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Several Convenient Methods for the Synthesis of 2-Amido Substituted Furans

Albert Padwa,* Kenneth R. Crawford, Paitoon Rashatasakhon, and Mickea Rose

Department of Chemistry, Emory University, Atlanta, Georgia 30322

chemap@emory.edu

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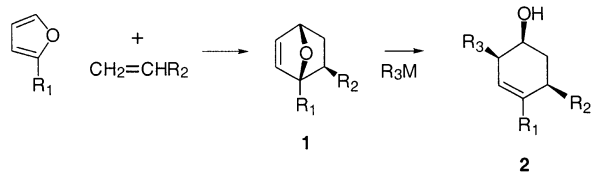
Several new methods for the synthesis of differently substituted 2-amidofurans are described. The thermolysis of furan-2-carbonyl azide results in a Curtius rearrangement and the resulting furanyl isocyanate was trapped with various organometallic reagents. A second method consists of a C−N cross-coupling reaction of a bromo-substituted furan with various amides, carbamates, and lactams. The CuI-catalyzed cross-coupling reaction between furanyl bromides and amides furnished 2- and 3-substituted amidofurans in 45−95% yield. The third protocol used involves the reaction of cyclic carbinol amides with triflic anhydride. The reaction proceeds under very mild conditions to provide α-(trifluoromethyl)sulfonamido-substituted furans in high yield. The resulting iminium ion derived from the reaction of the hydroxy pyrrolidinone with Tf_2O undergoes a facile ring opening as a consequence of the adjacent hydroxyl group to produce an imino triflate intermediate. Subsequent cyclization of this highly electrophilic imine with the oxygen atom of the adjacent carbonyl group leads to an imino dihydrofuran that reacts further with another equivalent of Tf_2O to give the observed product.

Furans[1] and isobenzofurans[2] have frequently been employed as dienes in the Diels−Alder reaction to afford substituted 7-oxabicyclo[2.2.1]heptanes (**1**) that serve as key intermediates in the synthesis of a variety of natural products.[3−10] The large number of selective transformations possible with the oxabicyclic system endow this nucleus with impressive versatility. A crucial synthetic transformation employing these intermediates (Scheme 1) involves the cleavage of the oxygen bridge to produce functionalized cyclohexene derivatives **2**. Many groups have developed different approaches including *β*-elimination of suitable derivatives,[11] treatment with strong acids,[12] reductive elimination of *endo* functionalities (R_2 = Cl or SO_2Ph),[13] fragmentation,[14] hydrolytic ring openings,[15] and alkylative bridge cleavage reactions.[16]

SCHEME 1



Several years ago we began a synthetic program to provide general access to a variety of alkaloids by [4+2]-cycloaddition chemistry of substituted 2-amidofurans.[17] Our synthetic strategy was to take advantage of an intramolecular Diels−Alder reaction of an alkenyl-substituted furanyl carbamate derivative (IMDAF).[18,19] Not only do IMDAF reactions allow for the preparation

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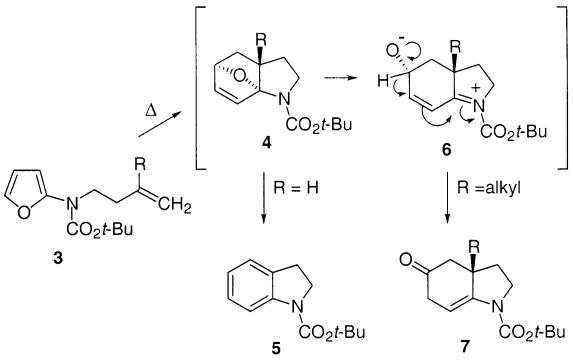
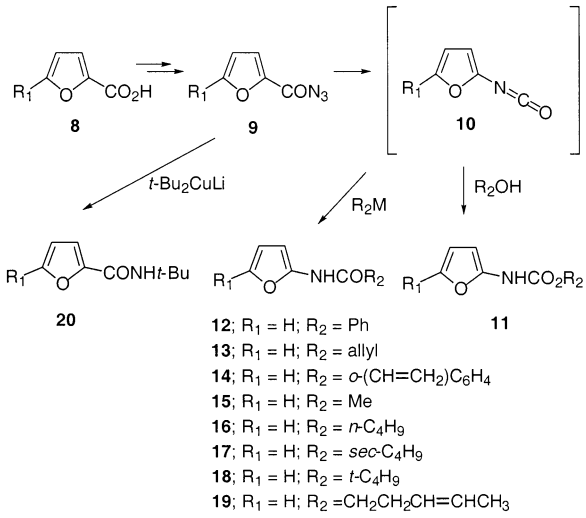
SCHEME 2



SCHEME 3



of complex oxygenated polycyclic compounds, but they often proceed at lower temperatures than their intermolecular counterparts. Even more significantly, unactivated π-bonds are reactive toward the internal cycloaddition reaction. Indeed, we discovered that the IMDAF reaction of a series of furanamide derivatives (i.e., **3**) occurred smoothly to furnish cyclized aromatic carbamates **5** as the only isolable products in high yield when monosubstituted alkenyl tethers were used (Scheme 2).[17] When the alkenyl group possesses a substituent other than hydrogen at the 2-position of the π-bond, the thermal reaction furnished a rearranged hexahydroindolinone (i.e., **7**). With this system, the initially formed cycloadduct **4** cannot aromatize. Instead, ring opening of the oxabicyclic intermediate occurs to generate zwitterion **6**, which undergoes a subsequent proton elimination by tautomerization to give the rearranged ketone **7**.[19]

To further probe the cycloaddition method for target-oriented synthesis, we required a diverse range of stable secondary and tertiary amidofurans. No broadly applicable method exists for the synthesis of this class of compounds. Consequently, we decided to develop several methods for the preparation of various 2-amido-substituted furans with the intention of using these substrates as reactive dienes for alkaloid synthesis. The present paper documents the results of these studies.

Results and Discussion

(a) The Isocyanate Approach. Previously, we had used a Curtius reaction to prepare various furano carbamate derivatives via a transient isocyanate intermediate (Scheme 3). This involved the preparation of furan-2-carbonyl azide (**9**) using a procedure described by Edwards and Singleton in 85% yield.[20] Thermolysis of **9** in an alcoholic solvent resulted in Curtius rearrangement to give isocyanate **10**, which reacted further with the alcoholic solvent to furnish the furanyl carbamate **11** in high yield. We thought that it might also be possible to use this method to prepare a series of 2-amidofurans containing tethered π-bonds. Our investigations began by heating a sample of furanyl acyl azide **9** (R_1 = H) in a benzene/toluene mixture at 90 °C so as to generate isocyanate **10**. After being cooled to 0 °C, the solution was allowed to react with several Grignard reagents. Thus, treatment of **10** with phenylmagnesium bromide afforded furan **12** in 63% yield. In a like manner, the reaction with allylmagnesium bromide gave **13** but only in 21% yield. The addition of an ortho-substituted aromatic Grignard to isocyanate **10** was also studied. 2-Vinylphenylmagnesium bromide was prepared by treating 2-bromostyrene with magnesium turnings in ether and was allowed to react with isocyanate **10** at 0 °C. The only product that could be isolated corresponded to the desired amidofuran **14**, but in a modest 32% yield.

So that a cross-section of additional information could be obtained regarding the trapping of furanyl isocyanate **10** with other organometallic reagents, we investigated its reaction with a series of alkyl cuprates. Exposure of a freshly prepared solution of **10** to methyl cuprate in ether at 0 °C furnished amide **15** in 60% yield. Similarly, the reaction of **10** with *n*-butyl, *sec*-butyl, and *tert*-butyl cuprates gave furanyl amides **16**, **17**, and **18** in 50%, 44%, and 45% yield, thereby demonstrating that cuprate reagents can also be used as nucleophiles in these trapping reactions. Hex-4-enoic acid furan-2-ylamide (**19**) was also prepared but in only 32% yield from isocyanate **10** and the cuprate derived from *trans*-1-iodo-3-pentene. Finally, treatment of acyl azide **9** with *tert*-butyl copper lithium also proceeded very smoothly to give the isomeric furanyl amide **20** in 58% isolated yield.

(b) The Copper-Catalyzed Amidation Approach. Since the above method, which makes use of the reaction of furano isocyanate **10** with various organometallic reagents, only proceeded in modest yield, we decided to investigate an alternate approach toward the desired 2-amido-substituted furan. Disconnection of the C−N bond in **12**−**19** between the furan carbon and amide nitrogen represents an alternate and very appealing approach to this system. C−N cross-coupling of aryl halides with amines has been the subject of intense studies in recent years, primarily by the groups of Buchwald[21] and Hartwig.[22] Application of this methodology to various heteroaromatic compounds is still a relatively unexplored process.[23] There were only limited reports on the catalyzed amidation of thiophenes[24] and,

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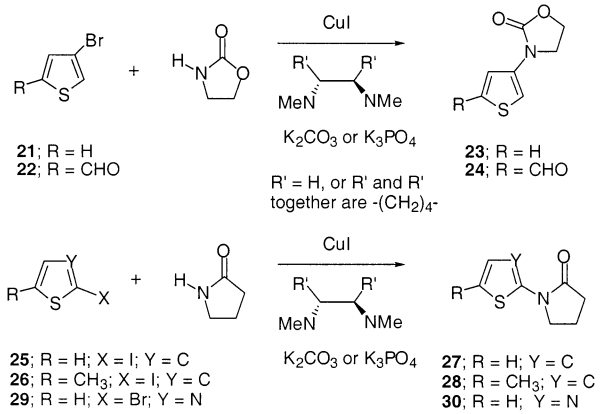
(20) Edwards, W.; Singleton, H. *J. Am. Chem. Soc.* **1938**, *60*, 540. We have had no dificulty with the handling of azide **9**. However, caution should be applied when working with acyl azides in general.

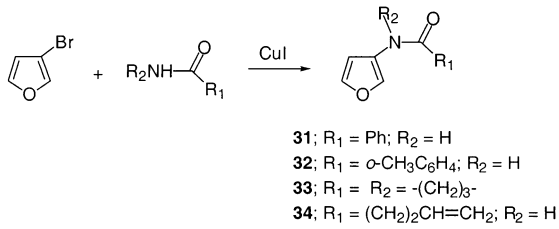
SCHEME 4



to the best of our knowledge, no examples with furans.[25] The first reported case of a Pd-catalyzed amination of a bromothiophene involved coupling with diarylamines, using a $Pd(OAc)_2/P(t\text{-}Bu)_3$ catalyst system.[26] These reactions required a strong base (NaO*t*-Bu) at 120 °C, making it incompatible with the broader range of functionality required. More recently, the Buchwald group demonstrated that the CuI-catalyzed amidation of aryl and heteroaryl halides provides an excellent complement to the Pd-catalyzed methodology.[21,27] Since the scope of this method toward heteroaromatics was quite limited, we became interested in determining whether the amidation reaction could be used to prepare various 2-amidofurans.

Encouraged by the facility with which thienyl halides undergo the C−N cross-coupling with various nitrogen sources, we set out to determine the optimal catalytic system using several classes of heteroaromatic compounds. After a thorough screening of various catalytic systems (including several Pd(0) catalysts and bis-phosphine ligand combinations), we found that Buchwald's CuI catalytic system gave the most consistent and promising results.[27] Thus, heating a mixture of 3-bromothiophenes **21** and **22** and 2-oxazolidone together with 1 mol % of air-stable CuI, 1-mol % of *N*,*N*′-dimethylethylenediamine, and a weak base in dioxane at 110 °C afforded the expected coupling products **23** and **24** in 99% and 85% yield, respectively (Scheme 4). The C−N cross-coupling reaction also occurred in high yield when the 2-iodo-substituted thiophenes **25** and **26** were used affording 2-thien-2-ylamides **27** (99%) and **28** (90%). A similar amidation also took place with thiazole **29** furnishing the related pyrrolidinone **30** (58%). In general, 1−10 mol % of CuI in combination with 10 mol % of *N*,*N*′-dimethylethylenediamine or racemic *trans*-*N*,*N*′-dimethylcyclohexanediamine worked best. As a base, either K_3PO_4 or K_2CO_3 was used with dioxane as solvent at 90−110 °C for 12−24 h.

SCHEME 5



Having established an effective catalytic system for the amidation of 2- and 3-amido-substituted thiophenes, we next focused on whether the related halogenated furans would undergo the C−N cross-coupling reaction. The reactions were conducted under conditions similar to those used for the thiophene couplings. When 3-bromofuran was used as the starting substrate, the cross-coupling reaction proceeded in high yield (80−98%) with benzamide, *o*-toluamide, or 2-pyrrolidinone as the nitrogen source, giving 3-furanyl amides **31**−**33** as the only isolable products (Scheme 5). Likewise, the coupling of 3-bromofuran and 4-pentenamide furnished the expected amide **34** in 82% yield. Most importantly, the C−N cross-coupling reaction with the 2-bromofuran isomer also provided the desired amides. Thus, the reaction of 2-bromofurans **35**−**37** with both benzamide and 2-pyrrolidinone gave the furanyl-substituted amides **38**−**41** in 67−99% yield, thereby demonstrating that oxygenated substituents on the heteroaromatic ring can be readily tolerated. 4-Pentenamide also underwent the cross-coupling reaction with 2-bromofuran to give the secondary amide **42** in 43% yield. Heating a sample of **42** at 110 °C in toluene for 3 h afforded the known 2-quinolone **44** via the initially formed [4+2]-cycloadduct **43** (Scheme 6).

The above results clearly demonstrate that 2- and 3-amido-substituted thiophenes and furans can be prepared from the C−N cross-coupling reaction of various bromo heteroaromatics with amides and lactams. The route is flexible and allows for the preparation of highly substituted amido heteroaromatic substrates.

(c) The Cyclic Carbinol Amide−Triflic Anhydride Approach. For the past decade our research group has had a continuing interest in the cyclization chemistry of *N*-acyliminium ions derived from α-alkoxy amides.[28] The α-amidoalkylation/cyclization sequence of *N*-acyliminium ions represents a powerful method for the synthesis of nitrogenated heterocyclic compounds.[29,30] During the course of our studies in this general area, we had been investigating the acid-induced cyclization chemistry of 5-hydroxy-5-methyl pyrrolidinones such as **46**. This

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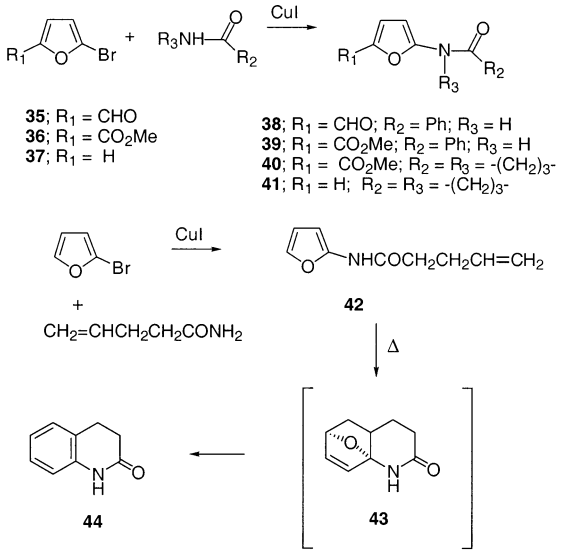
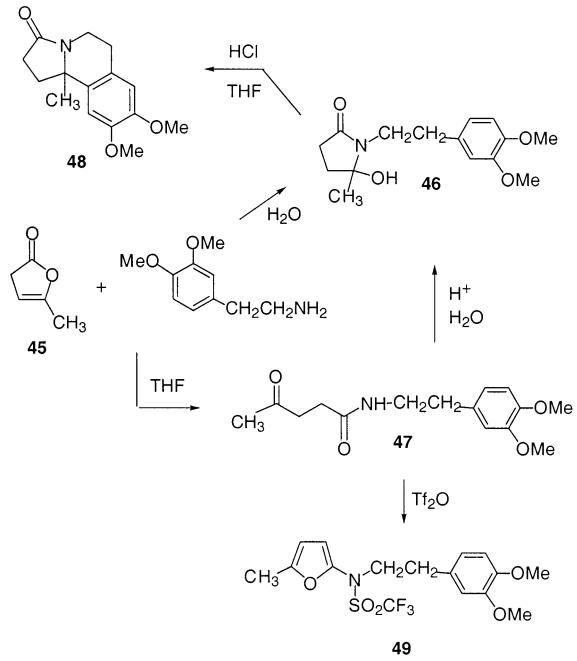
SCHEME 6

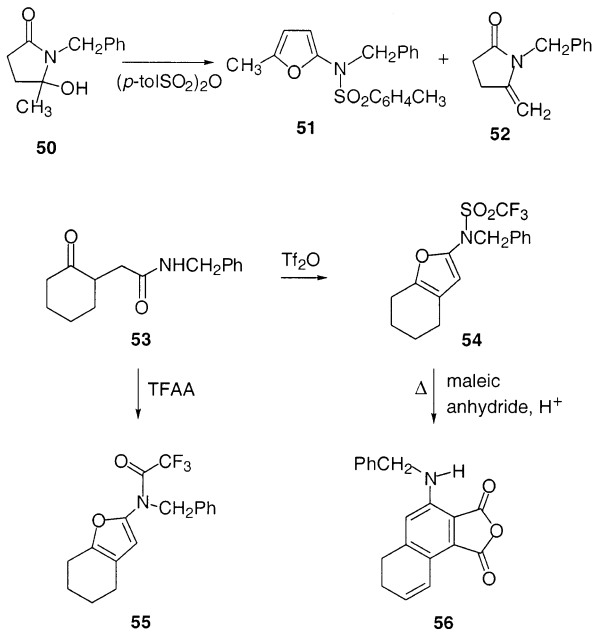


SCHEME 7



compound was readily prepared from the reaction of α-angelica lactone (**45**) with 3,4-dimethoxyphenethylamine under aqueous conditions (Scheme 7).[31] We noted that when the reaction was carried out under anhydrous conditions (i.e., THF as solvent), the isomeric γ-keto amide **47** was obtained as the exclusive product in 75% yield. Subjecting a sample of **47** to the aqueous acidic conditions resulted in the formation of the same cyclic carbinol amide (i.e., **46**) as that obtained from α-angelica lactone. On the other hand, when **47** was treated with

SCHEME 8



10% HCl in THF, isoquinolinone **48** was formed as the major product in 70% yield. Using these conditions, the initially formed *N*-acyliminium ion derived from **46** undergoes a well-established electrophilic aromatic substitution reaction with the tethered benzenoid ring. Since it is known that the judicious choice of a Lewis acid can often influence the outcome of the cyclization reaction,[32] we opted to study the conversion of **46** to **48** in greater detail using a variety of Lewis acids. Most interestingly, when a sample of **46** (or **47**) was allowed to stir with 2 equiv of triflic anhydride and pyridine in CH_2Cl_2, α-trifluoromethylsulfonamido furan **49** was formed in 90% yield. A related product was obtained with the corresponding *N*-benzyl hydroxy lactam **50**, which afforded sulfonamido furan **51** in 60% yield. We also investigated the cyclization of **50** using *p*-tosyl anhydride as the electrophile (Scheme 8). In this case, the related *p*-toluenesulfonamido furan **51** was formed but only in 23% isolated yield. Another product that was also obtained (9%) corresponded to enamide **52**, which is the simple dehydration product of **50**. No other characterizable products could be obtained from the crude reaction mixture.

This unanticipated furan cyclization led us to study the reaction in more detail since we were very interested in using this method for the synthesis of various *N*-alkenyl-substituted 2-amido furans. With this in mind, we next subjected the related cyclic ketoamide **53** to the triflic anhydride/pyridine conditions and were pleased to note that α-trifluoromethylsulfonamido furan **54** was isolated in 93% yield. Interestingly, cyclization to the furanyl amide system also occurred when trifluoro-acetic anhydride was used as the acylating agent. In this case, the trifluoroacetyl-substituted amidofuran **55** was obtained in 77% yield. As was anticipated from our earlier studies,[33] sulfonamido furan **54** was found to undergo a

(29) For reviews see: Speckamp, W. N. *Recl. Trav. Chim. Pays-Bas* **1981**, *100*, 345. Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367. Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, UK, 1991; Vol. 2, pp 1047−1082.

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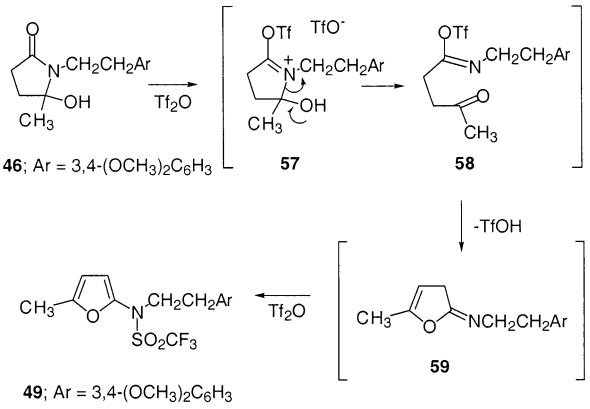
SCHEME 9



smooth intermolecular Diels−Alder reaction when heated with maleic anhydride at 120 °C to give the substituted dihydronaphthylamine **56** as the major product. The initial [4+2]-cycloadduct was not isolated, as it rapidly underwent ready ring opening of the oxabicyclic ring followed by dehydration and then partial oxidation under the themal conditions employed.

Recently, Charette and co-workers have demonstrated that secondary and tertiary amides can be activated with triflic anhydride to generate the corresponding iminium salts which can react further with various nucleophiles.[34] Iminium triflates were originally used by Ghosez as precursors of ketiminium ions which can function as electrophilic substrates in [2+2]-cycloadditions.[35] It would seem that when a hydroxy pyrrolidinone such as **46** is used as the tertiary amide, the resulting iminium ion (i.e., **57**) derived from the reaction of **46** with triflic anhydride undergoes a facile ring opening as a consequence of the adjacent hydroxyl group to produce imino triflate **58** (Scheme 9). Subsequent cyclization of this highly electrophilic imine[36] with the oxygen atom of the adjacent carbonyl group results in the formation of imino dihydrofuran **59**. This transient species reacts further with another equivalent of triflic anhydride to give the observed furan **49**.

In conclusion, three different procedures have been developed for the synthesis of various 2-amido-substituted furans. One method involves the thermolysis of furan-2-carbonyl azide, which results in a Curtius rearrangement to produce a furanyl isocyanate intermediate. Trapping of this transient species with several different organometallic reagents delivers the desired 2-amidofuran in good to moderate yield. A second method consists of a C−N cross-coupling reaction of a bromosubstituted furan with various amides, carbamates, and lactams. After a thorough screening of various catalytic systems, we found that the CuI conditions recently described by Buchwald gave the most consistent and promising results. Finally, the third protocol examined consists of treating cyclic carbinol amides with triflic anhydride. The reaction proceeds under very mild conditions to provide α-trifluoromethylsulfonamido-substituted furans in high yield. In one case, the resulting sulfonamidofuran underwent a bimolecular Diels−Alder cycloaddition with maleic anhydride to furnish an aromatic sulfonamide derivative. We are further evaluating the [4+2]-cycloaddition of these novel furans for alkaloid synthesis and additional results in this area will be reported in due course.

Experimental Section

Melting points are uncorrected. Mass spectra were determined at an ionizing voltage of 70 eV. Unless otherwise noted, all reactions were performed in flame-dried glassware under an atmosphere of dry argon. Solutions were evaporated under reduced pressure with a rotary evaporator and the residue was chromatographed on a silica gel column with an ethyl acetate/hexane mixture as the eluent unless specified otherwise. All solids were recrystallized from ethyl acetate/hexane for analytical data.

Furan-2-carbonyl Azide (9). To a solution containing 67.8 g (0.6 mol) of 2-furoic acid in 500 mL of benzene was added 66 mL (0.9 mol) of thionyl chloride. The mixture was heated at reflux for 18 h. After concentration under reduced pressure, the residue was distilled under water aspirator to give 67.5 g (86%) of furan-2-carbonyl chloride [bp 79−80 °C (35 mm)][37] as a colorless liquid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.65 (dd, 1H, J = 3.8 and 1.6 Hz), 7.50 (dd, 1H, J = 3.8 and 0.8 Hz), and 7.76 (dd, 1H, J = 1.6 and 0.8 Hz). To a solution of 66.6 g (0.5 mol) of the above acid chloride in 200 mL of ether at 0 °C was added dropwise a solution containing 33 g (0.5 mol) of sodium azide in 150 mL of water. The mixture was stirred at 0 °C for 15 min, then warmed to room temperature and stirred for another 2 h. After removal of the ether under reduced pressure, the resulting suspension was filtered and washed with cold water. The resulting white solid that formed was dried under vacuum to give 68.3 g (98%) of furan-2-carbonyl azide (**9**):[20] IR (neat) 3134, 2145, 1690, and 1292 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.56 (dd, 1H, J = 3.6 and 2.4 Hz), 7.27 (d, 1H, J = 2.4 Hz), and 7.66 (d, 1H, J = 3.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 112.6, 120.1, 145.6, 148.2, and 162.5. Anal. Calcd for $C_5H_3N_3O_2$: C, 43.80; H, 2.21; N, 30.65. Found: C, 43.62; H, 2.18; N, 30.76.

***N*-Furan-2-ylbenzamide (12).** A solution of 0.35 g (2.6 mmol) of azide **9** in 30 mL of a 2:1 benzene−toluene mixture was heated at reflux for 2 h. The solution was cooled to 0 °C and 0.9 mL (2.6 mmol) of a 3.0 M phenylmagnesium bromide solution was added dropwise. After the addition was complete, the mixture was stirred at room temperature for 1 h, quenched with a saturated NH_4Cl solution, extracted with ether, and dried over Na_2SO_4. Removal of the solvent under reduced pressure followed by flash silica gel chromatography gave 0.3 g (63%) of *N*-furan-2-ylbenzamide (**12**) as a pale yellow solid:[37] mp 121−122 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.35 (m, 1H), 6.42 (d, 1H, J = 2.8 Hz), 7.02 (m, 1H), 7.37 (t, 2H, J = 6.8 Hz), 7.45 (m, 1H), 7.82 (m, 1H), and 8.90 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 95.7, 111.4, 127.2, 128.5, 132.0, 133.1, 135.5, 145.4, and 164.0. Anal. Calcd for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.56; H, 4.91; N, 7.51.

But-3-enoic Acid Furan-2-ylamide (13). A solution of 1.0 g (7.6 mmol) of azide **9** in 60 mL of a 2:1 benzene−toluene mixture was heated at reflux for 2 h. After the mixture was cooled to 0 °C, 7 mL (7.6 mmol) of a 1.1 M allylmagnesium bromide solution was added dropwise. After the addition was

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complete, the mixture was stirred at room temperature for 1 h, quenched with a saturated NH_4Cl solution, extracted with ether, and dried over Na_2SO_4. Removal of the solvent under reduced pressure followed by flash silica gel chromatography gave 0.24 g (21%) of but-3-enoic acid furan-2-yl amide (**13**) as a pale yellow solid: mp 67−70 °C; IR (KBr) 3196, 3040, 1658, and 1582 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.18 (d, 2H, J = 7.2 Hz), 5.32−5.37 (m, 2H), 5.97−6.04 (m, 1H), 6.32 (d, 1H, J = 3.2 Hz), 6.37 (dd, 1H, J = 3.2 and 2.0 Hz), 7.05 (dd, 1H, J = 2.0 and 1.0 Hz), and 7.60 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 41.5, 95.5, 111.4, 120.7, 130.4, 135.4, 145.0, and 167.2. Anal. Calcd for $C_8H_9NO_2$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.47; H, 6.05; N, 9.21.

***N*-Furan-2-yl-2-vinylbenzamide (14).** To a suspension of 0.15 g (6.2 mmol) of magnesium turnings in 10 mL of ether at room temperature were added dropwise 0.5 mL (4.0 mmol) of 2-bromostyrene and one drop of 1,2-diiodoethane. The mixture was heated at reflux for 30 min and then stirred at room temperature for 18 h. The suspension was filtered through a pad of glass wool and the resulting 2-vinylphenylmagnesium bromide was used directly in the next step. A solution of 0.5 g (4.0 mmol) of azide **9** in 40 mL of a 2:1 benzene−toluene mixture was heated at reflux for 2 h. The resulting dark solution was cooled to 0 °C and cannulated into the above Grignard reagent solution at 0 °C. The mixture was warmed to room temperature, stirred for 1 h, diluted with ether, quenched with an aqueous NH_4Cl solution, extracted with ether, and dried over Na_2SO_4. Removal of the solvent under reduced pressure followed by flash silica gel chromatography gave 0.27 g (32%) of *N*-furan-2-yl-2-vinylbenzamide (**14**) as a pale yellow solid: mp 92−93 °C; IR (KBr) 3241, 1656, and 1551 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.40 (d, 1H, J = 11.2 Hz), 5.73 (dd, 1H, J = 9.4 and 1.0 Hz), 6.41 (t, 1H, J = 2.4 Hz), 6.46 (d, 1H, J = 3.2 Hz), 7.05−7.12 (m, 2H), 7.30 (t, 1H, J = 7.6 Hz), 7.43 (t, 1H, J = 7.4 Hz), 7.52−7.58 (m, 2H), and 8.16 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 95.3, 111.5, 117.6, 126.7, 127.6, 127.8, 130.9, 133.5, 134.3, 135.4, 136.4, 145.2, and 164.9. Anal. Calcd for $C_{13}H_{11}NO_2$: C, 73.22; H, 5.20; N, 6.57. Found: C, 73.48; H, 5.25; N, 6.52.

***N*-Furan-2-ylacetamide (15).** To a suspension of 0.25 g (2.8 mmol) of CuCN in 10 mL of THF at −78 °C was added dropwise 4.0 mL (5.5 mmol) of a 1.4 M methyllithium solution and the mixture was stirred at −78 °C for 40 min. A solution of 0.4 g (2.8 mmol) of azide **9** in a mixture of 20 mL of benzene and 10 mL of toluene was heated at reflux for 2 h. The resulting dark solution was cooled to 0 °C and cannulated into the above cuprate solution. The mixture was warmed to room temperature, stirred for 1 h, diluted with ether, quenched with an aqueous NH_4Cl solution, and extracted with ether. The organic layer was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 0.2 g (60%) of *N*-furan-2-ylacetamide (**15**) as a white solid:[38] mp 92−94 °C; IR (KBr) 3196, 3033, and 1660 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.17 (s, 3H), 6.29−6.36 (m, 2H), 7.05 (t, 1H, J = 2.0 Hz), and 7.90 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.3, 103.6, 111.4, 135.4, 145.2, and 167.0. Anal. Calcd for $C_6H_7NO_2$: C, 57.59; H, 5.64; N, 11.19. Found: C, 57.60; H, 5.61; N, 11.29.

Pentanoic Acid Furan-2-ylamide (16). To a suspension of 0.25 g (2.8 mmol) of CuCN in 6 mL of THF at −78 °C was added dropwise 2.2 mL (5.5 mmol) of a 2.5 M *n*-BuLi solution and the mixture was stirred at −78 °C for 1 h. A solution of 0.4 g (2.8 mmol) of azide **9** in a mixture of 16 mL of benzene and 8 mL of toluene was heated at reflux for 2 h. The resulting dark solution was cooled to −5 °C and cannulated into the above cuprate solution. The mixture was warmed to room temperature, stirred for 1 h, diluted with ether, quenched with an aqueous NH_4Cl solution, and extracted with ether. The organic layer was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 0.2 g (50%) of pentanoic acid furan-2-ylamide (**16**) as a pale yellow solid: mp 87−89 °C; IR (KBr) 3253, 1666, and 1554 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.92 (t, 3H, J = 7.4 Hz), 1.38 (m, 2H), 1.69 (m, 2H), 2.37 (t, 2H, J = 7.6 Hz), 6.29 (d, 1H, J = 3.2 Hz), 6.35 (m, 1H), 7.02 (s, 1H), and 8.34 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 22.3, 27.5, 36.3, 95.2, 111.3, 135.1, 145.3, and 170.1; HRMS calcd for $C_9H_{13}NO_2$ 167.0946, found 167.0943.

***N*-Furan-2-yl-2-methylbutyramide (17).** To a suspension of 0.25 g (2.8 mmol) of CuCN in 7 mL of THF at −78 °C was added dropwise 4.3 mL (5.6 mmol) of a 1.3 M *sec*-BuLi solution and the mixture was stirred at −78 °C for 1 h. A solution of 0.4 g (2.8 mmol) of azide **9** in a mixture of 20 mL of benzene and 10 mL of toluene was heated at reflux for 2 h. The resulting dark solution was cooled to −5 °C and cannulated into the above cuprate solution. The mixture was warmed to room temperature, stirred for 1 h, diluted with ether, quenched with an aqueous NH_4Cl solution, and extracted with ether. The organic layer was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 0.2 g (44%) of *N*-furan-2-yl-2-methylbutyramide (**17**) as a white solid: mp 85−86 °C; IR (KBr) 3260, 1671, 1651, and 1555 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.96 (t, 3H, J = 7.4 Hz), 1.23 (d, 3H, J = 7.2 Hz), 1.47−1.58 (m, 1H), 1.72−1.82 (m, 1H), 2.23−2.32 (m, 1H), 6.33−6.34 (m, 1H), 6.38 (t, 1H, J = 2.6 Hz), 7.04 (t, 1H, J = 1.0 Hz), and 7.49 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.8, 17.3, 27.3, 43.2, 95.0, 111.5, 135.1, 145.2, and 172.8; HRMS calcd for $C_9H_{13}NO_2$ 167.0946, found 167.0943.

***N*-Furan-2-yl-2,2-dimethylpropionamide (18).** To a suspension of 0.25 g (2.8 mmol) of CuCN in 7 mL of THF at −78 °C was added dropwise 3.7 mL (5.6 mmol) of a 1.5 M *t*-BuLi solution and the mixture was stirred at −78 °C for 1 h. A solution of 0.4 g (2.8 mmol) of azide **9** in a mixture of 20 mL of benzene and 10 mL of toluene was heated at reflux for 2 h. The resulting dark solution was cooled to −5 °C and cannulated into the above cuprate solution. The mixture was warmed to room temperature, stirred for 1 h, diluted with ether, quenched with an aqueous NH_4Cl solution, and extracted with ether. The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was subjected to flash silica gel chromatography to give 0.21 g (45%) of *N*-furan-2-yl-2,2-dimethylpropionamide (**18**) as a white solid: mp 101−102 °C; IR (KBr) 3274, 1663, and 1529 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.30 (s, 9H), 6.32−6.34 (m, 1H), 6.37−6.38 (m, 1H), 7.04−7.05 (m, 1H), and 7.70 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.5, 39.2, 94.7, 111.6, 135.0, 145.5, and 174.5. Anal. Calcd for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.47; H, 7.78; N, 8.27.

Hex-4-enoic Acid Furan-2-ylamide (19). To a solution containing 1.2 g (6.1 mmol) of *trans*-1-iodo-3-pentene in 10 mL of ether at −78 °C was added dropwise 8.1 mL (12 mmol) of a 1.5 M *t*-BuLi solution. The mixture was stirred at −78 °C for 30 min, warmed to room temperature, and cannulated through a pad of glass wool into a suspension containing 0.25 g (2.8 mmol) of CuCN in 6 mL of THF at −78 °C. The mixture was stirred at −78 °C for 1 h. A solution of 0.4 g (2.8 mmol) of azide **9** in a mixture of 20 mL of benzene and 10 mL of toluene was heated at reflux for 2 h. The resulting dark solution was cooled to 0 °C and cannulated into the above cuprate solution. After being stirred at room temperature for 1 h, the mixture was diluted with ether, quenched with an aqueous NH_4Cl solution, and extracted with ether. The organic layer was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 0.17 g (32%) of hex-4-enoic acid furan-2-ylamide (**19**) as a white solid: mp 65−66 °C; IR (KBr) 3203, 3063, 1667, and 1560 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.66 (d, 3H, J = 6.0 Hz), 2.41 (br s, 4H), 5.44−5.55 (m, 2H), 6.31

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(d, 1H, J = 3.2 Hz), 6.34 (m, 1H), 7.04 (d, 1H, J = 0.8 Hz), and 7.61 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.9, 28.2, 36.5, 95.2, 111.5, 127.0, 129.0, 135.2, 145.0, and 168.8. Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.30; H, 7.32; N, 7.68.

Furan-2-carboxylic Acid *tert*-Butylamide (20). To a suspension of 0.25 g (2.8 mmol) of CuCN in 7 mL of THF at −78 °C was added dropwise 3.7 mL (5.6 mmol) of a 1.5 M *t*-BuLi solution and the mixture was stirred at −78 °C for 1 h. To the above solution was added dropwise a solution containing 0.38 g (2.8 mmol) of azide **9** in 15 mL of THF. The mixture was warmed to room temperature, diluted with ether, quenched with aqueous NH_4Cl solution, and extracted with ether. The organic layer was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 0.26 g (58%) of furan-2-carboxylic acid *tert*-butylamide (**20**) as a white solid:[39] mp 97−98 °C; IR (KBr) 3317, 1644, and 1537 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.46 (s, 9H), 6.20 (br s, 1H), 6.47 (dd, 1H, J = 3.4 and 1.8 Hz), 7.05 (dd, 1H, J = 3.4 and 1.0 Hz), and 7.39 (dd, 1H, J = 1.8 and 1.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.9, 51.4, 112.0, 113.4, 143.2, 148.7, and 157.7. Anal. Calcd for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.56; H, 7.90; N, 8.38.

General Procedure for Cu(I)-Catalyzed C−N Cross-Couplings. To a sample of CuI (0.1 mmol, 10 mol %) and K_2CO_3 (4.3 mmol) or K_3PO_4 (2.1 mmol) under argon was added 1,4-dioxane (3 mL) followed by *N*,*N*′-dimethylethylenediamine or (±)-*trans*-*N*,*N*′-dimethylcyclohexanediamine[40] (0.1 mmol, 10 mol %), the heteroaromatic halide (1.0 mmol), and the appropriate amide (1.2 mmol). The reaction mixture was heated at 110 °C for 24 h, cooled to 25 °C, diluted with CH_2Cl_2 (5 mL), filtered through a short plug of silica gel, and concentrated under reduced pressure. The crude residue was purified by flash chromatography to give the desired product.

***N*-Thien-3-yloxazolidone (23).** Using the general procedure for Cu(I)-catalyzed C−N cross-couplings described above, 3-bromothiophene (**21**) and 2-oxazolidone gave 0.17 g (99%) of *N*-thien-3-yloxazolidone (**23**): mp 91−92 °C; IR (film) 1731, 1115, and 1041 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.98−4.05 (m, 2H), 4.42−4.51 (m, 2H), 6.98 (dd, 1H, J = 3.2 and 1.6 Hz), 7.30 (dd, 1H, J = 5.3 and 3.2 Hz), and 7.41 (dd, 1H, J = 5.3 and 1.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 45.5, 61.6, 107.2, 119.6, 125.5, 136.7, and 154.9. Anal. Calcd for $C_7H_7NO_2S$: C, 49.69; H, 4.17; N, 8.28. Found: C, 49.48; H, 4.16; N, 8.23.

***N*-5-Formylthien-3-yloxazolidone (24).** Using the general procedure for Cu(I)-catalyzed C−N cross-couplings described above, 4-bromothiophene-2-carboxaldehyde (**22**) and 2-oxazolidone afforded 0.17 g (85%) of **24** as a white solid: mp 171−172 °C; IR (film) 1734, 1661, 1552, 1455, 1401, 1262, and 1111 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.98−4.10 (m, 2H), 4.42−4.54 (m, 2H), 7.64−7.78 (m, 1H), 8.28 (d, 1H, J = 2.0 Hz), and 9.92 (d, 1H, J = 1.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 45.1, 62.2, 116.9, 128.6, 138.0, 142.2, 154.7, and 184.4. Anal. Calcd for $C_8H_7NO_3S$: C, 48.72; H, 3.58; N, 7.10. Found: C, 48.87; H, 3.71; N, 6.88.

***N*-Thien-2-ylpyrrolidinone (27).** Using the general procedure for Cu(I)-catalyzed C−N cross-couplings described above, 2-bromothiophene (**25**) and 2-pyrrolidinone gave 0.17 g (99%) of *N*-thien-2-ylpyrrolidinone (**27**) as a white solid: mp 116−117 °C (lit.[24] mp 116−117 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.07−2.29 (m, 2H), 2.57 (t, 2H, J = 8.1 Hz), 3.82 (t, 2H, J = 7.2 Hz), 6.48 (dd, 1H, J = 3.6 and 1.2 Hz), and 6.75−6.95 (m, 2H).

***N*-5-Methylthien-2-ylpyrrolidinone (28).** Using the general procedure for Cu(I)-catalyzed C−N cross-couplings described above, 2-iodo-5-methylthiophene (**26**) and 2-pyrrolidinone gave 0.16 g (90%) of *N*-5-methylthien-2-ylpyrrolidinone (**28**) as a white solid: mp 136−137 °C; IR (film) 1675, 1506, 1409, 1301, and 1235 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.08−2.24 (m, 2H), 2.38 (s, 3H), 2.49−2.60 (m, 2H), 3.71−3.84 (m, 2H), 6.20−6.30 (m, 1H), and 6.42−6.52 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.7, 17.5, 31.0, 48.3, 110.1, 121.2, 131.6, 137.8, and 171.5. Anal. Calcd for $C_9H_{11}NOS$: C, 59.64; H, 6.12; N, 7.73. Found: C, 59.60; H, 6.13; N, 7.72.

***N*-Thiazol-2-ylpyrrolidinone (30).** Using the general procedure for Cu(I)-catalyzed C−N cross-couplings described above, 2-bromothiazole (**29**) and 2-pyrrolidinone afforded 0.1 g (58%) of **30** as beige crystals: mp 83−84 °C; IR (film) 3129, 3078, 1696, 1506, 1460, 1383, and 1173 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.10−2.30 (m, 2H), 2.65 (t, 2H, J = 8.0 Hz), 4.12 (t, 2H, J = 7.2 Hz), 6.97 (d, 1H, J = 3.8 Hz), and 7.43 (d, 1H, J = 3.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.0, 31.6, 47.8, 113.4, 137.4, 157.7, and 173.3. Anal. Calcd for $C_7H_8N_2OS$: C, 49.98; H, 4.79; N, 16.65. Found: C, 50.08; H, 4.97; N, 16.66.

***N*-Furan-3-ylbenzamide (31).** Using the general procedure for Cu(I)-catalyzed C−N cross-couplings described above, 3-bromofuran and benzamide afforded 0.17 g of **31** (98%): mp 147−148 °C (lit.[41] mp 141−142 °C); IR (film) 3278, 3109, 1650, 1568, and 1158 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.42−6.48 (m, 1H), 7.30−7.35 (m, 1H), 7.37−7.45 (m, 2H), 7.46−7.54 (m, 1H), 7.79−7.86 (m, 2H), 8.14−8.20 (m, 1H), and 8.23 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 104.8, 124.3, 127.0, 128.7, 131.8, 132.8, 133.7, 141.5, and 165.1. Anal. Calcd for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.38; H, 4.84; N, 7.44.

***N*-Furan-3-yl-*o*-tolylamide (32).** Using the general procedure for Cu(I)-catalyzed C−N cross-couplings described above, 3-bromofuran and *o*-tolylamide gave 0.17 g (86%) of **32**: mp 139−140 °C; IR (film) 1644, 1562, and 1163 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.41 (s, 3H), 6.34 (d, 1H, J = 1.2 Hz), 7.10−7.25 (m, 3H), 7.26−7.40 (m, 2H), 7.88 (br s, 1H), and 8.08 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.7, 104.6, 124.2, 125.7, 126.7, 130.2, 131.1, 132.6, 135.3, 136.5, 141.4, and 167.4. Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.62; H, 5.54; N, 6.94.

***N*-Furan-3-ylpyrrolidinone (33).** Using the general procedure for Cu(I)-catalyzed C−N cross-couplings described above, 3-bromofuran and 2-pyrrolidinone gave 0.12 g (80%) of **33**: mp 74−75 °C; IR (film) 1681, 1593, 1425, 1316, and 1173 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.08−2.24 (m, 2H), 2.44−2.56 (m, 2H), 3.61−3.73 (m, 2H), 6.63−6.70 (m, 1H), 7.28−7.35 (m, 1H), and 7.77−7.85 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.2, 31.3, 47.7, 103.9, 126.5, 130.9, 141.8, and 173.0. Anal. Calcd for $C_8H_9NO_2$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.65; H, 6.05; N, 9.30.

Pent-4-enoic Acid Furan-3-ylamide (34). Using the general procedure for Cu(I)-catalyzed C−N cross-couplings described above, 3-bromofuran and 4-pentenamide[42] afforded 0.14 g (82%) of pent-4-enoic acid furan-3-ylamide (**34**): mp 75−76 °C; IR (film) 1656, 1568, and 1168 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.37−2.52 (m, 4H), 4.99−5.15 (m, 2H), 5.79−5.92 (m, 1H), 6.29 (dd, 1H, J = 1.9 and 0.6 Hz), 7.29 (t, 1H, J = 1.9 Hz), and 8.00−8.20 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 29.4, 35.6, 104.6, 115.8, 124.1, 132.5, 136.6, 141.3, and 170.3; Anal. Calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.17; H, 6.70; N, 8.50.

***N*-5-Formylfuran-2-ylbenzamide (38).** Using the general procedure for Cu(I)-catalyzed C−N cross-couplings described above, 5-bromofuran-2-carboxaldehyde and benzamide afforded 0.17 g (98%) of **38**: mp 137−138 °C; IR (film) 1701, 1670, 1552, 1265, and 1035 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.84 (d, 1H, J = 3.9 Hz), 7.33 (d, 1H, J = 3.9 Hz), 7.47−7.56 (m, 2H), 7.61 (ddt, 1H, J = 7.2 and 1.2 Hz), 7.88−7.95 (m, 2H), 9.12 (br s, 1H), and 9.43 (s, 1H); ^{13}C NMR ($CDCl_3$, 100

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MHz) δ 97.6, 127.3, 129.0, 132.2, 133.0 (2), 145.3, 152.2, 163.6, and 175.6. Anal. Calcd for $C_{12}H_9NO_3$: C, 66.97; H, 4.22; N, 6.51. Found: C, 66.47; H, 4.29; N, 6.43.

***N*-5-Carbomethoxyfuran-2-ylbenzamide (39).** Using the general procedure for Cu(I)-catalyzed C−N cross-couplings described above, 5-bromo-2-furoic acid methyl ester and benzamide gave 0.17 g (67%) of *N*-5-carbomethoxyfuran-2-ylbenzamide (**39**): mp 130−131 °C (lit.[43] mp 128−129 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.81 (s, 3H), 6.66 (d, 1H, *J* = 3.6 Hz), 7.19 (d, 1H, *J* = 3.6 Hz), 7.40−7.50 (m, 2H), 7.50−7.60 (m, 1H), 7.84−7.94 (m, 2H), and 9.27 (s, 1H).

***N*-5-Carbomethoxyfuran-2-ylpyrrolidinone (40).** Using the general procedure for Cu(I)-catalyzed C−N cross-couplings described above, 5-bromo-2-furoic acid methyl ester and 2-pyrrolidinone gave 0.16 g (77%) of *N*-5-carbomethoxyfuran-2-ylpyrrolidinone (**40**) as a white solid: mp 137−138 °C; IR (film) 1706, 1539, 1316, and 1227 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.16 (p, 2H, *J* = 5.7 Hz), 2.52 (t, 2H, *J* = 5.7 Hz), 3.79 (s, 3H), 3.98 (t, 2H, *J* = 5.7 Hz), 6.54 (t, 1H, *J* = 2.8 Hz), and 7.15 (d, 1H, *J* = 2.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.2, 31.4, 46.3, 51.6, 95.9, 121.2, 136.7, 149.9, 158.9, and 172.6. Anal. Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.34; H, 5.24; N, 6.66.

***N*-Furan-2-ylpyrrolidinone (41).** Using the general procedure for Cu(I)-catalyzed C−N cross-couplings described above, 2-bromofuran and 2-pyrrolidinone afforded 0.14 g (82%) of **41**: mp 65−66 °C; IR (film) 1706, 1593, 1516, and 1419 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.00−2.17 (m, 2H), 2.40−2.53 (m, 2H), 3.76−3.88 (m, 2H), 6.26−6.37 (m, 2H), and 6.99−7.07 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.9, 31.1, 46.5, 94.1, 111.2, 135.3, 146.3, and 171.9. Anal. Calcd for $C_8H_9NO_2$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.61; H, 5.99; N, 9.27.

Pent-4-enoic Acid Furan-2-ylamide (42). Using the general procedure for Cu(I)-catalyzed C−N cross-couplings described above, 2-bromofuran and 4-pentenamide (2.4 equiv) afforded 0.07 g (43%) of pent-4-enoic acid furan-2-ylamide (**42**) as a pale yellow oil: IR (film) 1652, 1558, 1235, and 1145 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.42−2.50 (m, 4H), 5.03 (d, 1H, *J* = 10.4 Hz), 5.09 (d, 1H, *J* = 17.6 Hz), 5.73−5.92 (m, 1H), 6.29 (d, 1H, *J* = 3.2 Hz), 6.24−6.40 (m, 1H), 6.97−7.06 (m, 1H), and 8.19 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 29.4, 35.9, 95.6, 111.6, 116.1, 135.5, 136.8, 145.4, and 169.3; HRMS calcd for $C_9H_{11}NO_2$ 165.0790, found 165.0803.

1-[2-(3,4-Dimethoxyphenyl)ethyl]-5-hydroxy-5-methylpyrrolidin-2-one (46). A solution of 3,4-dimethoxyphenethylamine (1.0 g, 5.6 mmol) in water (0.5 mL) was added to α-angelica lactone **45** (0.5 g, 5.1 mmol) and the mixture was stirred at room temperature for 1 h. The solution was concentrated under reduced pressure, and the resulting residue was purified by flash chromatography on silica gel, using 20% acetone in $CHCl_3$ as the eluent. The major product **46** was obtained as a yellow oil in 80% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39 (s, 3H), 1.95−2.13 (m, 2H), 2.20−2.38 (m, 1H), 2.40−2.56 (m, 1H), 2.67−2.95 (m, 3H), 3.50−3.29 (m, 2H), 3.81 (s, 3H), 3.83 (s, 3H), and 6.68−6.80 (m, 3H). The spectral data of this compound are identical with those reported in the literature.[44]

4-Oxopentanoic Acid 2-(3,4-Dimethoxyphenethyl)-amide (47). To a solution of lactone **45** (0.5 g, 5.1 mmol) in 10 mL of THF at 0 °C was added 3,4-dimethoxyphenethylamine (1.0 g, 5.6 mmol) dropwise. The reaction mixture was allowed to warm to room temperature and was stirred for 2 h. The solvent was removed under reduced pressure and the residue was purified on silica gel, using 20% acetone in $CHCl_3$ as the eluent. The major product was obtained as a yellow solid in 98% yield: mp 83−85 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.18 (s, 3H), 2.35 (t, 2H, *J* = 6.4 Hz), 2.72 (t, 2H, *J* = 7.0 Hz), 2.75 (t, 2H, *J* = 6.4 Hz), 3.40 (dt, 2H, *J* = 7.0 and 5.8 Hz), 3.85 (s, 3H), 3.87 (s, 3H), 5.85 (br s, 1H), and 6.69−6.78 (m, 3H). The spectral data of this compound are identical with those reported in the literature.[44]

8,9-Dimethoxy-10*b*-methyl-1,5,6,10*b*-tetrahydro-2*H*-pyrrolo[2,1-*a*]isoquinolin-3-one (48). To a solution of the above amide **47** (1.0 mmol) in 5 mL of THF was added 2 mL of 10% HCl solution. The mixture was stirred at room temperature for 16 h, diluted with $CHCl_3$, and washed with water. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture was purified by flash silica gel chromatography, using 20% acetone in $CHCl_3$ as the eluent, to give **48** in 70% yield as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.51 (s, 3H), 2.05−2.17 (m, 1H), 2.34−2.41 (m, 1H), 2.44 (tt, 1H, *J* = 9.6 and 1.6 Hz), 2.59−2.70 (m, 2H), 2.85−2.94 (m, 1H), 3.03−3.11 (m, 1H), 3.86 (s, 3H), 3.88 (s, 3H), 4.24−4.32 (m, 1H), and 6.57 (s, 2H). The spectral data of this compound are identical with those reported in the literature.[45]

***N*-[2-(3,4-Dimethoxyphenyl)ethyl]-*C*,*C*,*C*-trifluoro-*N*-(5-methylfuran-2-yl)methanesulfonamide (49).** To a solution of **47** (0.15 g, 0.5 mmol) in 5 mL of CH_2Cl_2 at −78 °C was added pyridine (0.2 mL, 2.7 mmol) and then 0.2 mL (1.1 mmol) of triflic anhydride (Tf_2O). The crude reaction mixture was allowed to warm to room temperature over 30 min and was stirred at 25 °C for an additional 10 min. Water was added and the organic layer was separated. The aqueous layer was extracted with chloroform and the organic phase was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture was purified by flash chromatography on silica gel, using 20% Et_2O in hexane as the eluent, to give furan **49** in 90% yield (0.19 g) as a colorless oil: IR (neat) 1614, 1465, 1401, 1228, 1189, 1142, and 1029 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28 (s, 3H), 2.85 (dd, 2H, *J* = 8.3 Hz), 3.85 (s, 3H), 3.86 (s, 3H), 3.89 (dd, 2H, *J* = 8.3 Hz), 5.99 (dd, 1H, *J* = 3.2 and 1.3 Hz), and 6.17 (d, 1H, *J* = 3.2 Hz), 6.67 (d, 1H, *J* = 1.9 Hz), 6.70 (dd, 1H, *J* = 7.9 and 1.9 Hz), and 6.79 (d, 1H, *J* = 7.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 35.0, 54.1, 56.0, 107.5, 109.6, 111.5, 112.1, 120.1 (q, *J* = 322.5 Hz), 121.0, 129.4, 140.2, 148.1, 149.2, and 151.9. Anal. Calcd for $C_{16}H_{18}F_3NO_5S$: C, 48.85; H, 4.61; N, 3.56. Found: C, 48.55; H, 4.76; N, 3.68.

1-Benzyl-5-hydroxy-5-methylpyrrolidin-2-one (50). This lactam was prepared from lactone **45** and benzylamine by using a procedure similar to that employed for **46**. Pyrrolidinone **50** was obtained as a colorless oil in 67% yield: IR (neat) 1666, 1413, 1356, 1200, and 1098 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (s, 3H), 2.16−2.06 (m, 2H), 2.40−2.31 (m, 1H), 2.64−2.50 (m, 1H), 4.00 (br s, 1H), 4.31 (d, 1H, *J* = 15.3 Hz), 4.60 (d, 1H, *J* = 15.3 Hz), and 7.29−7.18 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δδ 27.2, 29.3, 35.1, 42.5, 90.7, 127.4, 127.9, 128.7, 138.7, and 175.6; HRMS calcd for $C_{12}H_{15}NO_2$ 205.1103, found 205.1099.

***N*-Benzyl-4-methyl-*N*-(5-methylfuran-2-yl)benzenesulfonamide (51).** To a solution of **46** (0.1 g, 0.5 mmol) in 5 mL of CH_2Cl_2 at −78 °C was added pyridine (0.4 mL, 4.9 mmol) and 0.36 g (1.1 mmol) of *p*-toluenesulfonic anhydride ((*p*-tol)$_2$O) The reaction mixture was allowed to warm to room temperature over 30 min and was stirred for an additional 30 min. Water was added and the organic layer was separated. The aqueous layer was extracted with chloroform and the organic phase was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel, using 50% Et_2O in hexane as the eluent, to give 0.04 g of furan **51** in 23% yield as a white solid: mp 91−92 °C; IR (neat) 1562, 1350, 1165, 1088, and 1016 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.14 (s, 3H), 2.45 (s, 3H), 4.61 (s, 2H), 5.81 (dd, 1H, *J* = 3.2 and 1.0 Hz), 5.85 (d, 1H, *J* = 3.2 Hz), 7.20−7.33 (m, 7H), and 7.64−7.70 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δδ 13.9, 21.8, 54.1, 107.1, 108.7, 127.9, 128.0, 128.5, 128.7, 129.7, 135.9,

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136.2, 143.3, 144.0, and 150.4. Anal. Calcd for $C_{19}H_{19}NO_3S$: C, 66.84; H, 5.61; N, 4.10. Found: C, 66.93; H, 5.62; N, 4.14.

The minor compound isolated from the chromatographic separation was identified as 1-benzyl-5-methylene-pyrrolidin-2-one (**52**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.52−2.65 (m, 2H), 2.67−2.80 (m, 2H), 4.12 (d, 1H, J = 1.8 Hz), 4.19 (d, 1H, J = 1.8 Hz), 4.68 (s, 2H), and 7.20−7.39 (m, 5H). The spectral data of this compound are identical with those reported in the literature.[46]

***N*-Benzyl-2-(2-oxo-cyclohexyl)acetamide (53).** To a solution of (2-oxo-cyclohexyl)acetic acid (1.1 g, 7.3 mmol) in CH_2Cl_2 (70 mL) was added benzylamine (0.9 mL, 8.0 mmol) and 1.5 g (8.0 mmol) of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI). The mixture was stirred at room temperature for 3 h and partitioned between water and chloroform. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel, using 10% acetone in $CHCl_3$ as the eluent. Keto amide **53** was obtained as a white solid in 80% yield: mp 110−112 °C; IR (KBr) 1694, 1637, 1547, 1453, and 1413 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (qd, 1H, J = 9.7 and 3.8 Hz), 1.46−1.60 (m, 1H), 1.65 (qt, 1H, J = 13.0 and 9.7 Hz), 1.75−1.84 (m, 1H), 2.01 (dd, 1H, J = 14.6 and 5.4 Hz), 2.05−2.14 (m, 2H), 2.31 (d, 1H, J = 5.7 Hz), 2.21−2.34 (m, 1H), 2.58 (dd, 1H, J = 14.6 and 7.3 Hz), 2.82−2.92 (m 1H), 4.27−4.39 (m, 2H), 6.53 (br s, 1H), and 7.16−7.30 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.3, 28.0, 34.4, 36.6, 42.0, 43.4, 47.7, 127.3, 127.6, 128.6, 138.5, 171.9, and 212.6. Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.41; H, 7.85; N, 5.71.

***N*-Benzyl-*C*,*C*,*C*-trifluoro-*N*-(4,5,6,7-tetrahydrobenzofuran-2-yl)methanesulfonamide (54).** To a solution of keto amide **53** (0.2 g, 0.8 mmol) in freshly distilled CH_2Cl_2 (10 mL) were added pyridine (0.7 mL, 8.2 mmol) and Tf_2O (0.3 mL, 1.7 mmol). The reaction mixture was stirred at room temperature for 12 h and was then quenched by the addition of water. The organic layer was separated and the aqueous layer was extracted with chloroform. The organic phase was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel, using 20% Et_2O in hexane as the eluent. Furan **54** was isolated as the major product in 93% yield (0.27 g) as a colorless oil: IR (neat) 1570, 1406, 1221, 1145, and 1029 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58−1.65 (m, 2H), 1.70−1.77 (m, 2H), 2.21−2.26 (m, 2H), 2.41−2.46 (m, 2H), 4.77 (s, 2H), 5.79 (s, 1H), and 7.18−7.30 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9, 22.8, 23.0, 56.4, 109.9, 118.5, 120.2 (q, J = 323.6 Hz), 128.7, 128.8, 129.0, 134.5, 139.3, and 150.5; HRMS calcd for $C_{16}H_{16}F_3NO_3S$ 359.0803, found 359.0793.

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***N*-Benzyl-2,2,2-trifluoro-*N*-(4,5,6,7-tetrahydrobenzofuran-2-yl)acetamide (55).** To a solution of ketoamide **53** (0.1 g, 0.4 mmol) in freshly distilled CH_2Cl_2 (4.0 mL) was added 0.3 mL (4.1 mmol) of pyridine and trifluoroacetic anhydride (TFAA) (0.1 mL, 0.9 mmol). The reaction mixture was stirred at room temperature for 6 h and the reaction was quenched by the addition of water. The organic layer was separated and the aqueous layer was extracted with chloroform. The organic phase was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel, using 20% Et_2O in hexane as the eluent. Furan **55** was isolated as the major product in 77% yield (0.1 g) as a colorless oil: IR (neat) 1716, 1577, 1210, and 1161 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.66−1.90 (m, 4H), 2.30−2.39 (m, 2H), 2.49−2.58 (m, 2H), 4.83 (s, 2H), 5.81 (s, 1H), and 7.24−7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9, 22.9, 23.0, 54.0, 108.2, 116.3 (q, J = 286.8 Hz), 118.2, 128.2, 128.7, 128.9, 135.4, 141.4, 149.8, and 157.9 (q, J = 35.5 Hz); HRMS calcd for $C_{17}H_{16}F_3NO_2$ 323.1133, found 323.1138.

4-Benzylamino-6,7-dihydronaphtho[1,2-*c*]furan-1,3-dione (56). A solution of furan **54** (0.1 g, 0.3 mmol) and maleic anhydride (0.3 g, 2.8 mmol) in toluene (3 mL) was heated at 120 °C in a sealed tube for 24 h. The reaction mixture was allowed to cool to room temperature and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel, using 20% Et_2O in hexane as the eluent. The major product **56** was obtained as a red-orange solid in 19% yield: mp 203−205 °C; IR (KBr) 1807, 1754, 1309, and 1204 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30−2.36 (m, 2H), 2.79 (t, 2H, J = 7.6 Hz), 4.52 (d, 2H, J = 6.0 Hz), 6.17 (dt, 1H, J = 9.8 and 4.4 Hz), 6.55 (t, 1H, J = 5.4 Hz), 6.67 (br s, 1H), 7.20 (d, 1H, J = 9.8 Hz), and 7.29−7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.9, 28.9, 46.9, 107.7, 116.6, 122.0, 123.8, 124.1, 127.2, 128.0, 129.2, 131.4, 137.4, 146.6, 148.4, 163.8, and 165.3; HRMS calcd for $C_{19}H_{15}NO_3$ 305.1052, found 305.1050.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for new compounds lacking elemental analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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