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Chemoselective Aromatic Azido Reduction with Concomitant Aliphatic Azide Employing Al/Gd Triflates/NaI and ESI-MS Mechanistic Studies

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Abstract: Aluminium and gadolinium triflates catalyze the chemoselective reduction of aromatic azides to the corresponding amines in combination with sodium iodide. This mild chemoselective method has been applied to the synthesis of various aryl amines, C2-azido-substituted pyrrolo[2,1-*c*]-[1,4]benzodiazepines, and fused[2,1-*b*]quinazolinones by an intramolecular azido reduction tandem cyclization reaction. Interestingly, this methodology selectively reduces aryl azides with enhanced yields and proceeds in shorter reaction times than previous strategies. The mechanistic aspects have been investigated and the intermediates associated with this selective transformation have been intercepted and characterized by online monitoring of the reaction by ESI-MS.

Keywords: amines · azides · cyclization · heterocycles · mass spectrometry · reduction

Introduction

The interconversion of aryl azides into anilines has received modest interest in synthetic chemistry, and the azides are mostly obtained from anilines through their diazonium salts.[1,2] However, inspite of their explosive properties, organic azides are valuable intermediates in organic synthesis.[1,3] Recently, they have been extensively used in 'click' chemistry[4] for the synthesis of 1,2,3-triazoles, tetrazoles, anilines, *N*-alkylated anilines,[5] and nitrenes. They have also found use in peptide synthesis as excellent protecting groups.[6] In the literature, various procedures are available for the synthesis of amines, however, the reduction of azides is the most attractive method because of their easy accessibility.[7] A variety of reducing reagents have been reported in the literature[2] for the transformation of azides into amines. The most prominent ones are $LiAlH_4$,[8] borohydrides,[9] triphenylphosphine,[10] metal-catalyzed hydrogenations,[11] and radical initiators.[12] These methods are applicable to many synthetic conditions, but the majority of them have several drawbacks, including tedious work-up, long reaction times, harsh reaction conditions, and poor selectivity. Accordingly, these drawbacks have stimulated the search for better catalysts that could be superior to the existing ones with regard to selectivity, handling, toxicity, and environmental compatibility.

Previous studies have shown that Lewis acids like $TiCl_4$[13] in combination with NaI offer a useful alternative to existing methods for the reduction of amines, *N*-oxides, and nitrones. Based on this analogy, we previously developed a procedure for the reduction of azides to the corresponding amines by employing $FeCl_3$ in combination with NaI. However, in the present-day context, the requirement for greener and efficient Lewis acid promoters in organic transformations has encouraged the development of environmentally friendly methodologies.

In recent years, the use of metal triflates such as Al-$(OTf)_3$, Gd$(OTf)_3$, Yt$(OTf)_3$, Cu$(OTf)_2$, and Dy$(OTf)_3$ in many organic transformations has grown significantly. The

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most prominent metal catalyst is aluminium triflate since it is stable to air and moisture. It is used in Friedel–Crafts alkylation reactions[14a] and is a highly chemoselective heterogeneous catalyst for the dithioacetalization of carbonyl compounds.[14b] Recently, it was found to be an efficient catalyst for epoxide ring-opening,[14c,d] the esterification of carboxylic acids with alcohols,[14e] thiol protection,[14f] the silylation of alcohols and phenols,[14g] and it has also been used as a co-catalyst in biodegradable polymerization reactions.[14h] Recently, some facile methods for the acylation of alcohols, phenols, and thiols have been developed in this laboratory by using $Al(OTf)_3$ as the catalyst.[15] This prompted us to develop new methodologies involving metal triflates in combination with NaI for promoting different transformations, which has led us to report a new protocol for the reduction of aryl azides by employing metal triflate and NaI combinations. In addition, the chemoselectivity of this reagent system has also been examined for different types of substrates.

Various mechanisms have been proposed for such metal-assisted reduction of azides.[16,17] Comprehensive mechanistic investigations usually require kinetic data gained by monitoring over long timescales, usually by UV, IR, or NMR spectroscopy. However, these techniques are often not suitable for the short timescales required for investigating transient species as unequivocal assignments of UV and IR bands or NMR peaks and couplings, particularly for more complex or transient structures, may be challenging and sometimes unfeasible. Electrochemical techniques have also been used to monitor short-lived species, but they provide limited structural information on the detected intermediates. On the other hand, molecular analysis by mass spectrometry (MS) has greatly benefited from the development of electrospray ionization (ESI)[18] because molecules and supramolecules[19] of high polarity, molecular complexity, and/or mass can be easily ionized by ESI for investigation by MS. ESI is an interesting "ion-fishing" technique because it gently transfers preformed ions directly from solution to the gas phase. ESI-MS (and its tandem version ESI-MS/MS) is rapidly becoming the technique of choice for solution mechanistic studies in chemistry and biochemistry[20] and in high-throughput screening of homogeneous catalysis reactions.[21] In this context, we were interested in employing the online ESI-MS technique to trap and characterize the transient species that are involved in the metal-assisted ($Al(OTf)_3$/NaI) reduction of aryl azido compounds.

Results and Discussion

Most recently, Marcantoni and co-workers[17] reported a versatile method for aliphatic azido reductions using $CeCl_3 \cdot 7H_2O$ (1.5 equiv)/NaI (9 equiv) at reflux for 24 h and also studied the effect of microwave irradiation. However, it is well known that a number of amines or imines decompose at higher temperatures and in prolonged reactions. Sometimes they even dimerize in the presence of acid or ester groups. Therefore we have previously reported some mild and efficient azido reduction methods using a variety of reagent systems.[22] As a continuation of these efforts, and with a view particularly to extending the applicability of NaI to the reduction of aryl azides to the corresponding amino compounds in a chemoselective manner, the reactions of aryl azides in the presence of metal triflate catalysts and NaI are described herein for the first time.

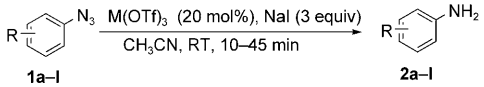
Optimization of the reaction conditions: To demonstrate the generality of this method initially we investigated the scope of these azido reductions under optimized reaction conditions by using a variety of solvents, for example, CH_2Cl_2, CH_3CN, THF, MeOH, and EtOH, with the aim of increasing the yields, shorten the reaction time, and to obtain a clean product. Of the solvents tested, CH_3CN was generally more efficient than other solvents. Notably, the best conversions and yields were achieved with CH_3CN as solvent (up to 95% conversion, 90% yield in the reaction of **2a**; Table 1). The chemoselectivity of the azido reduction process was also most efficient in CH_3CN as solvent. The efficiency of these solvents based on conversions and yields decreases in the order $CH_3CN > CH_2Cl_2 > THF > MeOH > EtOH$.

Next, various metal triflates were examined and the results are summarized in Table 1. The soft Lewis acid metal triflates tested were $Al(OTf)_3$, $Gd(OTf)_3$, $Yt(OTf)_3$, $Dy(OTf)_3$, and $Cu(OTf)_2$, in combination with NaI. In most cases the yields were significantly improved when the reaction was performed with $Al(OTf)_3$ (20 mol%) as the catalyst (Table 1, 78–92%). We also observed the chemoselective formation of the desired products when $Gd(OTf)_3$ (20 mol%) was employed as the catalyst (Table 1, 52–75%). Inferior results were obtained when other catalysts ($Yt(OTf)_3$, 25%; $Dy(OTf)_3$, 15%) were used, even with an excess of the reagent (40–50 mol%) and prolonged reaction times (12 h). However, a complicated mixture was obtained when $Cu(OTf)_2$ was used as the catalyst for this reaction.

Selective reduction of various aryl azido compounds: The required azido starting materials (**1a–l**) were obtained according to reported methods.[22b,c] Compounds **2a–l** were prepared from **1a–l** in good-to-moderate yields (52–92%) by using NaI (3 equiv) and $Al(OTf)_3$ or $Gd(OTf)_3$ (20 mol%) in CH_3CN at ambient temperature for 10–45 min (Table 1). These reactions were monitored by observing the disappearance of the starting material, as indicated by TLC. Note that reduction of aliphatic azido compounds **1b** and **1c** fail to give the corresponding amines **2b** and **2c** despite the use of excess reagents (1 equiv of $Al(OTf)_3$ and 5 equiv of NaI) and prolonged reaction times (24 h) under similar reaction conditions (Table 1). Thus, it was concluded that this methodology is exclusively applicable to the reduction of aryl azides.

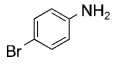
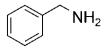
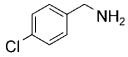
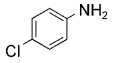
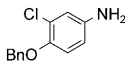
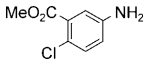
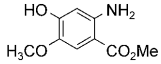
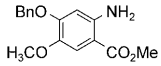
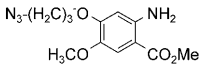
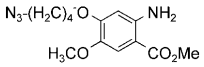
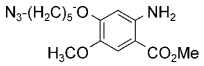
Interestingly, our results for **2j–l** (70–92% yields; Table 1) have revealed that the aromatic azido groups were reduced chemoselectively when an aliphatic azido group is present in the same substrate, with no trace of the corresponding ali-

Table 1. Chemoselective reduction of aryl azides (**1a–l**) to the corresponding amines (**2a–l**) employing Al/Gd-$(OTf)_3$ (20 mol%) with NaI.[a]



1a–l
M = Al or Gd

2a–l

Entry	Product	$Al(OTf)_3$: *t* [min]/ yield[b,c] [%]	$Gd(OTf)_3$: *t* [min]/ yield[b,c] [%]
2a		10/90	22/58
2b		ND[d]	ND
2c		ND	ND
2d		10/88	30/61
2e		15/85	45/55
2f		15/82	25/55
2g		10/78	30/60
2h		12/88	35/52
2i		18/90	30/55
2j		10/90	25/75
2k		10/92	25/70
2l		15/90	25/72

[a] All reactions were conducted at room temperature with 0.5 mmol of **1a–l**, 3.0 equiv of NaI, and 20 mol% of Al/Gd$(OTf)_3$ in 2 mL of CH_3CN for 10–45 min. [b] Isolated yields (purified by column chromatography). [c] All compounds were characterized by ^1H NMR and IR spectroscopy and HRMS. [d] No product was detected.

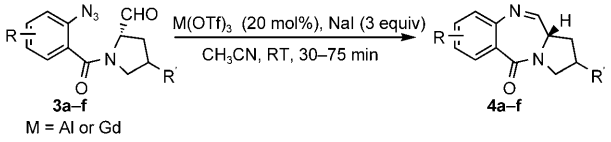
phatic amino products. Further, it was interesting to observe that the azido derivative **1e** with a carboxylic acid functionality fail not dimerize upon reduction using this reagent system. In addition, with **2e**, **2f**, and **2i** (Table 1), even the *O*-benzyl protection remained intact after the reduction process. Moreover, most of these reactions with various substrates provide good yields and clean products through a facile work-up, as depicted in Table 1.

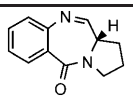
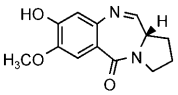
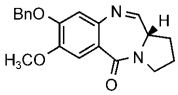
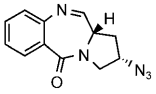
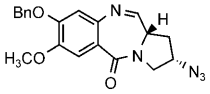
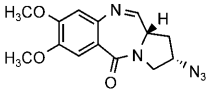
In the light of these successful results, we became interested in applying this chemoselective method to the synthesis of pyrrolo[2,1-*c*][1,4]benzodiazepines (PBDs) and its derivatives. It is well known that PBDs are a class of DNA-interactive potent antitumor antibiotics, gene regulators, and DNA probes.[23] According to structure–activity relationship (SAR) studies, C2-hydroxy substitution and C2 *exo* and *endo* unsaturation plays an enormous role in enhancing the DNA binding affinity and cytotoxicity of these compounds, for example, naturally occurring chicamycin A and B,[24a] neothramycin A and B,[24b] abbeymycin,[24c] and tomaymycin.[25] Therefore, we decided to apply this chemoselective protocol to the synthesis of C2-azido-substituted PBDs to probe its DNA-binding ability and anticancer activity. In our ongoing research program we have been involved in the development of new methodologies in solution as well as in solid-phase systems for the synthesis of bioactive natural products, including pyrrolobenzodiazepines[26] and fused quinazolinones.[27]

The functionalized imines **4a–f** (42–88% yields) were produced by the reduction of substituted 2-azidobenzoyl-(azido)prolinecarbaldehydes **3a–f** in the presence of NaI (3 equiv) and $Al(OTf)_3$ or Gd-$(OTf)_3$ (20 mol%) at ambient temperature for 30–75 min (Table 2). The advantage of this route is its ability to carry out a chemoselective azido reduction tandem cyclization for the synthesis of this class of compounds. Interestingly, the C-ring azido-substituted PBDs **4d–f** were obtained in yields of 80–86% with $Al(OTf)_3$ (20 mol%) and 55–68% with $Gd(OTf)_3$ (20 mol%; Table 2). This chemoselective route gave improved results compared with previously reported methods with respect to time and yields. Encouraged by these results, this protocol was applied to the synthesis of natural product DC-81 (**4b**) and benzylated DC-81 (**4c**; Table 2) under similar reaction conditions.

During the course of our studies, this approach was also employed in the preparation of PBD-5,11-diones. These PBD-5,11-diones are important intermediates in the synthesis of naturally occurring and synthetically modified PBD imines, such as tomaymycin and chicamycin.[28] In this work, we applied the same procedure as described earlier to the reduction of substrates **5a–j** to obtain the corresponding PBD-5,11-diones **6a–j** by an azido reduction tandem cyclization process. The results in Table 3 reveal that this procedure gave improved yields of 75–90% with $Al(OTf)_3$ and 50–75% with $Gd(OTf)_3$ using NaI. Compounds **5f–h** were selectively reduced to the corresponding amines, which underwent tandem cyclization reactions to afford **6f–h** in moderate-to-excellent yields with $Al(OTf)_3$ (80–90%) and Gd-$(OTf)_3$ (60–68%).

Table 2. Chemoselective aryl azido reduction for the synthesis of PBD-imines **4a–f** employing Al/Gd(OTf)$_3$ (20 mol%) and NaI.[a]



Entry	Product	Al(OTf)$_3$: t [min]/ yield[b,c] [%]	Gd(OTf)$_3$: t [min]/ yield[b,c] [%]
4a		30/88	45/50
4b		45/75	75/42
4c		30/80	50/45
4d		30/85	60/68
4e		35/86	65/60
4f		40/80	60/55

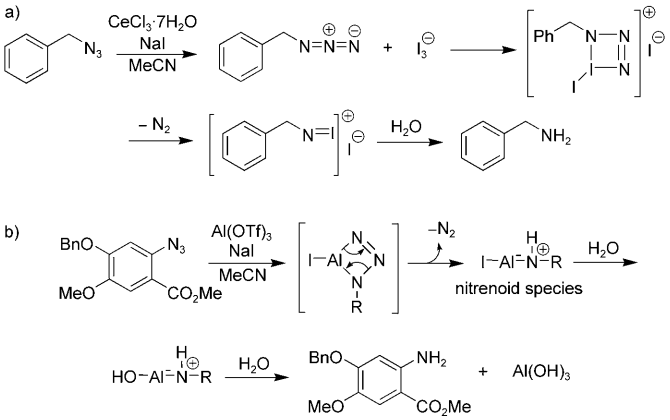
[a] All reactions were performed at ambient temperature with 0.5 mmol of **3a–f**, 3.0 equiv of NaI, and 20 mol% of Al/Gd(OTf)$_3$ in 2 mL of CH_3CN for 30–75 min. [b] Isolated yields (purified by column chromatography). [c] All the compounds were characterized by $^1H/^{13}C$ NMR and IR spectroscopy and HRMS.

Furthermore, it has been our long-term interest to explore both the selective reduction of aryl azides and intramolecular azido reductive cyclization reactions. To undertake such studies, the present chemoselective method was further extended to the synthesis of fused [2,1-*b*]quinazolinones. Recently, vasicinone and its analogues were synthesized[29] and evaluated for their bronchodilatory activity.[30] This class of compounds, particularly deoxyvasicinone, is found in nature and is reported to possess various pharmacological properties, such as antitumor[31] and antimycobacterial[32] activity, and is used extensively in indigenous medicine for colds, coughs, and asthma.[30]

The substituted azidobenzoyl precursors **7a–g** were reduced by employing the same reagent system as described earlier to afford the corresponding cyclized products **8a–g** in moderate-to-good yields using Al(OTf)$_3$ (82–95%) and Gd(OTf)$_3$ (38–62%) with NaI, as reported in Table 4.

Mechanistic studies: We monitored the reactions by ESI-MS(/MS) experiments in an attempt to intercept ionic intermediates and thereby collect mechanistic information that could allow optimization of the reaction conditions. By employing ESI(+)-MS, we monitored the reaction of the azide **1b** with $CeCl_3 \cdot 7H_2O$ in MeCN, a reaction that was expected to yield the amine **2b** (Scheme 1). ESI-MS has been shown to be a useful technique for carrying out mechanistic studies[33] because it transfers ions directly from the solution to the gas phase smoothly and efficiently (no or little dissociation), thereby providing snapshots of the ion composition of the reaction solutions. We have used this technique extensively to investigate the mechanisms of some major reactions.[34–36]

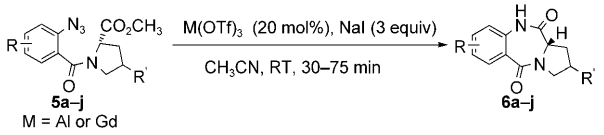
To clarify the mechanism of the reduction reactions and provide experimental evidence for the catalytic cycle proposed in Scheme 1,[16] we investigated the reduction of azides promoted by $CeCl_3$ by using mass spectrometry techniques. The reaction mixture was electrosprayed by the ESI source operated in the positive ion mode, and the cationic species were monitored online by MS analysis. We also monitored the reaction by ESI-MS in the negative ion mode, but no metal anions were detected. ESI is known for its ability to transfer ions to the gas phase without inducing undesirable side-reactions. Indeed,

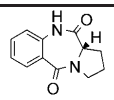
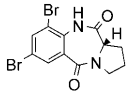
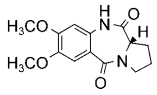
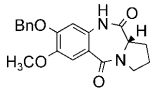
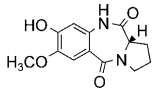
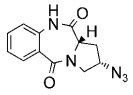
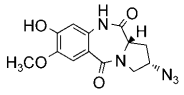
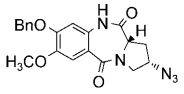
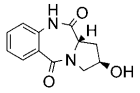
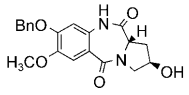


Scheme 1. Proposed mechanism for the conversion of aryl azides into amines by using a) $CeCl_3$,[16] and b) Al(OTf)$_3$/NaI based on an ESI(+)-MS(/MS) analysis.

the ESI-MS spectra collected for such reactions are extraordinarily clean and mechanistically enlightening. A number of ions were detected that could be attributed to the species shown in Figure 1. The isotopic patterns of the ions matched those calculated for the suggested species, particularly those containing multi-isotope elements such as iodine and nitro-

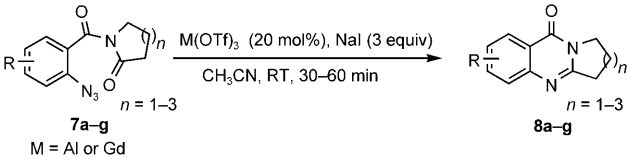
Table 3. Chemoselective aryl azido reduction with Al/Gd(OTf)$_3$ (20 mol%) for the synthesis of PBD-5,11-diones **6a–j**.[a]

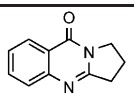
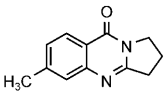
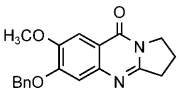
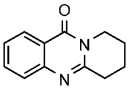
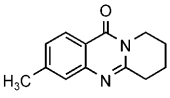
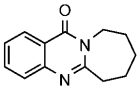
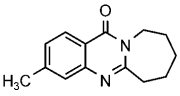


Entry	Product	Al(OTf)$_3$: t [min]/ yield[b,c] [%]	Gd(OTf)$_3$: t [min]/ yield[b,c] [%]
6a		30/89	45/75
6b		30/84	45/65
6c		35/82	50/62
6d		35/90	55/65
6e		40/77	75/55
6f		30/90	60/62
6g		35/80	50/68
6h		32/86	55/60
6i		45/79	70/50
6j		50/75	75/55

[a] All reactions were performed at ambient temperature with 0.5 mmol of **5a–j**, 3.0 equiv of NaI, and 20 mol% of Al/Gd(OTf)$_3$ in 2 mL of CH_3CN for 30–75 min. [b] Isolated yields (purified by column chromatography). [c] All the compounds were characterized by $^1H/^{13}C$ NMR and IR spectrocopy and HRMS.

Table 4. Synthesis of fused quinazolinones **8a–g** by an azido reduction tandem cyclization process by using Al/Gd(OTf)$_3$ (20 mol%).[a]



Entry	Product	Al(OTf)$_3$: t [min]/ yield[b,c] [%]	Gd(OTf)$_3$:t [min]/ yield[b,c] [%]
8a		30/95	40/55
8b		30/92	45/50
8c		35/95	55/38
8d		40/88	45/50
8e		40/90	40/62
8f		45/85	60/40
8g		50/82	55/60

[a] All reactions were performed at ambient temperature with 0.5 mmol of **7a–g**, 3.0 equiv of NaI, and 20 mol% of Al/Gd(OTf)$_3$ in 2 mL of CH_3CN for 30–60 min. [b] Isolated yields (purified by column chromatography). [c] All the compounds were characterized by $^1H/^{13}C$ NMR and IR spectroscopy and HRMS.

gen. The m/z values reported are those of the most abundant isotopologue ions. The m/z 387 ion is likely to be the species proposed by Marcantoni and co-workers.[17] ESI-(+)-MS/MS shows that the species with m/z 387 dissociates by loss of N_2 and iodine to give $PhCH_2N{=}I^+$ with m/z 232. This ion is therefore likely formed by the mechanism proposed in Scheme 1a and is also sampled from solution.

Proposed mechanism: We then studied the reaction with Al(OTf)$_3$. In the presence of aluminium complexes, it was noted that azido compounds might give the corresponding metal–azide adducts (not detected) prior to forming metal–nitrenoid species. It has been reported that azides can produce metal–nitrenoid species and our results show that the the azido reduction of aromatic azides follows a similar mechanism (Scheme 1b).[37–39] The mechanism in which the metal azide compound is formed cannot be rationalized in a straightforward way, however, a possible route to the nitrenoid species involves metal azide dissociation with N_2 loss followed by a ligand-exchange process with water to give species with m/z 330 $[R{-}N{=}AlOH{+}H]^+$, m/z 440 $[R{-}N{=}AlI{+}H]^+$, and m/z 446 $[R{-}N{=}AlOTf{+}H]^+$, as shown in Figure 1b. Organic azides, depending on the experimental conditions and the nature of the metal as well as the azide, may react with the metal complex to give a metal–imido species or a metal–azide adduct. The formation of a metal–nitrogen bond may occur by coordination of the terminal N_γ or N_α atom or by oxidative addition of the azido group. To predict the coordinating mode of the organic azide it is important to remember that the nitrogen in the α position is more basic than the terminal unsubstituted one. A possible mechanism that accommodates the features of the new reac-

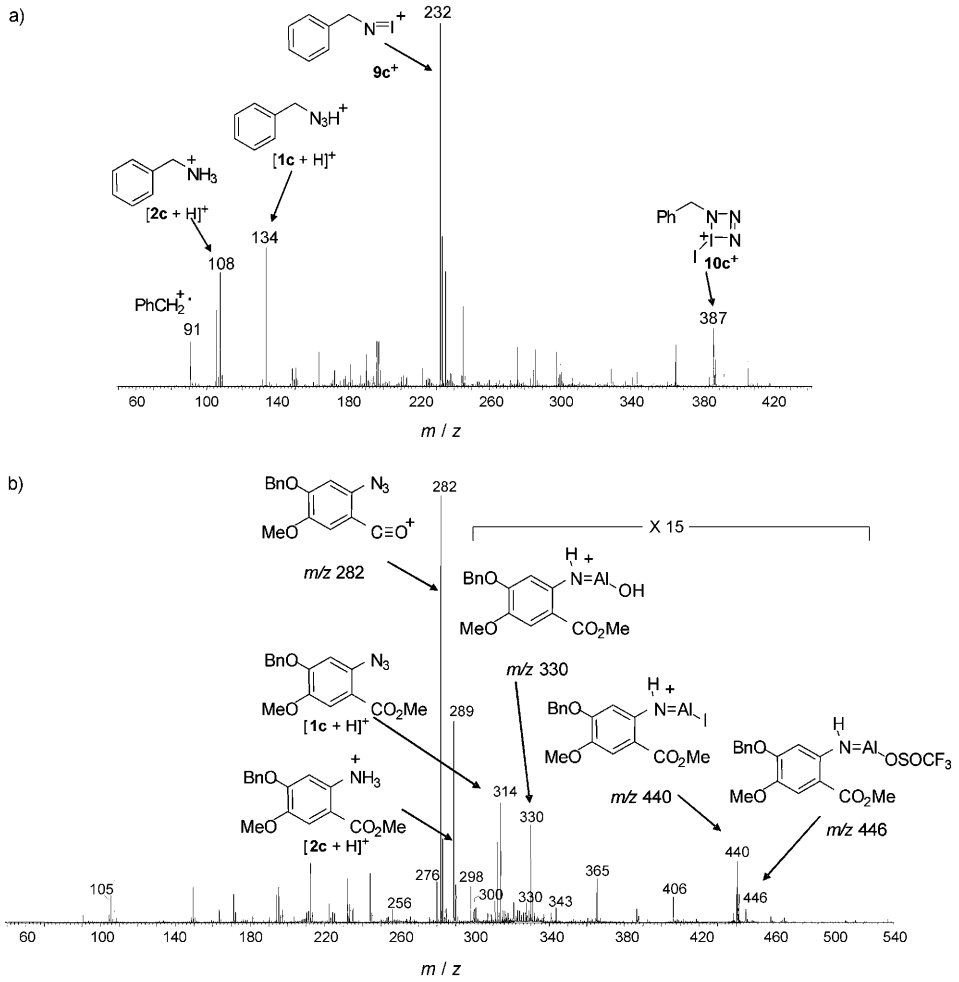


Figure 1. Online ESI(+)-MS spectra of a) the reaction of benzylamine with $CeCl_3$/NaI and b) the reaction of **1b** with $Al(OTf)_3$/NaI. Note that several cationic N=Al intermediates are detected in this new protocol.

tion is illustrated in Scheme 1b and is corroborated by the data collected in the online ESI-MS experiments.

In other words, nonaromatic azido reduction reactions are slower under triflate conditions and the products formed from azides **1b** and **1c** were observed in very low yields. For methyl 4-benzyloxy-5-methoxy-2-azidobenzoate (**1i**), we observed a sharp decrease in the reaction rate, which indicates that the presence of an electron-donating group on the azide slows the reaction. This data is consistent with the electrophilic behavior of the coordinated azide in the transition state, as expected. It is widely accepted that aryl azides can generate metal–nitrene (imido) intermediates in the presence of a suitable metal ion.[40] Structurally related iodoimine adducts have also been proposed on the basis of kinetic data as active intermediates in both the Mn/salen-catalyzed sulfimidation of sulfides[39] and in the Mn/porphyrin-catalyzed aziridination of olefins.[41] The collected data also explains why when $Al(OTf)_3$ was used in the reaction with subtrates containing aliphatic and aromatic azides, the reaction took place selectively with the aromatic azides.

Conclusions

We have reported a new catalytic system for the chemoselective reduction of functionalized aryl azides with concomitant aliphatic azides by using a variety of metal triflates with sodium iodide. Both the synthetic and mechanistic aspects of the reaction have been investigated and the formation of some transient species has been explained. This selective reduction of aryl azides to the corresponding amines is interesting and useful as it takes place in a shorter time than previous strategies and gives clean final products in moderate-to-excellent yields. This protocol is clearly superior to previous methods that used heavy metals and hazardous reagents as well as giving lower yields in longer reaction times. Moreover, this approach has been used for the preparation of imine-containing PBDs and their 5,11-diones as well as bioactive fused quinazolinones by the intramolecular azido reductive tandem cyclization process. Finally, we anticipate that this method may find use in combinatorial library synthesis due to its efficiency and operational simplicity.

Experimental Section

General methods: Purchased chemical reagents were used without further purification. Anhydrous THF, CH_2Cl_2, CH_3CN, MeOH, EtOH, and DMF to be used in reactions were prepared by distillation under nitrogen over sodium/benzophenone, CaH_2, sodium/P_2O_5, and CaH_2/molecular sieves, respectively. Solvents for extraction and column chromatography were distilled prior to use. Sodium azide was handled with care for the preparation of various substituted 2-azidobenzoic acids by wearing safety glasses, facemask, and gloves, and the reactions were performed in a fume hood. Infrared spectra were recorded on a Thermo Nicolet Nexus 670 and the wave numbers are expressed in cm^{-1}. Melting points were measured with an Eletrothermal apparatus. ^1H and ^{13}C NMR spectra were recorded on Gemini 200, Avance 300, and Unity 400 spectrometers using tetramethylsilane as the internal standard. Chemical shifts are reported in parts per million (ppm) downfield from tetramethyl silane. Spin multiplicities are described as s (singlet), br s (broad singlet), d (doublet), dd (double doublet), t (triplet), q (quartet), or m (multiplet). Coupling constants are reported in hertz (Hz). Mass spectra were recorded on a Quattro-LC spectrometer (ESI); for molecular weights above 400 on an LSIMS-VG-Autospec (FAB) spectrometer, and below 400 on a GC MS-

QP Zoloplus (Shimadzu) (EI-MS). The mechanistic studies were carried out by using a Micromass Q-tof instrument. Column chromatography was performed by using 100–200 mesh silica gel. TLC analyses were performed with silica gel plates using iodine, $KMnO_4$ and a UV lamp for visualization.

Procedure for the chemoselective reduction of aryl azide 1j to amine 2j: NaI (0.031 g, 0.490 mmol) and $Al(OTf)_3$ (0.015 g, 20 mol%) or $Gd(OTf)_3$ (0.019 g, 20 mol%) were added to a stirred solution of **1j** (0.050 g, 0.163 mmol) in CH_3CN (2 mL) at ambient temperature. The combined reaction mixture was stirred at the same temperature for 10 min and the completion of the reaction was monitored by the disappearance of the starting material, as indicated by TLC. Next, the solvent was removed under reduced pressure and excess of NaI was quenched with saturated sodium thiosulfate ($Na_2S_2O_3$). The resulting product was extracted with ethyl acetate (3×20 mL), washed with $NaHCO_3$ solution (20 mL) and brine (20 mL), and then dried over anhydrous Na_2SO_4. The final product was further purified by short-length column chromatography through silica gel (100–200 mesh) using ethyl acetate/hexane (8:10) as eluent to give the desired compound **2j** in good yields (90% with $Al(OTf)_3$ and 75% with $Gd(OTf)_3$). M.p. 69–71 °C; ^{1}H NMR (200 MHz, 25 °C, $CDCl_3$, TMS): δ = 7.23 (s, 1H), 6.07 (s, 1H), 4.03 (t, J = 6.04 Hz, 2H), 3.83 (s, 3H), 3.77 (s, 3H), 3.53 (t, J = 6.04 and 6.79 Hz, 2H), 2.02–2.14 ppm (m, 2H); ^{13}C NMR (75 MHz, 25 °C, $CDCl_3$, TMS): δ = 187.8, 173.7, 166.6, 160.1, 133.0, 122.1, 120.2, 84.4, 76.2, 71.4, 67.2, 47.9 ppm; IR (KBr): $\tilde{\nu}$ = 3470, 3384, 2927, 2089, 1683, 1623, 1594, 1532, 1514, 1464, 1431, 1388, 1254, 1201, 1171, 1083, 1027, 971, 880, 828, 780, 628 cm^{-1}; HRMS (ESI): m/z: calcd. for $C_{12}H_{16}N_4O_4Na$: 303.1069; found: 303.1076 $[M]^{+\cdot}$.

1-Amino-4-bromobenzene (2a): Brown solid; m.p. 60–62 °C; ^{1}H NMR (200 MHz, 25 °C, $CDCl_3$, TMS): δ = 7.24 (d, J = 8.72 Hz, 2H), 6.55 (d, J = 8.72 Hz, 2H), 3.67 ppm (brs, 2H); ^{13}C NMR (50 MHz, 25 °C, $CDCl_3$, TMS): δ = 146.0, 131.8, 117.1, 109.0 ppm; IR (KBr): $\tilde{\nu}$ = 3477, 3381, 3183, 1877, 1610, 1489, 1288, 1180, 1124, 1061, 833 cm^{-1}; ESI (MS): m/z: 172 $[M+H]^{+\cdot}$.

1-Amino-4-chlorobenzene (2d): White solid; m.p. 70–71 °C; ^{1}H NMR (300 MHz, 25 °C, $CDCl_3$, TMS): δ = 7.12 (d, J = 8.87 Hz, 2H), 6.63 (d, J = 8.87 Hz, 2H), 3.67 ppm (brs, 2H); ^{13}C NMR (75 MHz, 25 °C, $CDCl_3$, TMS): δ = 116.5, 123.7, 129.5, 144.8 ppm; IR (KBr): $\tilde{\nu}$ = 3477, 3375, 3198, 1880, 1618, 1509, 1288, 1180, 1079, 1015, 647, 546 cm^{-1}; ESI (MS): m/z: 127 $[M+H]^{+\cdot}$.

2-Amino-3-benzyloxybenzoic acid (2e): Brown solid; m.p. 141–142 °C; ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$, TMS): δ = 7.47 (d, J = 9.29 Hz, 1H), 7.26–7.36 (m, 5H), 6.86 (d, J = 8.80 Hz, 1H), 6.72 (brs, 1H), 6.49 (t, J = 7.82 and 8.31 Hz, 1H), 5.64 (brs, 1H), 5.00 ppm (s, 2H); ^{13}C NMR (50 MHz, 25 °C, $CDCl_3$, TMS): δ = 174.4, 173.1, 146.1, 142.4, 136.6, 128.2, 123.6, 115.0, 114.5, 109.6, 76.9, 70.7, 22.6 ppm; IR (KBr): $\tilde{\nu}$ = 3491, 3348, 3064, 3029, 2922, 2866, 1673, 1612, 1577, 1463, 1399, 1275, 1214, 1158, 1087, 1041, 902, 845, 796 cm^{-1}; HRMS (ESI): m/z: calcd. for $C_{14}H_{13}NO_3Na$: 266.0793; found: 266.0796 $[M]^{+\cdot}$.

1-Amino-4-benzyloxy-3-chlorobenzene (2f): White solid; m.p. 57–58 °C; ^{1}H NMR (300 MHz, 25 °C, $CDCl_3$, TMS): δ = 7.47 (d, J = 7.46 Hz, 2H), 7.40 (t, J = 7.46 Hz, 2H), 7.29 (t, J = 7.47 Hz, 1H), 6.81 (d, J = 8.76 Hz, 1H), 6.77 (d, J = 3.27 Hz, 1H), 6.52 (dd, J = 8.72 and 3.12 Hz, 1H), 5.11 (s, 2H), 3.46 ppm (brs, 2H); ^{13}C NMR (75 MHz, 25 °C, $CDCl_3$, TMS): δ = 146.9, 141.5, 138.8, 128.4, 128.3, 127.5, 124.3, 116.9, 117.2, 113.9, 72.1 ppm; IR (KBr): $\tilde{\nu}$ = 3409, 3301, 3208, 3061, 3032, 2911, 2859, 1627, 1509, 1272, 1225, 1012, 921, 855, 747, 696 cm^{-1}; (ESI) MS: m/z: 234 $[M+H]^{+\cdot}$.

Methyl 5-amino-2-chlorobenzoate (2g): Yellow semi-liquid; ^{1}H NMR (200 MHz, 25 °C, $CDCl_3$, TMS): δ = 7.22 (d, J = 8.48 Hz, 1H), 7.16 (d, J = 3.32 Hz, 1H), 6.77 (dd, J = 8.48 and 3.21 Hz, 1H), 3.96 (s, 3H), 3.77 ppm (brs, 2H); ^{13}C NMR (50 MHz, 25 °C, $CDCl_3$, TMS): δ = 167.1, 146.7, 132.6, 131.1, 122.2, 119.2, 117.8, 52.9 ppm; IR (KBr): $\tilde{\nu}$ = 3458, 3366, 3228, 3010, 2947, 2838, 1727, 1628, 1611, 1488, 1444, 1334, 1044, 988, 788, 656 cm^{-1}; (ESI) MS: m/z: 186 $[M+H]^{+\cdot}$.

Methyl 2-amino-4-hydroxy-5-methoxybenzoate (2h): Off-white solid; m.p. 148–149 °C; ^{1}H NMR (200 MHz, 25 °C, $CDCl_3$, TMS): δ = 7.22 (s, 1H), 6.15 (s, 1H), 5.48 (brs, 2H), 3.84 (s, 3H), 3.83 ppm (s, 3H); IR (KBr): $\tilde{\nu}$ = 3410, 3304, 3000, 2958, 2850, 1670, 1598, 1576, 1508, 1446, 1302, 1231, 1175, 1061, 1023, 952, 869, 843, 784, 629, 448 cm^{-1}; HRMS (ESI): m/z: calcd. for $C_9H_{12}NO_4$: 198.0766; found: 198.0774 $[M+H]^{+\cdot}$.

Methyl 2-amino-4-benzyloxy-5-methoxybenzoate (2i): Brown solid; m.p. 131–132 °C; ^{1}H NMR (200 MHz, 25 °C, $CDCl_3$, TMS): δ = 7.24–7.39 (m, 6H), 6.08 (s, 1H), 5.08 (s, 2H), 3.82 (s, 3H), 3.80 (s, 3H), 1.26 ppm (d, J = 15.86 Hz, 2H); IR (KBr): $\tilde{\nu}$ = 3468, 3356, 3030, 2947, 1676, 1617, 1587, 1560, 1514, 1462, 1426, 1384, 1303, 1258, 1200, 1170, 992, 872, 835, 740, 695 cm^{-1}; HRMS (ESI): m/z: calcd. for $C_{16}H_{17}NO_4Na$: 310.1055; found: 310.1073 $[M]^{+\cdot}$.

Methyl 2-amino-4-(4-azidobutyloxy)-5-methoxybenzoate (2k): Reddish brown solid; m.p. 82–84 °C; ^{1}H NMR (200 MHz, 25 °C, $CDCl_3$, TMS): δ = 7.22 (s, 1H), 6.04 (s, 1H), 3.98 (t, J = 5.14 and 6.61 Hz, 2H), 3.82 (s, 3H), 3.76 (s, 3H), 3.37 (t, J = 5.87 and 6.61 Hz, 2H), 1.74–1.95 ppm (m, 4H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$, TMS): δ = 167.9, 154.0, 146.8, 140.6, 113.2, 102.1, 100.1, 67.8, 51.3, 51.1, 26.1, 25.7 ppm; IR (KBr): $\tilde{\nu}$ = 3471, 3361, 2923, 2852, 2099, 1743, 1678, 1621, 1589, 1561, 1513, 1464, 1434, 1395, 1249, 1206, 1175, 864, 777 cm^{-1}; HRMS (ESI): m/z: calcd. for $C_{13}H_{18}N_4O_4Na$: 317.1225; found: 317.1218 $[M]^{+\cdot}$.

Methyl 2-amino-4-(5-azidopentyloxy)-5-methoxybenzoate (2l): Reddish brown solid; m.p. 102–104 °C; ^{1}H NMR (300 MHz, 25 °C, $CDCl_3$, TMS): δ = 7.22 (s, 1H), 6.06 (s, 1H), 3.95 (t, J = 6.04 and 6.79 Hz, 2H), 3.83 (s, 3H), 3.77 (s, 3H), 3.29 (t, J = 6.04 and 6.79 Hz, 2H), 1.82–1.91 (m, 2H), 1.51–1.73 ppm (m, 4H); ^{13}C NMR (75 MHz, 25 °C, $CDCl_3$, TMS): δ = 187.3, 173.5, 166.0, 160.0, 132.5, 121.3, 119.4, 87.4, 75.8, 70.4, 47.7, 47.6, 42.4 ppm; IR (KBr): $\tilde{\nu}$ = 3470, 3364, 2944, 2867, 2096, 1682, 1622, 1594, 1561, 1514, 1466, 1430, 1385, 1252, 1201, 1169, 1082, 1006, 887, 827, 765 cm^{-1}; HRMS (ESI): m/z: calcd. for $C_{14}H_{20}N_4O_4Na$: 331.1382; found: 331.1389 $[M]^{+\cdot}$.

(11a*S*)-1,2,3,11a-Tetrahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (4a): $[\alpha]_D^{25}$ = +343 (c = 0.4 in $CHCl_3$); ^{1}H NMR (200 MHz, 25 °C, $CDCl_3$, TMS): δ = 8.05 (d, J = 7.43 Hz, 1H), 7.79 (d, J = 4.46 Hz, 1H), 7.53 (t, J = 6.69 Hz, 1H), 7.28–7.38 (m, 2H), 3.36–3.94 (m, 3H), 2.26–2.38, (m, 2H), 2.02–2.16 ppm (m, 2H); MS (EI): m/z: 200 $[M]^{+\cdot}$.

DC-81 (4b): $[\alpha]_D^{25}$ = +281 (c = 0.02 in $CHCl_3$) {lit.:[42] $[\alpha]_D$ = +135 (c = 0.2 in $CHCl_3$)}; ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$, TMS): δ = 7.67 (d, J = 4.41 Hz, 1H), 7.52 (s, 1H), 6.90 (s, 1H), 3.96 (s, 3H), 3.42–3.87 (m, 3H), 2.12–2.32 (m, 2H), 1.81–2.10 ppm (m, 2H); MS (EI): m/z: 246 $[M]^{+\cdot}$.

(11a*S*)-8-Benzyloxy-7-methoxy-1,2,3,11a-tetrahydro-5*H*-pyrrolo[2,1-*c*]-[1,4]benzodiazepin-5-one (4c): $[\alpha]_D^{25}$ = +138 (c = 0.1 in $CHCl_3$); ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$, TMS): δ = 7.50 (d, J = 2.97 Hz, 1H), 7.08–7.42 (m, 6H), 6.74 (s, 1H), 4.98–5.15 (m, 2H), 3.87 (s, 3H), 3.38–3.80 (m, 3H), 2.09–2.26 (m, 2H), 1.81–2.01 ppm (m, 2H); MS (EI): m/z: 336 $[M]^{+\cdot}$.

(2*S*,11a*S*)-2-Azido-1,2,3,11a-tetrahydro-5*H*-pyrrolo[2,1-*c*]-[1,4]benzodiazepin-5-one (4d): M.p. 101–104 °C; $[\alpha]_D^{23}$ = −138 (c = 0.5 in MeOH); ^{1}H NMR (200 MHz, 25 °C, [D$_6$]DMSO, TMS): δ = 7.55–7.60 (d, J = 6.01 Hz, 1H), 7.15–7.25 (m, 2H), 6.90–7.00 (m, 1H), 6.75–6.80 (m, 1H), 4.25–4.30 (m, 1H), 3.90–4.00 (m, 2H), 3.50–3.60 (m, 1H), 3.20–3.30 (m, 1H), 2.20–2.30 ppm (m, 1H); IR (KBr): $\tilde{\nu}$ = 3311, 2103, 1618, 1448, 1211, 1145, 638 cm^{-1}; HRMS (EI): m/z: calcd. for $C_{12}H_{11}N_5O$: 241.0963; found: 241.0966 $[M]^{+\cdot}$.

(2*S*,11a*S*)-2-Azido-8-benzyloxy-7-methoxy-1,2,3,11a-tetrahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (4e): M.p. 122–124 °C; $[\alpha]_D^{23}$ = −158 (c = 0.5 in MeOH); ^{1}H NMR (300 MHz, 25 °C, [D$_6$]DMSO, TMS): δ = 7.63 (d, J = 7.28 Hz, 1H), 7.33–7.52 (m, 6H), 6.98 (s, 1H), 5.02 (s, 2H), 4.22–4.27 (m, 1H), 4.10–4.15 (m, 1H), 3.99 (s, 3H), 3.88 (m, 1H), 3.52 (m, 1H), 2.28 ppm (m, 2H); IR (KBr): $\tilde{\nu}$ = 3322, 2842, 2098, 1622, 1528, 1452, 1209, 1148, 647 cm^{-1}; ESI (MS): m/z: 378 $[M+H]^{+\cdot}$.

(2*S*,11a*S*)-2-Azido-7,8-dimethoxy-1,2,3,11a-tetrahydro-5*H*-pyrrolo[2,1-*c*]-[1,4]benzodiazepin-5-one (4f): M.p. 115–117 °C; $[\alpha]_D^{23}$ = −141 (c = 0.5 in MeOH); ^{1}H NMR (400 MHz, 25 °C, [D$_6$]DMSO, TMS): δ = 7.60 (d, J = 4.58 Hz, 1H), 7.38 (s, 1H), 6.94 (s, 1H), 4.23–4.28 (m, 1H), 4.11–4.17 (m, 1H), 4.00 (s, 3H), 3.92 (s, 3H), 3.72–3.80 (m, 1H), 3.55 (m, 1H), 2.91–3.08 (m, 1H), 2.32 ppm (m, 1H); IR (KBr): $\tilde{\nu}$ = 2928, 2847, 2103, 1621, 1512, 1448, 1210, 742, 642 cm^{-1}; ESI (MS): m/z: 302 $[M+H]^{+\cdot}$.

(11a*S*)-2,3,5,10,11,11a-Hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (6a): White solid; m.p. 218–219 °C; $[\alpha]_D^{23}$ = +201 (c = 1.0 in MeOH); ^{1}H NMR (200 MHz, 25 °C, $CDCl_3$, TMS): δ = 9.22 (brs, 1H),

7.96 (d, J=6.57 Hz, 1H), 7.46 (t, J=6.57 and 7.30 Hz, 1H), 7.21–7.28 (m, 1H), 7.03 (d, J=8.03 Hz, 1H), 4.05 (d, J=6.57 Hz, 1H), 3.75–3.86 (m, 1H), 3.51–3.65 (m, 1H), 2.71–2.82 (m, 1H), 1.98–2.08 ppm (m, 3H); ^{13}C NMR (50 MHz, 25 °C, $CDCl_3$, TMS): δ=171.2, 163.3, 135.1, 132.2, 130.8, 124.3, 123.0, 121.0, 56.8, 46.8, 26.1, 23.2; IR (KBr): $\tilde{\nu}$=3223, 2952, 2873, 1688, 1625, 1476, 1449, 1413, 1268, 1213, 1154, 1103 cm^{-1}; HRMS (ESI): m/z: calcd. for $C_{12}H_{12}N_2O_2Na$: 239.0796; found: 239.0806 $[M]^{+\cdot}$.

(11a*S*)-7,9-Dibromo-2,3,5,10,11,11a-hexahydro-1*H*-pyrrolo[2,1-*c*]-[1,4]benzodiazepine-5,11-dione (6b): White solid; m.p. 162–165 °C; $[\alpha]_D^{23}$=+321 (c=1.0 in MeOH); ^{1}H NMR (200 MHz, 25 °C, $CDCl_3$+[D$_6$]DMSO, TMS): δ=9.05 (brs, 1H), 7.94 (d, J=1.84 Hz, 1H), 7.86 (d, J=1.84 Hz, 1H), 4.00 (d, J=6.44 Hz, 1H), 3.71–3.81 (m, 1H), 3.44–3.58 (m, 1H), 2.70 (m, 1H), 1.99–2.03 ppm (m, 3H); ^{13}C NMR (50 MHz, 25 °C, $CDCl_3$, TMS): δ=188.9, 182.3, 157.4, 152.9, 151.6, 149.4, 137.5, 135.5, 76.1, 67.0, 45.7, 42.8 ppm; HRMS (ESI): m/z: calcd. for $C_{12}H_{10}N_2O_2NaBr_2$: 394.9006; found: 394.9002 $[M]^{+\cdot}$.

(11a*S*)-7,8-Dimethoxy-2,3,5,10,11,11a-hexahydro-1*H*-pyrrolo[2,1-*c*]-[1,4]benzodiazepine-5,11-dione (6c): White solid; m.p. 178–180 °C; $[\alpha]_D^{23}$=+303 (c=1.0 in MeOH); ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$, TMS): δ=8.71 (brs, 1H), 7.42 (s, 1H), 6.48 (s, 1H), 4.03–4.10 (m, 1H), 3.93 (s, 3H), 3.90 (s, 3H), 3.72–3.82 (m, 1H), 3.52–3.65 (m, 1H), 2.70–2.78 (m, 1H), 1.98–2.06 ppm (m, 3H); ^{13}C NMR (50 MHz, 25 °C, $CDCl_3$, TMS): δ=190.6, 184.8, 171.6, 165.7, 149.3, 138.5, 131.4, 123.3, 96.5, 76.3, 75.6, 66.7, 45.6, 43.0 ppm; HRMS (ESI): m/z: calcd. for $C_{14}H_{16}N_2O_4$: 277.1188; found: 277.1184 $[M]^{+\cdot}$.

(11a*S*)-8-Benzyloxy-7-methoxy-2,3,5,10,11,11a-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (6d): White solid; m.p. 172–173 °C; $[\alpha]_D^{23}$=+239 (c=1.0 in MeOH); ^{1}H NMR (200 MHz, 25 °C, $CDCl_3$, TMS): δ=8.81 (s, 1H), 7.26–7.40 (m, 6H), 6.49 (s, 1H), 5.10 (s, 2H), 4.00 (d, J=6.44 Hz, 1H), 3.91 (s, 3H), 3.47–3.78 (m, 2H), 2.63–2.71 (m, 1H), 1.90–2.05 ppm (m, 3H); ^{13}C NMR (50 MHz, 25 °C, $CDCl_3$, TMS): δ=170.8, 165.0, 149.4, 146.6, 135.7, 129.4, 128.5, 128.0, 127.1, 119.4, 112.3, 105.8, 76.9, 76.6, 708, 56.7, 56.1, 47.2, 26.1, 23.5 ppm; IR (KBr): $\tilde{\nu}$=3356, 2962, 2928, 2844, 1679, 1636, 1601, 1519, 1441, 1288, 1177, 1121, 1022, 883, 756, 697 cm^{-1}; HRMS (ESI): m/z: calcd. for $C_{20}H_{20}N_2O_4Na$: 375.1320; found: 375.1333 $[M]^{+\cdot}$.

(11a*S*)-8-Hydroxy-7-methoxy-2,3,5,10,11,11a-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (6e): White solid; m.p. 254–255 °C; $[\alpha]_D^{25}$=+276 (c=0.5 in MeOH); ^{1}H NMR (200 MHz, 25 °C, $CDCl_3$, TMS): δ=7.80 (brs, 1H), 7.40 (s, 1H), 6.50 (s, 1H), 6.00–6.10 (brs, 1H), 4.00–4.10 (m, 1H), 3.95 (s, 3H), 3.70–3.80 (m, 1H), 3.55–3.65 (m, 1H), 2.70–2.80 (m, 1H), 1.90–2.10 ppm (m, 3H); ^{13}C NMR (50 MHz, 25 °C, $CDCl_3$, TMS): δ=175.1, 170.1, 155.1, 149.5, 135.8, 122.5, 117.0, 112.8, 61.5, 60.7, 51.7, 30.7, 28.2 ppm; IR (KBr): $\tilde{\nu}$=2960, 2925, 2843, 1683, 1631, 1607, 1521, 1438, 1284, 1204, 1173, 1115, 1060, 1025, 884, 757 cm^{-1}; HRMS (ESI): m/z: calcd. for $C_{13}H_{14}N_2O_4$: 263.1031; found: 263.1040 $[M+H]^{+\cdot}$.

(2*S*,11a*S*)-2-Azido-2,3,5,10,11,11a-hexahydro-1*H*-pyrrolo[2,1-*c*]-[1,4]benzodiazepine-5,11-dione (6f): M.p. 217–220 °C; $[\alpha]_D^{23}$=+596 (c=1 in MeOH); ^{1}H NMR (200 MHz, 25 °C, $CDCl_3$+[D$_6$]DMSO, TMS): δ=10.20 (s, 1H), 7.85–95 (d, J=10.32 Hz, 1H), 7.40–7.45 (m, 1H), 7.10–7.20 (m, 2H), 4.25–4.35 (m, 1H), 4.05–4.15 (m, 1H), 3.80–3.95 (dd, J=6.21 and 13.70 Hz, 1H), 3.60–3.70 (m, 1H), 3.00–3.10 (m, 1H), 2.25–2.40 ppm (m, 1H); ^{13}C NMR (50 MHz, 25 °C, $CDCl_3$+[D$_6$]DMSO, TMS): δ=169.5, 164.8, 135.5, 131.5, 129.8, 124.4, 123.2, 120.4, 56.9, 55.5, 14.29 ppm; IR (KBr): $\tilde{\nu}$=2933, 2107, 1689, 1617, 1451, 1383, 1213, 1046, 750 cm^{-1}; HRMS (EI): calcd. for $C_{12}H_{11}N_5O_2$: 257.0912; found: 257.0917 $[M]^{+\cdot}$.

(2*S*,11a*S*)-2-Azido-8-hydroxy-7-methoxy-2,3,5,10,11,11a-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (6g): M.p. 116–118 °C; $[\alpha]_D^{23}$=+399 (c=1 in MeOH); ^{1}H NMR (200 MHz, 25 °C, $CDCl_3$, TMS): δ=10.10 (brs, 1H), 7.28 (s, 1H), 6.62 (s, 1H), 4.32 (m, 1H), 4.06 (dd, J=6.79 and 2.26 Hz, 1H), 3.87 (s, 3H), 3.48 (d, J=12.83 Hz, 1H), 3.62 (d, J=12.84 Hz, 1H), 3.02 (d, J=14.35 Hz, 1H), 2.25–2.34 ppm (m, 1H); IR (KBr): $\tilde{\nu}$=3448, 2925, 2853, 2105, 1732, 1681, 1628, 1497, 1425, 1355, 1271, 1215, 1116, 1023, 875, 790, 755, 696, 663, 634 cm^{-1}; HRMS (ESI): m/z: calcd. for $C_{13}H_{13}N_5O_4Na$: 326.0865; found: 326.0871 $[M]^{+\cdot}$.

(2*S*,11a*S*)-2-Azido-8-benzyloxy-7-methoxy-2,3,5,10,11,11a-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (6h): M.p. 173–175 °C; $[\alpha]_D^{25}$=+411 (c=1 in MeOH); ^{1}H NMR (300 MHz, 25 °C, $CDCl_3$, TMS): δ=9.36 (brs, 1H), 7.28–7.40 (m, 6H), 6.59 (s, 1H), 5.08 (m, 2H), 4.28 (m, 1H), 4.10 (dd, J=6.79 and 7.55 Hz, 1H), 3.89 (s, 3H), 3.74–3.80 (dd, J=7.55 and 5.28 Hz, 1H), 3.62 (d, J=12.84 Hz, 1H), 3.02 (d, J=14.35 Hz, 1H), 2.25–2.34 ppm (m, 1H); ^{13}C NMR (75 Hz, 25 °C, $CDCl_3$, TMS): δ=170.8, 165.7, 151.8, 135.8, 129.9, 128.7, 128.3, 127.4, 117.9, 112.5, 105.7, 70.9, 57.9, 56.2, 56.0, 52.6, 30.6; IR (KBr): $\tilde{\nu}$=3221, 2924, 2854, 2100, 1744, 1693, 1606, 1510, 1492, 1430, 1375, 1310, 1261, 1226, 1117, 1021, 873, 788, 753, 697, 643 cm^{-1}; HRMS (ESI): m/z: calcd. for $C_{20}H_{19}N_5O_4Na$: 416.1334; found: 416.1332 $[M]^{+\cdot}$.

(2*R*,11a*S*)-2-Hydroxy-2,3,5,10,11,11a-hexahydro-1*H*-pyrrolo[2,1-*c*]-[1,4]benzodiazepine-5,11-dione (6i): Semi-liquid; $[\alpha]_D^{23}$=+252 (c=1.0, MeOH); ^{1}H NMR (200 MHz, 25 °C, $CDCl_3$+[D$_6$]DMSO, TMS): δ=10.20 (brs, 1H), 7.85–8.00 (m, 1H), 7.40–7.50 (m, 1H), 7.08–7.26 (m, 2H), 4.60–4.70 (m, 1H), 4.40–4.55 (m, 1H), 4.10–4.26 (m, 1H), 3.85–3.95 (m, 1H), 3.50–3.62 (m, 1H), 2.78–2.95 (m, 1H), 2.00–2.10 ppm (m, 1H); ^{13}C NMR (50 MHz, 25 °C, $CDCl_3$+[D$_6$]DMSO, TMS): δ=169.6, 165.0, 135.3, 131.2, 128.2, 125.4, 123.4, 120.5, 67.1, 54.7, 53.3, 33.8 ppm; HRMS (ESI): m/z: calcd. for $C_{12}H_{12}N_2O_3Na$: 255.0745; found: 255.0751 $[M]^{+\cdot}$.

(2*R*,11a*S*)-8-Benzyloxy-7-methoxy-2-hydroxy-2,3,5,10,11,11a-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (6j): Semi-liquid; $[\alpha]_D^{23}$=−42 (c=0.5, MeOH); ^{1}H NMR (200 MHz, 25 °C, $CDCl_3$, TMS): δ=10.11 (brs, 1H), 7.43 (s, 1H), 7.32 (m, 5H), 6.51 (s, 1H), 5.01 (s, 2H), 4.31 (m, 1H), 4.05 (m, 1H), 3.81 (s, 3H), 3.60–3.65 (m, 2H), 1.90–1.98 (m, 2H), 1.21 ppm (m, 1H); ^{13}C NMR (75 MHz, 25 °C, $CDCl_3$, TMS): δ=172.1, 166.3, 152.8, 146.7, 138.1, 131.2, 129.9, 119.4, 112.7, 108.5, 80.1, 70.2, 68.9, 56.9, 55.3, 40.3, 38.2 ppm; ESI (MS): m/z: 369 $[M+H]^{+\cdot}$.

1,2,3,9-Tetrahydropyrrolo[2,1-*b*]quinazolin-9-one (8a): White solid; m.p. 104–106 °C; ^{1}H NMR (300 MHz, 25 °C, $CDCl_3$, TMS) δ=8.24 (dd, J=1.5 and 8.3 Hz, 1H), 7.57–7.70 (m, 2H), 7.38–7.52 (m, 1H), 4.16–4.21 (t, J=7.5 Hz, 2H), 3.12–3.18 (t, J=7.5 Hz, 2H), 2.24–2.34 ppm (m, 2H); HRMS (EI): m/z: calcd. for $C_{11}H_{10}N_2O$: 186.0793; found: 186.0789 $[M]^{+\cdot}$.

6-Methyl-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolin-9-one (8b): M.p. 99–101 °C; ^{1}H NMR (200 MHz, 25 °C, $CDCl_3$, TMS): δ=8.03 (s, 1H), 7.51 (s, 2H), 4.20 (t, J=7.52 Hz, 2H), 3.20 (t, J=7.85 Hz, 2H), 2.50 (s, 3H), 2.34 ppm (q, J=7.31 and 7.83 Hz, 2H); EI (MS): m/z: 200 $[M]^{+\cdot}$.

6-Benzyloxy-7-methoxy-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolin-9-one (8c): White solid; m.p. 157–158 °C; ^{1}H NMR (200 MHz, 25 °C, $CDCl_3$, TMS): δ=7.53 (s, 1H), 7.25–7.46 (m, 5H), 7.00 (s, 1H), 5.22 (s, 2H), 4.16 (t, J=7.34 Hz, 2H), 3.99 (s, 3H), 3.10 (t, J=7.34 and 8.08 Hz, 2H), 2.18–2.34 ppm (m, 2H); ^{13}C NMR (50 MHz, 25 °C, $CDCl_3$, TMS): δ=176.8, 173.1, 168.4, 164.5, 155.4, 148.0, 147.4, 146.7, 133.3, 128.3, 125.0, 115.6, 89.9, 75.3, 65.7, 51.6, 49.1, 39.1, 31.5 ppm; IR (KBr): $\tilde{\nu}$=2955, 2931, 2849, 1662, 1611, 1501, 1453, 1401, 1371, 1288, 1261, 1175, 1137, 1076, 1028, 846, 777 cm^{-1}; HRMS (ESI): m/z: calcd. for $C_{19}H_{18}N_2O_3Na$: 345.1225; found: 345.1200 $[M]^{+\cdot}$.

6,7,8,9-Tetrahydro-11*H*-pyridino[2,1-*b*]quinazolin-11-one (8d): M.p. 96–98 °C; ^{1}H NMR (200 MHz, 25 °C, $CDCl_3$, TMS) δ=8.21 (d, J=8.0 Hz, 1H), 7.70 (t, J=7.4 Hz, 1H), 7.67 (d, J=8.0 Hz, 1H), 7.41 (t, J=7.40 Hz, 1H), 4.07 (t, J=6.04 Hz, 2H), 3.06 (t, J=6.45 Hz, 2H), 1.90–2.10 ppm (m, 4H); HRMS (EI): m/z: calcd. for $C_{12}H_{12}N_2O$: 200.0944; found: 200.0932 $[M]^{+\cdot}$.

3-Methyl-6,7,8,9-tetrahydro-11*H*-pyridino[2,1-*b*]quinazolin-11-one (8e): ^{1}H NMR (200 MHz, 25 °C, $CDCl_3$, TMS): δ=8.01 (s, 1H), 7.55 (s, 2H), 4.12 (t, J=5.07 Hz, 2H), 3.08 (t, J=5.0 Hz, 2H), 2.51 (s, 3H), 1.90–2.20 ppm (m, 4H); EI (MS): m/z: 214 $[M]^{+\cdot}$.

7,8,9,10-Tetrahydroazepino[2,1-*b*]quinazolin-12(6*H*)-one (8f): M.p. 96–98 °C; ^{1}H NMR (200 MHz, 25 °C, $CDCl_3$, TMS): δ=8.25 (d, J=8.04 Hz, 1H), 7.70 (t, J=7.46 Hz, 1H), 7.66 (d, J=8.08 Hz, 1H), 7.44 (t, J=7.42 Hz, 1H), 4.43 (d, J=6.05 Hz, 2H), 3.03 (d, J=6.42 Hz, 2H), 1.81 ppm (s, 6H); EI (MS): m/z: 214 $[M]^{+\cdot}$.

3-Methyl-7,8,9,10-tetrahydroazepino[2,1-*b*]quinazolin-12(6*H*)-one (8g): M.p. 68–70 °C; ^{1}H NMR (200 MHz, 25 °C, $CDCl_3$, TMS): δ=8.02 (s, 1H), 7.43 (s, 2H), 4.35 (d, J=5.06 Hz, 2H), 3.05 (d, J=6.44 Hz, 2H), 2.47 (s, 3H), 1.80 ppm (s, 6H); EI (MS): m/z: 228 $[M]^{+\cdot}$.

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