JOC The Journal of Organic Chemistry

Article

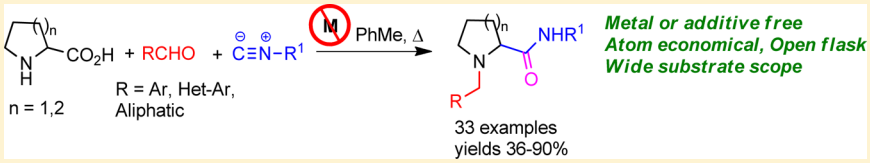
pubs.acs.org/joc

Regioselective Metal-Free Decarboxylative Multicomponent Coupling of α-Amino Acids, Aldehydes and Isonitriles Leading to *N*-Substituted Azacyclic-2-carboxamides with Antithrombotic Activity

Shashikant U. Dighe, Anil Kumar K. S., Smriti Srivastava, Pankaj Shukla, Surendra Singh, Madhu Dikshit,* and Sanjay Batra*

Medicinal and Process Chemistry Division and Pharmacology Division, CSIR-Central Drug Research Institute, BS-10/1, Sector 10, Jankipuram Extension, Sitapur Road, PO Box 173, Lucknow, 226031 Uttar Pradesh, India

Supporting Information



ABSTRACT: An atom-economical regioselective synthesis of *N*-substituted prolinamides or *N*-substituted piperidine-2-carboxamides via a metal-free decarboxylative multicomponent coupling between L-proline or pipecolic acid, aldehydes, and isonitriles is described. The cascade event involves sequential imine formation, decarboxylation, isonitrile insertion, and hydrolysis to afford the product in one-pot. Two of the prolinamides were found to display appreciable antithrombotic activity via inhibition of platelet aggregation.

INTRODUCTION

Decarboxylative coupling reactions leading to C−C bond formation have emerged as exciting options for accomplishing valuable synthetic transformations.[1,2] Though these reactions are often performed in the presence of transition metals, the condensation of α-amino acids with a variety of aldehydes and ketones to afford azomethine ylides can be achieved under metal-free conditions.[3] Despite their remarkable reactivity, azomethine ylides have found applications mostly in 3 + 2 cycloaddition reactions and 1,5- or 1,7-electrocyclizations.[4] Nonetheless recent work of Li's, Seidel's, and Wang's groups have demonstrated the utility of α-amino acid derived azomethine ylides for the synthesis of a variety of α-functionalized saturated cyclic amines. In a remarkably regioselective protocol, they have achieved three-component coupling reactions of α-amino acids, aldehydes, and various nucleophiles under metal-free conditions or under the influence of copper or iron catalysts (Figure 1).[5−7]

Prolinamide forms subunits of many natural products and pharmacologically active compounds.[8,9] We have earlier reported the potent antithrombotic and antiaggregation properties of prolinamide derivatives.[10] Moreover chiral prolinamides are successfully employed in asymmetric aminocatalytic reactions.[11] Coupling of proline and amine component for the formation of the prolinamide requires a variety of coupling reagents and anhydrous conditions and produces stoichiometric amounts of waste.[12] Thus, development of a new synthetic protocols for prolinamide synthesis employing readily available starting materials is an attractive synthetic target. Considering the widespread use of isonitriles for multicomponent reactions

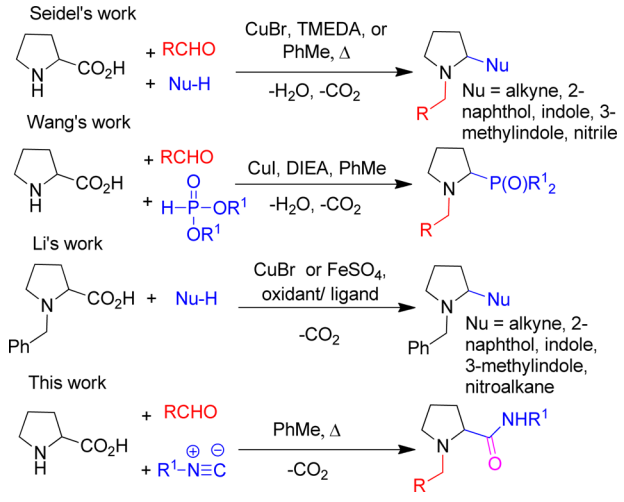


Figure 1. Synthesis of α-functionalized saturated cyclic amines via decarboxylative coupling of α-amino acids.

(MCR) and in our interest in decarboxylative reactions and isonitrile insertions,[13−15] we envisioned that decarboxylative MCR between L-proline, aldehyde, and isonitrile would offer a new metal-free approach to *N*-substituted prolinamides. It is worth mentioning that Ugi et al. have reported a four-component MCR between an α-amino acid, aldehyde, isonitrile

Received: September 9, 2014
Published: November 19, 2014

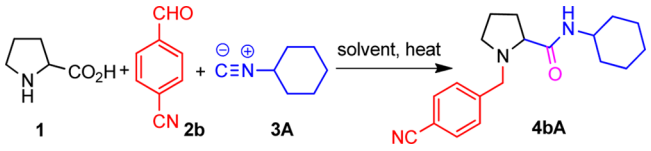
dx.doi.org/10.1021/jo502029k | J. Org. Chem. 2015, 80, 99−108

and alcohol to produce 1,1′-iminodicarboxylic acid derivatives.[16] However, the isonitrile insertion in α-amino acids via azomethine ylides remain unexplored, and we disclose our results related to this study herein.

RESULTS AND DISCUSSION

Our study began with the reaction of 1.2 equiv of L-proline (**1**), 1.0 equiv (0.2 g) of 4-cyanobenzaldehyde (**2b**), and 1.2 equiv of cyclohexyl isonitrile (**3A**) in toluene or *n*-BuOH at 200 °C under microwave irradiation for 20 min (Table 1, entries 1−2).

Table 1. Optimization of the Decarboxylative MCR[a] of Proline, 4-Cyanobenzaldehyde, and Cyclohexyl Isonitrile



entry	solvent (mL)	additive	mode/temp °C	time	yield **4bA**(%)[c]
1	PhMe (2)		μW/200	20 min	*d*
2	*n*-BuOH (2)		μW/200	20 min	*d*
3	PhMe (2)		μW/100	20 min	45
4	*n*-BuOH (2)		μW/100	20 min	12
5	PhMe (2)	H_2O	μW/100	20 min	41
6	PhMe (2)	$PhCO_2H$	μW/100	20 min	20
7[b]	PhMe (5)		T/110	4 h	85
8[b]	xylene (5)		T/140	4 h	81
9[b]	*n*-BuOH (5)		T/115	4 h	46
10[b]	MeCN (5)		T/85	4 h	53
11[b]	DMF (5)		T/110	4 h	
12[b]	DMSO (5)		T/110	2 h	

[a]All reactions were performed using 0.21 g (1.83 mmol) of L-proline, 0.2 g (1.52 mmol) of 4-cyanobenzaldehyde, and 0.23 mL (1.83 mmol) of cyclohexyl isonitrile. [b]T = Thermal heating. [c]Yields of chromatographically pure product. [d]Not detected.

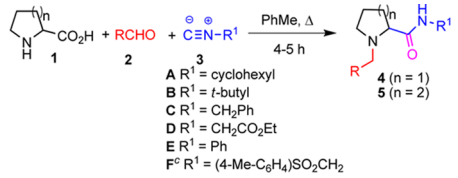
Both reactions resulted in a mixture of inseparable products, which prompted us to investigate the reaction at reduced temperature. Fortunately, an identical product in 43% and 12% yields was isolated from the reactions performed at 100 °C in toluene and *n*-BuOH, respectively (entries 3 and 4). On the basis of the spectroscopic analysis, this product was established to be the prolinamide **4bA**. Since the formation of amide would have involved hydrolysis (*vide infra*), to increase the yield of the product the reaction was conducted in the presence of water but with no impact (entry 5). Earlier, Seidel et al. discovered that addition of an acid during analogous reactions protonates the dipole leading to the iminium ion, which allows a facile nucleophilic attack.[6b] This finding inspired us to perform the MCR in the presence of benzoic acid in toluene (entry 6). Unfortunately **4bA** was isolated in only 20% yield, and therefore the use of acid was abandoned. To improve the yield of **4bA**, we next evaluated the reaction under conventional thermal conditions. To our delight, the reaction at 110 °C using toluene as solvent was complete in 4 h to afford **4bA** in 85% yield (entry 7). Screening of different solvents for the reaction under heating revealed that formation of **4bA** in toluene was comparable to xylene but superior to *n*-BuOH and MeCN (entries 8−10), whereas DMF and DMSO failed to produce any isolable product (entries 11−12). Therefore, the optimized conditions for the decarboxylative MCR that worked best were L-proline (1.2 equiv), aldehyde (1.0 equiv), and isonitrile (1.2 equiv) in toluene at 110 °C for 4 h.

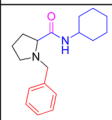
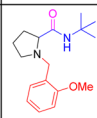
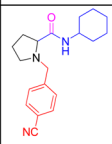
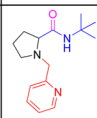
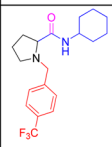
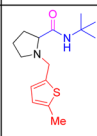
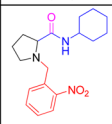
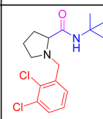
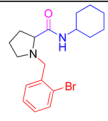
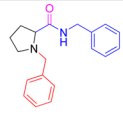
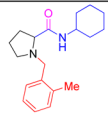
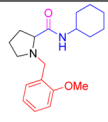
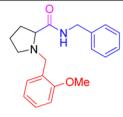
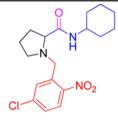
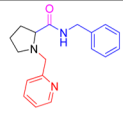
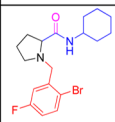
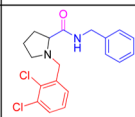
With the optimized conditions in hand, we set out to test the scope of the protocol with different aldehydes and isonitriles to afford *N*-alkyl prolinamides and the results are summarized in Table 2. Initially the reactions were performed using cyclohexyl isonitrile (**3A**) as the isonitrile component and making changes in aldehydes (**2**). It was found that all benzaldehydes (**2a,c−i**) gave the products (**4aA**, **4cA−4iA**) in moderate to good yields. The nature of the substitution present on the phenyl ring did not have any significant impact on the outcome, because both electron withdrawing and electron donating substituents gave the product in 78−85% yields. However, when pyridine-2-carbaldehyde (**2j**) and 5-methyl-thiophene-2-carbaldehyde (**2k**) were employed, the yields of the respective products (**4jA−4kA**) were only 51% and 54%. When aliphatic aldehydes (**2l−m**) were used as the reactant, we found that the products (**4lA−2mA**) were isolated in low yields. In particular, with hexanal (**2m**) the yield of the isolated prolinamide **4mA** was 36%. We observed that monitoring of the reaction with **2m** and column chromatography of **4mA** was too cumbersome. Next we employed several commercially available isonitriles, **3B−3E**, in the protocol and observed that in all cases except for the phenylisonitrile (**3E**), the products were isolated in good yields. In general, we discovered that benzaldehydes bearing nitrile or halogen as substituent furnished corresponding prolinamides in excellent yields, whereas the heteroaromatic aldehydes gave products in relatively lower yields. Notably we discovered that tosylmethylisonitrile (**3F**) failed to undergo reaction with **2a** or **2b** to yield the corresponding products. The success of the protocol with L-proline prompted us to test its scope with other α-amino acids. Therefore, the reaction of pipecolic acid with **2a** and **3A** was performed under the optimized conditions, and it was pleasing to note that the corresponding product **5aA** was isolated in 42% yield. Subsequently, pipecolic acid was also reacted with **2a**,**b** and **3B** to yield the corresponding amides **5aB** and **5bB** albeit in moderate yields. In contrast when sarcosine was used as the substrate, we failed to observe the formation of corresponding amide.

The plausible mechanism for the formation of prolinamide is analogous to the one proposed by Li et al.[5] and Seidel et al.[6] and is delineated in Scheme 1. In the first step, cyclic α-amino acid is condensed with the arylaldehyde resulting in imine (**I**) with the loss of water molecule. This is followed by thermal decarboxylation to form the azomethine ylide (**II**), which is a zwitterionic species. This species undergoes nucleophilic insertion of isonitrile to furnish the intermediate **III**, which on hydrolysis furnished the observed product **4**. The water liberated during the formation of the imine is required for the hydrolysis to generate the amide bond. This was ascertained by carrying out the reaction successfully even by using dry toluene under moisture-free conditions. Additionally, performing the reaction in the presence of activated molecular sieves under inert conditions to remove the liberated water reduced the yield of **4bA** to 12% and produced a known bicyclic compound **6** as the major product (Scheme 2). To provide further evidence that the oxygen of the amide bond is from the water that is liberated during the imine formation, in a control experiment, the reaction between proline, 4-cyanobenzaldehyde (**2b**), and cyclohexyl isonitrile (**3A**) was performed in dry toluene in the presence of $H_2{}^{18}O$ (97%) under conventional heating under inert conditions. On completion, the reaction mixture was directly subjected to mass spectral analysis, which displayed the presence of a mixture

dx.doi.org/10.1021/jo502029k | J. Org. Chem. 2015, 80, 99−108

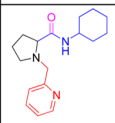
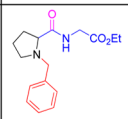
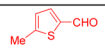
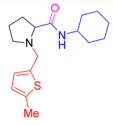
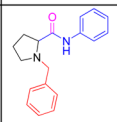
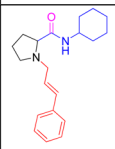
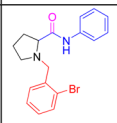
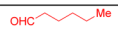
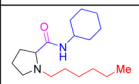
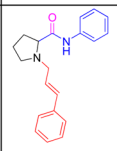
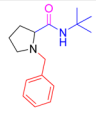
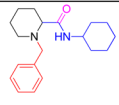
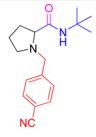
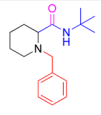
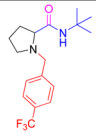
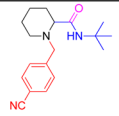
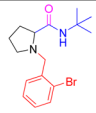
Table 2. Scope of the Protocol for the Synthesis of *N*-Substituted Prolinamides[a,b]



entry	aldehyde	isonitrile	Product **4/5** (yield %)	entry	aldehyde	isonitrile	Product **4/5** (yield %)
1		A	 **4aA** (62)	18		B	 **4gB** (62)
2		A	 **4bA** (85)	19		B	 **4jB** (65)
3		A	 **4cA** (80)	20		B	 **4kB** (63)
4		A	 **4dA** (78)	21		B	 **4lB** (88)
5		A	 **4eA** (84)	22		C	 **4aC** (60)
6		A	 **4fA** (82)	23		C	 **4eC** (76)
7		A	 **4gA** (78)	24		C	 **4gC** (70)
8		A	 **4hA** (71)	25		C	 **4jC** (60)
9		A	 **4iA** (68)	26		C	 **4lC** (83)

dx.doi.org/10.1021/jo502029k | *J. Org. Chem.* 2015, 80, 99−108

Table 2. continued

entry	aldehyde	isonitrile	Product **4/5** (yield %)	entry	aldehyde	isonitrile	Product **4/5** (yield %)
10		A	 **4jA** (51)	27		D	 **4aD** (66)
11		A	 **4kA** (54)	28		E	 **4aE** (60)
12		A	 **4lA (52%)**	29		E	 **4eE** (44)
13		A	 **4mA** (36%)	30		E	 **4lE** (49)
14		B	 **4aB** (77)	31		A	 **5aA** (42)
15		B	 **4bB** (90)	32		B	 **5aB** (48)
16		B	 **4cB** (86)	33		B	 **5bB** (58)
17		B	 **4eB** (86)				

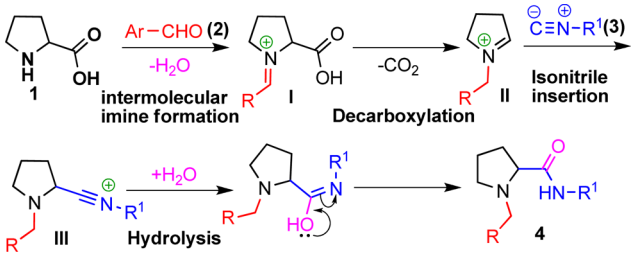
[a]Reactions were performed with L-proline **1** (1.2 equiv), arylaldehyde **2** (0.2 g, 1.0 equiv), and isonitrile **3** (1.2 equiv) in PhMe for 4−5 h at 110 °C. [b]Yields are determined after column chromatography. [c]TosMIC (**3F**) did not undergo reaction under the optimized conditions; therefore there is no product corresponding to it.

of ^{16}O (311 amu) and ^{18}O (313 amu) prolinamide **4bA** (see Supporting Information). Next we also performed the reaction in the presence of molecular sieves and D_2O. The reaction was complete in 4 h to afford the prolinamide **4bA** in 63% yield with no evidence of **6**. On the basis of the ^1H NMR spectrum, we observed approximately 46% deuterium incorporation in amide functionality. These experiments inferred that the water released during the imine formation is used for hydrolysis step (Scheme 3).

In order to investigate the antithrombotic properties of the prepared prolinamides, they were initially assessed for their

dx.doi.org/10.1021/jo502029k | J. Org. Chem. 2015, 80, 99−108

Scheme 1. Plausible Mechanism for the Formation of Prolinamide via Isonitrile Insertion



ability to protect the mice (*in vivo*) against collagen−epinephrine induced pulmonary thromboembolism at 30 μM/kg dose using aspirin and clopidogrel as the reference drugs.[10] It was found that compounds **4eA**, **4iA**, **4cB**, **4eB**, **4gB**, **4kB**, and **4jC** exhibited 40% protection whereas aspirin and clopidogrel displayed 40% and 60% at 170 and 70 μM/kg dose, respectively (Table 3). Investigations toward the effect of these compounds on bleeding time revealed that whereas **4iA**, **4cB**, **4gB**, **4kB**, and **4jC** exhibited a mild prolongation in bleeding time, **4eA** and **4eB** did not induce major effect on hemostasis, and it was considerably less in comparison to the standard antiplatelet drugs aspirin and clopidogrel. In order to probe the possible mode of antithrombotic action of these compounds, the *in vitro* investigations against collagen, adenosine diphosphate (ADP), thrombin receptor activating peptide (SFLLRN), or arachidonic acid induced human platelet aggregation were carried out. The result of this study showed that these compounds affect only collagen induced platelet aggregation. Among all evaluated compounds, **4eA** and **4eB** carrying 2-bromo substitution on the phenyl ring were the best potential leads since they inhibited aggregation in a concentration dependent manner with IC_{50} of 29.9 and 19.8 μM, respectively, and had no effect on thrombin time (TT), prothrombin time (PT), and activated partial thromboplastin time (aPTT). In contrast, compounds **4iA**, **4cB**, **4gB**, **4kB**, and **4jC** displayed inhibition at a higher concentration, which might be due to the poor solubility of these compounds in aqueous buffer. Further from the *in vivo* investigations in mice model of $FeCl_3$ induced arterial thrombosis, it was observed that **4eA** and **4eB** after 1 h of oral administration prolonged the time to occlusion (TTO) of carotid artery by 1.5- and 1.7-fold compared with 2.2-fold for clopidogrel.

Table 3. Results of Biological Assays of the Synthesized Compound

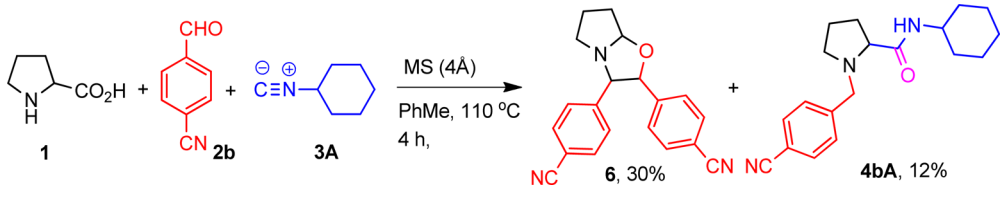
entry	compd no.	in vivo % protection at 30 μM/kg	fold increase in bleeding time[d]	IC_{50} (μM)
1	aspirin[a]	40	2.2	>30
2	clopidogrel[b]	60	2.3	
3	**4aA**	10		*e*
4	**4bA**	30		*e*
5	**4cA**	20		*e*
6	**4dA**	30		*e*
7	**4eA**	40	1.4	29.9
8	**4fA**	20		*e*
9	**4gA**	*c*		
10	**4hA**	20		*e*
11	**4iA**	40	1.3	>30
12	**4jA**	30		*e*
13	**4kA**	30		*e*
14	**4lA**	*c*		
15	**4mA**	*c*		
16	**4aB**	20		*e*
17	**4bB**	20		*e*
18	**4cB**	40	2.2	>30
19	**4eB**	40	1.3	19.8
20	**4gB**	40	2.0	>30
21	**4jB**	10		*e*
22	**4kB**	40	1.5	>30
23	**4lB**	20		*e*
24	**4aC**	20		*e*
25	**4eC**	30		*e*
26	**4gC**	*c*		
27	**4jC**	40	1.8	>30
28	**4lC**	*c*		
29	**4aD**	*c*		
30	**4aE**	*c*		
31	**4bE**	*c*		
32	**4lE**	*c*		

[a]At 170 μM/kg. [b]At 70 μM/kg. [c]Not done. [d]Only compounds showing 40% protection were evaluated for effect on the bleeding time. [e]No inhibition at 30 μM.

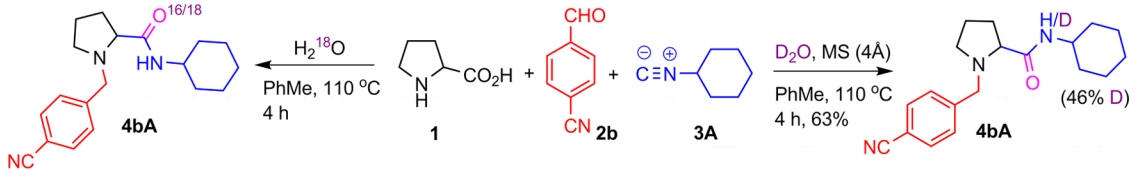
CONCLUSIONS

In summary, we have developed a metal-free decarboxylative multicomponent reaction involving L-proline or pipecolic acid, aldehydes, and isonitriles for the synthesis of *N*-substituted-2-prolinamides or *N*-substituted-piperidine-2-carboxamides.

Scheme 2. Reaction Performed in the Presence of Molecular Sieves Only



Scheme 3. Reaction Performed in the Presence of $H_2{}^{18}O$ and D_2O To Demonstrate the Hydrolysis Step



dx.doi.org/10.1021/jo502029k | J. Org. Chem. 2015, 80, 99−108

This reaction proceeds via a cascade process involving intermolecular imine formation, decarboxylation, isonitrile insertion, and hydrolysis to furnish the product. The protocol described herein is attractive because it is metal- or additive-free and can be readily performed via commercially available reagents. The antithrombotic assessment of products led to identification of two prolinamides with appreciable activity that is attributable to collagen induced platelet aggregation.

EXPERIMENTAL SECTION

General. All experiments were monitored by analytical thin layer chromatography (TLC) performed on precoated silica gel plates. After elution, plate was visualized under UV illumination at 254 nm for UV active materials. Further visualization was achieved by staining with $KMnO_4$ and charring on a hot plate. Column chromatography was performed on silica gel (230−400 mesh) by standard techniques eluting with solvents as indicated. IR spectra were recorded using a FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on 400 MHz spectrometer, using TMS as an internal standard (chemical shifts in δ). Peak multiplicities of NMR signals were designated as s (singlet), bs (broad singlet), d (doublet), dd (doublet of doublet), t (triplet), m (multiplet), etc. The ESI-MS were recorded on an ion trap mass spectrometer, and the HRMS spectra were recorded as ESI-HRMS on a Q-TOF LC-MS/MS mass spectrometer. Commercial grade reagents and solvents were used without further purification. $H_2{}^{18}O$ (97%) was purchased from Cambridge Isotope Laboratories, USA. All reactions were carried out in flame-dried reaction vessels with Teflon screw caps. The reactions via microwave heating were carried out in Biotage initiator 2.5 microwave synthesizer under sealed vessel conditions using the temperature control mode and the magnetic stirring option. The temperature in this instrument is determined by a calibrated external infrared sensor. The experimental studies involving human platelet rich plasma and Swiss mice were performed in accordance with the Indian Council of Medical Research, New Delhi, norms and GCP guidelines. Ethical committees of King Gorge's Medical University, Lucknow, and CSIR-CDRI approved the protocols used for the experiments, and informed consent was obtained from all the healthy subjects.

General Procedure for the Synthesis of Pyrrolidine-2-carboxamides as Exemplified for 1-(4-Cyanobenzyl)-*N*-cyclohexylpyrrolidine-2-carboxamide (4bA). To a stirred solution of aldehyde **2b** (0.2 g, 1.52 mmol) and L-proline (0.21 g, 1.83 mmol) in dry toulene (5.0 mL) was added cyclohexyl isonitrile **3A** (0.23 mL, 1.83 mmol) at room temperature. The reaction mixture was stirred at 110 °C for 5 h. After the reaction was completed (as determined by TLC), it was quenched with water (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layer was dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to obtain a residue. The residue was purified through column chromatography on silica gel using hexanes/EtOAc (6:4, v/v) as eluent to furnish **4bA** (0.382 g, 82%) as a colorless oil.

*1-Benzyl-N-cyclohexylpyrrolidine-2-carboxamide (**4aA**).*[17] Yield: 62% (0.334 g from 0.2 g); colorless oil; R_f = 0.48 (hexanes/EtOAc, 6:4, v/v). IR (neat) ν_{max}: 1217, 1520, 1660, 3345 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12−1.38 (m, 7H), 1.59−1.72 (m, 4H), 1.85−1.89 (m, 2H), 2.22−2.38 (m, 2H), 3.02−3.06 (m, 1H), 3.21 (dd, J_1 = 5.1 Hz, J_2 = 5.1 Hz, 1H), 3.48 (d, J = 12.8 Hz, 1H), 3.71−3.79 (m, 1H), 3.88 (d, J = 12.9 Hz, 1H), 7.28−7.36 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): 23.1, 24.4, 24.7, 25.5, 29.9, 32.5, 47.2, 54.6, 58.7, 67.7, 127.1, 127.4, 128.5, 128.6, 128.7, 137.1, 172.3. MS (ESI+): m/z = 287.1. ESI-HR-MS calculated for $C_{18}H_{26}N_2O$ (M^+ + H): 287.2123. Found: 287.2119.

*1-(4-Cyanobenzyl)-N-cyclohexylpyrrolidine-2-carboxamide (**4bA**).*[17] Yield: 85% (0.395 g from 0.2 g); colorless oil; R_f = 0.42 (hexanes/EtOAc, 6:4, v/v). IR (neat) ν_{max}: 891, 1251, 1657, 3351 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.02−1.14 (m, 3H), 1.26−1.34 (m, 2H), 1.52−1.87 (m, 8H), 2.13−2.30 (m, 2H), 2.93−2.96 (m, 1H), 3.11 (dd, J_1 = 5.3 Hz, J_2 = 5.3 Hz, 1H), 3.46 (d, J = 13.6 Hz, 1H), 3.61−3.69 (m, 1H), 3.84 (d, J = 13.6 Hz, 1H), 7.05 (s, 1H), 7.32 (d, J = 8.2 Hz, 2H), 7.57 (dd, J_1= 1.7 Hz, J_2 = 1.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 24.1, 24.6, 24.7, 25.5, 30.7, 33.4, 47.3, 54.1, 59.5, 67.8, 111.3, 118.6, 129.2, 132.4, 144.2, 173.0. MS (ESI+): m/z = 312.1. ESI-HR-MS calculated for $C_{19}H_{25}N_3O$ (M^+ + H): 312.2076. Found: 312.2077.

*N-Cyclohexyl-1-(4-(trifluoromethyl)benzyl)pyrrolidine-2-carboxamide (**4cA**).* Yield: 80% (0.325 g from 0.2 g); colorless oil; R_f = 0.44 (hexanes/EtOAc, 6:4, v/v). IR (neat) ν_{max}: 1067, 1214, 1526, 1669, 2858, 3409 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.14−1.67 (m, 3H), 1.26−1.32 (m, 2H), 1.57−1.60 (m, 2H), 1.67−1.71 (m, 4H), 1.88−2.06 (m, 5H), 2.39 (t, J = 4.4 Hz, 1H), 3.41−3.43 (m, 1H), 3.61 (d, J = 2.3 Hz, 1H), 4.19 (d, J = 9.7 Hz, 1H), 7.57 (d, J = 8.1 Hz, 2H), 7.63 (d, J = 8.1 Hz, 2H), 7.78 (d, J = 6.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 24.6, 24.7, 25.3, 25.5, 29.6, 32.4, 32.5, 33.7, 48.5, 54.1, 57.4, 66.5, 122.4, 125.2, 125.8, 130.4, 142.3, 173.5. MS (ESI+): m/z = 355.1. ESI-HR-MS calculated for $C_{19}H_{25}F_3N_2O$ (M^+ + H): 355.1997. Found: 355.1995.

*N-Cyclohexyl-1-(2-nitrobenzyl)pyrrolidine-2-carboxamide (**4dA**).* Yield: 78% (0.427 g from 0.25 g); brown oil; R_f = 0.43 (hexanes/EtOAc, 6:4, v/v). IR (neat) ν_{max}: 859, 1528, 1648, 3379 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.05−1.20 (m, 3H), 1.29−1.32 (m, 2H), 1.55−1.78 (m, 7H), 1.84−1.90 (m, 1H), 2.16−2.26 (m, 1H), 2.30−2.37 (m, 1H), 2.92−2.96 (m, 1H), 3.16 (dd, J_1 = 4.8 Hz, J_2 = 4.8 Hz, 1H), 3.54−3.60 (m, 1H), 3.85 (dd, J_1 = 12.0 Hz, J_2 = 12.0 Hz, 2H), 7.28 (s, 1H), 7.41−7.42 (m, 2H), 7.53−7.57 (m, 1H), 7.82 (dd, J_1 = 1.1 Hz, J_2 = 1.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 22.8, 23.8, 23.9, 24.4, 29.8, 31.5, 31.8, 46.6, 53.9, 56.4, 123.4, 127.5, 130.4, 131.8, 148.6, 171.9. MS (ESI+): m/z = 332.1. ESI-HR-MS calculated for $C_{18}H_{25}N_3O_3$ (M^+ + H): 332.1974. Found: 332.1973.

*1-(2-Bromobenzyl)-N-cyclohexylpyrrolidine-2-carboxamide (**4eA**).* Yield: 84% (0.330 g from 0.2 g); pale yellow oil; R_f = 0.45 (hexanes/EtOAc, 6:4, v/v). IR (neat) ν_{max}: 1252, 1646, 3312 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86−0.98 (m,1H), 1.06−1.16 (m, 2H), 1.26−1.34 (m, 2H), 1.55−1.72 (m, 5H), 1.73−1.82 (m, 2H), 1.87−1.95 (m, 1H), 2.19−2.23 (m, 1H), 2.45−2.52 (m, 1H), 3.11 (t, J = 6.7 Hz, 1H), 3.22 (dd, J_1= 4.1 Hz, J_2 = 4.1 Hz, 1H), 3.56−3.58 (m,1H), 3.78 (dd, J_1 = 13.1 Hz, J_2 = 13.1 Hz, 2H), 7.14−7.16 (m, 1H), 7.25−7.32 (m, 3H), 7.54 (dd, J_1 = 1.1 Hz, J_2 = 1.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 24.2, 24.8, 24.9, 25.5, 31.1, 32.7, 33.1, 47.4, 54.8, 60.2, 67.3, 124.9, 127.6, 129.0, 131.2, 133.0, 137.8, 173.5. MS (ESI+): m/z = 365.0. ESI-HR-MS calculated for $C_{18}H_{25}BrN_2O$ (M^+ + H): 365.1229. Found: 365.1242.

*N-Cyclohexyl-1-(2-methylbenzyl)pyrrolidine-2-carboxamide (**4fA**).*[17] Yield: 82% (0.335 g from 0.2 g); pale yellow; R_f = 0.49 (hexanes/EtOAc, 6:4, v/v). IR (neat) ν_{max}: 928, 1159, 1520, 1654, 3412 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22−1.78, (m, 3H), 1.34−1.38 (m, 2H), 1.61−1.73 (m, 4H), 1.85−1.88 (m, 2H), 2.21−2.24 (m, 1H), 2.33 (bs, 1H),2.36 (s, 3H), 3.05 (t, J = 1.7 Hz, 1H), 3.18 (dd, J_1 = 4.9 Hz, J_2 = 5.0 Hz, 1H), 3.44 (d, J = 12.8 Hz, 1H), 3.44−3.78 (m, 1H), 3.84 (d, J = 12.8 Hz, 1H), 7.16−7.19 (m, 3H), 7.28−7.31 (m,1H), 7.37 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 18.8, 23.6, 24.4, 24.3, 24.9, 30.5, 32.1, 32.5, 46.8, 54.2, 59.6, 66.7, 124.3, 126.9, 128.4, 130.5, 132.4, 134.1, 172.9. MS (ESI+): m/z = 301.2. ESI-HR-MS calculated for $C_{19}H_{28}N_2O$ (M^+ + H): 301.2280. Found: 301.2282.

*N-Cyclohexyl-1-(2-methoxybenzyl)pyrrolidine-2-carboxamide (**4gA**).* Yield: 78% (0.362 g from 0.2 g); colorless oil; R_f = 0.46 (hexanes/EtOAc, 6:4, v/v). IR (neat) ν_{max}: 919, 1161, 1529, 1648, 3422 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.08−1.21, (m, 3H), 1.29−1.41(m, 3H), 1.57−1.68 (m, 4H), 1.77−1.86 (m, 4H), 2.13−2.24 (m, 1H), 2.97−3.02 (m, 1H), 3.12 (dd, J_1 = 4.9 Hz, J_2 = 5.0 Hz, 1H), 3.40 (d, J = 12.8 Hz, 1H), 3.66−3.72 (m, 1H), 3.78 (d, J = 12.8 Hz, 1H), 3.86 (s, 3H), 7.14 (d, J = 7.3 Hz, 2H), 7.23 (d, J = 8.1 Hz, 2H), 7.38 (d, J = 8.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 24.1, 24.6, 24.7, 25.5, 30.7, 32.9, 33.1, 47.3, 53.9, 59.6, 64.7, 67.3, 110.9, 126.6, 128.6, 135.6, 136.8, 138.4, 147.9, 174.1. MS (ESI+): m/z = 317.1. ESI-HR-MS calculated for $C_{19}H_{28}N_2O_2$ (M^+ + H): 317.2229. Found: 317.2187.

*1-(5-Chloro-2-nitrobenzyl)-N-cyclohexylpyrrolidine-2-carboxamide (**4hA**).* Yield: 71% (0.28 g from 0.2 g); colorless oil; R_f = 0.41 (hexanes/EtOAc, 6:4, v/v). IR (neat) ν_{max}: 1263, 1648, 3334 cm^{-1}.

dx.doi.org/10.1021/jo502029k | J. Org. Chem. 2015, 80, 99−108

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.05−1.19 (m, 3H), 1.25−1.37 (m, 2H), 1.57−1.62 (m, 2H),1.66−1.73 (m, 4H), 2.22−2.32 (m, 1H), 2.42−2.49 (m, 1H), 3.05−3.09 (m, 1H), 3.27 (dd, J_1 = 4.6 Hz, J_2 = 4.6 Hz, 1H), 3.63−3.71 (m, 1H), 3.87 (dd, J_1 = 13.8 Hz, J_2 = 13.8 Hz, 2H), 7.18 (d, J = 8.1 Hz, 1H), 7.55 (d, J = 8.6 Hz, 1H), 8.11 (dd, J_1 = 2.7 Hz, J_2 = 2.7 Hz, 1H), 8.26 (d, J = 2.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 24.2, 24.9, 25.5, 25.6, 30.9, 33.9, 47.5, 54.6, 57.3, 67.9, 123.5, 125.4, 130.7, 138.3, 141.1, 146.7, 172.9. MS (ESI+): m/z = 366.1. ESI-HR-MS calculated for $C_{18}H_{24}ClN_3O_3$ (M^+ + H): 366.1584. Found: 366.1588.

1-(2-Bromo-5-fluorobenzyl)-N-cyclohexylpyrrolidine-2-carboxamide (**4iA**). Yield: 68% (0.255 g from 0.2 g); colorless oil; R_f = 0.42 (hexanes/EtOAc, 6:4, v/v). IR (neat) ν_{max}: 1258, 1650, 3332 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.08−1.26 (m, 1H), 1.29−1.36 (m, 2H), 1.58−1.71 (m, 6H), 2.19−2.29 (m, 1H), 2.43−2.49 (m, 1H), 3.13 (t, J = 6.9 Hz, 1H), 3.21−3.24 (m, 1H), 2.19−2.23 (m, 1H), 2.45−2.52 (m, 1H), 3.11 (t, J = 6.7 Hz, 1H), 3.22 (dd, J_1 = 4.1 Hz, J_2 = 4.1 Hz, 1H), 3.58−3.66 (m,1H), 3.57 (s,2H), 6.86−6.90 (m, 1H), 7.08 (dd, J_1 = 2.8 Hz, J_2 = 2.8 Hz, 2H), 7.21 (d, J = 6.9 Hz, 1H), 7.50 (dd, J_1 = 5.3 Hz, J_2 = 5.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 24.2, 24.7, 24.8, 24.9, 25.5, 31.1, 47.4, 54.7, 59.9, 67.6, 116.0 (d, J = 22.0 Hz), 117.7 (d, J = 23.0 Hz), 134.1, 134.2, 140.0, 140.1, 160.7, 173.3. MS (ESI+): m/z = 383.1. ESI-HR-MS calculated for $C_{18}H_{24}BrFN_2O$ (M^+ + H): 383.1134. Found: 383.1136.

N-Cyclohexyl-1-(pyridin-2-ylmethyl)pyrrolidine-2-carboxamide (**4jA**). Yield: 51% (0.274 g from 0.2 g); colorless oil; R_f = 0.31 (hexanes/EtOAc, 6:4, v/v). IR (neat) ν_{max}: 928, 1072, 1522, 1653, 3409 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.07−1.33 (m, 5H), 1.55−1.89 (m, 8H), 2.18−2.25 (m, 1H), 2.46−2.48 (m, 1H), 3.06 (t, J = 8.0 Hz, 1H), 3.26−3.30 (m, 1H), 3.69 (s, 1H), 3.81 (dd, J_1 = 12.0 Hz, J_2 = 12.0 Hz, 2H), 7.16−7.23 (m, 2H), 7.63 (t, J = 8.0 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 24.2, 24.7, 25.7, 29.7, 30.7, 32.8, 33.0, 47.4, 53.2 61.1, 67.4, 122.3, 122.7, 136.6, 149.5, 158.6, 173.4. MS (ESI+): m/z = 288.1. ESI-HR-MS calculated for $C_{17}H_{25}N_3O$ (M^+ + H): 288.2076. Found: 288.2066.

N-Cyclohexyl-1-((5-methylthiophen-2-yl)methyl)pyrrolidine-2-carboxamide (**4kA**). Yield: 54% (0.262 g. from 0.2 g); colorless oil; R_f = 0.31 (hexanes/EtOAc, 6:4, v/v). IR (neat) ν_{max}: 1061, 1215, 1519, 1648, 2312 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.88−1.22 (m, 4H), 1.35−1.38 (m, 2H), 1.58−1.72 (m, 1H), 1.84−1.86 (m, 1H), 2.16−2.22 (m, 1H), 2.44 (s, 3H), 3.09−3.18 (m, 2H), 3.63 (d, J = 13.7 Hz, 1H), 3.72−3.74 (m, 1H), 3.88 (d, J = 13.7 Hz, 1H), 6.55 (dd, J_1 = 1.1 Hz, J_2 = 1.1 Hz, 2H), 6.65 (d, J = 3.3 Hz, 1H), 7.39 (d, J = 8.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 15.4, 24.1, 24.7, 25.6, 28.4, 29.6, 30.7, 32.9, 33.1, 47.3, 53.7, 54.1, 66.9, 76.8, 77.2, 77.5, 124.6, 125.5, 139.4, 139.9, 173.4. MS (ESI+): m/z = 307.0. ESI-HR-MS calculated for $C_{17}H_{26}N_2OS$ (M^+ + H): 307.1844. Found: 307.1841.

1-Cinnamyl-N-cyclohexylpyrrolidine-2-carboxamide (**4lA**). Yield: 52% (0.246 g from 0.2 g); colorless oil; R_f = 0.43 (hexanes/EtOAc, 6:4, v/v). IR (neat) ν_{max}: 890, 961, 1251, 1653, 3333 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.16−1.22 (m, 2H), 1.37−1.47 (m, 2H), 1.61−1.68 (m, 4H), 1.77−1.89 (m, 4H), 2.16−2.19 (m, 1H), 2.22−2.45 (m, 1H), 3.12−3.22 (m, 3H), 3.23−3.25 (m, 1H), 3.40−3.76 (m, 1H), 4.33 (dd, J_1 = 1.3 Hz, J_2 = 1.3 Hz, 1H), 6.20−6.26 (m,1H), 6.53 (d, J = 15.8 Hz, 1H), 7.24−7.37 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): 22.2, 24.8, 24.9, 25.6, 30.8, 33.2, 33.3, 47.3, 54.1, 57.6, 67.1, 126.4, 126.5, 126.7, 127.7, 128.6, 129.4, 132.6, 136.9, 173.7. MS (ESI +): m/z = 313.3. ESI-HR-MS calculated for $C_{20}H_{28}N_2O$ (M^+ + H): 313.2280. Found: 313.2264.

N-Cyclohexyl-1-hexylpyrrolidine-2-carboxamide (**4mA**). Yield: 36% (0.202 g from 0.2 g); colorless oil; R_f = 0.47 (hexanes/EtOAc, 6:4, v/v). IR (neat) ν_{max}: 942, 1245, 1660, 3330 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (t, J = 6.3 Hz, 3H), 1.27−1.38 (m, 7H), 1.62−1.96 (m, 12H), 2.09−2.19 (m, 2H), 2.29−2.37 (m, 2H), 3.17−3.27 (m, 3H), 3.74 (bs, 2H), 7.43 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.2, 22.7, 24.2, 24.7, 24.8, 25.7, 27.3, 29.8, 30.6, 31.8, 33.1, 33.2, 34.1, 47.1, 53.9, 56.1, 173.5. MS (ESI+): m/z = 281.9. ESI-HR-MS calculated for $C_{17}H_{32}N_2O$ (M^+ + H): 281.2593. Found: 281.2585.

1-Benzyl-N-tert-butylpyrrolidine-2-carboxamide (**4aB**).[18] Yield: 77% (0.377 g from 0.2 g); colorless oil; R_f = 0.50 (hexanes/EtOAc, 6:4, v/v). IR (neat) ν_{max}: 1554, 1648, 3348 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (s, 9H), 1.66−1.75 (m, 2H), 1.81−1.86 (m, 1H), 2.16−2.22 (m, 1H), 2.31−2.37 (m, 1H), 3.03−3.06 (m, 2H), 3.63 (dd, J_1 = 12.9 Hz, J_2 = 12.9 Hz, 2H), 7.25−7.36 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): 23.9, 28.4, 30.7, 50.1, 54.2, 59.9, 68.1, 126.9, 127.3, 128.4, 128.5, 128.6, 138.8, 173.9. MS (ESI+): m/z = 261.0. ESI-HR-MS calculated for $C_{16}H_{24}N_2O$ (M^+ + H): 261.1967. Found: 261.1972.

N-tert-Butyl-1-(4-cyanobenzyl)pyrrolidine-2-carboxamide (**4bB**). Yield: 90% (0.377 g from 0.2 g); colorless oil; R_f = 0.47 (hexanes/EtOAc, 6:4, v/v). IR (neat) ν_{max}: 929, 1067, 1655, 2400, 3363 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31 (s, 9H), 1.69−1.91 (m, 3H), 2.19−2.29 (m, 1H), 2.34−2.41 (m, 1H), 3.01−3.11 (m, 2H), 3.73 (dd, J_1 = 13.3 Hz, J_2 = 13.3 Hz, 2H), 7.18 (s, 1H), 7.41 (d, J = 7.8 Hz, 2H), 7.61 (d, J = 7.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 24.8, 28.7, 30.7, 50.3, 54.1, 59.9, 68.2, 112.5, 119.2, 129.7, 133.0, 144.2, 173.8. MS (ESI+): m/z = 286.1. ESI-HR-MS calculated for $C_{17}H_{23}N_3O$ (M^+ + H): 286.1919. Found: 286.1929.

N-tert-Butyl-1-(4-(trifluoromethyl)benzyl)pyrrolidine-2-carboxamide (**4cB**). Yield: 86% (0.324 g from 0.2 g); colorless oil; R_f = 0.44 (hexanes/EtOAc, 6:4, v/v). IR (neat) ν_{max}: 1119, 1256, 1665, 3329 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (s, 9H),1.69−1.87 (m, 3H), 2.19−2.25 (m, 1H),2.32−2.38 (m, 1H), 3.05 (t, J = 5.4 Hz, 2H), 3.78 (dd, J_1= 13.3 Hz, J_2 = 13.3 Hz, 2H), 7.16 (s, 1H), 7.39 (d, J = 7.9 Hz, 2H), 7.59 (d, J = 7.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 23.9, 28.6, 30.7, 50.2, 54.3, 59.5, 68.3, 125.5, 125.6, 126.8, 128.8, 142.9, 173.5. MS (ESI+): m/z = 329.1. ESI-HR-MS calculated for $C_{17}H_{23}F_3N_2O$ (M^+ + H) 329.1841. Found: 329.1844.

1-(2-Bromobenzyl)-N-tert-butylpyrrolidine-2-carboxamide (**4eB**). Yield: 86% (0.365 g from 0.2 g); pale yellow oil; R_f = 0.50 (hexanes/EtOAc, 6:4, v/v). IR (neat) ν_{max}: 1253, 1656, 3326 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.14 (s, 9H), 1.69−1.77 (m, 2H), 1.84−1.90 (m, 1H), 2.15−2.25 (m, 1H), 2.46−2.52 (m, 1H), 3.08 (dd, J_1 = 4.1 Hz, J_2 = 4.1 Hz, 1H), 3.15 (t, J = 7.5 Hz, 1H), 3.66 (dd, J_1 = 13.0 Hz, J_2 = 13.1 Hz, 2H), 7.11−7.15 (m, 2H), 7.23−7.31 (m, 2H), 7.54 (d, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 24.2, 28.5, 31.2, 49.8, 55.1, 60.3, 68.0, 124.9, 127.6, 129.0, 131.1, 132.9, 137.9, 173.6. MS (ESI+): m/z = 339.0. ESI-HR-MS calculated for $C_{16}H_{23}BrN_2O$ (M^+ + H): 339.1072. Found: 339.1075.

N-tert-Butyl-1-(2-methoxybenzyl)pyrrolidine-2-carboxamide (**4gB**). Yield: 62% (0.330 g from 0.25 g); colorless oil; R_f = 0.45 (hexanes/EtOAc, 6:4, v/v). IR (neat) ν_{max}: 1116, 1549, 1639, 3321 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (s, 9H), 1.68−1.75 (m, 2H), 1.82−1.88 (m, 1H), 2.17−2.23 (m, 1H), 2.38−2.45 (m, 1H), 3.03−3.09 (m, 2H), 3.72 (dd, J_1 = 9.9 Hz, J_2 = 12.9 Hz, 2H), 3.85 (s, 3H), 6.88−6.94 (m, 2H), 7.24−7.32 (m, 2H), 7.32 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 23.9, 28.6, 30.9, 49.9, 54.2, 54.5, 55.4, 67.9, 110.6, 120.5, 127.0, 128.5, 130.6, 157.7, 174.1. MS (ESI+): m/z = 291.1. ESI-HR-MS calculated for $C_{17}H_{26}N_2O_2$ (M^+ + H): 291.2073. Found: 291.2077.

N-tert-Butyl-1-(pyridin-2-ylmethyl)pyrrolidine-2-carboxamide (**4jB**). Yield: 79% (0.384 g from 0.2 g); colorless oil; R_f = 0.3 (hexanes/EtOAc, 6:4, v/v). IR (neat) ν_{max}: 1059, 1217, 1523, 1650, 3408 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.29 (s, 9H), 1.75−1.77 (m, 2H), 1.87−1.91 (m, 1H), 2.17−2.25 (m, 1H), 2.45−2.52 (m, 1H), 3.08−3.19 (m, 2H), 3.81 (dd, J_1 = 13.4 Hz, J_2 = 13.4 Hz, 2H), 7.18−7.23 (m, 1H), 7.25−7.29 (m, 1H), 7.64−7.69 (m, 2H), 8.56 (t, J = 4.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 24.2, 28.8, 30.8, 50.3, 54.6, 61.5, 68.2, 122.4, 122.8, 136.7, 140.7, 158.9, 173.9. MS (ESI+): m/z = 262.1. ESI-HR-MS calculated for $C_{15}H_{23}N_3O$ (M^+ + H): 262.1919. Found: 262.1917.

N-tert-Butyl-1-((5-methylthiophen-2-yl)methyl)pyrrolidine-2-carboxamide(**4kB**). Yield: 63% (0.279 g from 0.2 g); colorless oil; R_f = 0.43 (hexanes/EtOAc, 6:4, v/v). IR (neat) ν_{max}: 1554, 1664, 3348 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35 (s, 9H), 1.72−1.75 (m, 2H), 1.83−1.87 (m, 1H), 2.17−2.22 (m, 1H), 2.35−2.39 (m, 1H), 2.46 (s, 3H), 3.04−3.07 (m, 1H), 3.13 (t, J = 6.6 Hz, 1H), 3.76 (dd, J_1= 13.8 Hz, J_2 = 13.7 Hz, 2H), 6.56−6.57 (m, 1H), 6.67 (d, J = 3.2 Hz, 1H), 7.33 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 15.4, 24.0, 28.7,

dx.doi.org/10.1021/jo502029k | J. Org. Chem. 2015, 80, 99−108

30.7, 50.2, 53.8, 54.2, 67.7, 124.6, 125.4, 139.4, 140.2, 173.7. MS (ESI+): m/z = 281.2. ESI-HR-MS calculated for $C_{15}H_{24}N_2OS$ (M^+ + H): 281.1688. Found: 281.1690.

N-tert-Butyl-1-(2,3-dichlorobenzyl)pyrrolidine-2-carboxamide ***(4lB)***. Yield: 88% (0.329 g from 0.2 g); colorless oil; R_f = 0.48 (hexanes/EtOAc, 6:4, v/v). IR (neat) ν_{max}: 1568, 1649, 3327 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.17 (s, 9H), 1.65−1.82 (m, 2H), 1.84−1.98 (m, 1H), 2.17−2.27 (m, 1H), 2.45−2.51 (m, 1H), 3.07 (dd, J_1= 4.2 Hz, J_2 = 4.2 Hz, 1H), 3.14 (t, J = 7.8 Hz, 1H), 3.80 (dd, J_1 = 12.9 Hz, J_2 = 12.9 Hz, 2H), 7.08 (s, 1H), 7.15−7.23 (m, 2H), 7.41 (dd, J_1 = 1.6 Hz, J_2 = 1.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 24.2, 28.5, 31.2, 49.9, 55.2, 58.8, 68.1, 127.4, 129.2, 129.7, 132.8, 133.4, 138.7, 173.7. MS (ESI+): m/z = 329.1. ESI-HR-MS calculated for $C_{16}H_{22}Cl_2N_2O$ (M^+ + H): 329.1187. Found: 329.1182.

N,1-Dibenzylpyrrolidine-2-carboxamide ***(4aC)***.[19] Yield: 60% (0.332 g from 0.2 g); colorless oil; R_f = 0.46 (hexanes/EtOAc, 6:4, v/v). IR (neat) ν_{max}: 1226, 1648, 3416 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.76−1.79 (m, 2H), 1.87−1.95 (m, 1H), 2.18−2.27 (m, 1H), 2.33−2.39 (m, 1H), 2.96−3.01 (m, 1H), 3.26 (dd, J_1 = 4.8 Hz, J_2 = 4.8 Hz, 1H), 3.64 (d, J_1 = 12.8 Hz, J_2 = 12.8 Hz, 2H), 4.38 (d, J = 5.8 Hz, 1H), 7.23−7.27 (m, 5H), 7.32−7.36 (m, 5H), 7.72 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 24.2, 30.7, 43.1, 54.0, 60.0, 65.2, 67.4, 126.9, 127.3, 127.4, 127.5, 127.6, 127.9, 128.5, 128.6, 128.7, 128.8, 138.4, 138.5, 141.2, 174.8. MS (ESI+): m/z = 295.2. ESI-HR-MS calculated for $C_{19}H_{22}N_2O$ (M^+ + H): 295.1810. Found: 295.1809.

N-Benzyl-1-(2-bromobenzyl)pyrrolidine-2-carboxamide ***(4eC)***. Yield: 76% (0.305 g from 0.2 g); colorless oil; R_f = 0.45 (hexanes/EtOAc, 6:4, v/v). IR (neat) ν_{max}: 1061, 1220, 1641, 3412 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.77−1.81 (m,2H), 1.97−2.02 (m, 1H), 2.25−2.31 (m, 1H), 2.46−2.48 (m, 1H), 3.03 (dd, J_1 = 7.2 Hz, J_2 = 1.4 Hz, 1H), 3.29−3.32 (m, 1H), 3.78 (dd, J_1 = 12.8 Hz, J_2 = 12.8 Hz, 2H), 4.21−4.24 (m, 1H), 4.39 (dd, J_1 = 6.2 Hz, J_2 = 6.3 Hz, 1H), 7.08−7.12 (m, 1H), 7.71−7.32 (m, 7H), 7.46 (dd, J_1 = 0.9 Hz, J_2 = 1.1 Hz, 1H), 7.79 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 24.3, 30.9, 42.9, 54.6, 60.1, 67.4, 124.7, 127.3, 127.5, 127.7, 128.6, 129.2, 131.4, 132.9, 137.5, 138.4. MS (ESI+): m/z = 373.0. ESI-HR-MS calculated for $C_{19}H_{21}BrN_2O$ (M^+ + H): 373.0916. Found: 373.0920.

N-Benzyl-1-(2-methoxybenzyl)pyrrolidine-2-carboxamide ***(4gC)***. Yield: 70% (0.329 g from 0.2 g); colorless oil; R_f = 0.44 (hexanes/EtOAc, 6:4, v/v). IR (neat) ν_{max}: 1539, 1649, 3345 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.71−1.78 (m, 2H), 1.97−2.01 (m, 1H), 2.27−2.32 (m, 1H), 2.35−2.42 (m, 1H), 2.87−2.92 (m, 1H), 3.27 (dd, J_1 = 5.1 Hz, J_2 = 5.1 Hz, 1H), 3.41 (d, J = 12.2 Hz, 1H), 3.55 (s, 3H), 4.04 (d, J = 12.2 Hz, 1H), 4.41 (dd, J_1 = 5.6 Hz, J_2 = 5.6 Hz, 1H), 4.57 (dd, J_1 = 6.5 Hz, J_2 = 6.5 Hz, 1H), 6.82 (d, J = 8.2 Hz, 1H), 6.88−6.92 (m, 1H), 7.17 (dd, J_1 = 1.7 Hz, J_2 = 1.7 Hz, 1H), 7.24−7.36 (m, 6H), 8.22 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 23.9, 30.9, 42.9, 54.1, 55.2, 55.5, 67.2, 110.6, 120.5, 126.8, 127.3, 127.4, 128.7, 128.9, 131.1, 138.9, 157.9, 175.0. MS (ESI+): m/z = 325.2. ESI-HR-MS calculated for $C_{20}H_{24}N_2O_2$ (M^+ + H): 325.1916. Found: 325.1913.

N-Benzyl-1-(pyridin-2-ylmethyl)pyrrolidine-2-carboxamide ***(4jC)***. Yield: 74% (0.408 g from 0.2 g); colorless oil; R_f = 0.25 (hexanes/EtOAc, 6:4, v/v). IR (neat) ν_{max}: 928, 1069, 1159, 1521, 1659, 3348 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.79−1.82 (m, 2H), 2.01−2.04 (m, 1H), 2.26−2.32 (m, 1H), 2.49−2.56 (m, 1H), 3.06−3.11 (m, 1H), 3.45 (dd, J_1 = 4.8 Hz, J_2 = 4.8 Hz, 1H), 3.85 (dd, J_1 = 13.4 Hz, J_2 = 13.4 Hz, 2H), 4.35−4.48 (m, 2H), 7.14 (d, J = 7.6 Hz, 2H), 7.26−7.32 (m, 5H), 7.56−7.60 (m, 1H), 8.41 (d, J = 4.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 24.4, 30.7, 43.1, 54.3, 61.2, 67.4, 122.3, 122.7, 127.2, 127.7, 128.5, 136.5, 138.7, 149.5, 158.5, 174.6. MS (ESI+): m/z = 296.1. ESI-HR-MS calculated for $C_{18}H_{21}N_3O$ (M^+ + H): 296.1763. Found: 296.1759.

N-Benzyl-1-(2,3-dichlorobenzyl)pyrrolidine-2-carboxamide ***(4lC)***. Yield: 83% (0.343 g from 0.2 g); colorless oil; R_f = 0.41 (hexanes/EtOAc, 6:4, v/v). IR (neat) ν_{max}: 1256, 1558, 1660, 3356 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.72−1.81 (m, 2H), 1.96−1.98 (m, 1H), 2.25−2.31 (m, 1H), 2.41−2.45 (m, 1H), 2.99−3.03 (m, 1H), 3.29 (dd, J_1 = 4.5 Hz, J_2 = 4.5 Hz, 1H), 3.81(dd, J_1 = 13.0 Hz, J_2 = 13.0 Hz, 2H), 4.21 (dd, J_1 = 5.6 Hz, J_2 = 5.6 Hz, 1H), 4.41 (dd, J_1 = 6.5 Hz, J_2 = 6.5 Hz, 1H), 7.11 (t, J = 7.7 Hz, 1H), 7.16−7.19 (m, 3H), 7.25−7.33 (m, 3H), 7.36 (dd, J_1 = 1.7 Hz, J_2 = 1.7 Hz, 1H), 7.68 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 24.3, 31.1, 43.1, 54.6, 58.5, 67.6, 127.4, 127.5, 127.7, 128.7, 129.3, 129.8, 132.6, 133.5, 138.4, 174.4. MS (ESI+): m/z = 363.1. ESI-HR-MS calculated for $C_{19}H_{20}Cl_2N_2O$ (M^+ + H): 363.1031. Found: 363.1034.

Ethyl 2-(1-Benzylpyrrolidine-2-carboxamido)acetate ***(4aD)***. Yield: 66% (0.361 g from 0.2 g); brown oil; R_f = 0.41 (hexanes/EtOAc, 6:4, v/v). IR (neat) ν_{max}: 1639, 1741, 3418 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.17 (t, J = 7.2 Hz, 3H), 1.69−1.76 (m, 3H), 2.03−2.11 (m, 1H), 2.21−2.27 (m, 1H), 2.83−2.86 (m, 1H), 3.06 (dd, J_1 = 5.5 Hz, J_2 = 5.8 Hz, 1H), 4.03−4.13 (m, 1H), 7.23−7.34 (m, 5H), 8.16 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.5, 23.6, 30.2, 41.1, 53.2, 59.1, 60.9, 67.4, 127.4, 128.5, 129.4, 139.1, 170.4, 174.5. MS (ESI+): m/z = 291.0. ESI-HR-MS calculated for $C_{16}H_{22}N_2O_3$ (M^+ + H): 291.1709. Found: 291.1708.

1-Benzyl-N-phenylpyrrolidine-2-carboxamide ***(4aE)***. Yield: 60% (0.318 g from 0.2 g); colorless oil; R_f = 0.39 (hexanes/EtOAc, 6:4, v/v). IR (neat) ν_{max}: 950, 1259, 1560, 1663, 3335 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.76−1.77 (m, 1H), 2.05 (bs, 1H), 2.25−2.34 (m, 2H), 3.01−3.07 (m, 2H), 3.86 (bs, 1H), 4.70 (s, 2H), 7.11−7.12 (m, 1H), 7.27−7.38 (m, 7H), 7.61 (d, J = 7.2 Hz, 2H), 9.74 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 29.7, 30.7, 47.3, 61.1, 65.3, 119.3, 123.9, 126.9, 127.6, 128.5, 128.9, 137.8, 141.0, 173.4. MS (ESI+): m/z = 281.7. ESI-HR-MS calculated for $C_{18}H_{20}N_2O$ (M^+ + H): 281.1654. Found: 281.1653

1-(2-Bromobenzyl)-N-phenylpyrrolidine-2-carboxamide ***(4eE)***. Yield: 44% (0.172 g from 0.2 g); colorless oil; R_f = 0.37 (hexanes/EtOAc, 6:4, v/v). IR (neat) ν_{max}: 868, 961, 1240, 1544, 1657, 3369 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.75−1.85 (m, 1H), 2.03−2.22 (m, 1H), 2.23−2.40 (m, 2H), 2.49−2.55 (m, 1H), 3.85−3.95 (m, 1H), 3.90 (dd, J_1 = 13.0 Hz, J_2 = 12.8 Hz, 1H), 4.14 (dd, J_1 = 7.1 Hz, J_2 = 8.2 Hz, 1H), 4.77 (s, 2H), 7.04−7.20 (m, 3H), 7.27−7.36 (m, 2H), 7.50−7.66 (m, 4H), 9.34 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 22.6, 25.1, 29.7, 49.5, 65.1, 119.3, 121.8, 125.1, 127.6, 128.7, 128.9, 129.1, 132.6, 133.4, 139.7, 176.2. MS (ESI+): m/z = 359.5. ESI-HR-MS calculated for $C_{18}H_{19}BrN_2O$ (M^+ + H): 359.0759. Found: 359.0744.

1-Cinnamyl-N-phenylpyrrolidine-2-carboxamide ***(4lE)***. Yield: 49% (0.227 g from 0.2 g); colorless oil; R_f = 0.32 (hexanes/EtOAc, 6:4, v/v). IR (neat) ν_{max}: 951, 1255, 1560, 1668, 3325 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.77−1.81 (m, 2H), 1.97−2.01 (m, 1H), 2.19−2.27 (m, 1H), 2.47−2.53 (m, 1H), 3.25−3.32 (m, 3H), 3.46−3.52 (m, 1H), 6.22−6.29 (m, 1H), 6.55 (d, J = 15.7 Hz, 1H), 7.08 (d, J = 7.3 Hz, 1H), 7.19−7.34 (m, 7H), 7.58 (d, J = 7.8 Hz, 1H), 9.34 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 24.4, 30.7, 54.0, 57.5, 67.3, 119.4, 124.1, 126.2, 126.4, 127.7, 128.6, 128.9, 132.9, 136.6, 137.7, 172.9. MS (ESI+): m/z = 307.3. ESI-HR-MS calculated for $C_{20}H_{22}N_2O$ (M^+ + H): 307.1810. Found: 307.17990.

1-Benzyl-N-cyclohexylpiperidine-2-carboxamide ***(5aA)***. Yield: 42% (0.237 g from 0.2 g); colorless oil; R_f = 0.37 (hexanes/EtOAc, 6:4, v/v). IR (neat) ν_{max}: 869, 1259, 1498, 1662, 3306 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.90−1.30 (m, 3H), 1.31−1.41 (m, 4H), 1.57−1.72 (m, 4H), 1.77−1.95 (m, 4H), 2.60−2.69 (m, 3H), 3.11−3.14 (m, 1H), 3.67−3.87 (m, 3H), 7.26−7.36 (m, 5H), 7.82 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 24.1, 24.7, 24.8, 25.5, 25.8, 30.2, 32.8, 32.9, 45.7, 47.6, 60.4, 64.8, 126.8, 127.3, 128.4, 141.3, 173.2. MS (ESI+): m/z = 301.1. ESI-HR-MS calculated for $C_{19}H_{28}N_2O$ (M^+ + H): 301.2280. Found: 301.2256.

1-Benzyl-N-tert-butylpiperidine-2-carboxamide ***(5aB)***. Yield: 48% (0.248 g from 0.2 g); colorless oil; R_f = 0.34 (hexanes/EtOAc, 6:4, v/v). IR (neat) ν_{max}: 923, 1256, 1562, 1668, 3323 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.35 (s, 9H), 1.37−1.39 (m, 2H), 1.56−1.57 (m, 2H), 1.77−1.94 (m, 2H), 2.61−2.66 (m, 1H), 2.99−3.08 (m, 2H), 3.40 (bs, 2H), 7.28−7.36 (m, 5H), 7.56 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 23.9, 25.7, 28.7, 29.9, 45.7, 50.6, 60.8, 65.1, 126.9, 127.4, 128.5, 141.2, 173.3. MS (ESI+): m/z = 275.0. ESI-HR-MS calculated for $C_{17}H_{26}N_2O$ (M^+ + H): 275.2123. Found: 275.2118.

N-tert-Butyl-1-(4-cyanobenzyl)piperidine-2-carboxamide ***(5bB)***. Yield: 58% (0.264 g from 0.2 g); colorless oil; R_f = 0.32 (hexanes/EtOAc, 6:4, v/v). IR (neat) ν_{max}: 896, 1262, 1548, 1659, 3340 cm^{-1}.

dx.doi.org/10.1021/jo502029k | J. Org. Chem. 2015, 80, 99−108

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (s, 9H), 1.66−1.75 (s, 3H), 1.81−1.86 (m, 2H), 2.16−2.22 (m, 1H), 2.31−2.37 (m, 1H), 3.02−3.06 (m, 2H), 3.39 (d, J = 13.2 Hz, 1H), 3.64 (d, J = 13.2 Hz, 1H), 7.27 (bs, 1H), 7.38 (d, J = 7.9 Hz, 1H), 7.58 (d, J = 8.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 24.0, 26.8, 28.7, 30.7, 50.2, 53.8, 61.5, 67.7, 112.8, 119.6, 130.7, 133.8, 143.9, 173.6. MS (ESI+): m/z = 300.1. ESI-HR-MS calculated for $C_{18}H_{25}N_3O$ (M^+ + H): 300.2076. Found: 300.2061.

4,4′-(Hexahydropyrrolo[2,1-b]oxazole-2,3-diyl)dibenzonitrile[20] ***(6)***. Yield: 30% (0.036 g from 0.05 g); white solid; mp >200 °C; R_f = 0.42 (hexanes/EtOAc, 6:4, v/v). IR (neat) ν_{max}: 960, 1423, 1553, 1612 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.78−1.84 (m, 1H), 1.97−2.14 (m, 3H), 2.73−2.78 (m, 1H), 3.04−3.10 (m, 1H), 3.71 (d, J = 7.9 Hz, 1H), 4.55 (d, J = 7.9 Hz, 1H), 5.22 (dd, J_1 = 7.9 Hz, J_2 = 7.9 Hz, 1H), 7.24 (d, J = 8.5 Hz, 2H), 7.27 (d, J = 8.5 Hz, 2H), 7.54 (d, J = 6.5 Hz, 2H), 7.56 (d, J = 6.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 24.2, 31.7, 55.9, 78.7, 87.7, 99.3, 111.7, 112.4, 118.6, 118.8, 127.1, 128.1, 132.5, 132.6, 143.8, 146.3.

■ ASSOCIATED CONTENT

Supporting Information

Experiment to ascertain the *in situ* liberation of water for hydrolysis, procedures for bioassays, and copies of ^{1}H and ^{13}C NMR and HRMS spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*batra_san@yahoo.co.uk (SB).
*madhu_dikshit@cdri.res.in (MD).

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

S.U.D. acknowledges the financial support in the form of a fellowship from CSIR, New Delhi. Authors acknowledge the SAIF division for providing the spectroscopic data. M.D. acknowledges a financial grant from the CSIR-Network project BSC0102. Authors acknowledge the anonymous reviewers for their suggestions to improve the manuscript. This is CDRI Communication No. 8851.

■ REFERENCES

(1) For selected reviews, see: (a) Gooßen, L. J.; Rodriguez, N.; Gooßen, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 3100−3120. (b) Rodriguez, N.; Gooßen, L. J. *Chem. Soc. Rev.* **2011**, *40*, 5030−5048. (c) Dzik, W. I.; Lange, P. L.; Gooßen, L. J. *Chem. Sci.* **2012**, *3*, 2671−2678. (d) Cornella, J.; Larrosa, I. *Synthesis* **2012**, *44*, 653−676. (e) Gooßen, L. J.; Gooßen, K. *Top. Organomet. Chem.* **2013**, *44*, 121−142. (f) Park, K.; Lee, S. *RSC Adv.* **2013**, *3*, 14165−14182.

(2) For selected recent citations, see: (a) Tang, J.; Gooßen, L. J. *Org. Lett.* **2014**, *16*, 2664−2667. (b) Guntreddi, T.; Vanjari, R.; Singh, K. N. *Org. Lett.* **2014**, *16*, 3624−3627. (c) Suresh, R.; Muthusubramanian, S.; Kumaran, R. S.; Manickam, G. *Asian J. Org. Chem.* **2014**, *3*, 604−608. (d) Cahiez, G.; Moyeux, A.; Poizat, M. *Chem. Commun.* **2014**, *50*, 8982−8984. (e) Min, H.; Palani, T.; Park, K.; Hwang, J.; Lee, S. *J. Org. Chem.* **2014**, *79*, 6279−6285. (f) Mino, T.; Yoshizawa, E.; Watanabe, K.; Abe, T.; Hirai, K.; Sakamoto, M. *Tetrahedron Lett.* **2014**, *55*, 3184−3188. (g) Fromm, A.; van Wuellen, C.; Hackenberger, D.; Goossen, L. J. *J. Am. Chem. Soc.* **2014**, *136*, 10007−10023. (h) Xiong, H.-Y.; Yang, Z.-Y.; Chen, Z.; Zeng, J.-L.; Nie, J.; Ma, J.-A. *Chem.—Eur. J.* **2014**, *20*, 8325−8329. (i) Rouchet, J.-B.; Schneider, C.; Spitz, C.; Lefevre, J.; Dupas, G.; Fruit, C.; Hoarau, C. *Chem.—Eur. J.* **2014**, *20*, 3610−3615. (j) Chen, F.; Wong, N W. Y.; Forgione, P. *Adv. Synth. Catal.* **2014**, *356*, 1725−1730.

(3) (a) Rizzi, G. P. *J. Org. Chem.* **1970**, *35*, 2069−2072. (b) Grigg, R.; Thianpatanagul, S. *J. Chem. Soc., Chem. Commun.* **1984**, 180−181. (c) Grigg, R.; Aly, M. F.; Sridharan, V.; Thianpatanagul, S. *J. Chem. Soc., Chem. Commun.* **1984**, 182−183.

(4) For selected reviews on azomethine ylide chemistry, see: (a) Padwa, A. *1,3-Dipolar Cycloaddition Chemistry*; Wiley: New York, 1984; Vol. 2. (b) Gothelf, K. V.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 863−910. (c) Padwa, A.; Pearson, W. H. *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Wiley: Chichester, U.K., 2002; Vol. 59. (d) Najera, C.; Sansano, J. M. *Curr. Org. Chem.* **2003**, *7*, 1105−1150. (e) Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765−2810. (f) Pandey, G.; Banerjee, P.; Gadre, S. R. *Chem. Rev.* **2006**, *106*, 4484−4517. (h) Bonin, M.; Chauveau, A.; Micouin, L. *Synlett* **2006**, 2349−2363. (i) Nair, V.; Suja, T. D. *Tetrahedron* **2007**, *63*, 12247−12275. (j) Najera, C.; Sansano, J. M. *Top. Heterocycl. Chem.* **2008**, *12*, 117−145. (k) Stanley, L. M.; Sibi, M. P. *Chem. Rev.* **2008**, *108*, 2887−2902. (l) Nyerges, M.; Toth, J.; Groundwater, P. W. *Synlett* **2008**, 1269−1278. (m) Pineiro, M.; Pinho e Melo, T. M. V. D. *Eur. J. Org. Chem.* **2009**, 5287−5307. (n) Burrell, A. J. M.; Coldham, I. *Curr. Org. Synth.* **2010**, *7*, 312−331. (o) Adrio, J.; Carretero, J. C. *Chem. Commun.* **2011**, *47*, 6784−6794. (p) Muncipinto, G. Cycloaddition Reactions in Diversity-Oriented Synthesis: Basics and Applications. In *Organic Synthesis, Drug Discovery, and Chemical Biology*; Trabocchi, A., Ed.; John Wiley & Sons, Inc.: Hoboken, NJ, USA, 2013. (q) Narayan, R.; Potowski, M.; Jia, Z.-J.; Antonchick, A. P.; Waldmann, H. *Acc. Chem. Res.* **2014**, *47*, 1296−1310.

(5) Bi, H.-P.; Zhao, L.; Liang, Y.-M.; Li, C.-J. *Angew. Chem, Int. Ed.* **2009**, *48*, 792−795.

(6) (a) Das, D.; Richers, M. T.; Ma, L.; Seidel, D. *Org. Lett.* **2011**, *13*, 6584−6587. (b) Zhang, C.; Seidel, D. *J. Am. Chem. Soc.* **2010**, *132*, 1798−1799.

(7) Yang, D.; Zhao, D.; Mao, L.; Wang, L.; Wang, R. *J. Org. Chem.* **2011**, *76*, 6426−6431.

(8) For example: (a) Blunt, J. W.; Copp, B. R.; Keyzers, R. A.; Munro, M. H. G.; Princep, M. R. *Nat. Prod. Rep.* **2013**, *30*, 237−323. (b) Hou, Y.; Tianero, M. D. B.; Kwan, J. C.; Wyche, T. P.; Michel, C. R.; Ellis, G. A.; Rivera, E. V.; Braun, D. R.; Rose, W. E.; Schmidt, E. W.; Bugni, T. S. *Org. Lett.* **2012**, *14*, 5050−5053. (c) Pettit, G. R.; Smith, T. H.; Xu, J.-P.; Herald, D. L.; Flahive, E. J.; Anderson, C. R.; Belcher, P. E.; Knight, J. C. *J. Nat. Prod.* **2011**, *74*, 1003−1008. (d) Adams, B.; Pörzgen, P.; Pittman, E.; Yoshida, W. Y.; Westenburg, H. E.; Horgen, F. D. *J. Nat. Prod.* **2008**, *71*, 750−754.

(9) For example: (a) St. Laurent, D. R.; Serrano-Wu, M. H.; Belema, M.; Ding, M.; Fang, H.; Gao, M.; Goodrich, J. T.; Krause, R. G.; Lemm, J. A.; Liu, M.; Lopez, O. D.; Nguyen, V. N.; Nower, P. T.; O'Boyle, D. R., II; Pearce, B. C.; Romine, J. L.; Valera, L.; Sun, J.-H.; Wang, Y.-K.; Yang, F.; Yang, X.; Meanwell, N. A.; Snyder, L. B. *J. Med. Chem.* **2014**, *57*, 1976−1994. (b) Furet, P.; Guagnano, V.; Fairhurst, R. A.; Imbach-Weese, P.; Bruce, I.; Knapp, M.; Fritsch, C.; Blasco, F.; Blanz, J.; Aichholz, R.; Hamon, J.; Fabbro, D.; Caravatt, G. *Bioorg. Med. Chem.* **2013**, *23*, 3741−3748. (c) Moore, B. P.; Chung, D. H.; Matharu, D. S.; Golden, J. E.; Maddox, C.; Rasmussen, L.; Noah, J. W.; Sosa, M. I.; Ananthan, S.; Tower, N. A.; White, E. L.; Jia, F.; Prisinzano, T. E.; Aubé, J.; Jonsson, C. B.; Severson, W. E. *J. Med. Chem.* **2012**, *55*, 8582−8587. (d) Rabey, F. M.; Gadepalli, R. S. V. S.; Diano, S.; Cheng, Q.; Tabrizian, T.; Gailani, D.; Rimoldi, J. M.; Madar, Z. S. *Curr. Med. Chem.* **2012**, *19*, 4194−4206. (e) Chobanian, H.; Biftu, T.; Pio, B.; Wu, Z. WO 2014081618 A1, 2014; *Chem. Abstr. 161*, 39572. (f) Caravatti, G.; Fairhurst, R. A.; Furet, P.; Guagnano, V.; Imbach, P. US 20090163469 A1, 2009; *Chem. Abstr. 151*, 101486.

(10) Kumar, A. K. S.; Misra, A.; Siddiqi, T. I.; Srivastava, S.; Jain, M.; Bhatta, R. S.; Barthwal, M.; Dikshit, M.; Dikshit, D. K. *Eur. J. Med. Chem.* **2014**, *81*, 456−472.

(11) For example: (a) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Wiley-VCH: Weinheim, Germany, 2005. (b) Tang, Z.; Jiang, F.; Cui, X.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, Y.-D. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5755−5760. (c) Chen, J.-R.; Lu, H.-H.; Li,

X.-Y.; Cheng, L.; Wan, J.; Xiao, W.-J. *Org. Lett.* **2005**, *7*, 4543−4545. (d) Dalko, P. I., Ed. *Enantioselective Organocatalysis*; Wiley-VCH: Weinheim, Germany, 2007. (e) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138−6171. (f) Bisai, V.; Bisai, A.; Singh, V. K. *Tetrahedron* **2012**, *68*, 4541−4580. (g) Liu, L.; Gao, M.-N.; Li, Y.; Li, Z.; Song, L.; Liu, Z.-W.; Xue, D.; Liu, Z.-T. *Curr. Org. Chem.* **2013**, *17*, 1563−1568. (h) Delaney, J. P.; Brozinskia, H. L.; Henderson, L. C. *Org. Biomol. Chem.* **2013**, *11*, 2951−2960. (i) Guan, Z.; Luo, Y.; Zhang, B.-Q.; Heinen, K.; Yang, D.-C.; He, Y.-H. *Tetrahedron: Asymmetry* **2014**, *25*, 802−812. (j) Moles, F. J. N.; Guillena, G.; Najera, C. *RSC Adv.* **2014**, *4*, 9963−9966. (k) Wang, Y.; Ji, S.; Wei, K.; Lin, J. *RSC Adv.* **2014**, *4*, 30850−30856.

(12) Pattabiraman, V.; Bode, J. W. *Nature* **2011**, *480*, 471−479.

(13) For selected reviews on isonitrile insertions, see: (a) Lang, S. *Chem. Soc. Rev.* **2013**, *42*, 4867−4880. (b) Qiu, G.; Ding, Q.; Wu, J. *Chem. Soc. Rev.* **2013**, *42*, 5257−5269. (c) Vlaar, T.; Ruijter, E.; Maes, B. U. W.; Orru, R. V. A. *Angew. Chem., Int. Ed.* **2013**, *52*, 7084−7097. (d) Chakrabarty, S.; Choudhary, S.; Doshi, A.; Liu, F.-Q.; Mohan, R.; Ravindra, M. P.; Shah, D.; Yang, X.; Fleming, F. F. *Adv. Synth. Catal.* **2014**, *356*, 2135−2196.

(14) (a) Bhowmik, S.; Pandey, G.; Batra, S. *Chem.—Eur. J.* **2013**, *19*, 10487−10491. (b) Pandey, G.; Bhowmik, S.; Batra, S. *Org. Lett.* **2013**, *15*, 5044−5047. (c) Yadav, V. D.; Dighe, S. U.; Batra, S. *RSC Adv.* **2014**, *4*, 57587−57590.

(15) Pandey, G.; Bhowmik, S.; Batra, S. *RSC Adv.* **2014**, *4*, 41433−41436.

(16) Ugi, I.; Demharter, A.; Hõri, W.; Schmid, T. *Tetrahedron* **1996**, *52*, 11657−11664.

(17) Cheng, H.; Smith, C. R.; Wang, Y.; Parrott, T. J.; Dress, K. R.; Nair, S. K.; Hoffman, J. E.; Le, P. T. Q.; Kupchinsky, S. W.; Yang, Y.; Cripps, S. J.; Huang, B. WO 2005108359 A1, 2005; *Chem. Abstr. 143*, 478200.

(18) O'Neil, I. A.; Miller, N. D.; Peake, J.; Barkley, J. V.; Low, C. M. R.; Kalindjian, S. B. *Synlett* **1993**, 515−518.

(19) Traverse, J. F.; Zhao, Y.; Hoveyda, A. H.; Snapper, M. L. *Org. Lett.* **2005**, *7*, 3151−3154.

(20) Ghorai, M. K.; Samanta, S.; Das, S. *Chem.—Asian J.* **2013**, *2*, 1026−1030.