JOC The Journal of Organic Chemistry

ARTICLE

pubs.acs.org/joc

A One-Pot Azido Reductive Tandem Mono-N-Alkylation Employing Dialkylboron Triflates: Online ESI-MS Mechanistic Investigation

Nagula Shankaraiah,[‡] Nagula Markandeya,[§] Vunnam Srinivasulu,[†] Kokkonda Sreekanth,[†] Ch. Sanjeeva Reddy,[*,§] Leonardo S. Santos,[#] and Ahmed Kamal[*,†,⊥]

[†]Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500 607, India

[‡]National Institute of Pharmaceutical Education and Research (NIPER), Hyderabad-500 037, India

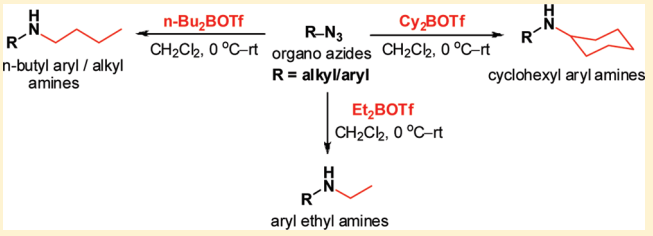
[§]Department of Chemistry, Kakatiya University, Warangal 506 009, A.P, India

[#]Laboratory of Asymmetric Synthesis, Chemistry Institute of Natural Resources, University of Talca, Talca, P.O. Box 747, Chile

[⊥]Catalytic Chemistry Chair, Chemistry Department, College of Science, King Saud University, Riyadh, Saudi Arabia

Supporting Information

ABSTRACT: An efficient one-pot reductive tandem mono-N-alkylation of both aromatic and aliphatic azides using dialkylboron triflates as alkylating agents has been examined under standardized reaction conditions. This methodology after optimization has been employed toward the syntheses of various secondary alkyl as well as aryl amines, including the synthesis of N10-butylated pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones via in situ azido reductive-cyclization process. This protocol is particularly attractive to provide an environmentally benign and practical method for mono-N-alkylation from organic azides without the use of toxic catalysts or corrosive alkylating agents. In addition, 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/MS.



INTRODUCTION

There is considerable interest in the conversion of primary amines into N-alkylated amines for the construction of a vast range of natural products, bioactive molecules, and industrial materials.[1] Secondary amine building blocks are also interesting organic compounds because of their physiological activity and their potential as organic intermediates in the field of bioorganic chemistry.[2] With this increasing repertoire of applications, developing efficient methods for the synthesis of N-alkylated amines has drawn much attention in recent years. However, many different ways to alkylate amines have been reported,[3] which are mostly reductive methods for imines,[4] amides,[5] direct alkylation by halide,[6] displacement of sulfonate[7] or tosylate,[8] epoxide ring-opening,[9] and reductive amination of carbonyls.[10] These methods are applicable to many synthetic conditions, but the majority of them have several drawbacks such as the use of toxic and corrosive alkylating reagents[11] and the frequent generation of wasteful salts as byproduct that are undesirable in view of the environmental concerns.[12] Moreover, the reaction conditions are often drastic (high temperature, basic conditions, etc.), including tedious workup, long reaction times, and poor selectivity. To overcome these difficulties, development of a convenient protocol for mono-N-alkylation is an important synthetic goal for chemists.

However, despite their explosive properties, organic azides are valuable intermediates in organic synthesis.[13−15] In recent years, they have been extensively used in 'click' chemistry[16] for the synthesis of 1,2,3-triazoles, tetrazoles, anilines, and N-alkylated anilines.[17] Brown and co-workers[18a−f] efficiently reported the use of R_3B and their halogenated organoborohydrates ($BHCl_2 \cdot SMe_2$, $BHBr_2 \cdot SMe_2$, etc.) for the reductive N-alkylation of organic azides into their corresponding secondary amines. Most of these azido reductive mono-N-alkylation reaction procedures are reported and performed under reflux conditions apart from the use of xylene as the solvent in a number of the cases. It is also known that a number of amines or imines decompose at higher temperatures and prolonged reaction times. Carboni and co-workers[18g] studied reductive N-alkylation reactions with alkyldichloroboranes by using functionalized azides as substrates. Herein, we report an entirely new, direct one-pot azido reduction with concomitant mono-N-alkylation of both aromatic and aliphatic azides using dialkylboron triflates. Such tandem reactions offer an effective and convenient one-pot process for the synthesis of various N-alkylated amine motifs. In this connection, we have explored different types of dialkylboron triflates such as Bu_2-BOTf, Et_2BOTf, and Cy_2BOTf which are used for the azido-reductive mono-N-alkylation process under mild reaction conditions. Among the above triflates, one of the triflates, namely

Received: May 9, 2011
Published: July 21, 2011

diethylboron triflate, was freshly prepared in situ by mixing of Et_3B and trifluoromethanesulfonic acid.

It is well-known that the use of metal triflates in many organic transformations has grown significantly in the last two decades. Recently, we developed a facile chemoselective azido-reductive cyclization approach by using various metal triflates in combination with NaI and studied their mechanistic aspects.[19] The dialkylboron triflates are particularly useful reagents for the enolization of carbonyl compounds, including ketones, thioesters, and acyloxazolidinones.[20] The most prominent metal Lewis acid catalyst is Bu_2BOTf, since it is stable and especially used in Evan's aldol reaction.[21] Moreover, Bu_2BOTf is found to be an efficient catalyst in regioselective reductive ring-opening of benzylidene acetals in carbohydrates.[22] Benjamin and co-workers reported anti-aldol additions of Oppolzer's sultam that is efficiently promoted by Et_2BOTf.[23] The Cy_2BOTf is also found to be an effective metal catalyst for the enolization of carboxylic esters.[24] However, very few applications have been reported by employing dialkylboron triflates.

RESULTS AND DISCUSSION

This investigation began from our curiosity based on Brown's azido reductive mono-N-alkylation approach by using different types of R_3B or R_2BCl. Herein, it was considered of interest to utilize various Lewis acid-assisted dialkylboron triflates (Bu_2BOTf, Et_2BOTf, and Cy_2BOTf) for the reductive mono-N-alkylation of aromatic azides. Moreover, this aromatic azido reduction reaction was carried out in a one-pot manner with tandem mono-N-alkylation within a short period of time at room temperature and interestingly without the use of catalyst. On this success, the applicability of this procedure toward the mono-N-alkylation of aliphatic primary azides was also explored. Thus, to investigate the generality of this application, we initially optimized the reaction conditions by using a variety of solvents, for example CH_3CN, THF, CH_2Cl_2, Et_2O, and toluene, with the aim to increase yields, shorten reaction times, and to obtain clean products. In nonpolar solvent such as toluene, the reactions were slower and yields were unsatisfactory. Similar results were obtained in Et_2O due to poor solubility of the substrates. Among the solvents examined, CH_2Cl_2 gave the most favorable results with good conversions as well as yields. Then employing CH_2Cl_2, we investigated the requirement of the optimum amount of dialkylboron triflates (Bu_2BOTf, Et_2BOTf, and Cy_2BOTf). These studies suggested that 1 equiv of triflate is sufficient for the reductive mono-N-alkylation of both aliphatic as well as aromatic azides. However, the di-N-alkylated (*tert*-amine) product was also observed considerably when the reaction was performed with excess dialkylboron triflate, such as diethyl or di-n-butylboron triflate. Similarly, when this reaction was performed with an excess of Cy_2BOTf, it did not produce the tertiary amine as a side product probably because of the steric aspect of this triflate.

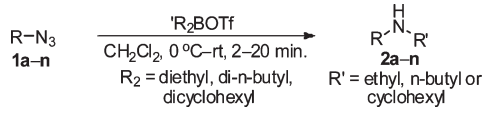
These reactions are considerably spontaneous compared to the related reactions with the corresponding trialkylboranes. In contrast to trialkylboranes, dialkylchloroboranes, even dialkylboron triflates containing a secondary alkyl group, readily react with organic azides to give good to excellent yields of secondary amines after hydrolysis mainly due to the increase in Lewis acidic nature of the dialkylboron triflates. Earlier, it was pointed out by Brown that the reaction of hindered azides with hindered trialkylboranes completely fails.[18e] However in another case, the present reactions proceed well even with sterically hindered organic azides, employing Cy_2BOTf and Bu_2BOTf.

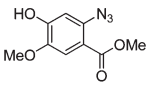
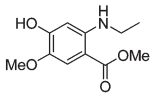
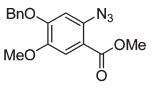
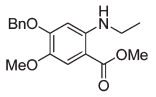
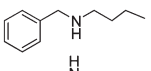
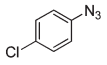
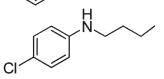
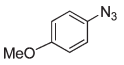
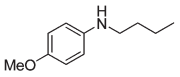
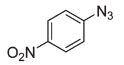
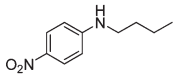
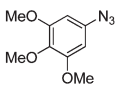
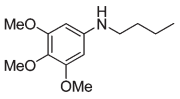
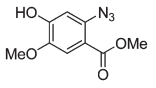
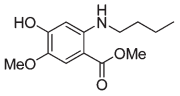
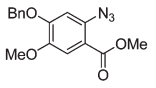
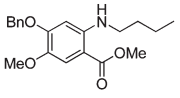
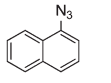
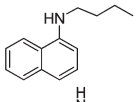
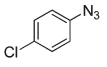
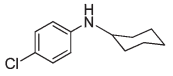
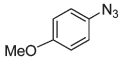
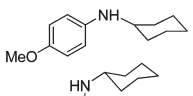
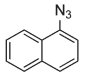
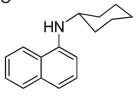
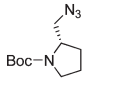
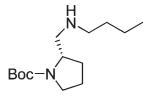
This development suggests that diethyl or di-n-butylboron triflates might be provide a spontaneous reaction with organic azides. As these results were encouraging, a series of organic azides were investigated and these results are summarized in Table 1. It was observed that with less hindered organoboranes or azides (such as diethyl or di-n-butyl), the reaction is rapid, evolving gas, at room temperature whereas in more hindered cases, such as as dicyclohexyl, the reaction is slightly slower and requires about 20 min for the completion of the reaction.

On the basis of the interesting findings of this investigation, a variety of organoboranes were reacted with different organic azides, thus providing a general synthetic procedure for the secondary amines. The required azido starting materials (**1a**−**n**) were obtained according to our previously reported methods.[25] The reactions were conducted by adding the corresponding dialkylboron triflate (1.0 mmol) to a stirred solution of azides (1.0 mmol) in CH_2Cl_2 as a solvent at 0 °C to ambient temperature for 5−20 min, and all the reactions were monitored by observing the disappearance of the starting material, as indicated by TLC. We further validated the reaction conditions by considering the reaction of various substituted azido derivatives with different dialkylboron triflates. In this protocol, one of the noncommercial boronates Et_2BOTf[23] was freshly prepared for the mono-N-alkylation of substrates (entries **1a** and **1b**) as shown in Table 1. The mono-N-alkylated secondary amines **2a**−**n** were obtained from **1a**−**n** in good to excellent yields (80−95%), and the results are summarized in Table 1. Substituted azido derivatives (entries **1a**, **1b**, **1h**, and **1i**) bearing both electron-donating as well as electron-withdrawing groups in the aromatic ring proceeded smoothly and selectively to the corresponding mono-N-alkylated anilines (entries **2a**, **2b**, **2h**, and **2i**) in good yields (80−88%, Table 1). It is noteworthy that reducible functional groups such as nitro (entry **1f**) and ester (entries **1a**, **1b**, **1h**, and **1i**) survived with this protocol. The observations were similar in cases of more electron-donating groups in the aromatic ring such as trimethoxy substitution (entry **1g**, Table 1), which gave 88% yield. The reaction of nitro-substituted azido benzene (entry **1f**, Table 1) proceeded smoothly and gave cleaner mono-N-alkylated aniline (90% yield, entry **2f**). In the case of the *p*-chloro-azido benzene (**1d**) the reaction proceeded very well with excellent yield (entry **2d**, 95%). Mono-*N*-cyclohexyl aniline derivatives (80−85% yields, entries **2k**−**m**, Table 1) were also obtained significantly by employing similar reaction conditions. However, the reaction time is prolonged up to 20 min, which is due to the bulky group of Cy_2BOTf. The aliphatic azido compounds (entry **1c** and **1n**, Table 1) were also converted to their corresponding secondary amines (entry **2c** and **2n**). Interestingly, a Boc-protected mono-N-butylated proline secondary amine building block (entry **2n**, Table 1) was obtained efficiently without changing its stereochemistry, confirmed by optical rotation of the pure product **2n**. Indeed, it is plausible to achieve mono-*N*-alkyl anilines via a one-pot process without the separation of the aniline intermediate.

In our ongoing research program, we have been involved in the development of new azido reductive methodologies in solution as well as of solid-phase systems for the preparation of bioactive natural products, such as pyrrolobenzodiazepines[26] and their derivatives. In this context, we explored this reaction protocol toward the synthesis of not only the secondary amines but also mono-N-alkylation followed by a tandem ring-closing

Table 1. One-Pot Synthesis of Mono-N-alkylated Derivatives (2a−n) from Organic Azides (1a−n) Employing Dialkylboron Triflates



entry	organo azides (**1a–n**)	*N*-alkyl amines (**2a–n**)[a,b]	time (min)	yield (%)[c]
a			5	85
b			5	88
c			2	90
d			2	95
e			2	92
f			4	90
g			2	88
h			3	80
i			5	82
j			2	90
k			20	82
l			20	80
m			20	85
n			10	80

[a] All reactions were conducted at 0 °C to rt with 1.0 mmol of **1a−n**, 1.0 mmol of dialkylboron triflates (Bu_2BOTf, Et_2BOTf, and Cy_2BOTf) in 2 mL of CH_2Cl_2 for 2−20 min. [b] All compounds were characterized by $^1H/^{13}C$ NMR and HRMS. [c] Isolated yields (purified by column chromatography).

reaction process. The main objective was to utilize this mono-N-alkylation approach for the introduction of an additional pharmacophoric scaffold in the bioactive molecules, such as pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones (PBDs) in a one-pot manner. These are well-known naturally occurring antitumor antibiotics that are produced by various *Streptomyces* species and exert their biological activity by interacting with DNA in a sequence-selective manner.[27] PBD-5,11-diones have been employed as intermediates in the synthesis of naturally occurring and synthetically modified PBD imines, such as tomaymycin and chicamycin. This tricyclic PBD ring system has been used for a number of pharmaceutical applications, such as a template for the design and assembly of antituberculosis agents,[28] peptidomimetics,[29] anxiolytic drugs,[30] anticonvulsants,[31] and herbicides.[32]

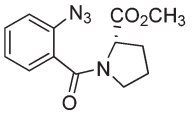
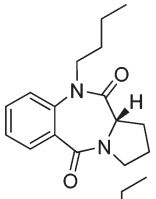
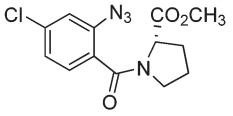
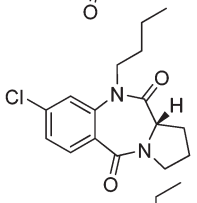
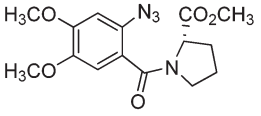
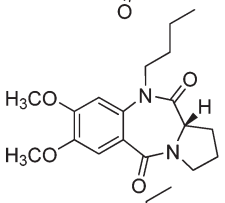
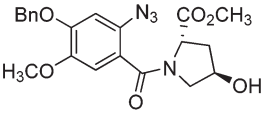
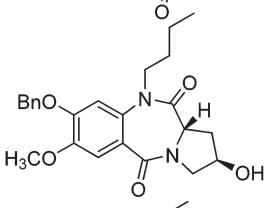
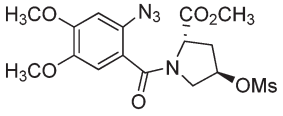
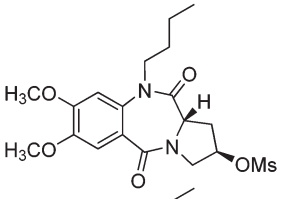
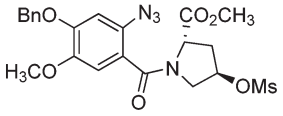
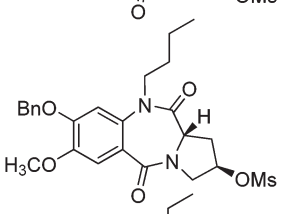
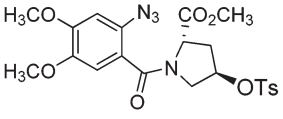
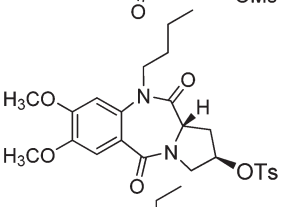
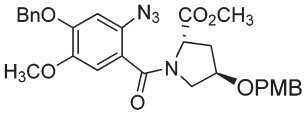
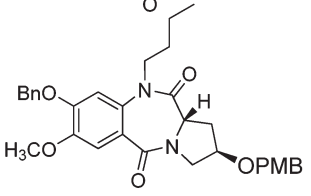
The key intermediates **3a−h** were synthesized by employing our earlier reported methods.[19,33] The mono-N10-butylated PBD-5,11-diones (**4a−h**) were obtained in an efficient manner by employing Bu_2BOTf as the alkylating agent and yields ranged from 72% to 92% as depicted in Table 2. However, during this reaction process, a considerable number of the mono-N10-butylated benzoylproline esters (**5a−h**) were observed in almost 70% yield within a period of 5 min; the other final compounds (**4a−h**) were obtained in 30% yield as shown in Scheme 1, and no trace of *tert*-amines was observed. Next, this reaction mixture was treated with NaH as base dissolved in THF solvent at room temperature for 30 min to provide the final cyclized compounds **4a−h**. This protocol was successfully applied for the synthesis of the A-aromatic ring/C-C2-substituted N10-butylated PBD-5,11-diones in good yields (entries **4d−h**, Table 2) ranging from 72% to 88%. It is interesting to note that the substrates such as C2-mesylated (entries **3e** and **3f**, Table 2), C2-tosylated (entry **3g**), and C2-OPMB protected (entry **3g**) intermediates were efficiently converted to their mono-N10-butylated ring-closing dilactams (entries **4e−h**, Table 2) by employing this protocol without any deprotection. However, it was observed that when this reaction was carried out with C2-OTBDMS protected precursor, the OTBDMS group was completely deprotected under similar reaction conditions. Then, this direct one-pot azido-reductive mono-N-alkylation approach was also applied chemoselectively for the synthesis of (*S*)-1-(2-(butylamino)-benzoyl)-*N*-methoxy-*N*-methylpyrrolidine-2-carboxamide (**7**) from precursor **6**[33a] with n-Bu_2BOTf as shown in Scheme 2. As a result, the Weinreb amide protection is not effected by using this di-n-butylboron triflate. This key intermediate is also one of the very important precursors for the synthesis of PBD-carbinols as an essential pharmacophoric scaffold.

Mechanistic Studies. In the reaction proposed by Brown and co-workers, organic azides lead to secondary amines upon reaction with dialkylboranes, which could involve reversible coordination of the azide with trialkylborane followed by loss of N_2 with subsequent (or concurrent) migration of the alkyl group from boron to nitrogen[18e,f] and thereby affording the final product after hydrolysis.

Complete mechanistic investigations generally require kinetic data obtained by monitoring over long time scales, frequently by UV, IR, or NMR spectroscopy. However, these techniques are often not appropriate for the short time scales required for investigating transient species, as unequivocal assignments of UV and IR bands or NMR peaks and couplings, principally for more complex or transient structures, may be challenging and sometimes impossible. 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, during the last two decades there has been

dx.doi.org/10.1021/jo200931m |*J. Org. Chem.* 2011, 76, 7017–7026

Table 2. One-Pot Synthesis of N10-Butylated Pyrrolo[2,1-*c*][1,4]benzodiazepin-5,11-diones (4a−h) Using Bu_2BOTf as Alkylating Agent

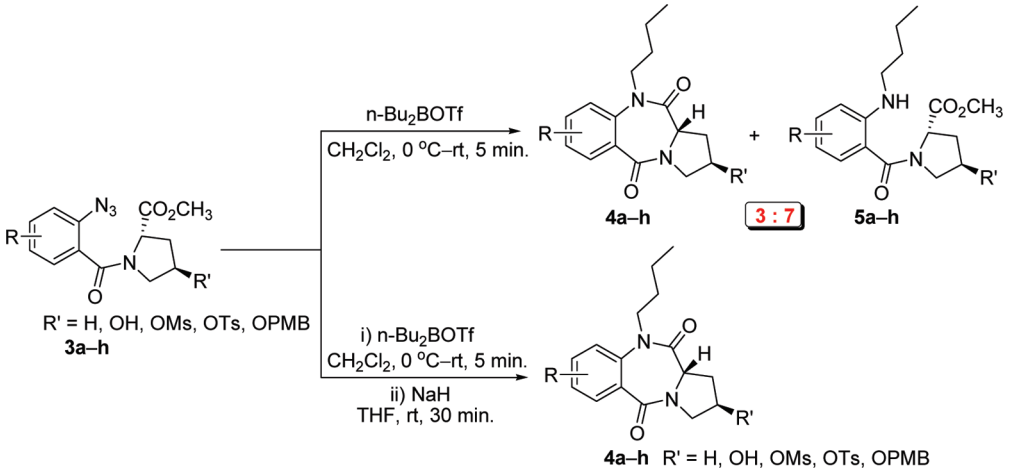
entry	reactants (**3a**–**h**)	products (**4a**–**h**)[a,b]	time (min)	yield (%)[c]
a			35	92
b			35	92
c			35	85
d			35	72
e			35	88
f			35	85
g			35	82
h			35	78

[a] All reactions were conducted at 0 °C to rt with 1.0 mmol of **3a**−**h** and 1.0 mmol of Bu_2BOTf in 2 mL of CH_2C1_2 for 5 min. Later this reaction mixture was stirred with NaH (2 equiv) in THF (3 mL) for 30 min. [b] All compounds were characterized by $^1H/^{13}C$ NMR and HRMS. Isolated yields represent purification by column chromatography.

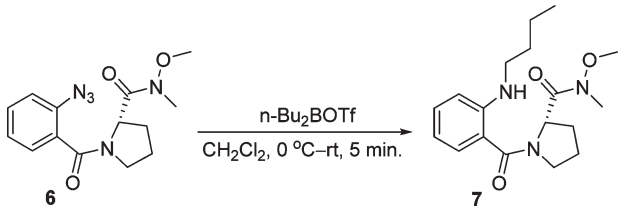
considerable growth in the development of electrospray ionization (ESI) for molecular analysis by mass spectrometry (MS) as a practical method in the study of reaction mechanisms.[34,35] ESI is an interesting 'ion-fishing' technique because it gently transfers

dx.doi.org/10.1021/jo200931m |*J. Org. Chem.* 2011, 76, 7017–7026

Scheme 1. Synthesis of N10-Butylated Pyrrolo[2,1-*c*][1,4]benzodiazepin-5,11-diones



Scheme 2. One-Pot Azido-Reductive Tandem Mono-N-alkylation for the Synthesis of (*S*)-1-(2-(Butylamino)benzoyl)-*N*-methoxy-*N*-methylpyrrolidine-2-carboxamide by Employing Bu_2BOTf



preformed ions directly from solution to the gas phase,[36] and it is rapidly becoming the technique of choice for fast screening of intermediates directly from solution[37] and in high throughput screening of homogeneous catalysis reactions, providing hitherto unavailable chemical information to mechanistic studies.[35] In this context, we became interested in employing the online ESI-MS technique to identify and characterize the species that are involved in the synthetic route for the one-pot azido reduction through dialkylboron triflates.

We monitored the reaction via ESI-MS(/MS) experiments by attempting to intercept ionic intermediates and collect the mechanistic information that could guide the optimization of reaction conditions. We monitored the reaction of **1i** and Bu_2BOTf solution by direct infusion with reaction times around 15 s via ESI-MS operating in the positive ion mode. However, no intermediates were detected, mainly due to the short lifetime of these intermediates. Thus, direct ESI-MS was discarded as the technique for this mechanistic study.[38] Microreactors coupled to an ESI-MS ion source have been used by us to organic reaction mechanistic studies, thus allowing the interception of transient and short lifetime compounds.[35,37a,37c] Since ESI-MS can transfer the ions directly from solution to gas phase with efficiency and gentleness (no or little dissociation), reaction times around 0.33 s can be screened through coupling the microreactor depicted in the insert of Figure 1, thus providing proper snapshots of the ion composition of the reaction solutions in shorter reaction times. We have been using this technique extensively to investigate the mechanisms of several reactions.[39] Thus, to study the mechanism of alkylation reaction, we employed a microreactor coupled to ESI-MS by attempting to "fish" the previously proposed intermediates (Figure 1 and Scheme 3). Figure 1a shows the ESI-MS spectrum of **1i** in neat CH_2Cl_2 wherein the major ion detected in the mass spectrum corresponds to $[\mathbf{1i} - N_2 + H]^+$ of m/z 286.1070 (calculated 286.1079) and $[\mathbf{1i} + H]^+$ of m/z 314.1135 (calculated 314.1146). At this stage, it was not possible to obtain the net protonated azide **1i** (Figure 1a) because of the great lability of the N_3 group. Those ions were then mass-selected and structurally characterized via CID with argon in ESI-MS/MS measurements affording neutral losses of N_2 followed by CH_3OH as the main fragmentation pathway (spectra not shown). Then, we investigated the formation of the intermediate species in a reaction solution that was prepared by online mixing of **1i** with Bu_2BOTf via the microreactor (insert in Figure 1) following Brown's procedure. The reaction of **1i** solution with Bu_2BOTf/CH_2Cl_2 using the microreactor resulted in a very clean spectrum (Figure 1b) displaying two cationic species that were easily identified by their absolute masses at reaction times of 0.33 s: $[\mathbf{8} + H]^+$ (m/z 588.2165, calculated 588.2163) and $[\mathbf{9} + H]^+$ (m/z 560.2105, calculated 560.2096). After addition of water to the reaction mixture, the final product of the reaction was obtained as $[\mathbf{2i} + H]^+$ of m/z 344.1870 (calculated 344.1862). According to ESI-MS data, strong evidence for the currently accepted mechanism has been collected, thus confirming the proposals initially made by Brown and co-workers.

CONCLUSION

In summary, we have investigated and presented a valuable alternative methodology for selective azido-reductive direct mono-N-alkylation of both aromatic and aliphatic azides using dialkylboron triflates as alkylating agents. This methodology is particularly attractive, as it provides secondary amine building blocks as pharmacophoric scaffolds for drug discovery. Moreover, the one-pot azido-reductive mono-N-alkylation followed by a tandem cyclization sequence is an innovative development for the synthesis N10-butylated PBD-5,11-diones. Furthermore, the presented protocol is facile and environmentally benign.

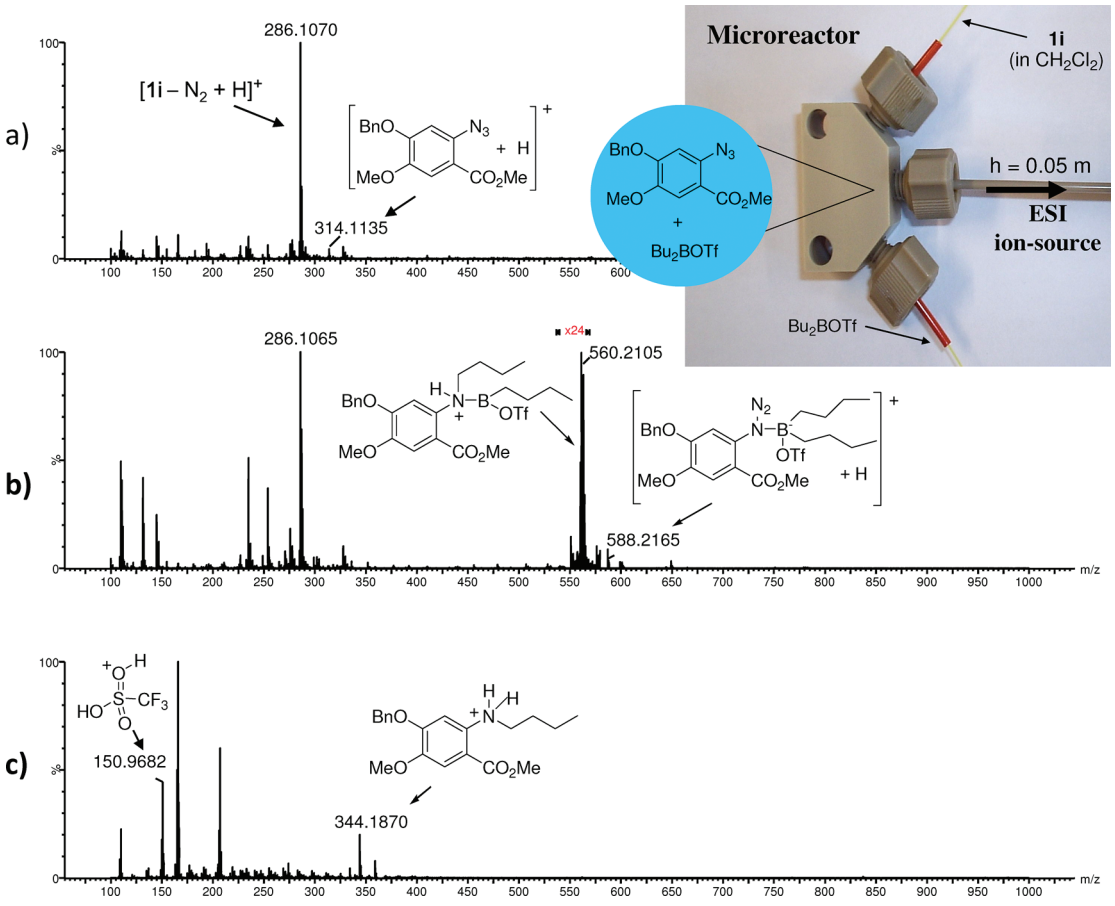
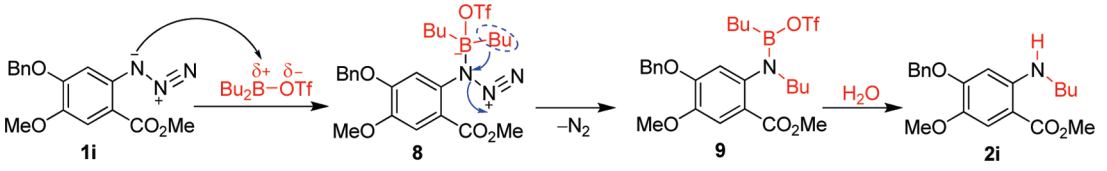


Figure 1. ESI(+)-MS spectra for the reaction of **1i** with Bu_2BOTf: (a) **1i** in CH_2Cl_2 (control experiment); (b) online monitoring of the mixture of **1i** and Bu_2BOTf at 0.33 s of reaction time and interception of intermediates **8** and **9**; (c) production of **2i** after addition of H_2O. Other unidentified ions/compounds are mainly hydrated triflates, and these are mostly water and solvent clusters of the triflate of *m*/*z* 150.9 (favorably ionized under positive-ion ESI).

Scheme 3. Proof of the Mechanism for the Conversion of Aryl Azide into N-Alkylated Aniline by Using Bu_2BOTf as an Alkylating Agent Based on ESI(+)-MS(/MS) Online Monitoring



EXPERIMENTAL SECTION

General Methods. Purchased chemical reagents were used without further purification. Anhydrous CH_2Cl_2, THF, CH_3CN, toluene, and ether 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. FT-IR spectra for all the compounds were recorded by using thin film as well as KBr disk. ^1H and ^{13}C NMR spectra were recorded on 200, 300, and 400 MHz spectrometers using tetramethylsilane as the internal standard (Note: Most of the compounds of 'NH' protons did not appear in ^1H NMR spectra because of D_2O exchange). 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 by electrospray ionization mass spectrometry (ESI-MS), and the online mechanistic studies were carried out by using ESI(+)-MS(/MS) in a Q-Tof Micro equipment. Column chromatography was performed by using 60−120 mesh silica gel. TLC analyses were performed with silica gel plates using iodine, $KMnO_4$, and a UV lamp for visualization.

General Reaction Procedure for the Preparation of Compounds 2a−n. A dry 25 mL round-bottom flask equipped with a septum inlet and magnetic stirring bar was flushed with nitrogen. A 2 mL amount of dry CH_2Cl_2 and 1.0 mmol of dialkylboron triflate were added to a round-bottom flask at 0 °C, and 1.0 mmol of organic azide (**1a**−**n**) dissolved in 2 mL of dry CH_2Cl_2 was added by using a syringe. Later, the reaction mixture was monitored by observing the disappearance of the

dx.doi.org/10.1021/jo200931m |J. Org. Chem. 2011, 76, 7017–7026

starting material, as indicated by TLC. After the nitrogen gas evolution had ceased, the solution was cooled to 0 °C and very carefully hydrolyzed by slowly adding 3−5 mL of H_2O and additionally an excess of H_2O was added and the precipitate removed by filtration. The combined aqueous layers and precipitate were washed with saturated $NaHCO_3$ solution and followed by brine wash. The mono-N-alkylated amines were extracted with EtOAc. The crude products were purified by column chromatography (60−120 mesh silica gel) using EtOAc:hexane as eluent.

*Methyl 2-(Ethylamino)-4-hydroxy-5-methoxybenzoate (**2a**).* Triethylborane (1 mL, 1 M in hexane, 1.0 mmol) solution was added to freshly distilled triflouromethanesulfonic acid (88 μL, 1.0 mmol). The reaction mixture was stirred at room temperature for 1 h in which the solution appeared as homogeneous pale yellow/orange. Then, it was cooled to 0 °C, and methyl 2-azido-4-hydroxy-5-methoxybenzoate (**1a**, 223 mg, 1.0 mmol) in dry CH_2Cl_2 (5 mL) was added. Later, the reaction mixture was monitored by observing the disappearance of the starting material, as indicated by TLC. After 5 min, this reaction mixture was quenched with saturated $NaHCO_3$ solution, another 10 mL of CH_2Cl_2 was added, and the precipitate was removed by filtration. The organic phase was separated and dried over anhydrous Na_2SO_4. The crude product thus obtained was purified by column chromatography using a silica gel (60−120 mesh) pad employing ethyl acetate/hexane (30:70) as eluent to afford the brownish crystalline solid **2a** (191 mg, 85%). Mp: 70−72 °C; FT-IR: (cm^{-1}) 3525, 3471, 3384, 2924, 2853, 1655, 1590, 1538, 1429, 1393, 1335, 1278, 1242, 1176, 1085, 1025, 957, 866, 827, 772; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.32 (s, 1H), 7.25 (s, 1H), 6.33 (br, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.20 (q, 2H), 1.35 (t, 3H, J = 7.17 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.5, 152.2, 148.7, 136.8, 112.9, 100.8, 97.2, 56.5, 51.2, 37.8, 14.5; HRMS (ESI): m/z Calcd for $C_{11}H_{16}NO_4$ 226.1106, found 226.1116 $[M + H]^+$.

*Methyl 4-(Benzyloxy)-2-(ethylamino)-5-methoxybenzoate (**2b**).* Reddish brown solid. Mp: 90−92 °C; FT-IR: (cm^{-1}) 3352, 2924, 2855, 1668, 1582, 1516, 1456, 1366, 1238, 1165, 1104, 994, 909, 862, 810, 774, 743, 701; ^1H NMR (400 MHz, $CDCl_3$): δ= 7.26−7.46 (m, 6H), 6.09 (s, 1H), 5.16 (s, 2H), 3.80 (s, 6H), 3.07−3.12 (m, 2H), 1.25 (t, 2H, J = 7.05 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.5, 154.5, 148.3, 139.3, 136.5, 128.6, 127.9, 127.1, 114.6, 100.9, 96.5, 70.5, 56.8, 51.1, 37.6, 14.4; HRMS (ESI): m/z Calcd for $C_{18}H_{22}NO_4$ 316.1548, found 316.1554 $[M + H]^+$.

*N-Benzylbutan-1-amine (**2c**).* To a stirred solution of Bu_2BOTf (1.46 mL, 1.502 mmol) in dry CH_2Cl_2 (2 mL), 1-(azidomethyl)benzene (**1c**, 200 mg, 1.502 mmol) dissolved in dry CH_2Cl_2 (2 mL) was added at 0 °C and stirred at room temperature for 2 min. The reaction mixture was neutralized with saturated aqueous $NaHCO_3$ solution, extracted the organic layer, dried over Na_2SO_4 and evaporated under reduced pressure. The crude product thus obtained was purified by column chromatography through silica gel (60−120 mesh) pad employing ethyl acetate/hexane (80:20) as eluent to afford the compound **2c** (220 mg, 90%). White solid. Mp: 54−56 °C; FT-IR: (cm^{-1}) 3419, 3074, 2924, 2852, 1604, 1438, 1383, 1240, 1170, 1032, 750, 639; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.26−7.36 (m, 5H), 4.38 (br, 1H), 3.89 (s, 2H), 2.67−2.72 (t, 2H, J = 7.54 Hz), 1.52−1.61 (m, 2H), 1.22−1.40 (m, 2H), 0.88−0.93 (t, 3H, J = 7.17 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 133.5, 129.4, 128.9, 128.7, 52.1, 47.4, 29.2, 19.9, 13.5; HRMS (ESI): m/z Calcd for $C_{11}H_{18}N$ 164.1439, found 164.1432 $[M + H]^+$.

*N-Butyl-4-chloroaniline (**2d**).* Reddish brown liquid. FT-IR: (cm^{-1}) 3417, 2958, 2928, 2866, 1600, 1501, 1399, 1318, 1256, 1176, 1141, 1092, 813, 763; ^1H NMR (200 MHz, $CDCl_3$): δ = 7.06 (d, 2H, J = 8.81 Hz), 6.46 (d, 2H, J = 8.81 Hz), 3.50 (br, 1H), 3.05 (t, 2H, J = 6.61 Hz), 1.33−1.66 (m, 4H), 0.96 (t, 3H, J = 7.34 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.9, 128.9, 121.5, 113.7, 43.7, 31.4, 20.2,13.8; HRMS (ESI): m/z Calcd for $C_{10}H_{15}NCl$ 184.0893, found 184.0890 $[M + H]^+$.

*N-Butyl-4-methoxyaniline (**2e**).* Reddish brown liquid, FT-IR: (cm^{-1}) 3372, 2957, 2868, 1671, 1603, 1511, 1462, 1295, 1244, 1177, 1146, 1033, 827, 756; ^1H NMR (200 MHz, $CDCl_3$): δ = 6.73 (d, 2H, J = 8.81 Hz), 6.49 (d, 2H, J = 8.81 Hz), 3.71 (s, 3H), 3.07 (t, 2H, J = 6.61 Hz), 1.33−1.66 (m, 4H), 0.96 (t, 3H, J = 7.34 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.9, 142.7, 114.8, 113.9, 55.7, 44.7, 31.7, 20.3, 13.9; HRMS (ESI): m/z Calcd for $C_{11}H_{17}NONa$ 202.1193, found 202.1199 $[M + Na]^+$.

*N-Butyl-4-nitroaniline (**2f**).* Brown solid. Mp: 54−56 °C; FT-IR: (cm^{-1}) 3345, 2957, 2869, 1605, 1473, 1298, 1189, 1109, 834, 752, 659; ^1H NMR (200 MHz, $CDCl_3$): δ = 8.06 (d, 2H, J = 9.55 Hz), 6.49 (d, 2H, J = 8.81 Hz), 4.83 (s, 1H), 3.23 (q, 2H), 1.39−1.72 (m, 4H), 0.98 (t, 3H, J = 7.34 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.5, 137.6, 126.4, 110.8, 43.1, 31.1, 20.1, 13.7; HRMS (ESI): m/z Calcd for $C_{10}H_{14}N_2O_2$-Na 217.0952, found 217.0962 $[M + Na]^+$.

*N-Butyl-3,4,5-trimethoxyaniline (**2g**).* Dark brown liquid. FT-IR: (cm^{-1}) 3401, 2925, 1603, 1320, 1112; ^1H NMR (200 MHz, $CDCl_3$): δ = 6.52 (s, 1H), 5.93 (s, 1H), 5.78 (s, 1H), 3.58−4.12 (m, 9H), 3.03−3.23 (m, 2H), 1.28−1.82 (m, 4H), 0.78−1.03 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.8, 145.3, 129.7, 90.1, 61.0, 55.8, 44.0, 31.6, 20.2, 13.8. HRMS (ESI): m/z Calcd for $C_{13}H_{22}NO_3$ 240.1599, found 240.1610 $[M + H]^+$.

*Methyl 2-(Butylamino)-4-hydroxy-5-methoxybenzoate (**2h**).* Reddish brown solid. Mp: 72−74 °C; FT-IR: (cm^{-1}) 3360, 2926, 2854, 1742, 1677, 1589, 1521, 1462, 1435, 1377, 1309, 1237, 1195, 1092, 1031, 867, 765; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.35 (s, 2H), 6.55 (s, 1H), 3.86 (s, 6H), 3.17 (t, 2H, J = 6.98 Hz), 1.65−1.75 (m, 2H), 1.39−1.51 (m, 2H), 0.98 (t, 3H, J = 7.17 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.6, 152.4, 149.1, 136.8, 127.7, 113.1, 97.2, 56.6, 51.2, 42.9, 31.3, 20.3, 13.9. HRMS (ESI): m/z Calcd for $C_{13}H_{20}NO_4$ 254.1392, found 254.1388 $[M + H]^+$.

*Methyl 4-(Benzyloxy)-2-(butylamino)-5-methoxybenzoate (**2i**).* White solid. Mp: 81−83 °C; FT-IR: (cm^{-1}) 3351, 2955, 2927, 2864, 1674, 1619, 1586, 1523, 1460, 1442, 1384, 1363, 1336, 1270, 1245, 1221, 1200, 1173, 1097, 1034, 1004, 967, 872, 772, 738, 697; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.25−7.42 (m, 6H), 6.11 (s, 1H), 5.16 (s, 2H), 3.80 (s, 6H), 3.04 (t, 2H, J = 6.79 Hz), 1.58 (qt, 2H), 1.36−1.48 (m, 2H), 0.95 (t, 3H, J = 6.79 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.5, 154.5, 148.4, 139.3, 136.5, 128.6, 127.9, 127.1, 114.5, 101.0, 96.6, 70.5, 56.9, 51.2, 42.9, 31.2, 20.3, 13.8; HRMS (ESI): m/z Calcd for $C_{20}H_{26}NO_4$ 344.1862, found 344.1870 $[M + H]^+$.

*N-Butylnaphthalen-1-amine (**2j**).* Dark brown solid. Mp: 72−74 °C; FT-IR: (cm^{-1}): 3432, 3057, 2956, 2927, 2863, 1623, 1582, 1526, 1476, 1408, 1375, 1343, 1283, 1218, 1183, 1028, 766; ^1H NMR (200 MHz, $CDCl_3$): δ = 7.70−7.75 (m, 2H), 7.13−7.43 (m, 4H), 6.49−6.58 (m, 1H), 4.22 (br, 1H), 3.22 (t, 2H, J = 6.61 Hz), 1.69−1.83 (m, 2H), 1.43−1.63 (m, 2H), 0.98−1.06 (t, 3H, J = 7.34 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.5, 134.2, 128.6, 126.6, 125.6, 124.5, 123.3, 119.7, 117.0, 104.2, 43.9, 31.5, 20.5, 13.9; HRMS (ESI): m/z Calcd for $C_{14}H_{18}N$ 200.1439, found 200.1431 $[M + H]^+$.

*4-Chloro-N-cyclohexylaniline (**2k**).* To a stirred solution of Cy_2BOTf (424 mg, 1.302 mmol) in dry CH_2Cl_2 (2 mL) was added *p*-chloro-azido benzene (**1k**, 200 mg, 1.302 mmol) dissolved in dry CH_2Cl_2 (2 mL) at 0 °C, and the mixture was stirred at room temparature for 20 min. The reaction mixture was neutralized with saturated aqueous $NaHCO_3$ solution, extracted the organic layer, dried over Na_2SO_4, and evaporated under reduced pressure. The crude product thus obtained was purified by column chromatography through silica gel (60−120 mesh) pad employing ethyl acetate/hexane (80:20) as eluent to afford the compound **2k** as brown liquid. FT-IR: (cm^{-1}) 3401, 2928, 2853, 1601, 1504, 1320, 1117, 772, 747, 691; ^1H NMR (200 MHz, $CDCl_3$): δ = 6.98 (d, 2H, J = 8.79 Hz), 6.37 (d, 2H, J = 8.06 Hz), 3.43 (s, 1H), 3.08−3.16 (m, 1H), 2.24 (t, 1H, J = 7.34 Hz), 1.92−1.99 (m, 4H), 1.73 (tt, 3H, J = 3.66, 4.39 Hz), 1.53−1.62 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.4, 129.2, 116.8, 113.1, 51.7, 33.5, 25.9, 25.0. HRMS (ESI): m/z Calcd for $C_{12}H_{17}NCl$ 210.1049, found 210.1054 $[M + H]^+$.

*N-Cyclohexyl-4-methoxyaniline (**2l**).* Reddish brown liquid. FT-IR: (cm^{-1}) 3446, 2924, 1509, 772; ^1H NMR (200 MHz, $CDCl_3$): δ = 6.72

(d, 2H, J = 8.81 Hz), 6.49 (d, 2H, J = 9.55 Hz), 3.73 (s, 3H), 3.06−3.21 (m, 1H), 2.38 (br, 1H), 2.04 (dd, 2H, J = 2.93, 12.49 Hz), 1.58−1.80 (m, 3H), 1.00−1.46 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.0, 140.9, 115.1, 114.8, 55.7, 53.0, 33.3, 25.8, 24.9. HRMS (ESI): m/z Calcd for $C_{13}H_{20}NO$ 206.1544, found 206.1538 $[M + H]^+$.

N-Cyclohexylnaphthalen-1-amine (**2m**). Dark brown solid. Mp: 76−78 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.67−7.75 (m, 2H), 7.09−7.38 (m, 4H), 6.57 (d, 1H, J = 7.01 Hz), 4.18 (br, 1H), 3.40−3.49 (m, 1H), 2.14−2.21 (m, 2H), 1.64−1.90 (m, 3H), 1.1−1.56 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.4, 128.6, 126.5, 125.5, 124.4, 123.3, 119.7, 116.6, 104.7, 51.7, 33.2, 29.6, 26.0, 25.0. HRMS (ESI): m/z Calcd for $C_{16}H_{20}N$ 226.1595, found 226.1593 $[M + H]^+$.

(S)-tert-Butyl 2-((Butylamino)methyl)pyrrolidine-1-carboxylate (**2n**). White solid. Mp: 54−56 °C; $[\alpha]^{25}_D$ = −26.62 (c = 0.0015, $CHCl_3$); FT-IR: (cm^{-1}) 3435, 2925, 2854, 2103, 1683, 1417; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.02−4.90 (dd, 1H, J = 7.79, 10.95 Hz), 3.39 (t, 2H, J = 6.98, 7.17 Hz), 2.40 (t, 2H, J = 8.12 Hz), 2.06−1.97 (m, 4H), 1.46−1.25 (m, 14H), 0.95 (t, 2H, J = 7.17, 7.36 Hz), 0.87 (t, 2H, J = 6.42, 6.79 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.2, 81.9, 55.2, 53.4, 49.4, 47.8, 33.7, 31.8, 29.6, 23.6, 22.6, 19.5, 17.5, 14.0; HRMS (ESI): m/z Calcd for $C_{14}H_{29}N_2O_2$ 257.2229, found 257.2220 $[M + H]^+$.

(S)-10-Butyl-2,3-dihydro-1H-benzo[e]pyrrolo[1,2-a][1,4]diazepine-5,11(10H,11aH)-dione (**4a**). Brown solid. Mp: 93−94 °C; $[\alpha]^{25}_D$ = +121.36 (c = 0.0012, $CHCl_3$); FT-IR: (cm^{-1}): 2926, 2872, 1670, 1641, 1600, 1455, 1405, 1288, 1242, 1154, 1082, 958, 843, 768, 709; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.92 (d, 1H, J = 7.28 Hz), 7.52 (t, 1H, J = 7.28 Hz), 7.29 (qt, 2H), 4.19−4.25 (m, 1H), 4.01 (d, 1H, J = 6.24 Hz), 3.78−3.82 (m, 1H), 3.53−3.65 (m, 2H), 2.73 (d, 1H, J = 11.45 Hz), 2.09−2.18 (m, 1H), 1.94−2.03 (m, 2H), 1.41−1.59 (m, 2H), 1.20−1.27 (m, 2H), 0.85 (t, 3H, J = 7.28 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.1, 164.9, 139.3, 131.8, 130.9, 130.1, 125.7, 122.4, 57.2, 47.9, 46.4, 29.9, 26.5, 23.7, 19.8, 13.5; HRMS (ESI): m/z Calcd for $C_{16}H_{21}N_2O_2$ 273.1603, found 273.1599 $[M + H]^+$.

(S)-10-Butyl-8-chloro-2,3-dihydro-1H-benzo[e]pyrrolo[1,2-a][1,4]-diazepine-5,11(10H,11aH)-dione (**4b**). Yellowish solid. Mp: 70−72 °C; $[\alpha]^{25}_D$ = +162.037 (c = 0.0011, $CHCl_3$); FT-IR: (cm^{-1}) 2926, 2858, 1681, 1639, 1590, 1440, 1372, 1280, 1235, 1204, 1157, 1094, 1027, 924, 841, 801, 770, 710; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.86 (d, 1H, J = 7.28 Hz), 7.26 (t, 2H, J = 7.28 Hz), 4.23 (qt, 1H), 3.98 (d, 1H, J = 6.24 Hz), 3.76−3.80 (m, 1H), 3.51−3.62 (m, 2H), 2.71−2.76 (m, 1H), 2.09−2.20 (m, 1H), 1.95−2.04 (m, 2H), 1.53−1.62 (m, 2H), 1.41−1.51 (m, 2H), 0.89 (t, 3H, J = 7.28 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.9, 164.2, 140.5, 137.7, 131.6, 129.5, 126.0, 122.6, 57.3, 48.2, 46.6, 29.9, 26.6, 23.8, 19.8, 13.5; HRMS (ESI): m/z Calcd for $C_{16}H_{20}N_2O_2Cl$ 307.1213, found 307.1202 $[M + H]^+$.

(S)-10-Butyl-7,8-dimethoxy-2,3-dihydro-1H-benzo[e]pyrrolo[1,2-a][1,4]diazepine-5,11(10H,11aH)-dione (**4c**). White crystalline solid. Mp: 118−120 °C; $[\alpha]^{25}_D$ = +22.123 (c = 0.0011, $CHCl_3$); FT-IR: (cm^{-1}) 3445, 2945, 2872, 1678, 1629, 1518, 1435, 1370, 1252, 1211, 1115, 1013, 874, 783, 726; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31 (s, 1H), 6.66 (s, 1H), 4.22−4.32 (m, 1H), 4.01 (d, 1H, J = 6.04 Hz), 3.94 (s, 3H), 3.89 (s, 3H), 3.71−3.77 (m, 1H), 3.45−3.57 (m, 2H), 2.73 (d, 1H, J = 10.95 Hz), 2.09−2.33 (m, 1H), 1.88−2.05 (m, 2H), 1.38−1.49 (m, 2H), 1.18−1.30 (m, 2H), 0.87 (t, 3H, J = 7.18 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.1, 164.9, 151.55, 146.7, 132.2, 123.7, 111.2, 105.5, 57.4, 56.1, 56.0, 48.0, 46.4, 29.9, 26.5, 23.8, 19.8, 13.6; HRMS (ESI): m/z Calcd for $C_{18}H_{25}N_2O_4$ 333.1814, found 333.1819 $[M + H]^+$.

(2R,11aS)-8-(Benzyloxy)-10-butyl-2-hydroxy-7-methoxy-2,3-dihydro-1H-benzo[e]pyrrolo[1,2-a][1,4]diazepine-5,11(10H,11aH)-dione (**4d**). Colorless viscous liquid. $[\alpha]^{25}_D$ = +147.327 (c = 0.011, $CHCl_3$); FT-IR: (cm^{-1}) 3414, 2929, 1660, 1617, 1422, 1261, 1220, 1182, 722. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34−7.39 (m, 6H), 6.65 (s, 1H), 5.13−5.34 (m, 2H), 4.59−4.69 (m, 1H), 4.15−4.24 (m, 1H), 3.94 (s, 3H), 3.60−3.65 (m, 2H), 3.25−3.40 (m, 2H), 2.90−3.01 (m, 1H), 2.33−2.43 (m, 1H), 1.97−2.13 (m, 1H), 1.22− 1.38 (m, 2H), 1.03−1.15 (m, 2H), 0.78 (t, 3H, J = 7.36 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.4, 165.5, 150.3, 147.3, 135.9, 131.9, 128.7, 128.2, 126.8, 114.2, 111.6, 108.3, 71.1, 69.2, 56.3, 53.7, 49.4, 48.2, 34.8, 30.6, 19.7, 13.6. HRMS (ESI): m/z calcd for $C_{24}H_{29}N_2O_5$ 425.2010, found 425.2037 $[M + H]^+$.

(2R,11aS)-10-Butyl-2-hydroxy-7,8-dimethoxy-2,3-dihydro-1H-benzo-[e]pyrrolo[1,2-a][1,4]diazepine-5,11(10H,11aH)-dione (**4e**). Pale yellow viscous liquid. $[\alpha]^{25}_D$ = +201.230 (c = 0.012, $CHCl_3$); FT-IR: (cm^{-1}) 2957, 1663, 1637, 1603, 1518, 1442, 1361, 1268, 1176, 1025, 964.4, 901, 752, 530. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32 (s, 1H), 6.68 (s, 1H), 5.29−5.39 (m, 1H), 4.12−4.32 (m, 1H), 3.95 (s, 3H), 3.90 (s, 3H), 3.39−3.71 (m, 2H), 3.13−3.24 (m, 2H), 3.02 (s, 3H), 2.38−2.49 (m, 1H), 1.19−1.55 (m, 5H), 0.90 (t, 3H, J = 7.55 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.6, 165.3, 152.1, 147.1, 133.1, 122.4, 114.3, 111.4, 78.2, 56.3, 55.7, 51.6, 48.6, 38.6, 33.5, 29.8, 29.7, 19.8, 13.7. HRMS (ESI): m/z calcd for $C_{19}H_{27}N_2O_7S$ 427.1538, found 427.1548 $[M + H]^+$.

(2R,11aS)-8-(Benzyloxy)-10-butyl-7-methoxy-5,11-dioxo-2,3,5,10,11,11a-hexahydro-1H-benzo[e]pyrrolo[1,2-a][1,4]diazepin-2-yl Methanesulfonate (**4f**). Pale yellow liquid. $[\alpha]^{25}_D$ = +158.521 (c = 0.015, $CHCl_3$); FT-IR: (cm^{-1}) 2929, 1641, 1635, 1603, 1435, 1355, 1173, 1035, 771; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33−7.38 (m, 5H), 7.28−7.31 (m, 1H), 6.63 (s, 1H), 5.12−5.25 (m, 2H), 4.32−4.34 (m, 1H), 4.17−4.20 (m, 1H), 3.97 (s, 3H), 3.74−3.75 (m, 2H), 3.40−3.44 (m, 2H), 3.00 (s, 3H), 2.37−2.41 (m, 1H), 1.51−1.57 (m, 1H), 1.33−1.39 (m, 2H), 1.08−1.12 (m, 2H), 0.82 (t, 3H, J = 7.00 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.3, 165.0, 150.6, 147.5, 135.8, 132.6, 128.7, 128.2, 126.8, 122.3, 111.6, 108.3, 78.0, 71.0, 56.1, 55.5, 51.5, 48.3, 38.4, 33.3, 29.6, 19.6, 13.5; HRMS (ESI): m/z calcd for $C_{25}H_{30}N_2O_7SNa$ 525.1671, found 525.1661 $[M + Na]^+$.

(2R,11aS)-10-Butyl-7,8-dimethoxy-5,11-dioxo-2,3,5,10,11,11a-hexahydro-1H-benzo[e]pyrrolo[1,2-a][1,4]diazepin-2-yl 4-Methylbenzenesulfonate (**4g**). Colorless viscous liquid. $[\alpha]^{25}_D$ = +124.423 (c = 0.010, $CHCl_3$); FT-IR: (cm^{-1}). 2930, 1642, 1605, 1517, 1455, 1364, 1258, 1219, 1122, 1017, 772; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.77−7.79 (m, 1H), 7.36 (s, 2H), 6.94 (s, 1H), 6.73 (s, 2H), 5.36−5.42 (m, 1H), 4.17−4.35 (m, 1H), 3.93 (s, 6H), 3.70−3.72 (m, 2H), 3.45 (t, 2H, J = 7.00 Hz), 2.45 (s, 3H), 1.86−2.15 (m, 2H), 1.29−1.38 (m, 2H), 1.18−1.24 (m, 2H), 0.81 (3H, J = 7.00 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.1, 161.5, 151.7, 147.0, 133.0, 130.7, 130.0, 127.8, 127.0, 112.5, 111.5, 105.8, 78.3, 56.8, 56.0, 55.6, 48.5, 29.8, 23.7, 19.8, 13.7; HRMS (ESI): m/z calcd for $C_{25}H_{30}N_2O_7SNa$ 525.1671, found 525.1690 $[M + Na]^+$.

(2R,11aS)-8-(Benzyloxy)-10-butyl-7-methoxy-2-(4-methoxybenzyloxy)-2,3-dihydro-1H-benzo[e]pyrrolo[1,2-a][1,4]diazepine-5,11(10H,11aH)-dione (**4h**). Colorless viscous liquid. $[\alpha]^{25}_D$ = +94.723 (c = 0.02, $CHCl_3$); FT-IR: (cm^{-1}) 2928, 2870, 1634, 1602, 1510, 1115, 720 ; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.31−7.40 (m, 5H), 7.22−7.26 (m, 2H), 6.86 (d, 3H, J = 9.00 Hz), 6.64 (s, 1H), 5.15−5.28 (m, 2H), 4.42−4.49 (m, 3H), 4.11−4.26 (m, 1H), 3.95 (s, 3H), 3.79 (s, 3H), 3.70−3.75 (m, 2H), 3.46 (t, 2H, J = 7.00 Hz), 2.01− 2.16 (m, 2H), 1.52−1.59 (m, 2H), 1.30−1.43 (m, 2H), 0.91 (t, 3H, J = 7.00 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.5, 165.3, 152.8, 150.3, 147.3, 135.9, 130.8, 129.7, 129.3, 128.7, 128.2, 127.9, 126.8, 113.8, 111.6, 108.3, 75.7, 72.5, 71.2, 56.2, 56.1, 55.2, 50.6, 48.1, 38.6, 31.5, 19.1, 13.8; HRMS (ESI): m/z calcd for $C_{32}H_{36}N_2O_6Na$ 567.2471, found 567.2461 $[M + Na]^+$.

(S)-Methyl 1-(2-(Butylamino)benzoyl)pyrrolidine-2-carboxylate (**5a**). Brown liquid. $[\alpha]^{25}_D$ = +345.00 (c = 0.0011, $CHCl_3$); FT-IR: (cm^{-1}) 3378, 2957, 2871, 1742, 1676, 1629, 1584, 1517, 1456, 1404, 1320, 1288, 1200, 1091, 1036, 921, 799, 751; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.14−7.19 (m, 2H), 6.53−6.59 (m, 2H), 5.49 (br, 1H), 4.62 (br, 1H), 3.75 (s, 3H), 3.64−3.69 (m, 1H) 3.45−3.56 (m, 1H), 3.09 (t, 2H, J = 6.79 Hz), 2.24−2.36 (m, 1H), 1.84−2.06 (m, 3H), 1.64 (qt, 2H), 1.38−1.51 (m, 2H), 0.96 (t, 3H, J = 6.79 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.9, 170.1, 146.7, 131.2, 127.6, 119.4, 114.9, 110.9, 58.7,

52.3, 49.4, 43.1, 31.52, 29.4, 25.2, 20.3, 13.9; HRMS (ESI): m/z Calcd for $C_{17}H_{25}N_2O_3$ 305.1865, found 305.1869 $[M + H]^+$.

*S)-1-(2-(Butylamino)benzoyl)-N-methoxy-N-methylpyrrolidine-2-carboxamide (**7**).* Brown liquid, $[\alpha]^{25}_D = +305.00$ ($c = 0.001$, $CHCl_3$); FT-IR: (cm^{-1}) 3341, 2928, 2869, 2125, 1636, 1520, 1460, 1410, 1317, 1250, 1167, 1095, 999, 754; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.18−7.22 (m, 2H), 6.58−6.62 (m, 2H), 5.58 (s, 1H), 5.08 (s, 1H), 3.87 (s, 3H), 3.63−3.73 (m, 1H) 3.36−3.48 (m, 1H), 3.24 (s, 3H), 3.06−3.16 (m, 2H), 2.26−2.39 (m, 1H), 1.90−2.04 (m, 2H), 1.81−1.88 (m, 1H), 1.62−1.70 (m, 2H), 1.38−1.46 (m, 2H), 0.93 (t, 3H, J = 7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.7, 163.8, 145.9, 130.6, 130.2, 127.3 114.9, 110.3, 60.9, 56.1, 48.5, 42.8, 30.8, 29.2, 28.8, 24.6, 19.9, 13.4; HRMS (ESI): m/z Calcd for $C_{18}H_{27}N_3O_3Na$ 356.1950, found 356.1934 $[M + Na]^+$.

■ ASSOCIATED CONTENT

Supporting Information. Detailed experimental procedure and compound characterization with $^1H/^{13}C$ NMR and HRMS. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Tel: +91-40-27193157; fax: +91-40-27193189; e-mail: ahmedkamal@iict.res.in (A.K.); tel: 9849077509; e-mail: chsrkuc@yahoo.co.in (C.S.R.).

■ ACKNOWLEDGMENT

N.M.K., V.S., and K.S., are thankful to CSIR, New Delhi, for awarding of research fellowships. L.S.S. thanks FONDECYT (1110022), IFS (F/4195-1) and the Organization for the Prohibition of Chemical Weapons for the support of this research.

■ REFERENCES

(1) (a) Patai, S. *The Chemistry of Amino, Nitroso, Nitro and Related Groups*; Wiley: New York, 1996. (b) Salvatore, R. N.; Yoon, C. H.; Jung, K. W. *Tetrahedron* **2001**, *57*, 7785–7811.

(2) (a) Byun, E.; Hong, B.; De Castro, Kathlia., A.; Lim, M.; Rhee., H. *J. Org. Chem.* **2007**, *72*, 9815–9817. (b) Bhanushali, M. J.; Nandurkar, N. S.; Bhor, M. D.; Bhanage, B. M. *Tetrahedron Lett.* **2007**, *48*, 1273–1276. (c) Morris, D. R.; Morton, L. J., Eds. *Polyamines in Biology and Medicine*; Marcel Dekker, Inc.: New York, 1981.

(3) Olsen, C. A.; Franzyk, H.; Jaroszewski, J. W. *Synthesis* **2005**, 2631−2653, and references cited therein.

(4) (a) Sasaki, Y.; Murphy, W. A.; Heiman, M. L.; Lance, V. A.; Coy, D. H. *J. Med. Chem.* **1987**, *30*, 1162–1166. (b) Sasaki, Y.; Coy, D. H. *Peptides* **1987**, *8*, 119–121. (c) Meyer, J. P.; Davis, P.; Lee, K. B.; Porreca, F.; Yamamura, H. I.; Hruby, V. J. *J. Med. Chem.* **1995**, *38*, 3462–3468. (d) Gazal, S.; Gellerman, G.; Gilon, C. *Peptides* **2003**, *24*, 1847–1852.

(5) (a) Dankwardt, S. M.; Smith, D. B.; Porco, J. A.; Nguyen, C. H. *Synlett* **1997**, 854–856. (b) Kan, T.; Kobayashi, H.; Fukuyama, T. *Synlett* **2002**, 1338–1340.

(6) (a) Zuckermann, R. N.; Kerr, J. M.; Kent, S. B. H.; Moos, W. H. *J. Am. Chem. Soc.* **1992**, *114*, 10646–10647. (b) Barn, D. R.; Morphy, J. R.; Rees, D. C. *Tetrahedron Lett.* **1996**, *37*, 3213–3216. (c) Byk, G.; Frederic, M.; Scherman, D. *Tetrahedron Lett.* **1997**, *38*, 3219–3222.

(7) (a) Virgilio, A. A.; Schürer, S. C.; Ellman, J. A. *Tetrahedron Lett.* **1996**, *37*, 6961–6964. (b) Souers, A. J.; Virgilio, A. A.; Schürer, S. S.; Ellman, J. A.; Kogan, T. P.; West, H. E.; Ankener, W.; Vanderslice, P. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2297–2302. (c) Souers, A. J.; Virgilio, A. A.; Rosenquist, A.; Fenuik, W.; Ellman, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 1817–1825.

(8) Sajjadi, Z.; Lubell, W. D. *J. Pept. Res.* **2005**, *65*, 298–310.

(9) (a) Rossé, G.; Ouertani, F.; Schröder, H. *J. Comb. Chem.* **1999**, *1*, 397–401. (b) Bryan, W. M.; Huffman, W. F.; Bhatnagar, P. K. *Tetrahedron Lett.* **2000**, *41*, 6997–7000. (c) Wong, J. C.; Sternson, S. M.; Louca, J. B.; Hong, R.; Schreiber, S. L. *Chem. Biol.* **2004**, *11*, 1279–1291. (d) Tremblay, M. R.; Wentworth, P.; Lee, G. E.; Janda, K. D. *J. Comb. Chem.* **2000**, *2*, 698–709.

(10) Lee, O.-Y.; Law, K.-L.; Ho, C.-Y.; Yang, D. *J. Org. Chem.* **2008**, *73*, 8829–8837.

(11) Ono, Y. *Pure Appl. Chem.* **1996**, *68*, 367–375.

(12) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: Oxford, 1998.

(13) (a) Scriven, E. F. V.; Turnbull, R. *Chem. Rev.* **1988**, *88*, 297–368. (b) Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem.* **2005**, *117*, 5320–5374. *Angew. Chem., Int. Ed.* **2005**, *44*, 5188–5240. (c) *The Chemistry of the Azido Group*;Patai, S., Ed.; Wiley: New York, 1971. (d) *Azides and Nitrenes: Reactivity and Utility*; Scriven, E. F. V., Ed.; Academic Press: New York, 1984. (e) Larock, R. C. *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*; VCH, Weinheim, 1989; p 409.

(14) (a) Liu, Q.; Tor, Y. *Org. Lett.* **2003**, *5*, 2571–2572. (b) Rodrigues, J. A. R.; Abramovitch, R. A.; de Souse, J. D. F.; Leiva, G. C. *J. Org. Chem.* **2004**, *69*, 2920–2928.

(15) (a) *The Chemistry of the Azido Group*; Patai, S., Ed.; Wiley: New York, 1971. (b) *The Chemistry of Halides, Pseudo-halides and Azides, Supplement D*; Patai, S.; Rappoport, Z., Eds.; Wiley: New York, 1983. (c) *Chemistry of Halides, Pseudo-Halides and Azides, Part 1*; Patai, S., Ed.; Wiley: New York, 1995. (d) *Chemistry of Halides, Pseudo-Halides and Azides, Part 2*; Patai, S., Ed.; Wiley: New York, 1995.

(16) (a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004–2021. (b) Moses, J. E.; Moorhouse, A. D. *Chem. Soc. Rev.* **2007**, *36*, 1249–1262. (c) Kamal, A.; Shankaraiah, N.; Reddy, Ch. R.; Prabhakar, S.; Markandeya, N.; Srivastava, H. K.; Sastry, G. N. *Tetrahedron* **2010**, *66*, 5498–5506. (d) Kamal, A.; Prabhakar, S.; Shankaraiah, N.; Reddy, C. R.; Reddy, P. V. *Tetrahedron Lett.* **2008**, *49*, 3620–3624. (e) Kamal, A.; Shankaraiah, N.; Devaiah, V.; Reddy, K. L.; Juvekar, A.; Sen, S.; Kurian, N.; Zingde, S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1468–1473.

(17) (a) Demmer, O.; Dijkgraaf, I.; Schottelius, M.; Wester, H.-J.; Kessler, H. *Org. Lett.* **2008**, *10*, 2015–2018. (b) Sajiki, H.; Ikawa, T.; Hirota, K. *Org. Lett.* **2004**, *6*, 4977–4980.

(18) (a) Salunkhe, A. M.; Ramachandran, P. V.; Brown, H. C. *Tetrahedron* **2002**, *58*, 10059–10064. (b) Brown, H. C.; Salunkhe, A. M.; Singaram, B. *J. Org. Chem.* **1991**, *56*, 1170–1175. (c) Brown, H. C.; Midland, M. M.; Levy, A. B. *Tetrahedron* **1987**, *43*, 4079–4088. (d) Brown, H. C.; Midland, M. M.; Levy, A. B. *J. Am. Chem. Soc.* **1973**, *95*, 2394–2396. (e) Brown, H. C.; Midland, M. M.; Levy, A. B. *J. Am. Chem. Soc.* **1972**, *94*, 2114–2115. (f) Suzuki, A.; Sono, S.; Itoh, M.; Brown, H. C.; Midland, M. M. *J. Am. Chem. Soc.* **1971**, *93*, 4329–4330. (g) Carboni, B.; Vaultier, M.; Carrié, R. *Tetrahedron* **1987**, *43*, 1799–1810.

(19) Kamal, A.; Markandeya, N.; Shankaraiah, N.; Reddy, Ch. R.; Prabhakar, S.; Reddy, Ch. S.; Eberlin, M. N.; Santos, L. S. *Chem.—Eur. J.* **2009**, *15*, 7215–7224.

(20) (a) Guindon, Y.; Prévost, M.; Mochirian, P.; Guérin, B. *Org. Lett.* **2002**, *4*, 1019–1022. (b) Kim, B. M.; Williams, S. F.; Masamune, S. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2 (Heathcock, C. H., Ed.), Chapter 1.7, p 239. (c) Cowden, C. J.; Paterson, I. *Org. React.* **1997**, *51*, 1–200.

(21) (a) Evans, D. A.; Côté, B.; Coleman, P. J.; Connell, B. T. *J. Am. Chem. Soc.* **2003**, *125*, 10893–10898. (b) Evans, D. A.; Coleman, P. J.; Côté, B. *J. Org. Chem.* **1997**, *62*, 788–789. (c) Das, S.; Li, L.-S.; Sinha, S. C. *Org. Lett.* **2004**, *6*, 123–126.

(22) (a) Hernández-Torres, J. M.; Achkar, J.; Wei, A. *J. Org. Chem.* **2004**, *69*, 7206–7211. (b) Lu, J.; Chan., T.-H. *Tetrahedron Lett.* **1998**, *39*, 355–358.

(23) (a) The non-commercial Et_2BOTf was prepared following the procedure described by: Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber,

T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099–3111. (b) Benjamin, H. F.; Gelman, D. M.; Perlmutter, P.; Vounatsos, F. Tetrahedron. *Asymmetry* **2006**, *17*, 1152–1155.

(24) (a) Abiko, A.; Liu, J.-F.; Masamune, S. *J. Org. Chem.* **1996**, *61*, 2590–2591. (b) Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Syntheses via Boranes*; Wiley-Interscience: New York, 1975; p 28. (c) Brown, H. C.; Ganesan, K.; Dhar, R. K. *J. Org. Chem.* **1993**, *58*, 147–153.

(25) Kamal, A.; Shankaraiah, N.; Reddy, K. L.; Devaiah, V. *Tetrahedron Lett.* **2006**, *47*, 4253–4257.

(26) (a) Kamal, A.; Reddy, K. L.; Devaiah, V.; Shankaraiah, N.; Rao, M. V. *Mini-Rev. Med. Chem.* **2006**, *6*, 69–87. (b) Shankaraiah, N.; Markandeya, N.; Moraga, M. E.; Arancibia, C.; Kamal, A.; Santos, L. S. *Synthesis* **2009**, 2163–2170. (c) Kamal, A.; Shankaraiah, N.; Markandeya, N.; Reddy, Ch. S. *Synlett* **2008**, 1297–1300. (d) Kamal, A.; Shankaraiah, N.; Prabhakar, S.; Reddy, R. C.; Markandeya., N.; Reddy, K. L.; Devaiah, V. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2434–2439. (e) Kamal, A.; Shankaraiah, N.; Devaiah, V.; Reddy, K. L. *Tetrahedron Lett.* **2006**, *47*, 9025–9028.

(27) (a) Kamal, A.; Rao, M. V.; Laxman, N.; Ramesh, G.; Reddy, G. S. K. *Curr. Med. Chem.: Anti-Cancer Agents* **2002**, *2*, 215–254. (b) Kamal, A.; Azeeza, S.; Bharathi, E. V.; Malik, M. S.; Shetti, R. V. *Mini-Rev. Med. Chem.* **2010**, *10*, 405–435.

(28) Kamal, A.; Reddy, K. L.; Devaiah, V.; Shankaraiah, N.; Reddy, G. S. K.; Raghavan, S. *J. Comb. Chem.* **2007**, *9*, 29–42.

(29) Blackburn, B. K.; Lee, A.; Baier, M.; Kohl, B.; Olivero, A. G.; Matamoros, R.; Robarge, K. D.; McDowell, R. S. *J. Med. Chem.* **1997**, *40*, 717–729.

(30) Wright, W. B.; Brabander, H. J.; Greenblatt, E. N.; Day, I. P.; Hardy, R. A. *J. Med. Chem.* **1978**, *21*, 1087–1089.

(31) Di Martino, G.; Massa, S.; Corelli, F.; Pantaleoni, G.; Fanini, D.; Palumbo, G. *Eur. J. Med. Chem.* **1983**, *18*, 347–350.

(32) Karp, G. M.; Manfredi, M. C.; Guaciaro, M. A.; Ortlip, C. L.; Marc, P.; Szamosi, I. T. *J. Agric. Food Chem.* **1997**, *45*, 493–500.

(33) (a) Kamal, A.; Shankaraiah, N.; Markandeya, N.; Reddy, K. L.; Reddy, S. C. *Tetrahedron Lett.* **2008**, *49*, 1465–1468.

(34) Cole, R. B. In *Electrospray and MALDI Mass Spectrometry: Fundamentals, Instrumentation, Practicalities, and Biological Applications*, 2nd ed.; John Wiley: New York, 2010.

(35) Santos, L. S. *In Reactive Intermediates: MS Investigations in Solution*; Wiley-VCH: Weinheim, 2010.

(36) de la Mora, J. F.; Van Berkel, G. J.; Enke, C. G.; Cole, R. B.; Martinez-Sanchez, M.; Fenn, J. B. *J. Mass Spectrom.* **2000**, *35*, 939–952.

(37) (a) Santos, L. S.; Knaack, L.; Metzger., J. O. *Int. J. Mass Spectrom.* **2005**, *246*, 84–104. (b) Chen, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 2832–2847. (c) Santos, L. S. *Eur. J. Org. Chem.* **2008**, 235–253.

(38) Santos, L. S.; Pavam, C. H.; Almeida, W. P.; Coelho, F.; Eberlin, M. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 4330–4333.

(39) (a) Santos, L. S.; Metzger, J. O. *Angew. Chem., Int. Ed.* **2006**, *45*, 977–981. (b) Santos, L. S.; Metzger, J. O. *Rapid Commun. Mass Spectrom.* **2008**, *22*, 898–904. (c) Santos, L. S.; Rosso, G. B.; Pilli, R. A.; Eberlin, M. N. *J. Org. Chem.* **2007**, *72*, 5809–5812. (d) Silva, B. V.; Violante, F. A.; Pinto, A. C.; Santos, L. S. *Rapid Commun. Mass Spectrom.* **2011**, *25*, 423–428.