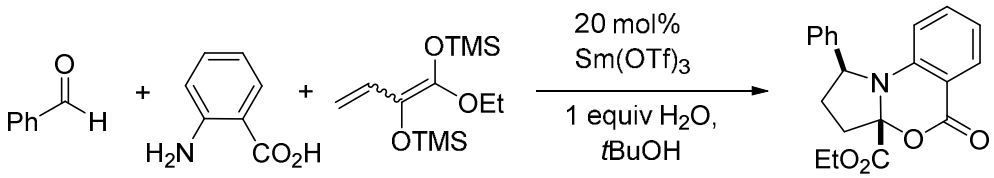
We reasoned that this powerful and straightforward synthesis of fused pyrrolidines could be extended to other heterocyclic frameworks in the event that other imines with a secondary nucleophilic site would participate in this process as well. We now report our findings on the one-pot, highly diastereoselective synthesis of related pyrrolo[1,2-*a*]benzoxazinones and pyrrolo[1,2-*a*]quinazolinones by application of this strategy.[16]

RESULTS AND DISCUSSION

As an alternative to *ortho*-hydroxy aniline we envisioned anthranilic acid as a suitable amine component for our three-component cycloannulation strategy which was expected to give rise to pyrrolobenzoxazinones as the final products. Thus, we started our investigations with the model reaction of anthranilic acid (1.0 equiv.), benzaldehyde (1.2 equiv.), and 1,2-*bis*-silyldienediolate (2.0 equiv.) **1** in *t*BuOH and in the presence of various lanthanide triflates (20 mol%) and H_2O (1 equiv.). Water-tolerant Lewis acids such as $Yb(OTf)_3$ and in particular $Sm(OTf)_3$ turned out to be the most suitable catalysts for

this transformation in terms of yield and selectivity. Thus, $Sm(OTf)_3$ furnished pyrrolo[1,2-*a*]benzoxazinone **3a** with 71% yield as mainly the *cis*-stereoisomer (89:11 *cis*/*trans*) after 4 h at rt while $Yb(OTf)_3$ gave rise to the product with comparable yield but slightly reduced selectivity of 85:15 *cis*/*trans* (Scheme 2).

Scheme 2. Preliminary Studies for the Synthesis of *cis*-3a



1 71%, *dr* 89:11 **3a**

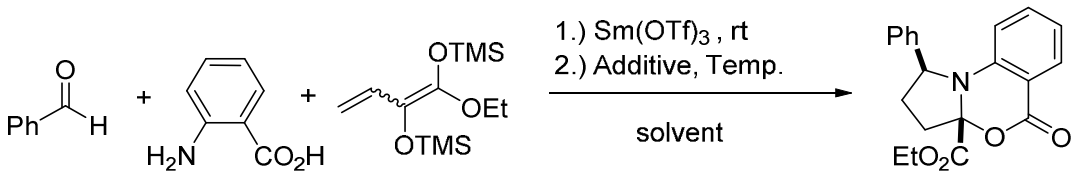
When we attempted to apply this strategy to other pyrrolobenzoxazinones we obtained the desired products in good yields, but unfortunately with no diastereoselectivity whatsoever. Eventually, we were able to trace this phenomenon back to a precipitation of the *cis*-stereoisomer **3a** during cyclization which led to its enrichment, but occurred only in this specific case. Therefore, other conditions were required to obtain the pyrrolobenzoxazinones selectively.

As the diastereoselectivity of this process is determined in the cyclization, the second step of this sequence, we attempted to add various acidic and basic additives after completion of the vinylogous Mannich reaction in order to speed up the cyclization at potentially lower temperatures.[15] However, the use of tetra-*n*-butylammonium fluoride to facilitate the desilylation gave only low yields in the solvent mixture CH_2Cl_2/*t*BuOH (2:1), which was important to dissolve both the starting materials and the product (Table 1, entry 1). Brønsted acids proved to be more efficient. Thus, trifluoroacetic acid mediated the second step at rt in very good yields, albeit with no selectivity (entry 2). Lowering the temperature to -20°C improved the selectivity slightly to 57:43 (*cis*/*trans*; entry 3). Variation of the solvent mixture lead to undesired precipitation, no reaction or no selectivity (entries 4-7). We next investigated the influence of the Brønsted acid on the diastereoselectivity. Among the acids

investigated, 2,4-dinitrobenzenesulfonic acid (DNBSA) gave the best result with a ratio of 85:15 favoring the *cis*-isomer and a combined yield of 61% (entries 8-13).

We assume that the pronounced kinetic *cis*-selectivity is established during nucleophilic addition of the pendent carboxylic acid moiety onto the *in situ*-generated iminium ion and is most likely a result of non-bonding interactions in the transition state between the 5-pyrrolidine substituent (Ph) and the anthranylic acid moiety.

Table 1. Optimization Studies for the [3+2]-Cycloannulation Process towards 3a[a]



1 **3a**

Entry	Additive	Solvent	Temp. (T)	Yield [%][b]	*dr*[c]
1	TBAF	CH_2Cl_2/*t*BuOH (2:1)	rt	22	50:50
2	TFA	CH_2Cl_2/*t*BuOH (2:1)	rt	88	50:50
3	TFA	CH_2Cl_2/*t*BuOH (2:1)	-20°C	83	57:43
4	TFA	toluene/*t*BuOH (2:1)	-20°C	84	66:37[d]
5	TFA	Et_2O/*t*BuOH (2:1)	-20°C	61	70:30[d]
6	TFA	MeOH	-20°C	-	-
7	TFA	MeCN	-20°C	79	50:50
8	TfOH	CH_2Cl_2/*t*BuOH (2:1)	-20°C	99	55:45
9	HCl(Et_2O)	CH_2Cl_2/*t*BuOH (2:1)	-20°C	99	63:37
10	DNBSA	CH_2Cl_2/*t*BuOH (2:1)	-20°C	61	85:15
11	*p*TsOH	CH_2Cl_2/*t*BuOH (2:1)	-20°C	64	83:17
12	MsOH	CH_2Cl_2/*t*BuOH (2:1)	-20°C	81	71:29

13	DNBA	CH_2Cl_2/*t*BuOH (2:1)	-20°C	84	70:30
14	DNBSA[e]	CH_2Cl_2/*t*BuOH (2:1)	-20°C	62	85:15
15	DNBSA[f]	CH_2Cl_2/*t*BuOH (2:1)	-20°C	58	81:19
16	**DNBSA[g]**	**CH_2Cl_2/*t*BuOH (2:1)**	**-20°C**	**83**	**88:12**

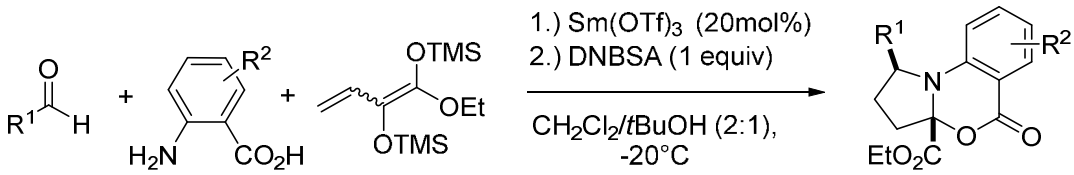
[a]Reaction conditions: anthranilic acid (0.20 mmol), aldehyde (1.20 equiv.), *bis*-silyldienediolate **1** (2.00 equiv.), $Sm(OTf)_3$ (20 mol%) in 1.2 mL solvent mixture containing 1.0 equiv. H_2O for 30 sec at rt, additive (2 equiv.) for max. 2 h. [b]Isolated yield of chromatographically purified material. [c]*dr* of crude product determined by NMR. [d]*cis*-isomer precipitates. [e]1.00 equiv. DNBSA. [f]0.50 equiv. DNBSA. [g]step 1 at -20°C, 1.00 equiv. DNBSA.

The amount of DNBSA could be further reduced to one equivalent with identical results and only a slightly extended reaction time (Table 1, entry 14). The reaction is even possible with 0.5 equivalents of DNBSA, albeit with a slightly decreased yield and selectivity (entry 15). Lowering the temperature of the first step to -20°C further improved both the yield to 83% and the diastereoselectivity to 88:12 (entry 16) We assume that the bulky Brønsted acid DNBSA reinforces the above mentioned non-bonding interactions in the transition state of the cyclization leading to an enhanced diastereoselectivity.

With these optimal conditions in hand we studied the scope of this stereocontrolled [3+2]-cycloheteroannulation process. It turned out that a variety of different aromatic and aliphatic aldehydes were tolerated leading to the corresponding pyrrolobenzoxazinones **3** in generally good to excellent yields (Table 2). The products could be obtained as single stereoisomers upon chromatographic separation of the minor isomers. Various alkyl-substituted and condensed aromatic aldehydes furnished the products in good yields up to 96% and excellent *cis*-selectivities of up to 95:5 (entries 1-6). Halogenated aromatic aldehydes could be successfully applied as well and delivered products **3g** and **3h** in excellent yields and good diastereoselectivities (entries 7 and 8). When the electronic nature of the aromatic system was modulated by electronwithdrawing groups, the selectivity of the process decreased

to 72:28 (entries 9-11). Aliphatic aldehydes could be employed as well under these conditions. Thus, cyclohexane carbaldehyde gave rise to the formation of pyrrolobenzoxazinone **3l** which was obtained in excellent yield and 94:6-diastereoselectivity (entry 12). However, subjecting pivalic aldehyde carrying a very bulky alkyl group to this transformation produced a 1:1-ratio of both diastereomers in 80% yield indicating that the *tert*-butyl group was sterically too demanding (entry 13). Interestingly, simple flash chromatography converted this 1:1-mixture into a 26:74-*cis/trans*-mixture apparently through acid-catalyzed isomerization. The same effect was observed when the reaction was run directly at rt for 24 h in the second step which almost exclusively produced the thermodynamically more stable *trans*-stereoisomer (entry 14).

Table 2. Substrate Scope of the [3+2]-Cycloannulation toward Pyrrolobenzoxazinones 3[a]



Entry	Product	R^1	R^2	Yield[%][b]	*dr*[c]
1	**3a**	Ph	H	83	88:12
2	**3b**	2-Me-C_6H_4	H	88	95:5
3	**3c**	4-Me-C_6H_4	H	87	93:7
4	**3d**	4-Ph-C_6H_4	H	86	89:11
5	**3e**	1-naphthyl	H	88	89:11
6	**3f**	2-naphthyl	H	95	90:10
7	**3g**	4-Cl-C_6H_4	H	94	91:9
8	**3h**	4-Br-C_6H_4	H	96	89:11
9	**3i**	4-MeO-C_6H_4	H	90	86:14

10	**3j**	4-NC-C_6H_4	H	48	77:23
11	**3k**	3-furyl	H	73	72:28
12	**3l**	cyclohexyl	H	87	94:6
13	**3m**	*tert*-butyl	H	80	50:50
14	**3m**[d]	*tert*-butyl	H	58	3:97
15	**3n**	Ph	4-Me	80	94:6
16	**3o**	Ph	5-Me	94	89:11
17	**3p**	Ph	4-OMe	78	88:12
18	**3q**	Ph	4-Cl	45	86:14
19	**3r**	Ph	5-Br	99	89:11

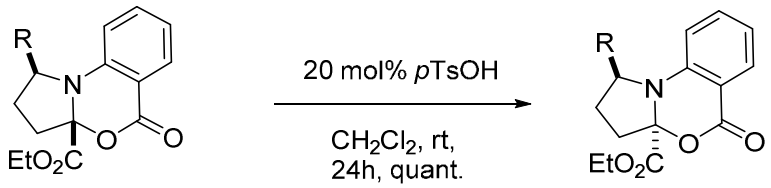
[a]Reaction conditions: amino acid (0.20 mmol), aldehyde (1.20 equiv.), *bis*-silyldienediolate **1** (2.00 equiv.), $Sm(OTf)_3$ (20 mol%) in 1.2 mL solvent mixture containing 1.0 equiv. H_2O for 30-50 min at -20°C, addition of DNBSA for 1.5-7 h at -20°C. [b]Isolated yield of pure material as *cis/trans*-mixture; [c]*dr* of crude product determined by NMR. [d] Entire reaction sequence at rt.

Variation in the anthranilic acid component was also possible and led to the formation of several differently substituted pyrrolobenzoxazinones **3n-r** (entries 15-19). Both electrondonating and electronwithdrawing groups were tolerated in the 4- and 5-position of the heterocycle giving rise to the products in typically good yields (45-99%) and selectivities (*dr* 86:14-94:6). Substitution in the 2-position of the heterocycle led to no product formation presumably on the basis of too much steric hindrance next to the reactive centers. The relative configuration of *cis*-pyrrolo[1,2-*a*]benzoxazinone **3a** was unambiguously determined by X-ray crystallography (see Supporting Information).[17]

Having developed conditions for the stereoselective formation of *cis*-configured pyrrolobenzoxazinones **3** under kinetically controlled conditions we wondered whether we could effectively isomerize the *N,O*-acetal structure and obtain a thermodynamic ratio of stereoisomers. In the case of the *t*Bu-substituted pyrrolobenzoxazinone **3m** it had already become apparent that the

substitution of the heterocycle affected the isomeric ratio and that large substituents rapidly shifted the equilibrium towards the *trans*-stereoisomer (Table 2, entries 13 and 14). Accordingly, we dissolved pyrrolobenzoxazinones **3a** and **3m** in CH_2Cl_2 and treated them each with *para*-toluenesulfonic acid at rt for 24 h until no further change in the isomeric ratio was observed. Whereas isomerically pure **3a** (R = Ph) produced a 1:1-ratio of *cis/trans*-stereoisomers, the 50:50-ratio of *cis*- and *trans*-**3m** (R = *t*Bu) was almost fully converted into the thermodynamically more stable *trans*-isomer in quantitative yield (Table 3). These results clearly reveal that (1) an acid-catalyzed isomerization process was possible and (2) that the thermodynamic ratio of diastereomers depended on the relative steric size of the pyrrolidine substituents.

Table 3. Isomerization under Thermodynamic Conditions.

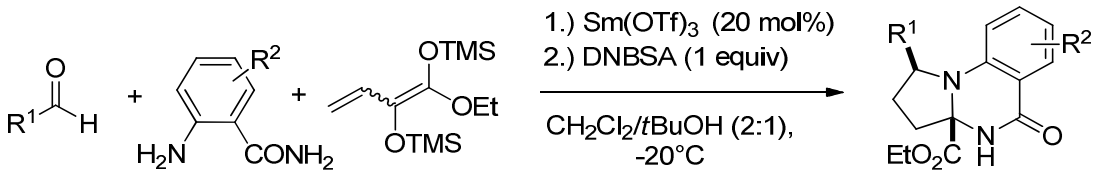


R	*dr* of starting material	*dr* of product
Ph	100:0	50:50
*t*Bu	50:50	4:96

After having established a reliable [3+2]-cycloannulation process for the synthesis of pyrrolobenzoxazinones we wondered whether we could extend this strategy towards the synthesis of the corresponding pyrroloquinazolinones by simply exchanging the anthranilic acid component for an anthranilic amide. Fortunately, the formerly optimized conditions could be completely adopted and excellent yields of the pyrroloquinazolinones **4** were obtained in this one-pot process, despite the occasional formation of quinazolinones as side products in trace amounts (<5%).[11,12,18] Thus, treating benzaldehyde, anthranilic amide, and *bis*-silyldienediolate **1** with 20 mol% $Sm(OTf)_3$ in CH_2Cl_2/*t*BuOH (2:1) for 5 min at -20°C with subsequent addition of 1 equiv. of DNBSA to the intermediate vinylogous Mannich product and stirring this mixture for 3 h at -20°C furnished pyrroloquinazolinone **4a** in 70%

isolated yield and as nearly one single diastereomer (*dr* > 98:2, Table 4, entry 1). Here the addition of DNBSA was not essential for the selectivity but slightly improved the yield from 62% to 70% (entry 2). Using this protocol a broad range of pyrroloquinazolinones **4** were obtained in this three-component [3+2]-cycloannulation process with typically good to excellent yields and as single stereoisomers (*dr* > 98:2) (Table 4). The comparably higher selectivity in the formation of pyrroloquinazolinones in contrast to the pyrrolobenzoxazinones above appears to result from the larger steric size of the amide moiety relative to the acid moiety and enhanced non-bonding interactions in the transition state of the cyclization accordingly.

Table 4. Substrate Scope of the [3+2]-Cycloannulation toward Pyrroloquinazolinones 4[a]



1 **4a-4q**

Entry	Product	R^1	R^2	Yield[%][b]
1	**4a**[c]	Ph	H	70
2	**4a**[d]	Ph	H	62
3	**4b**	2-Me-C_6H_4	H	79
4	**4c**	3-Me-C_6H_4	H	76
5	**4d**	4-Me-C_6H_4	H	70
6	**4e**	1-naphthyl	H	81
7	**4f**	2-naphthyl	H	76
8	**4g**	4-Cl-C_6H_4	H	73
9	**4h**	4-Br-C_6H_4	H	81
10	**4i**	4-F-C_6H_4	H	70

11	**4j**	4-MeO-C_6H_4	H	81
12	**4k**	4-NC-C_6H_4	H	82
13	**4l**	3-furyl	H	66
14	**4m**	Ph	4-Me	69
15	**4n**	Ph	5-Me	73
16	**4o**	Ph	4-MeO	72
17	**4p**	Ph	5-Cl	82
18	**4q**	Ph	5-Br	78

[a]Reaction conditions: anthranilic amides (0.20 mmol), aldehyde (1.20 equiv.), *bis*-silyldienediolate **1** (2.00 equiv.), $Sm(OTf)_3$ (20 mol%) in 1.2 mL solvent mixture containing 1.0 equiv. H_2O for 5 min at -20°C, addition of DNBSA for 1.5-7h at -20°C. [b]Isolated yield of chromatographically pure material; *dr* >98:2. [c]Isolation of quinazolinone **5** in 7% yield.[18] [d]Without DNBSA, 6h at -20°C.

Various tolyl aldehydes as well as naphthyl aldehydes were good substrates for this one-pot process and furnished the products with good yields in the range of 70-81% (Table 4, entries 2-7). Several electrondonating and electronwithdrawing substituents in different positions around the aromatic ring were readily tolerated and delivered the corresponding cycloannulation products with up to 82% yield (entries 8-12). Even the 3-furyl aldehyde-derived pyrroloquinazolinone **4l** was isolated in 66% yield as nearly one single isomer (entry 13). Furthermore, several substituted 2-aminobenzamides turned out to be applicable to this process and reacted to produce the heterocyclic products **4m**-**4q** with up to 82% yield (entries 14-18). The relative configuration of *cis*-pyrroloquinazolinone **4a** was again verified by an X-ray structure (see Supporting Information).[19]

CONCLUSION

In summary, we have reported a novel one-pot, three-component, Lewis-acid-catalyzed [3+2]-cycloheteroannulation process for the stereocontrolled synthesis of complex

pyrrolo[1,2-*a*]benzoxazinones **3** and pyrrolo[1,2-*a*]quinazolinones **4**. Starting from simple aldehydes, anthranilic acid or anthranilamide derivatives, respectively, and the new *bis*-silyldienediolate **1**, a highly efficient synthesis of a broad range of novel heterobicyclic compounds was developed. The products were obtained in good to excellent yields and with good diastereoselectivity in the case of the pyrrolobenzoxazinones and even as single diastereomers in the case of the pyrroloquinazolinones. It was further shown that the *N,O*-acetal moiety of the pyrrolobenzoxazinones could be readily isomerized under acidic conditions. Current investigations are directed towards the development of a catalytic, enantioselective process to furnish the products in enantiomerically enriched form.

EXPERIMENTAL SECTION

General. Unless otherwise noted, all reactions were carried out in dry solvents under argon atmosphere using standard vacuum line techniques. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 26°C. The signals were referenced to residual chloroform (7.26 ppm, ^{1}H, 77.2 ppm, ^{13}C). Chemical shifts are reported in ppm, multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet) and brs (broad singulet). High resolution mass spectra (HRMS) were recorded using ESI-FT-ICR. Solvents were distilled from the indicated drying reagents: dichloromethane (CaH_2), tetrahydrofuran (Na, benzophenone), diethyl ether (Na, benzophenone), toluene (Na, benzophenone). Methyl-*tert*-butyl ether, diethyl ether, ethyl acetate and hexane were technical grade and distilled from KOH. Flash column chromatography was performed by using silica gel (0.040-0.063 mm). Spots were monitored by thin-layer chromatography, visualized by UV (254 nm, 366 nm) and treated with phosphomolybdic acid staining solution. Compound **1** was synthesised according to known literature.[15]

General Procedure for Synthesis of Pyrrolobenzoxazinone 3a (Table 2, entry 1)

Anthranilic acid (27 mg, 0.20 mmol, 1.00 equiv.) and $Sm(OTf)_3$ (24 mg, 0.04 mmol, 0.20 equiv.) were dissolved in a solvent mixture of 1.2 mL *t*BuOH/CH_2Cl_2 (1:2) including 1.00 equiv. H_2O (3.6 µl). Benzaldehyde (24 µL, 0.24 mmol, 1.20 equiv.) was added and stirring continued for 5 min at rt. The

reaction mixture was cooled to -20 °C and nucleophile **1** (110 mg, 0.40 mmol, 2.00 equiv.) was added dropwise. Stirring was continued until full conversion of the intermediate was indicated by TLC (30 min). 2,4-Dinitrobenzene sulfonic acid (57 mg, 0.20 mmol, 1.00 equiv.) was added in one portion and stirring continued until full conversion of the product was indicated by TLC (4.5 h). 10 mL CH_2Cl_2 was added and the resulting suspension washed with 15 mL of a sat. $NaHCO_3$ solution. The aqueous phase was extracted several times with CH_2Cl_2 (10x) and the water removed by azeotropic destillation. The crude product was dissolved in CH_2Cl_2, filtered through Celite® and the solvent removed under reduced pressure (*dr* 88:12). Flash column chromatography (hexane/MTBE 10:1 to 6:1) gave pyrrolobenzoxazinone **3a** (56 mg, 83%, *dr* 90:10) as white solid. *cis*-Diastereomer: R_f (hexane/MTBE 2:1) 0.33; mp 174 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, 1H, J = 1.0, 8.0 Hz), 7.53 (d, 2H, J = 7.5 Hz), 7.41 (t, 2H, J = 7.5 Hz), 7.37–7.24 (m, 2H), 6.98 (t, 1H, J = 7.5 Hz), 6.54 (d, 1H, J = 8.0 Hz), 4.90 (dd, 1H, J = 2.5, 8.0 Hz), 4.24 (m, 2H), 2.86–2.74 (m, 2H), 2.51–2.39 (m, 1H), 2.18–2.04 (m, 1H), 1.25 (t, 3H, J = 7.0 Hz); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 169.6, 163.3, 145.9, 143.3, 135.3, 130.2, 128.9, 127.6, 126.3, 122.0, 117.8, 115.3, 97.0, 69.8, 62.9, 35.6, 34.3, 14.1; IR (KBr) ν 2980, 2957, 1742, 1718, 1605, 1570, 1485, 1468, 1354, 1300, 1274, 1188, 1096, 1031, 1019, 766 cm^{-1}; MS (ESI+) m/z $(M+H)^+$, 338.0, $(M+Na)^+$, 360.0; Anal. Calcd for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15; Found: C, 71.09; H, 5.68; N, 4.28. *trans*-Diastereomer: R_f (hexane/MTBE 2:1) 0.23; mp 101 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (dd, 1H, J = 8.0, 1.5 Hz), 7.34–7.21 (m, 6H), 6.81 (m, 1H), 6.41 (d, 1H, J = 8.0 Hz), 5.16 (dd, 1H, J = 2.5, 8.5 Hz), 4.20 (m, 2H), 2.68 (ddd, 1H, J = 13.0, 11.5, 8.0 Hz), 2.54 (ddd, 1H, J = 13.0, 8.0, 2.5 Hz), 2.07 (ddt, 1H, J = 12.0, 8.0, 2.5 Hz), 1.19 (t, 3H, J = 7.0 Hz); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 170.5, 163.6, 144.2, 141.5, 135.6, 131.1, 129.2, 127.9, 126.4, 119.9, 114.8, 112.9, 95.9, 62.8, 62.5, 34.3, 32.3, 14.2; IR (KBr) ν 3062, 2955, 2925, 2856, 1742, 1606, 1573, 1487, 1469, 1451, 1372, 1298, 1261, 1181, 1164, 1053, 1024, 761, 700, 691 cm^{-1}; MS (ESI+) m/z $(M+H)^+$, 338.0, $(M+Na)^+$, 360.0, $(2M+Na)^+$,697.2; HRMS (ESI+) m/z $(M+H)^+$ Calcd for $C_{20}H_{20}NO_4$ 338.13868; Found: 338.13856.

Pyrrolobenzoxazinone **3b**: *dr* 95:5, 62 mg (88%, *dr* 95:5), white solid. *cis*-Diastereomer: R_f (hexane/MTBE 2:1) 0.40; mp 122 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05–7.97 (m, 1H), 7.94–7.84 (m, 1H), 7.38–7.19 (m, 4H), 7.09–6.93 (m, 1H), 6.53 (d, 1H, *J* = 8.0 Hz), 5.05 (dd, 1H, *J* = 8.0, 2.5 Hz), 4.35–4.17 (m, 2H), 2.92–2.71 (m, 2H), 2.51–2.41 (m, 1H), 2.34 (s, 3H), 2.06–1.95 (m, 1H), 1.26 (t, 3H, *J* = 7.0 Hz); ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ 169.4, 163.5, 146.2, 141.1, 135.4, 134.0, 130.8, 130.2, 127.4, 126.5, 126.2, 122.3, 118.1, 115.7, 97.3, 67.7, 62.9, 35.3, 32.7, 19.4, 14.1; IR (KBr) ν 2983, 2929, 1744, 1728, 1484, 1467, 1363, 1349, 1317, 1285, 1241, 1158, 1103, 1058, 1029, 969, 789, 765, 747, 681 cm^{-1}; MS (ESI+) *m*/*z* $(M+H)^+$, 352.2, $(M+Na)^+$, 374.2, $(M+K)^+$, 390.1; Anal. Calcd for $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02; N, 3.99; Found: C, 71.52; H, 6.07; N, 3.69.

Pyrrolobenzoxazinone **3c**: *dr* 93:7, 61 mg (87%, *dr* 95:5), white solid. *cis*-Diastereomer: R_f (hexane/MTBE 2:1) 0.40; mp 107 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (dd, 1H, *J* = 8.0, 1.5 Hz), 7.41 (d, 2H, *J* = 8.0 Hz), 7.33–7.25 (m, 1H), 7.22 (d, 2H, *J* = 8.0 Hz), 6.97 (ddd, 1H, *J* = 8.0, 7.5, 0.5 Hz), 6.59–6.53 (m, 1H), 4.87 (dd, 1H, *J* = 8.0, 2.5 Hz), 4.23 (q, 2H, *J* = 7.0 Hz), 2.85–2.69 (m, 2H), 2.52–2.40 (m, 1H), 2.39 (s, 3H), 2.15–2.03 (m, 1H), 1.24 (t, 3H, *J* = 7.0 Hz); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 169.5, 163.4, 146.0, 140.3, 137.3, 135.3, 130.2, 129.6, 126.2, 121.9, 117.8, 115.3, 97.0, 69.6, 62.9, 35.6, 34.4, 21.2, 14.1; IR (KBr) ν 2986, 2939, 1741, 1728, 1607, 1484, 1469, 1359, 1345, 1286, 1242, 1184, 1104, 1053, 1029, 962, 785, 771, 688 cm^{-1}; MS (ESI+) *m*/*z* $(M+H)^+$, 352.2, $(M+Na)^+$, 374.2, $(M+K)^+$, 390.1; Anal. Calcd for $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02; N, 3.99; Found: C, 71.47; H, 6.25; N, 3.77.

Pyrrolobenzoxazinone **3d**: *dr* 89:11, 71 mg (86%, *dr* 91:9), white solid. *cis*-Diastereomer: R_f (hexane/MTBE 2:1) 0.37; mp 141 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (dd, 1H, *J* = 8.0, 1.5 Hz), 7.71–7.58 (m, 6H), 7.52 –7.43 (m, 2H), 7.42–7.29 (m, 2H), 7.07–6.97 (m, 1H), 6.63 (d, 1H, *J* = 8.0 Hz), 4.96 (dd, 1H, *J* = 2.5, 8.0 Hz), 4.37–4.19 (m, 2H), 2.93–2.75 (m, 2H), 2.54–2.43 (m, 1H), 2.23–2.12 (m, 1H), 1.27 (t, 3H, *J* = 7.0 Hz); ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ 169.5, 163.4, 146.0, 142.4, 140.7, 140.6, 135.4, 130.3, 129.0, 127.6, 127.5, 127.2, 126.8, 122.1, 117.9, 115.4, 97.0, 69.6, 63.0, 35.7, 34.4,

14.1; IR (KBr) ν 3030, 2982, 1747, 1607, 1486, 1468, 1362, 1281, 1240, 1184, 1171, 1104, 1056, 1032, 964, 764, 738, 699 cm^{-1}; MS (ESI+) *m*/*z* $(M+H)^+$, 414.2, $(M+Na)^+$, 436.2, $(M+K)^+$, 452.2, $(2M+Na)^+$, 849.4; HRMS (ESI+) *m*/*z* $(M+H)^+$ Calcd for $C_{26}H_{24}NO_4$ 414.16998; Found: 414.16986.

Pyrrolobenzoxazinone **3e**: *dr* 89:11, 68 mg (88%, *dr* 91:9), white foam. *cis*-Diastereomer: R_f (hexane/MTBE 2:1) 0.34; mp 65 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, 1H, *J* = 6.5 Hz), 8.04 (dd, 1H, *J* = 8.0, 1.5 Hz), 8.01–7.81 (m, 3H), 7.65–7.51 (m, 3H), 7.33–7.23 (m, 1H), 7.2 (m, 1H), 6.63 (d, 1H, *J* = 8.0 Hz), 5.60 (d, 1H, *J* = 9.0 Hz), 4.30 (q, 2H, *J* = 7.0 Hz, 3.12–2.95 (m, 1H), 2.75 (td, 1H, *J* = 13.0, 7.0 Hz), 2.56–2.44 (m, 1H), 2.21 (dd, 1H, *J* = 11.5, 7.0 Hz), 1.30 (t, 3H, *J* = 7.0 Hz); ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ 169.6, 163.6, 146.4, 137.9, 135.5, 134.3, 130.3, 130.1, 129.3, 128.4, 126.6, 126.0, 125.8, 124.1, 123.1, 122.6, 118.3, 116.0, 97.5, 68.1, 63.1, 35.7, 33.3, 14.2; IR (KBr) ν 2980, 2959, 2926, 1747, 1607, 1485, 1468, 1364, 1348, 1288, 1244, 1157, 1145, 1103, 1056, 803, 785, 765 cm^{-1}; MS (ESI+) *m*/*z* $(M+H)^+$, 388.2, $(M+Na)^+$, 410.2, $(M+K)^+$, 426.1; HRMS (ESI+) *m*/*z* $(M+H)^+$ Calcd for $C_{24}H_{22}NO_4$ 388.15433; Found: 388.15424.

Pyrrolobenzoxazinone **3f**: *dr* 90:10, 74 mg (95%, *dr* 92:8), white solid. *cis*-Diastereomer: R_f (hexane/MTBE 2:1) 0.37; mp 112 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07–8.00 (m, 2H), 7.91 (d, 1H, *J* = 8.5 Hz), 7.90–7.83 (m, 2H), 7.60 (dd, 1H, *J* = 8.5, 2.0 Hz), 7.52 (m, 2H), 7.28–7.23 (m, 1H), 6.99 (m, 1H), 6.58 (dd, 1H, *J* = 8.0, 0.5 Hz), 5.06 (dd, 1H, *J* = 7.5, 3.0 Hz), 4.30 (m, 2H), 2.90–2.79 (m, 2H), 2.55–2.46 (m, 1H), 2.24–2.17 (m, 1H), 1.29 (t, 3H, *J* = 7.0 Hz); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 169.5, 163.4, 146.0, 140.7, 135.4, 133.5, 133.0, 130.3, 129.0, 128.1, 127.9, 126.6, 126.2, 125.2, 124.4, 122.2, 118.0, 115.5, 97.1, 70.0, 63.0, 35.7, 34.2, 14.2; IR (KBr) ν 2979, 2926, 1746, 1607, 1484, 1468, 1368, 1350, 1327, 1290, 1241, 1193, 1103, 1057, 1031, 965, 822, 787, 753, 478 cm^{-1}; MS (ESI+) *m*/*z* $(M+H)^+$, 388.2, $(M+Na)^+$, 410.2, $(M+K)^+$, 426.1, $(2M+Na)^+$, 797.3; Anal. Calcd for $C_{24}H_{21}NO_4$: C, 74.40; H, 5.46; N, 3.62; Found: C, 74.21; H, 5.72; N, 3.29.

Pyrrolobenzoxazinone **3g**: *dr* 91:9, 70 mg (94%, *dr* 91:9), white solid. *cis*-Diastereomer: R_f (hexane/MTBE 2:1) 0.31; mp 144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, 1H, *J* = 1.5, 8.0 Hz),

7.51–7.45 (m, 2H), 7.40–7.35 (m, 2H), 7.32 (ddd, 1H, *J* = 8.0, 7.5, 1.5 Hz), 7.00 (m, 1H), 6.52 (dd, 1H, *J* = 8.0, 0.5 Hz), 4.86 (dd, 1H, *J* = 8.0, 2.5 Hz), 4.23 (m, 2H), 2.86–2.69 (m, 2H), 2.50–2.40 (m, 1H), 2.10–2.02 (m, 1H), 1.23 (t, 3H, *J* = 7.0 Hz); $^{13}C\{H\}$ NMR (75 MHz, $CDCl_3$) δ 169.5, 163.2, 145.8, 141.9, 135.4, 133.5, 130.4, 129.1, 127.8, 122.3, 117.8, 115.5, 97.0, 69.2, 63.0, 35.6, 34.3, 14.1; IR (KBr) ν 3058, 2989, 2942, 1743, 1729, 1608, 1486, 1470, 1354, 1317, 1286, 1245, 1212, 1162, 1148, 1104, 1055, 1030, 964, 790, 769 cm^{-1}; MS (ESI+) *m*/*z* $(M+H)^+$, 372.2, $(M+Na)^+$, 394.1, $(M+K)^+$, 410.1, $(2M+Na)^+$, 765.2; HRMS (ESI+) *m*/*z* $(M+Na)^+$ Calcd for $C_{20}H_{18}ClNO_4Na$ 394.08166; Found: 394.08162.

Pyrrolobenzoxazinone **3h**: *dr* 89:11, 80 mg (96%, *dr* 91:9), white solid. *cis*-Diastereomer: R_f (hexane/MTBE 2:1) 0.31; mp 154 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, 1H, *J* = 1.5, 8.0 Hz), 7.57–7.52 (m, 2H), 7.46–7.40 (m, 2H), 7.32 (ddd, 1H, *J* = 8.0, 7.5, 1.5 Hz), 7.01 (m, 1H), 6.52 (dd, 1H, *J* = 8.0, 0.5 Hz), 4.85 (dd, 1H, *J* = 8.0, 2.5 Hz), 4.23 (m, 2H), 2.87–2.68 (m, 2H), 2.51–2.38 (m, 1H), 2.11–2.01 (m, 1H), 1.24 (t, 3H, *J* = 7.0 Hz); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ 169.5, 163.2, 145.7, 142.4, 135.4, 132.1, 130.4, 128.1, 122.4, 121.6, 117.8, 115.5, 96.9, 69.3, 63.0, 35.6, 34.2, 14.1; IR (KBr) ν 3058, 2988, 2939, 1743, 1729, 1607, 1485, 1469, 1352, 1287, 1280, 1244, 1163, 1103, 1055, 1030, 1011, 964, 789, 768, 687 cm^{-1}; MS (ESI+) *m*/*z* $(M+H)^+$, 416.1, 418.1, $(M+Na)^+$, 438.1, 440.1, $(M+K)^+$, 454.0, 456.0, $(2M+Na)^+$, 855.1; HRMS (ESI+) *m*/*z* $(M+H)^+$ Calcd for $C_{20}H_{19}BrNO_4$ 416.04920; Found: 416.04905.

Pyrrolobenzoxazinone **3i**: *dr* 86:14, 66 mg (90%, *dr* 80:20), white solid. *cis*-Diastereomer: R_f (hexane/MTBE 2:1) 0.27; mp 101 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.99 (dd, 1H, *J* = 8.0, 1.5 Hz), 7.44 (m, 2H), 7.34–7.25 (m, 1H), 7.04–6.90 (m, 3H), 6.55 (d, 1H, *J* = 8.0 Hz), 4.85 (dd, 1H, *J* = 7.5, 3.0 Hz), 4.23 (m, 2H), 3.84 (s, 3H), 2.84–2.67 (m, 2H), 2.51–2.38 (m, 1H), 2.12–2.01 (m, 1H), 1.24 (t, 3H, *J* = 7.0 Hz); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ 169.6, 163.4, 159.2, 146.0, 135.4, 135.3, 130.3, 127.5, 122.0, 117.9, 115.3, 114.3, 97.0, 69.4, 62.9, 55.5, 35.7, 34.4, 14.1; IR (KBr) ν 2984, 2938, 2838, 1745, 1609, 1514, 1485, 1469, 1363, 1346, 1286, 1248, 1178, 1110, 1031, 835, 748, 687, 550 cm^{-1}; MS

(ESI+) *m/z* $(M+H)^+$, 368.2, $(M+Na)^+$, 390.2, $(M+K)^+$, 406.1; HRMS (ESI+) *m/z* $(M+H)^+$ Calcd for $C_{21}H_{22}NO_5$ 368.14925; Found: 368.14910.

Pyrrolobenzoxazinone **3j**: *dr* 77:23, 35 mg (48%, *dr* 76:24), white solid. *cis*-Diastereomer: R_f (hexane/MTBE 3:2) 0.18; mp 153°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, 1H, *J* = 8.0, 1.0 Hz), 7.71 (m, 4H), 7.34 (ddd, 1H, *J* = 8.5, 7.5, 1.5 Hz), 7.04 (m, 1H), 6.47 (dd, 1H, *J* = 8.0, 0.5 Hz), 4.93 (dd, 1H, *J* = 8.5, 2.0 Hz), 4.25 (m, 2H), 2.93–2.81 (m, 1H), 2.72 (ddd, 1H, *J* = 13.5, 12.0, 7.0 Hz), 2.48 (ddd, 1H, *J* = 13.5, 7.5, 2.5 Hz), 2.08 (ddt, 1H, *J* = 12.0, 7.0, 2.5 Hz), 1.24 (t, 1H, *J* = 7.0 Hz); ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ 169.4, 163.0, 148.7, 145.4, 135.6, 132.8, 130.5, 127.2, 122.7, 118.7, 117.7, 115.6, 111.7, 96.9, 69.4, 63.2, 35.6, 34.1, 14.1; IR (KBr) ν 2983, 2957, 2927, 1743, 1608, 1485, 1468, 1361, 1290, 1243, 1157, 1104, 1059, 1033, 970, 762, 686, 565 cm^{-1}; MS (ESI+) *m/z* $(M+H)^+$, 363.2, $(M+Na)^+$, 385.1, $(M+K)^+$, 401.1; HRMS (ESI+) *m/z* $(M+Na)^+$ Calcd for $C_{21}H_{18}N_2O_4Na$ 385.11588; Found: 385.11579.

Pyrrolobenzoxazinone **3k**: *dr* 72:28, 48 mg (73%, *dr* 69:31), white solid. *cis*-Diastereomer: R_f (hexane/MTBE 2:1) 0.38; mp 102 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (dd, 1H, *J* = 8.0, 1.5 Hz), 7.62–7.56 (m, 1H), 7.46 (t, 1H, *J* = 2.0 Hz,), 7.38 (m, 1H), 7.00 (m, 1H), 6.82 (dd, 1H, *J* = 8.0, 0.5 Hz), 6.47 (dd, 1H, *J* = 2.0, 1.0 Hz), 4.82 (m, 1H), 4.20 (m, 2H), 2.80 (ddd, 1H, *J* = 12.5, 11.5, 7.0 Hz), 2.72–2.57 (m, 1H), 2.47 (ddd, 1H, *J* = 12.5, 6.5, 2.0 Hz), 2.06 (ddt, 1H, *J* = 12.0, 7.0, 2.0 Hz), 1.21 (t, 3H, *J* = 7.0 Hz); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 169.7, 163.4, 145.9, 144.2, 140.4, 135.5, 130.4, 128.5, 122.1, 117.8, 115.3, 109.0, 96.6, 63.0, 62.7, 35.8, 33.0, 14.2; IR (KBr) ν 2985, 2956, 2875, 1747, 1725, 1607, 1487, 1470, 1363, 1331, 1298, 1289, 1191, 1169, 1097, 1033, 1017, 874, 806, 764, 758, 604 cm^{-1}; MS (ESI+) *m/z* $(M+H)^+$, 328.1, $(M+Na)^+$, 350.1, $(M+K)^+$, 366.1, $(2M+Na)^+$, 677.3; HRMS (ESI+) *m/z* $(M+H)^+$ Calcd for $C_{18}H_{18}NO_5$ 328.11795; Found: 328.11797.

Pyrrolobenzoxazinone **3l**: *dr* 94:6, 60 mg (87%, *dr* 90:10), yellowish oil. *cis*-Diastereomer: R_f (hexane/MTBE 2:1) 0.40; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (dd, 1H, *J* = 8.0, 1.5 Hz), 7.51–7.40 (m, 1H), 7.06–6.93 (m, 2H), 4.14 (m, 2H), 3.56 (t, 1H, *J* = 7.0 Hz), 2.74 (td, 1H, *J* = 13.5, 7.5 Hz), 2.39 (dd,

1H, *J* = 13.5, 7.5 Hz), 2.21 (tt, 1H, *J* = 12.5, 8.0 Hz), 2.02 (dd, 2H, *J* = 12.5, 7.5 Hz), 1.89–1.80 (m, 2H), 1.78–1.71 (m, 3H), 1.32–1.20 (m, 3H), 1.16 (t, 3H, *J* = 7.0 Hz), 1.13–1.00 (m, 2H); ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ 169.4, 163.6, 146.5, 135.2, 130.4, 121.4, 118.1, 115.1, 96.8, 72.4, 62.6, 43.5, 36.5, 31.8, 28.6, 26.8, 26.7, 26.5, 26.4, 14.0; IR (Film) ν 2979, 2926, 2852, 1749, 1735, 1484, 1467, 1450, 1367, 1287, 1268, 1243, 1232, 1200, 1163, 1139, 1099, 1031, 973, 756, 680 cm^{-1}; MS (ESI+) *m*/*z* $(M+H)^+$, 344.2, $(M+Na)^+$, 366.2, $(M+K)^+$, 382.1, $(2M+Na)^+$, 709.4; HRMS (ESI+) *m*/*z* $(M+H)^+$ Calcd for $C_{20}H_{26}NO_4$ 344.18563; Found: 344.18556.

Pyrrolobenzoxazinone **3m**: at -20°C: *dr* 50:50, 51 mg (80%, *dr* 25:75), at rt: *dr* 3:97, 37 mg (58%, *dr* 3:97) yellowish oil. *trans*-Diastereomer: R_f (hexane/MTBE 2:1) 0.48; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (dd, 1H, *J* = 8.0, 1.5 Hz), 7.41 (m, 1H), 6.98 (d, 1H, *J* = 8.0 Hz), 6.87 (t, 1H, *J* = 8.0 Hz), 4.07 (q, 2H, *J* = 7.0 Hz), 4.04 (d, 1H, *J* = 8.0 Hz), 2.63–2.52 (m, 1H), 2.45–2.25 (m, 2H), 2.11 (dd, 1H, *J* = 12.5, 7.5 Hz), 1.06 (t, 3H, *J* = 7.0 Hz), 0.98 (s, 9H); ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ 171.2 164.5, 147.6, 134.4, 130.7, 119.8, 116.2, 114.4, 97.7, 65.9, 62.3, 38.2, 34.7, 27.9, 25.2, 14.0; IR (KBr) ν 2957, 2910, 2874, 1742, 1481, 1363, 1292, 1241, 1197, 1165, 1111, 1054, 1020, 957, 760, 696 cm^{-1}; MS (ESI+) *m*/*z* $(M+H)^+$, 318.1, $(M+Na)^+$, 340.1, $(M+K)^+$, 356.1, $(2M+Na)^+$, 657.2; HRMS (ESI+) *m*/*z* $(M+Na)^+$ Calcd for $C_{18}H_{23}NO_4Na$ 340.15193; Found: 340.15192.

Pyrrolobenzoxazinone **3n**: *dr* 94:6, 56.5 mg (80%, *dr* 96:4), yellowish solid. *cis*-Diastereomer: R_f (hexane/MTBE 3:2) 0.38; mp 120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, 1H, *J* = 8.0 Hz), 7.55 (m, 2H), 7.42 (m, 2H), 7.34 (m, 1H), 6.81 (d, 1H, *J* = 8.0 Hz), 6.35 (s, 1H), 4.88 (dd, 1H, *J* = 8.0, 2.5 Hz), 4.24 (q, 2H, *J* = 7.0 Hz), 2.86–2.68 (m, 2H), 2.47–2.39 (m, 1H), 2.18 (s, 3H), 2.14–2.04 (m, 1H), 1.25 (t, 3H, *J* = 7.0 Hz); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 169.7, 163.5, 146.7, 146.2, 143.4, 130.2, 128.9, 127.6, 126.3, 123.5, 118.0, 112.8, 97.0, 69.8, 62.9, 35.5, 34.4, 22.1, 14.1; IR (KBr) ν 3060, 3027, 2982, 2927, 1747, 1722, 1615, 1574, 1496, 1464, 1453, 1364, 1297, 1243, 1198, 1051, 1030, 969, 773, 762, 704 cm^{-1}; MS (ESI+) *m*/*z* $(M+H)^+$, 352.2, $(M+Na)^+$, 374.2, $(M+K)^+$, 390.1, $(2M+Na)^+$, 725.2; HRMS (ESI+) *m*/*z* $(M+H)^+$ Calcd for $C_{21}H_{22}NO_4$ 352.15433; Found: 352.15468.

Pyrrolobenzoxazinone **3o**: *dr* 89:11, 66.0 mg (94%, *dr* 93:7), yellowish solid. *cis*-Diastereomer: R_f (hexane/MTBE 3:2) 0.53; mp 105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (dd, 1H, *J* = 2.0, 0.5 Hz), 7.53 (m, 2H), 7.41 (m, 2H), 7.34 (m, 1H), 7.10 (ddd, 1H, *J* = 8.50, 2.0, 0.5 Hz), 6.45 (d, 1H, *J* = 8.5 Hz), 4.83 (dd, 1H, *J* = 8.0, 2.5 Hz), 4.23 (q, 2H, *J* = 7.0 Hz), 2.85–2.72 (m, 2H), 2.49–2.38 (m, 1H), 2.27 (s, 3H), 2.15–2.04 (m, 1H), 1.25 (t, 3H, *J* = 7.0 Hz); ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ 169.6, 163.6, 143.7, 143.5, 136.3, 131.9, 130.0, 128.9, 127.6, 126.4, 118.2, 115.4, 97.3, 69.9, 62.8, 35.6, 34.3, 20.7, 14.1; IR (KBr) ν 3029, 2981, 2958, 2925, 1728, 1623, 1504, 1452, 1349, 1276, 1241, 1213, 1194, 1181, 1150, 1095, 1027, 822, 758, 702 cm^{-1}; MS (ESI+) *m*/*z* $(M+H)^+$, 352.2, $(M+Na)^+$, 374.2, $(M+K)^+$, 390.1, $(2M+Na)^+$, 725.2; HRMS (ESI+) *m*/*z* $(M+H)^+$ Calcd for $C_{21}H_{22}NO_4$ 352.15433; Found: 352.15441.

Pyrrolobenzoxazinone **3p**: *dr* 88:12, 57.5 mg (78%, *dr* 92:8), yellowish solid. *cis*-Diastereomer: R_f (hexane/MTBE 3:2) 0.26; mp 110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, 1H, *J* = 9.0 Hz), 7.54 (m, 2H), 7.40 (m, 2H), 7.32 (m, 1H), 6.51 (dd, 1H, *J* = 9.0, 2.5 Hz), 5.93 (d, 1H, *J* = 2.5 Hz), 4.89 (dd, 1H, *J* = 7.5, 4.0 Hz), 4.25 (m, 2H), 3.54 (s, 1H), 2.82–2.67 (m, 2H), 2.51–2.40 (m, 1H), 2.19–2.00 (m, 1H), 1.26 (t, 3H, *J* = 7.0 Hz);^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 169.9, 165.5, 163.3, 148.0, 143.3, 132.5, 129.1, 127.8, 126.6, 109.4, 107.9, 101.5, 96.7, 69.5, 62.9, 55.4, 36.0, 34.4, 14.2; IR (KBr) ν 2976, 2952, 2904, 1747, 1721, 1614, 1570, 1497, 1471, 1323, 1291, 1273, 1252, 1227, 1212, 1183, 1129, 1096, 1026, 841, 766, 703 cm^{-1}; MS (ESI+) *m*/*z* $(M+H)^+$, 368.2, $(M+Na)^+$, 390.2, $(M+K)^+$, 406.2, $(2M+Na)^+$, 757.2; HRMS (ESI+) *m*/*z* $(M+H)^+$ Calcd for $C_{21}H_{22}NO_5$ 368.14925; Found: 368.14938.

Pyrrolobenzoxazinone **3q**: *dr* 86:14, 33.5 mg (45%, *dr* 91:9), white solid. *cis*-Diastereomer: R_f (hexane/MTBE 2:1) 0.41; mp 125 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, 1H, *J* = 8.5 Hz), 7.53–7.47 (m, 2H), 7.47–7.39 (m, 2H), 7.39–7.32 (m, 1H), 6.96 (dd, 1H, *J* = 8.5, 2.0 Hz), 6.51 (d, 1H, *J* = 2.0 Hz), 4.91 (dd, 1H, *J* = 8.0, 2.5 Hz), 4.26 (m, 2H), 3.54 (s, 1H), 2.86–2.70 (m, 2H), 2.53–2.39 (m, 1H), 2.20–2.06 (m, 1H), 1.27 (t, 3H, *J* = 7.0 Hz); ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ 169.1, 162.6, 146.8, 142.5, 141.7, 131.7, 129.1, 127.9, 126.2, 122.6, 117.5, 113.6, 96.9, 69.8, 63.1, 35.5, 34.4, 14.1; IR (KBr) ν 2985, 2963, 2924, 1748, 1603, 1566, 1480, 1449, 1364, 1295, 1237, 1219, 1187, 1091, 1047,

1026, 970, 858, 771, 703 cm^{-1}; MS (ESI+) *m*/*z* $(M+H)^+$, 372.2, $(M+Na)^+$, 394.2, $(M+K)^+$, 410.1, $(2M+Na)^+$, 765.1; HRMS (ESI+) *m*/*z* $(M+H)^+$ Calcd for $C_{20}H_{19}ClNO_4$ 372.09971; Found: 372.09986.

Pyrrolobenzoxazinone **3r**: *dr* 89:11, 82.0 mg (>99%, *dr* 91:9), yellowish solid. *cis*-Diastereomer: R_f (hexane/MTBE 2:1) 0.42; mp 148 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, 1H, *J* = 2.5 Hz), 7.54–7.46 (m, 2H), 7.47–7.38 (m, 2H), 7.38–7.30 (m, 1H), 7.36 (dd, 1H, *J* = 8.5, 2.5 Hz), 6.41 (d, 1H, *J* = 8.5 Hz), 4.87 (dd, 1H, *J* = 8.0, 3.0 Hz), 4.26 (q, 2H, *J* = 7.0 Hz), 2.87–2.70 (m, 2H), 2.55–2.38 (m, 1H), 2.21–2.06 (m, 1H), 1.27 (t, 3H, *J* = 7.0 Hz); ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ 169.0, 162.1, 144.7, 142.8, 138.1, 132.7, 129.0, 127.9, 126.2, 119.5, 116.8, 114.5, 97.0, 69.8, 63.1, 35.5, 34.3, 14.1; IR (KBr) ν 2980, 2962, 1746, 1601, 1481, 1451, 1423, 1356, 1281, 1235, 1176, 1158, 1125, 1058, 1028, 967, 831, 780, 743, 700 cm^{-1}; MS (ESI+) *m*/*z* $(M+H)^+$, 416.2, 418.2, $(M+Na)^+$, 438.2, 440.2, $(M+K)^+$, 454.1, 456.1, $(2M+Na)^+$, 855.0; HRMS (ESI+) *m*/*z* $(M+H)^+$ Calcd for $C_{20}H_{19}BrNO_4$ 416.04920; Found: 416.04951.

General Procedure for Synthesis of Pyrroloquinazolinone 4a (Table 4, entry 1)

Anthranilic amide (27 mg, 0.20 mmol, 1.00 equiv.) and $Sm(OTf)_3$ (24 mg, 0.04 mmol, 0.20 equiv.) were dissolved in a solvent mixture of 1.2 mL *t*BuOH/CH_2Cl_2 (1:2) including 1.00 equiv. H_2O (3.6 µl). Benzaldehyde (24 µL, 0.24 mmol, 1.20 equiv.) was added and stirring was continued for 5 min at rt. The reaction mixture was cooled to -20 °C and nucleophile **1** (110 mg, 0.40 mmol, 2.00 equiv.) was added dropwise. Stirring was continued until full conversion of the intermediate was indicated by TLC (1 h). 2,4-Dinitrobenzene sulfonic acid (57 mg, 0.20 mmol, 1.00 equiv.) was added in one portion and stirring was continued at -20 °C until full conversion of the product was indicated by TLC (3 h). 10 mL CH_2Cl_2 was added and the resulting suspension was washed with 15 mL of sat. $NaHCO_3$ solution. The aqueous phase was extracted several times with CH_2Cl_2 (8x) and the water removed by azeotropic destillation. The crude product was dissolved in CH_2Cl_2, filtered through Celite® and the solvent removed under reduced pressure (*dr* >98:2). Flash column chromatography

(hexane/MTBE 2:1 to MTBE) gave pyrroloquinazolinone **4a** (47 mg, 70%, *dr* >98:2) as white solid. *cis*-Diastereomer: R_f (hexane/MTBE 1:4) 0.23; mp 154 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (dd, 1H, *J* = 8.0, 1.5 Hz), 7.66–7.54 (m, 2H), 7.46–7.27 (m, 3H), 7.25–7.16 (m, 1H), 6.97–6.87 (m, 1H), 6.58–6.49 (m, 1H), 4.88 (dd, 1H, *J* = 8.0, 3.0 Hz), 4.20 (q, 2H, *J* = 7.0 Hz), 2.84–2.59 (m, 2H), 2.31–2.20 (m, 1H), 2.14–2.04 (m, 1H), 1.23 (t, 3H, *J* = 7.0 Hz); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 172.0, 165.5, 146.6, 144.0, 133.9, 128.7,128.3, 127.3, 126.4, 120.6, 117.5, 117.4,79.2, 70.4, 62.3, 36.4, 34.6, 14.1; IR (KBr) ν 3208, 3062, 2981, 2903, 1737, 1671, 1605, 1483, 1451, 1373, 1300, 1265, 1217, 1156, 1087, 1029, 758, 702 cm^{-1}; MS (ESI+) *m*/*z* $(M+H)^+$, 337.2, $(M+Na)^+$, 359.2, $(M+K)^+$, 375.1, $(2M+Na)^+$, 695.3; HRMS (ESI+) *m*/*z* $(M+Na)^+$ Calcd for $C_{20}H_{20}N_2O_3Na$ 359.13661; Found: 359.13637.

Pyrroloquinazolinone **4b**: 55 mg (79%, *dr* >98:2), white solid. *cis*-Diastereomer: R_f (hexane/MTBE 1:3) 0.24; mp 149 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, 2H, *J* = 8.0 Hz), 7.37–7.17 (m, 5H), 6.98–6.91 (m, 1H), 6.52 (d, 1H, *J* = 8.0 Hz), 5.04 (dd, 1H, *J* = 8.5, 2.5 Hz), 4.24 (q, 2H, *J* = 7.0 Hz), 2.88–2.76 (m, 1H), 2.75–2.64 (m, 1H), 2.36 (s, 3H), 2.28 (ddd, 1H, *J* = 13.0, 7.0, 3.0 Hz), 2.02–1.93 (m, 1H), 1.27 (t, 3H, *J* = 7.0 Hz); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 172.0, 165.6, 146.9, 141.9, 133.9, 133.8, 130.7, 128.2, 127.2, 126.6, 126.5, 121.0, 117.9, 117.8, 79.4, 68.4, 62.3, 36.2, 32.9, 19.4, 14.2; IR (KBr) ν 3195, 3061, 2975, 2925, 2903, 1739, 1670, 1607, 1483, 1375, 1302, 1282, 1263, 1159, 1083, 1034, 1026, 761, 750 cm^{-1}; MS (ESI+) *m*/*z* $(M+H)^+$, 351.2, $(M+Na)^+$, 373.2, $(M+K)^+$, 389.1, $(2M+Na)^+$, 723.3; Anal. Calcd for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33; N, 7.99; Found: C, 71.73; H, 6.27; N, 7.74.

Pyrroloquinazolinone **4c**: 54 mg (76%, *dr* >98:2), white solid. *cis*-Diastereomer: R_f (hexane/MTBE 1:4) 0.31; mp 150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (dd, 1H, *J* = 8.0, 1.5 Hz), 7.38 (d, 1H, *J* = 7.5 Hz), 7.35 (brs, 1H), 7.29 (t, 1H, *J* = 8.0 Hz), 7.25–7.19 (m, 2H), 7.12 (d, 1H, *J* = 7.5 Hz), 6.94–6.86 (m, 1H), 6.55 (dd, 1H, *J* = 8.0, 0.5 Hz), 4.85 (dd, 1H, *J* = 8.0, 3.5 Hz), 4.26–4.14 (m, 2H), 2.80–2.62 (m, 2H), 2.39 (s, 3H), 2.29–2.20 (m, 1H), 2.13–2.04 (m, 1H), 1.24 (t, 3H, *J* = 7.0 Hz); ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ 172.1, 165.6, 146.8, 144.2, 138.5, 134.0, 128.8, 128.4, 128.2, 127.1, 123.6, 120.7, 117.6, 117.5, 79.3, 70.5, 62.4, 36.7, 34.8, 21.8, 14.3; IR (KBr) ν 3208, 3064, 2979, 2905, 1738, 1673,

1606, 1484, 1374, 1300, 1285, 1264, 1193, 1151, 1085, 1032, 787, 763, 703; MS (ESI+) *m*/*z* $(M+H)^+$, 351.2, $(M+Na)^+$, 373.2, $(M+K)^+$, 389.1, $(2M+Na)^+$, 723.3; Anal. Calcd for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33; N, 7.99; Found: C, 71.72; H, 6.33; N, 7.79.

Pyrroloquinazolinone **4d**: 49 mg (70%, *dr* >98:2), white solid. *cis*-Diastereomer: R_f (hexane/MTBE 1:4) 0.34; mp 173 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (dd, 1H, *J* = 8.0, 1.5 Hz), 7.46 (d, 2H, *J* = 8.0 Hz), 7.27–7.16 (m, 3H), 7.01 (brs, 1H), 6.91 (t, 1H, *J* = 8.0 Hz), 6.55 (d, 1H, *J* = 8.0 Hz), 4.86 (dd, 1H, *J* = 7.5, 3.0 Hz), 4.20 (q, 2H, *J* = 7.0 Hz), 2.81–2.58 (m, 2H), 2.38 (s, 3H), 2.26–2.16 (m, 1H), 2.12–2.02 (m, 1H), 1.24 (t, 3H, *J* = 7.0 Hz); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 172.0, 165.4, 146.7, 141.0, 137.0, 134.0, 129.5, 128.3, 126.3, 120.6, 117.4, 117.4, 79.2, 70.2, 62.3, 36.7, 34.7, 21.2, 14.2; IR (KBr) ν 3196, 3065, 2980, 2921, 2901, 1738, 1672, 1607, 1484, 1374, 1304, 1285, 1257, 1213, 1183, 1154, 1085, 1034, 1022, 755; MS (ESI+) *m*/*z* $(M+H)^+$, 351.2, $(M+Na)^+$, 373.2, $(M+K)^+$, 389.1, $(2M+Na)^+$, 723.3; Anal. Calcd for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33; N, 7.99; Found: C, 71.52; H, 6.04; N, 7.76.

Pyrroloquinazolinone **4e**: 63 mg (81%, *dr* >98:2), white solid. *cis*-Diastereomer: R_f (hexane/MTBE 1:3) 0.21; mp 184 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, 1H, *J* = 7.0 Hz), 8.02 (dd, 1H, *J* = 8.0, 1.5 Hz), 7.97–7.90 (m, 2H), 7.84 (d, 1H, *J* = 8.0 Hz), 7.60–7.49 (m, 3H), 7.23–7.16 (m, 1H), 7.01 (s, 1H), 6.98–6.92 (m, 1H), 6.61 (d, 1H, *J* = 8.0 Hz), 5.58 (d, 1H, *J* = 8.5 Hz), 4.26 (q, 2H, *J* = 7.0 Hz), 3.01 (tdd, 1H, *J* = 12.0, 9.0, 7.0 Hz), 2.62 (td, 1H, *J* = 7.0, 12.5 Hz), 2.31–2.14 (m, 2H), 1.29 (t, 3H, *J* = 7.0 Hz); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 172.1, 165.8, 147.0, 138.6, 134.1, 134.0, 130.0, 129.2, 128.2, 128.0, 126.3, 125.8, 125.7, 124.5, 123.1, 121.2, 118.2, 118.0, 79.4, 68.9, 62.4, 36.4, 33.5, 14.2; IR (KBr) ν 3244, 3060, 2980, 2935, 1734, 1671, 1605, 1483, 1382, 1371, 1301, 1281, 1266, 1203, 1193, 1154, 1090, 1039, 1028, 803, 781, 761 cm^{-1}; MS (ESI+) *m*/*z* $(M+H)^+$, 387.2, $(M+Na)^+$, 409.2, $(M+K)^+$, 425.2, $(2M+Na)^+$, 795.3; HRMS (ESI+) *m*/*z* $(M+Na)^+$ Calcd for $C_{24}H_{22}N_2O_3Na$ 409.15226; Found: 409.15211.

Pyrroloquinazolinone **4f**: 59 mg (76%, *dr* >98:2), white solid. *cis*-Diastereomer: R_f (hexane/MTBE 1:3) 0.17; mp 176 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 8.02 (dd, 1H, *J* = 8.0, 1.5 Hz), 7.93–

7.84 (m, 3H), 7.63 (dd, 1H, *J* = 8.5, 1.5 Hz), 7.55–7.47 (m, 2H), 7.33 (s, 1H), 7.21–7.15 (m, 1H), 6.96–6.89 (m, 1H), 6.59 (d, 1H, *J* = 8.0 Hz), 5.04 (dd, 1H, *J* = 8.0, 3.0 Hz), 4.26 (q, 2H, *J* = 7.0 Hz), 2.88–2.76 (m, 1H), 2.71 (ddd, 1H, *J* = 13.0, 10.0, 6.5 Hz), 2.30 (ddd, 1H, *J* = 13.0, 7.0, 4.0 Hz), 2.22–2.13 (m, 1H), 1.29 (t, 3H, *J* = 7.0 Hz); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ 172.1, 165.5, 146.6, 141.4, 134.0, 133.5, 133.0, 128.7, 128.4, 128.1, 127.8, 126.4, 126.0, 125.2, 124.5, 120.8, 117.6, 117.5, 79.3, 70.5, 62.4, 36.6, 34.5, 14.3; IR (KBr) ν 3203, 3060, 2978, 2925, 1739, 1673, 1606, 1483, 1373, 1299, 1282, 1264, 1213, 1193, 1155, 1083, 1033, 1019, 822, 751 cm^{-1}; MS (ESI+) *m*/*z* $(M+H)^+$, 387.2, $(M+Na)^+$, 409.2, $(M+K)^+$, 425.2, $(2M+Na)^+$, 795.3; HRMS (ESI+) *m*/*z* $(M+Na)^+$ Calcd for $C_{24}H_{22}N_2O_3Na$ 409.15226; Found: 409.15196.

Pyrroloquinazolinone **4g**: 54 mg (73%, *dr* >98:2), white solid. *cis*-Diastereomer: R_f (hexane/MTBE 1:4) 0.23; mp 148 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.97 (dd, 1H, *J* = 8.0, 1.5 Hz), 7.53 (d, 2H, *J* = 8.5 Hz), 7.42–7.32 (m, 2H), 7.28–7.19 (m, 1H), 7.10 (brs, 1H), 6.98 – 6.88 (m, 1H), 6.50 (d, 1H, *J* = 8.0 Hz), 4.84 (dd, 1H, *J* = 8.0, 3.0 Hz), 4.19 (q, 2H, *J* = 7.0 Hz), 2.83–2.68 (m, 1H), 2.61 (ddd, 1H, *J* = 13.0, 10.5, 6.5 Hz), 2.24 (ddd, 1H, *J* = 13.0, 6.5, 4.0 Hz), 2.03 (tdd, 1H, *J* = 9.5, 6.5, 3.5 Hz), 1.23 (t, 3H, *J* = 7.0 Hz); $^{13}C\{H\}$ NMR (75 MHz, $CDCl_3$) δ 172.0, 165.3, 146.4, 142.6, 134.1, 133.1, 128.9, 128.4, 127.9, 121.0, 117.6, 117.3, 79.2, 69.8, 62.5, 36.6, 34.6, 14.2; IR (KBr) ν 2980, 2934, 2904, 1738, 1669, 1607, 1574, 1487, 1375, 1355, 1300, 1283, 1262, 1218, 1155, 1088, 1014, 841, 759 cm^{-1}; MS (ESI+) *m*/*z* $(M+H)^+$, 371.2, $(M+Na)^+$, 393.1, $(M+K)^+$, 409.1, $(2M+Na)^+$, 763.2; HRMS (ESI+) *m*/*z* $(M+Na)^+$ Calcd for $C_{20}H_{19}ClN_2O_3Na$ 393.09764; Found: 393.09771.

Pyrroloquinazolinone **4h**: 68 mg (81%, *dr* >98:2), white solid. *cis*-Diastereomer: R_f (hexane/MTBE 1:4) 0.22; mp 157 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.97 (dd, 1H, *J* = 8.0, 1.5 Hz), 7.58–7.43 (m, 4H), 7.28–7.19 (m, 1H), 7.09 (brs, 1H), 6.98–6.89 (m, 1H), 6.50 (d, 1H, *J* = 8.0 Hz), 4.82 (dd, 1H, *J* = 8.0, 3.0 Hz), 4.19 (q, 2H, *J* = 7.0 Hz), 2.83–2.68 (m, 1H), 2.61 (ddd, 1H, *J* = 13.0, 10.5, 6.5 Hz), 2.23 (ddd, 1H, *J* = 13.0, 6.5, 4.0 Hz), 2.09–1.98 (m, 1H), 1.23 (t, 3H, *J* = 7.0 Hz); $^{13}C\{H\}$ NMR (75 MHz, $CDCl_3$) δ 172.0, 165.3, 146.4, 143.1, 134.1, 131.9, 128.4, 128.2, 121.2, 121.0, 117.6, 117.3, 79.2, 69.9, 62.5, 36.6, 34.5, 14.2; IR (KBr) ν 1737, 1661, 1607, 1486, 1372, 1299, 1283, 1264, 1218, 1190, 1154, 1086,

1033, 1011, 759 cm^{-1}; MS (ESI+) *m/z* $(M+H)^+$, 415.1, 417.1, $(M+Na)^+$, 437.1, 439.1, $(M+K)^+$, 453.1, 455.1, $(2M+Na)^+$, 853.1; Anal. Calcd for $C_{20}H_{19}BrN_2O_3$: C, 57.84; H, 4.61; N, 6.75; Found: C, 57.73; H, 4.44; N, 6.36.

Pyrroloquinazolinone **4i**: 50 mg (70%, *dr* >98:2), white solid. *cis*-Diastereomer: R_f (hexane/MTBE 1:4) 0.22; mp 135 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (dd, 1H, *J* = 8.0, 1.5 Hz), 7.62–7.50 (m, 2H), 7.29–7.18 (m, 2H), 7.13–7.03 (m, 2H), 6.97– 6.88 (m, 1H), 6.51 (d, 1H, *J* = 8.0 Hz), 4.85 (dd, 1H, *J* = 8.0, 3.0 Hz), 4.19 (q, 2H, *J* = 7.0 Hz), 2.83–2.57 (m, 2H), 2.25 (ddd, 1H, *J* = 11.0, 6.5, 4.0 Hz), 2.10–1.99 (m, 1H), 1.23 (t, 3H, *J* = 7.0 Hz); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 172.1, 165.4, 162.2 (d, *J* = 245.5 Hz), 146.5, 139.7 (d, *J* = 3.0 Hz), 134.0, 128.4, 128.0 (d, *J* = 8.0 Hz), 120.9, 117.6, 117.3, 115.6 (d, *J* = 21.5 Hz), 79.2, 69.8, 62.4, 36.5, 34.7, 14.2; IR (KBr) ν 3219, 3069, 2982, 2903, 1737, 1671, 1607, 1509, 1484, 1373, 1298, 1285, 1262, 1224, 1157, 1086, 1026, 1015, 836, 757 cm^{-1}; MS (ESI+) *m/z* $(M-CO_2Et)^+$, 281.1, $(M+H)^+$, 355.2, $(M+Na)^+$, 377.2, $(M+K)^+$, 393.1, $(2M+Na)^+$, 731.3; Anal. Calcd for $C_{20}H_{19}FN_2O_3$: C, 67.79; H, 5.40; N, 7.91; Found: C, 67.40; H, 5.39; N, 7.82.

Pyrroloquinazolinone **4j**: 59 mg (81%, *dr* 98:2), white solid. *cis*-Diastereomer: R_f (hexane/MTBE 1:4) 0.25; mp 148 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, 1H, *J* = 8.0, 1.5 Hz), 7.51–7.45 (m, 2H), 7.24–7.18 (m, 1H), 7.17–7.01 (m, 1H), 6.96–6.88 (m, 3H), 6.55 (d, 1H, *J* = 8.0 Hz), 4.84 (dd, 1H, *J* = 7.5, 3.5 Hz), 4.19 (q, 2H, *J* = 7.0 Hz), 3.83 (s, 3H), 2.77–2.60 (m, 2H), 2.28–2.18 (m, 1H), 2.09–2.02 (m, 1H), 1.23 (t, 3H, *J* = 7.0 Hz); ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ 172.1, 165.4, 158.9, 146.7, 136.0, 133.9, 128.3, 127.5, 120.6, 117.4, 117.3, 114.1, 79.1, 69.9, 62.3, 55.4, 36.6, 34.7, 14.2; IR (KBr) ν 2981, 2934, 2904, 1733, 1666, 1608, 1513, 1483, 1373, 1300, 1282, 1249, 1176, 1086, 1034, 758, 547 cm^{-1}; MS (ESI+) *m/z* $(M+H)^+$, 367.2, $(M+Na)^+$, 389.2, $(M+K)^+$, 405.1, $(2M+Na)^+$, 755.3; HRMS (ESI+) *m/z* $(M+Na)^+$ Calcd for $C_{21}H_{22}N_2O_4Na$ 389.14718; Found: 389.14681.

Pyrroloquinazolinone **4k**: 60 mg (82%, *dr* >98:2), white solid. *cis*-Diastereomer: R_f (hexane/MTBE 1:8) 0.15; mp 179 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (dd, 1H, *J* = 8.0, 1.5 Hz), 7.77–7.68 (m, 4H), 7.45 (brs, 1H), 7.28–7.21 (m, 1H), 6.98–6.93 (m, 1H), 6.43 (d, 1H, *J* = 8.0 Hz), 4.90 (dd, 1H, *J* = 8.5,

2.5 Hz), 4.19 (q, 2H, *J* = 7.0 Hz), 2.88–2.77 (m, 1H), 2.59 (ddd, 1H, *J* = 13.0, 11.0, 7.0 Hz), 2.29 (ddd, 1H, *J* = 13.0, 7.0, 3.5 Hz), 2.05 (ddt, 1H, *J* = 13.0, 6.5, 3.5 Hz), 1.22 (t, 3H, *J* = 7.0 Hz); $^{13}C\{H\}$ NMR (75 MHz, $CDCl_3$) δ 172.0, 165.3, 149.5, 146.1, 134.1, 132.7, 128.5, 127.3, 121.3, 118.9, 117.8, 117.3, 111.3, 79.2, 70.1, 62.6, 36.5, 34.4, 14.1; IR (KBr) ν 3202, 3069, 2982, 2937, 2900, 2226, 1738, 1676, 1607, 1482, 1372, 1302, 1280, 1264, 1218, 1162, 1151, 1084, 1020, 849, 764, 565, 550 cm^{-1}; MS (ESI+) *m/z* $(M\text{-}CO_2Et)^+$, 288.1, $(M+H)^+$, 362.2, $(M+Na)^+$, 384.2, $(M+K)^+$, 400.1, $(2M+Na)^+$, 745.3; HRMS (ESI+) *m/z* $(M+Na)^+$ Calcd for $C_{21}H_{19}N_3O_3Na$ 384.13186; Found: 384.13179.

Pyrroloquinazolinone **4l**: 43 mg (66%, *dr* >98:2), white solid. *cis*-Diastereomer: R_f (hexane/MTBE 1:4) 0.41; mp 132 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.95 (dd, 1H, *J* = 8.0, 1.5 Hz), 7.66–7.62 (m, 1H), 7.44 (t, 1H, *J* = 1.5 Hz), 7.34–7.28 (m, 1H), 7.00 (brs, 1H), 6.95–6.90 (m, 1H), 6.81 (dd, 1H, *J* = 8.0, 0.5 Hz), 6.44 (dd, 1H, *J* = 1.5, 1.0 Hz), 4.83–4.77 (m, 1H), 4.15 (q, 2H, *J* = 7.0 Hz), 2.70–2.54 (m, 2H), 2.27–2.20 (m, 1H), 2.06–1.99 (m, 1H), 1.20 (t, 3H, *J* = 7.0 Hz); $^{13}C\{H\}$ NMR (75 MHz, $CDCl_3$) δ 172.0, 165.4, 146.5, 143.8, 140.6, 134.1, 128.8, 128.3, 120.7, 117.3, 109.0, 78.7, 63.3, 62.4, 36.8, 33.1, 14.2; IR (KBr) ν 3212, 3066, 2980, 2904, 1739, 1670, 1606, 1484, 1373, 1301, 1286, 1262, 1212, 1182, 1159, 1089, 1026, 875, 766, 601; cm^{-1}; MS (ESI+) *m/z* $(M\text{-}CO_2Et)^+$, 253.1, $(M+H)^+$, 327.2, $(M+Na)^+$, 349.1, $(M+K)^+$, 365.1, $(2M+Na)^+$, 675.3; HRMS (ESI+) *m/z* $(M+Na)^+$ Calcd for $C_{18}H_{18}N_2O_4Na$ 349.11588; Found: 349.11576.

Pyrroloquinazolinone **4m**: 49 mg (69%, *dr* 98:2), white solid. *cis*-Diastereomer: R_f (hexane/MTBE 1:4) 0.25; mp 203 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, 1H, *J* = 8.0 Hz), 7.63–7.56 (m, 2H), 7.45–7.37 (m, 2H), 7.36–7.27 (m, 1H), 6.75 (dd, 1H, *J* = 8.0, 1.0 Hz), 6.56 (brs, 1H), 6.35 (s, 1H), 4.87 (dd, 1H, *J* = 8.0, 2.5 Hz), 4.20 (q, 2H, *J* = 7.0 Hz), 2.83–2.68 (m, 1H), 2.65–2.53 (m, 1H), 2.21–2.02 (m, 2H), 2.16 (s, 3H), 1.24 (t, 3H, *J* = 7.0 Hz); $^{13}C\{H\}$ NMR (75 MHz, $CDCl_3$) δ 172.1, 165.4, 146.8, 145.0, 144.1, 128.7, 128.3, 127.3, 126.4, 122.2, 117.7, 115.0, 79.3, 70.5, 62.4, 36.7, 34.6, 22.0, 14.2; IR (KBr) ν 3213, 2980, 2904, 1739, 1668, 1614, 1495, 1471, 1454, 1349, 1297, 1263, 1215, 1187, 1088, 1029, 1017, 778, 757, 703 cm^{-1}; MS (ESI+) *m/z* $(M\text{-}CO_2Et)^+$, 277.2, $(M+H)^+$, 351.2, $(M+Na)^+$, 373.2, $(M+K)^+$,

389.1, $(2M+Na)^+$, 723.4; HRMS (ESI+) *m*/*z* $(M+Na)^+$ Calcd for $C_{21}H_{22}N_2O_3Na$ 373.15226; Found: 373.15223.

Pyrroloquinazolinone **4n**: 51 mg (73%, *dr* >98:2), white solid. *cis*-Diastereomer: R_f (hexane/MTBE 1:4) 0.25; mp 154 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.61 (d, 2H, *J* = 7.5 Hz), 7.42 (t, 2H, *J* = 7.5 Hz), 7.33 (t, 1H, *J* = 7.5 Hz), 7.24 (brs, 1H), 7.06 (d, 1H, *J* = 8.0 Hz), 6.48 (d, 1H, *J* = 8.0 Hz), 4.84 (dd, 1H, *J* = 8.0, 2.0 Hz), 4.22 (q, 2H, *J* = 7.0 Hz), 2.84–2.72 (m, 1H), 2.71–2.62 (m, 1H), 2.31–2.20 (m, 1H), 2.28 (s, 3H), 2.14–2.06 (m, 1H), 1.26 (t, 3H, *J* = 7.0 Hz); ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ 172.2, 165.6, 144.5, 144.3, 134.9, 130.4, 128.7, 128.2, 127.3, 126.5, 117.8, 117.6, 79.3, 70.6, 62.3, 36.5, 34.7, 20.6, 14.2; IR (KBr) ν 3193, 3060, 1978, 2922, 2902, 1739, 1671, 1619, 1499, 1450, 1442, 1362, 1286, 1264, 1210, 1157, 1087, 1028, 822, 788, 758, 702, 541 cm^{-1}; HRMS (ESI+) *m*/*z* $(M+Na)^+$ Calcd for $C_{21}H_{22}N_2O_3Na$ 373.15226; Found: 373.15194.

Pyrroloquinazolinone **4o**: 53 mg (72%, *dr* >98:2), white solid. *cis*-Diastereomer: R_f (hexane/MTBE 1:4) 0.18; mp 197 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, 1H, *J* = 8.5 Hz), 7.59–7.54 (m, 2H), 7.42–7.35 (m, 2H), 7.32–7.27 (m, 1H), 6.70 (brs, 1H), 6.45 (dd, 1H, *J* = 8.5, 2.5 Hz), 5.97 (d, 1H, *J* = 2.5 Hz), 4.88 (dd, 1H, *J* = 8.0, 4.0 Hz), 4.21 (q, 2H, *J* = 7.0 Hz), 3.53 (s, 3H), 2.77–2.66 (m, 1H), 2.61 (ddd, 1H, *J* = 13.0, 9.0, 6.5 Hz), 2.25–2.17 (m, 1H), 2.12–2.04 (m, 1H), 1.25 (t, 3H, *J* = 7.0 Hz); ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ 172.3, 165.3, 164.5, 148.3, 143.9, 130.4, 128.9, 127.5, 126.6, 110.5, 107.5, 101.4, 79.3, 70.0, 62.5, 55.3, 37.0, 34.7, 14.3; IR (KBr) ν 3183, 3059, 2983, 2939, 2902, 1741, 1666, 1606, 1475, 1455, 1356, 1310, 1296, 1260, 1233, 1215, 1177, 1089, 1029, 849, 768, 759, 702 cm^{-1}; MS (ESI+) *m*/*z* $(M+H)^+$, 367.2, $(M+Na)^+$, 389.2, $(M+K)^+$, 405.1, $(2M+Na)^+$, 755.4; HRMS (ESI+) *m*/*z* $(M+Na)^+$ Calcd for $C_{21}H_{22}N_2O_4Na$ 389.14718; Found: 389.14699.

Pyrroloquinazolinone **4p**: 61 mg (82%, *dr* >98:2), white solid. *cis*-Diastereomer: R_f (hexane/MTBE 1:4) 0.35; mp 213 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, 1H, *J* = 2.5 Hz), 7.56–7.51 (m, 2H), 7.43–7.37 (m, 2H), 7.35–7.29 (m, 1H), 7.15 (dd, 1H, *J* = 8.5, 2.5 Hz), 6.80 (brs, 1H), 6.46 (d, 1H, *J* = 8.5 Hz), 4.85 (dd, 1H, *J* = 8.0, 3.5 Hz), 4.22 (q, 2H, *J* = 7.0 Hz), 2.79–2.70 (m, 1H), 2.66 (ddd, 1H, *J* = 13.0,

10.0, 6.0 Hz), 2.25–2.17 (m, 1H), 2.13–2.05 (m, 1H), 1.25 (t, 3H, J = 7.0 Hz); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ 171.7, 164.3, 145.1, 143.5, 134.1, 129.0, 128.0, 127.7, 126.4, 126.2, 118.9, 118.7, 79.3, 70.4, 62.7, 36.7, 34.7, 14.3; IR (KBr) ν 3192, 3060, 2978, 2899, 1737, 1673, 1604, 1483, 1442, 1359, 1280, 1265, 1217, 1156, 1095, 1027, 756, 702 cm^{-1}; MS (ESI+) m/z $(M+Na)^+$, 393.2, $(M+K)^+$, 409.1, $(2M+Na)^+$, 763.3; HRMS (ESI+) m/z $(M+Na)^+$ Calcd for $C_{20}H_{19}ClN_2O_3Na$ 393.09764; Found: 393.09760.

Pyrroloquinazolinone **4q**: 65 mg (78%, *dr* >98:2), white solid. *cis*-Diastereomer: R_f (hexane/MTBE 1:4) 0.42; mp 214 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, 1H, J = 2.5 Hz), 7.56–7.51 (m, 2H), 7.43–7.37 (m, 2H), 7.35–7.29 (m, 1H), 7.28 (dd, 1H, J = 8.5, 2.5 Hz), 7.09 (brs, 1H), 6.40 (d, 1H, J = 8.5 Hz), 4.85 (dd, 1H, J = 8.0, 3.5 Hz), 4.22 (q, 2H, J = 7.0 Hz), 2.79–2.69 (m, 1H), 2.66 (ddd, 1H, J = 13.0, 10.0, 6.5 Hz), 2.24 (ddd, 1H, J = 13.0, 8.0, 4.0 Hz), 2.14–2.06 (m, 1H), 1.25 (t, 3H, J = 7.0 Hz); $^{13}C\{H\}$ NMR (75 MHz, $CDCl_3$) δ 171.7, 164.3, 145.5, 143.5, 136.8, 131.0, 129.0, 127.7, 126.4, 119.1, 119.0, 113.3, 79.3, 70.3, 62.7, 36.6, 34.7, 14.3; IR (KBr) ν 3192, 3060, 2985, 2899, 1737, 1672, 1600, 1481, 1450, 1440, 1357, 1265, 1217, 1156, 1092, 1026, 987, 754, 702 cm^{-1}; MS (ESI+) m/z $(M+H)^+$, 415.1, 417.1, $(M+Na)^+$, 437.1, 439.1, $(M+K)^+$, 453.0, 455.0, $(2M+Na)^+$, 853.1; HRMS (ESI+) m/z $(M+Na)^+$ Calcd for $C_{20}H_{19}BrN_2O_3Na$ 437.04713; Found: 437.04710.

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SUPPORTING INFORMATION

^{1}H and ^{13}C-NMR spectra data for all new compounds and crystallographic data for compounds **3a** and **4a** (deposition numbers: CCDC 1403682 & 1403681). This material is available free of charge via the Internet at http://pubs.acs.org.

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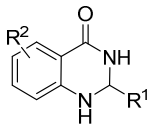
(16) A single example of the pyrrolobenzoxazinone synthesis has been included in a recent communication on the application of chip-based free-flow electrophoresis to organic synthesis, see: C. Benz, J. Appun, M. Boomhoff, C. Schneider, D. Belder, *Angew. Chem. Int. Ed.* **2015**, *54*, 2766.

(17) Crystallographic data for **3a**: CCDC 1403682 contains the supplementary crystallographic data and can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(18) Formation of known quinazolinones **5** was observed in trace amounts under the reaction conditions resulting from the condensation of aryl aldehydes and 2-aminobenzamides.



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(19) Crystallographic data for **4a**: CCDC 1403681 contains the supplementary crystallographic data and can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.