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# Expedient and Rapid Synthesis of 1,2,3-Triazolo[5,1-*c*]morpholines through Palladium−Copper Catalysis

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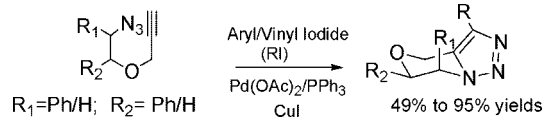


A one-pot approach using palladium−copper as catalyst has been developed for the synthesis of morpholines fused with 1,2,3-triazole. Good regioselectivity, mild reaction conditions, high yields and short reaction time are the hallmarks of this method.

Because of the abundance of medium-sized heterocyclic scaffolds in many natural products, drugs, and preclinical leads, synthesis of these compounds through novel methodologies that achieve the formation of multiple bonds in one operation is one of the major challenges in organic synthesis. Such processes need to avoid multiple steps, protection and deprotections, drain of resources, and long reaction times, thereby constituting environmentally benign and atom-economic methods. To this end, use of a catalytic amount of transition metals to trigger the process is being recognized as a powerful means. In this context, one particular area that has witnessed significant interest over the past few years is azide−alkyne cycloaddition. The importance of this reaction was enhanced significantly after the discovery of "click-reaction".[1]

Among the approaches to C−C and/or C−N bond-forming reactions leading to various heterocycles, 1,2,3-triazoles have received special interest because of their potent use ranging from medicinal chemistry[2] to material science.[3] More importantly, fused triazoles are of interest due to their various biological activities[4] and also clinical applications[5] (viz. alprazolam, estazolam, etc.). On the other hand, the morpholine moiety is found in a diverse range of bioactive agents including antidepressant, antileukemia, NK-1 receptor antagonist, fungicide, etc.[6] For example, reboxetine[6a] is used as an antidepressant drug to treat clinical depression, attention deficit disorder, panic disorder, hyperactivity, etc., and fenpropimorph[6d] is extensively used in agriculture as a fungicide, mainly to control fungal attacks in cereals. Presently the world drug index contains more than 100 drugs having this structural feature in different forms including scaffold, side-chain, fused-ring, etc. The reason behind the extensive use of the morpholine core by pharmaceutical industries is primarily the likely improvement in pharamacokinetics effected by this structural unit. Therefore, it would be attractive to develop a straightforward and convenient method for the synthesis of morpholines fused with 1,2,3-triazole, which would pave the way for the preparation of a wide variety of different bioactive compounds. Although there are numerous methods for the synthesis of individual 1,2,3-triazoles[7] and morpholines,[8] only a few methods exist in the literature for some specific 1,2,3-triazolo-morpholine analogs,[9] adopting multistep procedures through conventional reaction pathways. Therefore, there remains a need for a scalable, efficient, and general method for this important class of compounds, particularly using transition-metal-catalyzed one-pot reactions.

In the course of our research activities directed toward the synthesis of various heterocycles[10] of biological interests using

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(9) Pericas and co-workers synthesized 1,2,3-triazolo-morpholines through conventional thermal cycloaddition approach. For details, see:(a) Oliva, A. I.; Christmann, U.; Font, D.; Cuevas, F.; Ballester, P.; Buschmann, H.; Torrens, A.; Yenes, S.; Pericas, M. A. *Org. Lett.* **2008**, *10*, 1617. (b) Medaer, B. P.; Van Aken, K. J.; Hoornaert, G. J. *Tetrahedron* **1996**, *52*, 8813.

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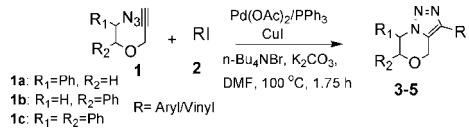
**SCHEME 1. Synthesis of 1,2,3-Triazolo[5,1-*c*]morpholines through Palladium−Copper Catalysis**



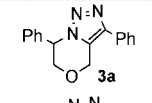
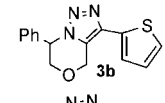
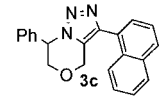
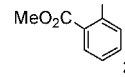
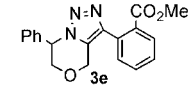
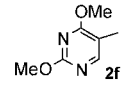
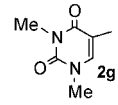
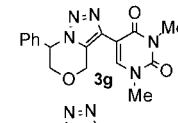
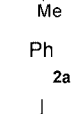
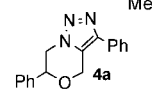
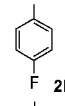
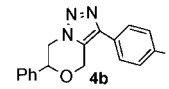
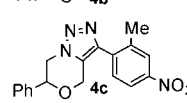
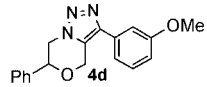
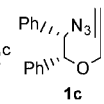
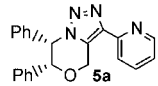
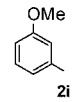
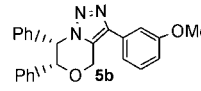
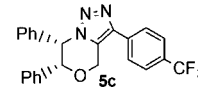

palladium catalyst, we have reported in the recent past the synthesis of 1,2,3-triazolo-isoindolines.[10a] This led us to envisage that *O*-propargylated-2-azidoethanol **1** would react with various aryl/vinyl iodides **2** under palladium−copper catalysis leading to carbon-substituted morpholines **3**−**5** fused with 1,2,3-triazoles (Scheme 1). The present report addresses several key issues related to azides: (a) their reactivity toward metal activated internal alkynes, (b) their regioselectivity in intramolecular cycloaddition that normally does not adjust to the structural requirements required for "click chemistry", and (c) the optimum catalytic reaction conditions. Herein we report our results obtained so far toward these goals.

At the outset, the reaction of **1a** with iodobenzene **2a** was tried under our previously reported[10a] reaction conditions [$Pd(PPh_3)_2Cl_2$/CuI/$Et_3N$/115 °C], expected to give the desired product **3a**. However, this produced the product in low yield (37%). This disappointing result prompted us to optimize the reaction conditions and catalysts. After screening various types of palladium catalyst (for details see Supporting Information), $Pd(OAc)_2/PPh_3$ along with CuI turned out to be the most effective catalytic system. Omission of either CuI or $PPh_3$ resulted in very low yield or no formation of desired products. Among the bases (inorganic and organic) and solvent systems examined, $K_2CO_3$ and DMF turned out to be superior compared to others. Resorting to heating without initial stirring for the requisite time period at room temperature lowered the product yields. The optimized reaction conditions were applied subsequently for the reactions between azido-alkynes **1a**−**c** and iodides **2a**−**k** resulting in the products **3**−**5** (entries 1−14, Table 1). The aryl, heteroaryl, and vinyl iodides employed in the reactions worked efficiently, furnishing good to excellent yields. Unfortunately, aryl bromides did not respond as coupling partner in these reactions. The reaction tolerated many functional groups including methoxy, carbomethoxy, methyl, trifluoromethyl, fluoro, nitro, etc. The presence of electron-withdrawing groups (EWGs) in the iodides **2** ensured better yields compared to electron-donating groups (see Table 2, entries 4, 5, 10, 14 vs 6, 11). Similarly, alkyne-azides **1a**−**c** having various substitutions were also found to be equally effective in our reaction conditions. Indeed, a single diastereomeric product **5** was obtained in the case of diphenyl-substituted alkyne-azide **1c** (see Table 2, entries 12−14). In contrast to the outcome (1,4-disubstituted triazole) of "click reaction", our method yielded regioselectively 1,5-disubstituted triazoles. No extrusion of nitrogen was observed during the course of the reaction.[11]

To investigate the scope of the reactions further, azido-alkynes **1a**−**b** were treated with 1,4-diiodobenzene **6** under these reaction conditions. Gratifyingly, the bis-heteroannulated products **7a**−**b** were formed regioselectively with good yields (Scheme 2). Thus, this method could also be applied for the synthesis of fascinating molecules having poly heteroannulated frameworks under one-pot reactions.

The structures of all new products were well secured by spectroscopic and analytical data. Mass spectral data supported intramolecular cycloaddition in preference to intermolecular cycloaddition, which would have led to cyclodimerization.[12] The

**TABLE 1. Scope of the Reaction for the Synthesis of 1,2,3-Triazolo[5,1-*c*]morpholines**[a]

| Entry | Azido-alkyne **1** | Iodide **2** (RI) R | Product[b] **3** | Yield (%) |
|---|---|---|---|---|
| 1 |  **1a** |  **2a** |  **3a** | 65 |
| 2 | **1a** |  **2b** |  **3b** | 53 |
| 3 | **1a** |  **2c** |  **3c** | 75 |
| 4 | **1a** |  **2d** |  **3d** | 90 |
| 5 | **1a** |  **2e** |  **3e** | 71 |
| 6 | **1a** |  **2f** |  **3f** | 59 |
| 7 | **1a** |  **2g** |  **3g** | 49 |
| 8 |  **1b** |  **2a** |  **4a** | 85 |
| 9 | **1b** |  **2h** |  **4b** | 57 |
| 10 | **1b** |  **2d** |  **4c** | 68 |
| 11 | **1b** |  **2i** |  **4d** | 61 |
| 12[c] |  **1c** |  **2j** |  **5a** | 95 |
| 13[c] | **1c** |  **2i** |  **5b** | 89 |
| 14[c] | **1c** |  **2k** |  **5c** | 77 |

[a] Reaction conditions: **1** (1.2 equiv), **2** (1.0 equiv), $Pd(OAc)_2$ (0.05 equiv), $PPh_3$ (0.20 equiv), CuI (0.10 equiv), $K_2CO_3$ (2.0 equiv), *n*-$Bu_4NBr$ (0.05 equiv) in dry DMF (5 mL) stirred at rt for 45 min and then heated at 100 °C for 1 h. [b] Satisfactory spectroscopic and analytical data were obtained for all new products. [c] Azido-alkyne **1c** and products **5a**−**c** are all in recemic mixture.

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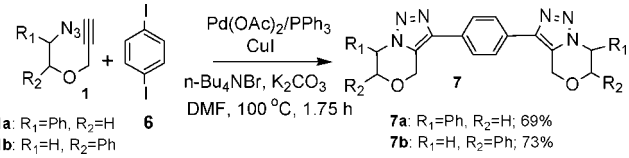
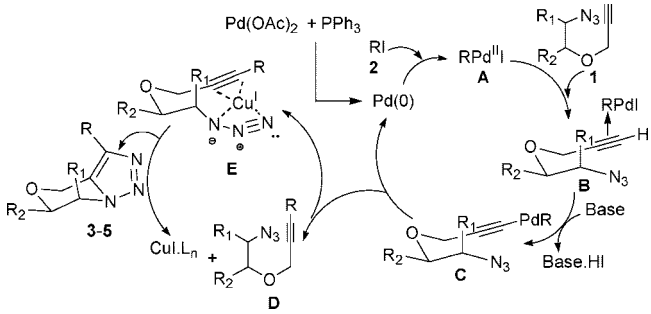
**SCHEME 2. Synthesis of Bis-heteroannulated Products 7a−b**




**SCHEME 3. Plausible Reaction Mechanism**




*cis*-stereochemistry of products **5a−c** was established through NOE between the adjacent protons of morpholine ring in NOESY spectra as well as their small coupling constants (∼2−3 Hz) in $^1$H NMR. Finally, the unambiguous structural confirmation came from X-ray diffraction analysis of a representative product **5b** (see structure in Supporting Information). Interestingly, careful scrutiny of the vicinal H−H coupling constants in morpholine ring of products **3** and **4** reveals that the *J* values are small (∼4−5 Hz) in products **3** but distinctly different (∼10−11 Hz) in products **4**. This observation suggests that the phenyl ring adjacent to the nitrogen prefers to adopt an axial-like conformation, whereas that next to the oxygen takes up the equatorial conformation.[13] The above structural conclusion was further supported by X-ray diffraction analysis of another product **3d** (see structure in Supporting Information).

A possible reaction mechanism, which accounts for the formation of products **3−5**, is shown in Scheme 3. In this connection, it is worth mentioning that the corresponding acyclic intermediates **D** were isolated with 65% and 88% yields, respectively, when the reactions of **1a** and **1b** were performed separately with phenyl iodide **2a** at room temperature for 45 min under the optimized reaction conditions but without using copper iodide. On the basis of this evidence, we believe that the formation of the intermediate internal alkyne **D** is not proceeding through conventional Sonogashira's coupling pathway[14] involving CuI; rather, it is following a palladium(0)-catalyzed copper-free Sonogashira pathway[15] as depicted in Scheme 3. The palladium(0) formed in situ[16] undergoes oxidative addition with aryl (or vinyl) iodides **2** to form RPd(II)I (**A**), which subsequently activates the triple bond of **1** through coordination as in intermediate species **B**. Activation of the triple bond is necessary[15b] for deprotonation of the acetylenic hydrogen that needs to be carried out in the next step by the employed base. Upon deprotonation, a palladium−acetylide complex **C** is formed, which undergoes reductive elimination[15c] to afford the acyclic intermediate **D** with regeneration of palladium(0), which makes the catalytic cycle active. The acyclic intermediate **D** would presumably be converted[17] to the desired cyclized product **3−5** through the copper-coordinated intermediate **E**. DMF could facilitate the cycloaddition as it is a dipolar aprotic solvent.

In conclusion, the aforementioned heteroannulation involves a two-step process carried out in one pot: (a) palladium(0)-catalyzed coupling reaction resulting in internal alkynes, followed by (b) copper(I)-catalyzed intramolecular cycloaddition between azide and internal alkyne, leading to 1,2,3-triazolo[5,1-*c*]morpholines **3−5**. In conjunction with other recent reports,[18] this method could expand the scope of "click chemistry", where cycloaddition of azide is applicable to terminal alkynes only. The reaction process was found to be general and highly regioselective, furnishing an array of compounds with moderate to excellent yield, starting from readily available or easily synthesized simple materials. The method is operationally simple and requires a short reaction time period. We believe this methodology should find broad applications in synthetic, combinatorial, and medicinal chemistry as well.

## Experimental Section

**General Procedure for the Synthesis of 1,2,3-Triazolo[5,1-*c*]morpholines (3−5).** A mixture of $Pd(OAc)_2$ (5 mg, 5 mol %) and $PPh_3$ (22 mg, 20 mol %) in dry DMF (4 mL) was stirred for 10 min under argon atmosphere. Iodo-compound **2** (0.416 mmol), $K_2CO_3$ (115 mg, 0.833 mmol), and tetrabutylammonium bromide (7 mg, 5 mol %) were added to it successively. The whole reaction mixture was then allowed to stir for another 10 min under argon atmosphere. A solution of azido-acetylene **1** (0.499 mmol) in dry DMF (2 mL) was added dropwise followed by CuI (8.0 mg, 10 mol %). The resulting mixture was flushed with argon carefully and stirred at room temperature for 45 min. After disappearance of starting materials (monitored by TLC), the whole mixture was allowed to heat at 100 °C for 1 h. Upon completion of the reaction, the solvent was removed in vacuum; the residue was mixed with water (10 mL) and then extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified through silica gel (100−200 mesh) column chromatography (ethyl acetate−petroleum ether) to afford the desired product.

**3,7-Diphenyl-6,7-dihydro-4*H*-[1,2,3]triazolo[5,1-*c*][1,4]oxazine (3a).** White solid (75 mg, 65% yield): mp 160−161 °C; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 4.12 (dd, $J$ = 5.1, 12.0 Hz, 1H), 4.31 (dd, $J$ = 4.0, 12.0 Hz, 1H), 5.18 (d, $J$ = 15.0 Hz, 1H), 5.27 (d, $J$ = 15.0 Hz, 1H,), 5.69 (t, $J$ = 4.2 Hz, 1H), 7.17−7.19 (m, 2H), 7.36−7.38 (m, 4H), 7.47 (t, $J$ = 7.4 Hz, 2H), 7.69 (d, $J$ = 7.2 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 59.7, 63.4, 69.9, 126.0, 126.8, 127.7, 127.8, 128.5, 128.7, 128.8, 130.6, 136.6, 140.9; IR (KBr) 3029, 2931, 2838, 1607, 1493, 1456 cm$^{-1}$; MS (FAB) *m*/*z* 278 $[M + H]^+$. Anal. Calcd for $C_{17}H_{15}N_3O$: C, 73.63; H, 5.45; N, 15.15. Found: C, 73.71; H, 5.52; N, 15.19.

(13) This perhaps arises from the fact that the axial N-C-Ph does not face any 1,3-diaxial interaction while it also avoids the 1,2-torsoinal strain with the neighboring N-N bond.

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(17) Intermediate species **D** (R = $R_1$ = Ph, $R_2$ = H) was isolated, and several control experiments were carried out under various reaction conditions. However, expected cycloaddition was completed within 1 h (with 91% yield of desired product **3a**), when the aforementioned intermediate **D** was heated in DMF at 100 °C in the presence of catalytic amount (10 mol %) of CuI only. Heating at 100 °C without CuI yielded the desired product **3a** (54%) along with the recovery of unreacted intermediate **D** (41%) even after 14h.

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**3-(2-Carbomethoxyphenyl)-7-phenyl-6,7-dihydro-4*H*-[1,2,3]triazolo[5,1-*c*][1,4]oxazine (3e).** White solid (99 mg, 71% yield): mp 124−126 °C; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 3.81 (s, 3H), 4.09 (dd, $J$ = 5.5, 12.1 Hz, 1H), 4.33 (dd, $J$ = 4.2, 12.0 Hz, 1H), 4.92 (d, $J$ = 15.3 Hz, 1H), 5.0 (d, $J$ = 15.0 Hz, 1H), 5.70 (t, $J$ = 4.6 Hz, 1H), 7.18−7.21 (m, 2H), 7.34−7.43 (m, 3H), 7.46−7.51 (m, 2H), 7.57−7.62 (m, 1H), 7.94 (d, $J$ = 7.8 Hz, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 52.2, 59.9, 63.1, 70.4, 126.8, 128.4, 128.6, 128.8, 129.3, 130.2, 130.6, 130.8, 131.7, 136.8, 140.3, 167.8; IR (KBr) 2987, 2952, 2849, 1715, 1591, 1495, 1452 cm$^{-1}$; ESI-MS $m/z$ 335.94 [M + H]$^+$, 357.92 [M + Na]$^+$, 373.89 [M + K]$^+$. Anal. Calcd for $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 12.53. Found: C, 68.18; H, 5.22; N, 12.44.

**3-(2-Methyl-4-nitrophenyl)-6-phenyl-6,7-dihydro-4*H*-[1,2,3]triazolo[5,1-*c*][1,4]oxazine (4c).** Light yellow solid (95 mg, 68% yield): mp 141−142 °C; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 2.58 (s, 3H), 4.39 (dd, $J$ = 11.1, 12.9 Hz, 1H), 4.81 (dd, $J$ = 3.0, 13.2 Hz, 1H), 4.98 (dd, $J$ = 3.0, 10.5 Hz, 1H), 5.06 (d, $J$ = 15.3 Hz, 1H), 5.17 (d, $J$ = 15.3 Hz, 1H), 7.35 (d, $J$ = 8.4 Hz, 1H), 7.46 (br, 5H), 8.10 (d, $J$ = 8.4 Hz, 1H), 8.19 (s, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 20.9, 51.2, 62.6, 75.4, 120.9, 125.8, 126.0, 128.8, 128.9, 129.1, 129.8, 136.1, 136.5, 139.1, 139.7, 147.3; IR (KBr) 3073, 2938, 1592, 1512, 1448 cm$^{-1}$; ESI-MS $m/z$ 337.01 [M + H]$^+$, 358.99 [M + Na]$^+$. Anal. Calcd for $C_{18}H_{16}N_4O_3$: C, 64.28; H, 4.79; N, 16.66. Found: C, 64.35; H, 4.86; N, 16.54.

**3-(3-Methoxyphenyl)-6-phenyl-6,7-dihydro-4*H*-[1,2,3]triazolo[5,1-*c*][1,4]oxazine (4d).** White solid (78 mg, 61% yield): mp 141−142 °C; IR (KBr) 2994, 2944, 2842, 1596, 1497, 1458, 1076 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 600 MHz) $\delta$ 3.86 (s, 3H), 4.28 (dd, $J$ = 10.5, 12.9 Hz, 1H), 4.66 (dd, $J$ = 3.0, 13.2 Hz, 1H), 4.86 (dd, $J$ = 3.3, 10.5 Hz, 1H), 5.13 (d, $J$ = 15.0 Hz, 1H), 5.33 (d, $J$ = 15.0 Hz, 1H), 6.89 (dd, $J$ = 1.8, 8.4 Hz, 1H), 7.08 (d, $J$ = 7.8 Hz, 1H), 7.33−7.36 (m, 2H), 7.40−7.42 (m, 1H), 7.44(d, $J$ = 4.2 Hz, 4H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 51.2, 55.2, 63.1, 75.0, 111.0, 113.8, 118.1, 126.0, 127.0, 128.8, 128.9, 129.9, 132.0, 136.7, 140.9, 160.0; ESI-MS $m/z$ 308.15 [M + H]$^+$, 330.15 [M + Na]$^+$.Anal. Calcd for $C_{18}H_{17}N_3O_2$ C, 70.34; H, 5.58; N, 13.67. Found: C, 70.28; H, 5.67; N, 13.61.

**3-(3-Methoxyphenyl)-6,7-diphenyl-6,7-dihydro-4*H*-[1,2,3]triazolo[5,1-*c*][1,4]oxazine (5b).** White solid (142 mg, 89% yield): mp 196−197 °C; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 3.90 (s, 3H), 5.30 (d, $J$ = 3.0 Hz, 1H), 5.34 (d, $J$ = 15.6 Hz, 1H), 5.62 (d, $J$ = 15.3 Hz, 1H), 5.85 (d, $J$ = 3.0 Hz, 1H), 6.64 (d, $J$ = 7.2 Hz, 2H), 6.93 (dd, $J$ = 1.9, 8.2 Hz, 1H), 7.01−7.02 (m, 2H), 7.08 (t, $J$ = 7.3 Hz, 2H), 7.14−7.23 (m, 5H), 7.38−7.43 (m, 2H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 55.3, 63.5, 64.3, 78.7, 111.1, 113.9, 118.2, 126.0, 127.4, 127.71, 127.74, 128.01, 128.08, 130.0, 132.1, 134.3, 135.8, 140.4, 160.0; IR (KBr) 3063, 3034, 2938, 2839, 1599, 1495, 1458 cm$^{-1}$; ESI-MS $m/z$ 405.97 [M + Na]$^+$. Anal. Calcd for $C_{24}H_{21}N_3O_2$ C, 75.18; H, 5.52; N, 10.96. Found: C, 75.11; H, 5.61; N, 11.03.

**3-(4-Trifluoromethylphenyl)-6,7-diphenyl-6,7-dihydro-4*H*-[1,2,3]triazolo[5,1-*c*][1,4]oxazine (5c).** White solid (135 mg, 77% yield): mp 249−250 °C; IR (KBr) 3038, 2851, 1620, 1454, 1121 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 5.31 (d, $J$ = 2.4 Hz, 1H), 5.37 (d, $J$ = 15.6 Hz, 1H), 5.65 (d, $J$ = 15.3 Hz, 1H), 5.87 (d, $J$ = 2.1 Hz, 1H), 6.66 (d, $J$ = 7.5 Hz, 2H), 7.01−7.03 (m, 2H), 7.09 (t, $J$ = 7.3 Hz, 2H), 7.16−7.24 (m, 4H), 7.75 (d, $J$ = 8.1 Hz, 2H), 7.86 (d, $J$ = 8.1 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 63.5, 64.4, 78.9, 126.04,126.08,127.7,127.8, 128.1, 128.2, 129.5, 129.9, 134.1, 134.3, 135.6, 139.4; ESI-MS $m/z$ 422.11 [M + H]$^+$, 444.08 [M + Na]$^+$, 460.07 [M + K]$^+$.Anal. Calcd for $C_{24}H_{18}F_3N_3O$ C, 68.40; H, 4.31; N, 9.97. Found: C, 68.36; H, 4.42; N, 10.06.

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**Supporting Information Available:** Experimental procedure, compound characterization, crystallographic data of compounds of **3d** and **5b**, and copies of $^1$H and $^{13}$C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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