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Intramolecular Carbonylative C-H Functionalization of 1,2,3-Triazoles for the Synthesis of Triazolo[1,5-*a*]indolones

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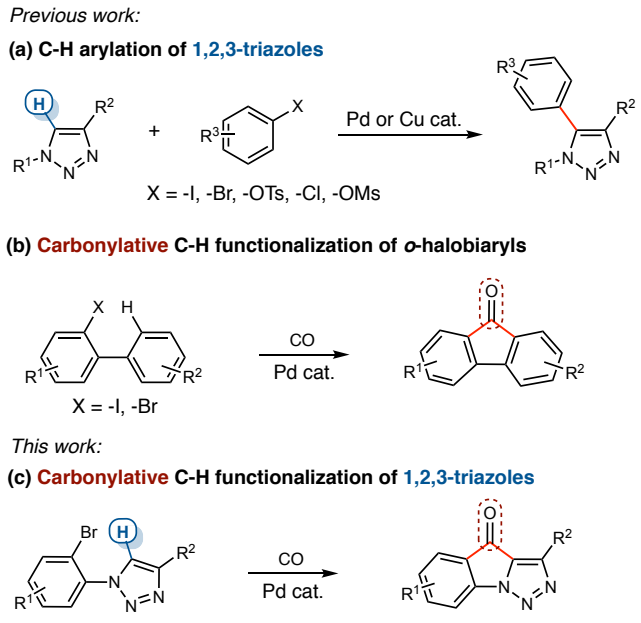
Abstract: This study presents a synthesis of 4*H*-[1,2,3]triazolo[1,5-*a*]indol-4-ones. The key step in the synthesis of this new heterocyclic scaffold is an intramolecular cyclization *via* an unprecedented carbonylative C-H functionalization of 1-(2-bromoaryl)-1,2,3-triazoles. Isotopic labeling of the carbonyl carbon atom is possible using near stoichiometric amounts of ^{13}CO. Additionally, an alternative pathway *via* carbonylative Sonogashira coupling followed by a two-step one pot azidation/cycloaddition is also investigated, giving rise to the same scaffold.

Keywords: 1,2,3-triazoles; carbonylation; C-H activation; heterocycles; isotopic labeling

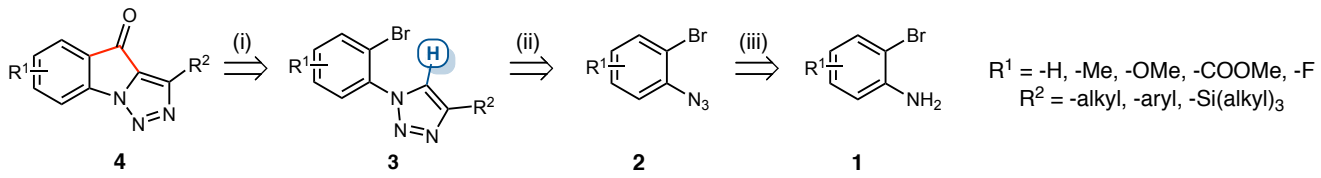
Over the past decade, transition metal-catalyzed C-H functionalization has emerged as a valuable strategy in organic synthesis.[1] This strategy is challenging, as it has to deal with the inertness of a C-H bond, but is also beneficial in terms of atom economy, since typical prefunctionalization steps (such as halogenation and borylation) can be circumvented by directly addressing a C-H bond. One relevant example for this study is the discovery of the direct arylation of 1,2,3-triazoles (Scheme 1a).[2]

While transition metal-catalyzed direct arylation is widely explored, the carbonylative equivalent still poses great scientific challenges to date.[3] This problem has partially been addressed by using activated substrates (*e.g.* polyfluoroarenes)[4] or intramolecular chelation (*e.g.* nitrogen coordination, directing group).[5] Other methods involve *in situ* formation of an organocuprate[6] or *in situ* halogenation.[7] One example is the pioneering work of the Larock group in 2000, discussing the intramolecular carbonylative C-H functionalization of *o*-halobiaryls for the synthesis of fluorenone derivates (Scheme 1b).[8] Recently, the scope of this transformation was expanded, as it turned out that (fused) 5-membered heterocycles were also suitable substrates.[9] Progress has also been made on the more challenging intermolecular transformation as the Arndtsen group developed a general procedure to perform carbonylative C-H functionalization on 5-membered nitrogen-containing heterocycles.[10]

To our surprise, neither intra- nor intermolecular carbonylative C-H functionalization of 1,2,3-triazoles has been reported to date. This type of transformation could however be a valuable new strategy towards highly substituted triazoles which are omnipresent since the discovery of the click reaction. In this report, we present our results of the first intramolecular carbonylative C-H functionalization of triazoles. This pathway gives direct access to a new heterocyclic scaffold: the triazolo[1,5-*a*]indolone (Scheme 1c).



Scheme 1. Transition metal-catalyzed (carbonylative) C-H functionalization.

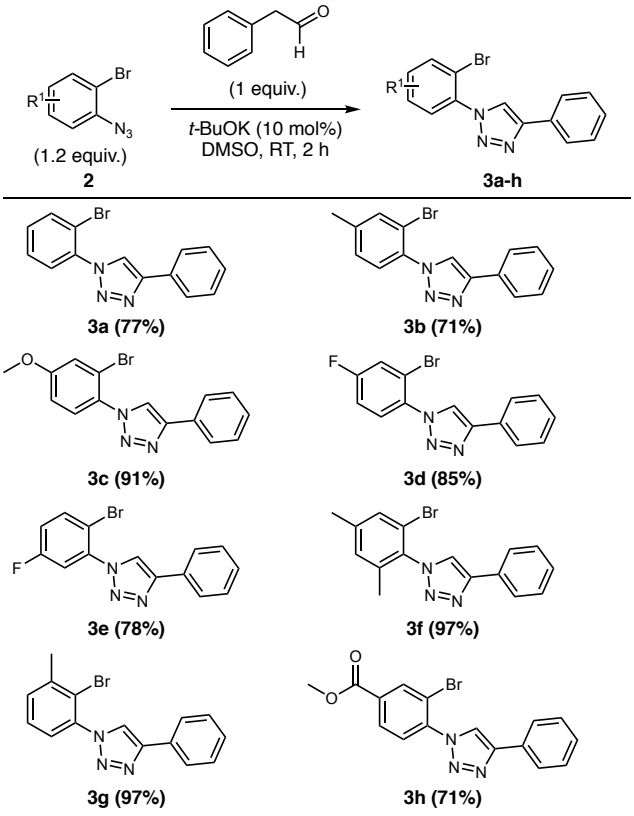


Scheme 2. Retrosynthetic strategy for the synthesis of triazolo[1,5-*a*]indolones: (i) carbonylative C-H functionalization, (ii) cycloaddition and (iii) functional group interconversion.

The triazolo[1,5-*a*]indolones were synthesized *via* a sequential procedure, using 2-bromoanilines as readily available starting materials (Scheme 2). First, 2-bromoanilines **1** were converted into their corresponding azides **2** in the presence of *tert*-butyl nitrite and azidotrimethylsilane (see ESI).[11]

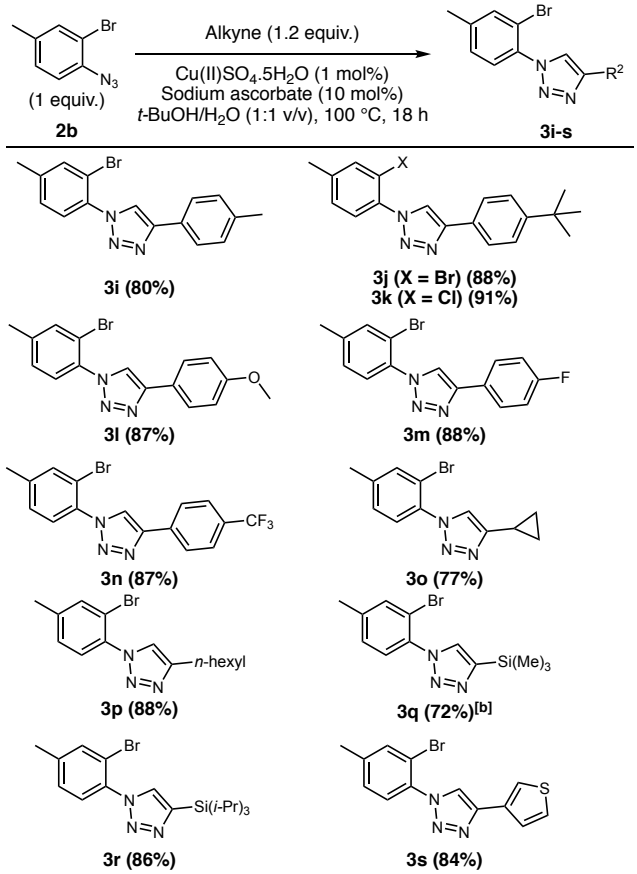
The second step, the cycloaddition of 2-bromophenyl azides **2** with alkynes or enolizable aldehydes to furnish 1-(2-bromophenyl)-1,2,3-triazoles **3**, is more challenging due to the steric hindrance of the *ortho*-bromo atom. In literature, only a few of these triazole containing precursors have been synthesized so far.[12] In order to generate a diverse library, two methods were employed. The first one is a metal-free enolate-mediated organocatalytic azide-aldehyde [3+2] cycloaddition.[12c] As demonstrated in Table 1, different R^1-substituents were introduced through cycloaddition of phenyl acetaldehyde with a variety of 2-bromophenyl azides **2** in the presence of potassium *tert*-butoxide in DMSO at room temperature. Both unsubstituted (**3a**) and substituted (**3b-3h**) 1- (2-bromophenyl)-1,2,3-triazoles were obtained in good to excellent yields, ranging from 71% to 97%. The second method – the copper-catalyzed azide-alkyne [3+2] cycloaddition (CuAAC) – could allow variation of the R^2-substituent (Table 2). However, upon reacting 2-bromo-4-methylphenyl azide **2b** with 4-ethynyltoluene using the original CuAAC conditions reported by Sharpless,[13] only 14% of the desired product **3i** was isolated, while vast amounts of starting material were still present. This observation could potentially be ascribed to the steric hindrance of the bromo substituent. In

Table 1. Organocatalytic azide-aldehyde [3+2] cycloaddition: azide substrate scope.[a]



[a] *Reaction conditions:* phenyl acetaldehyde (0.70 mmol), azide **2** (0.84 mmol), *t*-BuOK (10 mol%) in 2 mL of DMSO at room temperature for 2 hours. Isolated yields.

Table 2. Copper-catalyzed azide-alkyne [3+2] cycloaddition: alkyne substrate scope.[a]



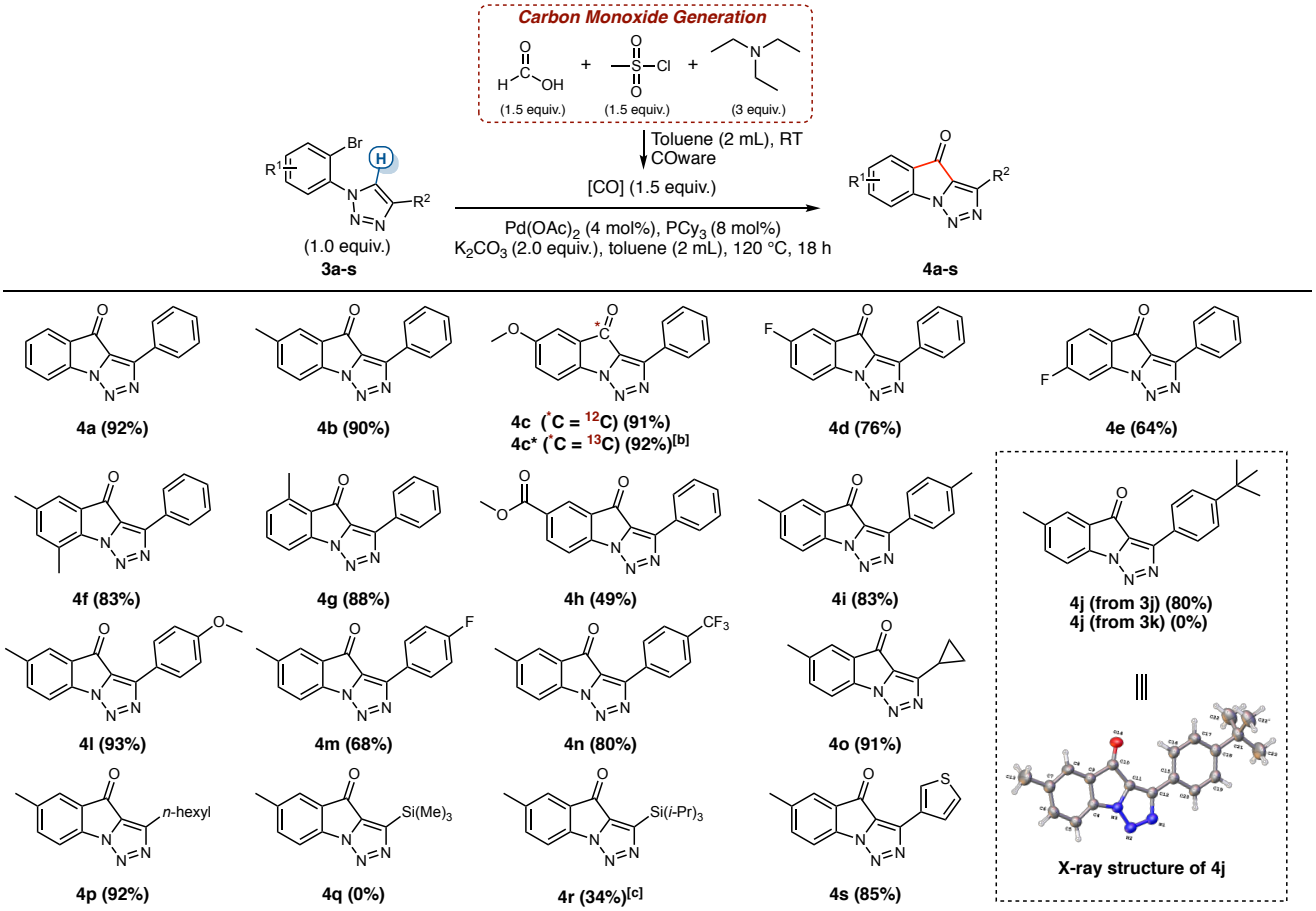
[a] *Reaction conditions:* 2-bromo-4-methylphenyl azide **2b** (0.70 mmol), alkyne (0.84 mmol), $Cu(II)SO_4.5H_2O$ (1 mol%) and sodium ascorbate (10 mol%) in 3 mL of *t*-BuOH/H_2O (1:1 v/v) at 100 °C for 18 hours. Isolated yields. [b] 4 equivalents of trimethylsilylacetylene were used.

order to get full conversion, a short optimization study was performed investigating the influence of the catalyst loading, the required amount of reducing agent and the reaction temperature. The details are summarized in the ESI. With the optimized conditions in hand (1 mol% $CuSO_4.5H_2O$ and 10 mol% sodium ascorbate in a *t*-BuOH/water mixture (1:1 v/v) for 18 hours at 100 °C), full conversion of the azide **2b** was achieved, yielding 80% of **3i**. Next, a variety of alkynes were employed to further investigate the scope of the cycloaddition. Aryl alkynes bearing a *t*-Bu (**3j** and **3k**), an OMe (**3l**), a F (**3m**) and a CF_3 (**3n**) group, were suitable for this transformation and gave excellent yields (87% - 91%). Also cyclopropylacetylene and 1-octyne afforded the desired products in satisfactory yields (77% for **3o** and 88% for **3p** respectively). Subsequently, two silylated acetylenes were tested. Cycloaddition of azide **2b** with 1.2 equivalents of trimethylsilylacetylene furnished **3q** in only 35% yield.[14] Gratifyingly, performing the same reaction with 4 equivalents of trimethylsilylacetylene afforded 72% of the desired product. In case of (triisopropylsilyl)acetylene, only 1.2 equivalents were required to obtain **3r** in an excellent yield of 86%. The scope was finalized with the heterocyclic 3-ethynylthiophene, which provided product **3s** in 84% yield.

Next, we speculated that the 1-(2-bromophenyl)-1,2,3-triazoles could serve as suitable substrates for the palladium-catalyzed intramolecular carbonylative ring closure, generating a new heterocyclic scaffold: the triazolo[1,5-*a*]indolone. Although carbon monoxide represents one of the most important C1 building blocks, safety issues constrain the direct utility of this highly toxic gas. Recently, we have published a study revealing a low-cost and robust carbon monoxide precursor based on formic acid, mesyl chloride and triethylamine.[15] This CO precursor can be used in a two-chamber reactor (COware),[16] in which the desired amount of CO is generated in one chamber and is consumed in the other (see ESI for details on the reaction setup and CO generation). This approach was previously applied in our group in the carbonylative assembly of helix mimetics.[17]

We started our investigation by screening different reaction conditions for the intramolecular carbonylative C-H functionalization of substrate **3j**. Full conversion was achieved in the presence of 4 mol% $Pd(OAc)_2$, 8 mol% PCy_3, 1.5 equiv. carbon monoxide and 2.0 equiv. potassium carbonate in toluene at 120 °C for 18 hours, yielding **4j** in 80% (Table 3). NMR and X-ray crystallography[18] confirmed the structure of this

Table 3. Intramolecular carbonylative C-H functionalization of 1-(2-bromophenyl)-1,2,3-triazoles generating triazolo[1,5-*a*]indolones.[a]



[a] *Reaction conditions:* 1-(2-bromophenyl)-1,2,3-triazole **3** (0.40 mmol), $Pd(OAc)_2$ (4 mol%), PCy_3 (8 mol%), K_2CO_3 (0.80 mmol) and CO (0.60 mmol) in 2 mL of dry degassed toluene for 18 h at 120 °C. See ESI for details on the reaction setup (COware)[16] and CO generation. Isolated yields. [b] ^{13}C-HCOOH was used to generate ^{13}CO. [c] Yield based on ^{1}H NMR.

compound. Under these conditions, we tried to convert the other synthesized triazoles **3a-s** into their corresponding triazolo[1,5-*a*]indolones. To our delight, unsubstituted and electron rich 1-(2-bromophenyl)-1,2,3-triazoles were excellent substrates as they provided the corresponding triazolo[1,5-*a*]indolones (**4a**, **4b**, **4c** and **4f**) in high yields, ranging from 83 to 92%. Even an *ortho*-substituted methyl with respect to the bromine yielded the desired compound **4g** in 88%. Electron deficient 1-(2-bromophenyl)-1,2,3-triazoles were more challenging as not only the desired triazolo[1,5-*a*]indolones were formed, but also considerable amounts of the corresponding benzoic acid derivative.[19] Nevertheless, **4d**, **4e** and **4h** were isolated in 76%, 64% and 49% yield respectively. The nature of the aryl substituent at the 4-position of the triazole could also be varied to furnish the corresponding triazolo[1,5-*a*]indolones in moderate to excellent yields (83%, 93%, 68% and 80% for **4i**, **4l**, **4m** and **4n** respectively). Triazoles with a cyclopropyl and a *n*-hexyl group turned out to be excellent substrates, yielding **4o** in 91% and **4p** in 92%. Subsequently, silylated triazoles were investigated. Unfortunately, the reaction of triazole **3q** did not provide compound **4q**, but a rather complex mixture. This could be ascribed to the instability of the trimethylsilyl group. Performing the same reaction with the more stable triisopropylsilyl group afforded an inseparable mixture of the starting material **3r** and the desired compound **4r**. Based on ^{1}H NMR, 34% of the **4r** was formed. Reaction of the thiophene substituted triazole **3s**, yielded substrate **4s** in 85%**.** The substrate scope was finalized with ^{13}C-carbonyl labeling of **4c**, using only near stoichiometric amounts of ^{13}CO.

We also wondered whether 1-(2-chlorophenyl)-1,2,3-triazoles were suitable substrates in this transformation. Unfortunately, upon reacting substrate **3k** under the same conditions, no conversion towards triazolo[1,5-*a*]indolone **4j** was observed and the starting material was fully recovered.

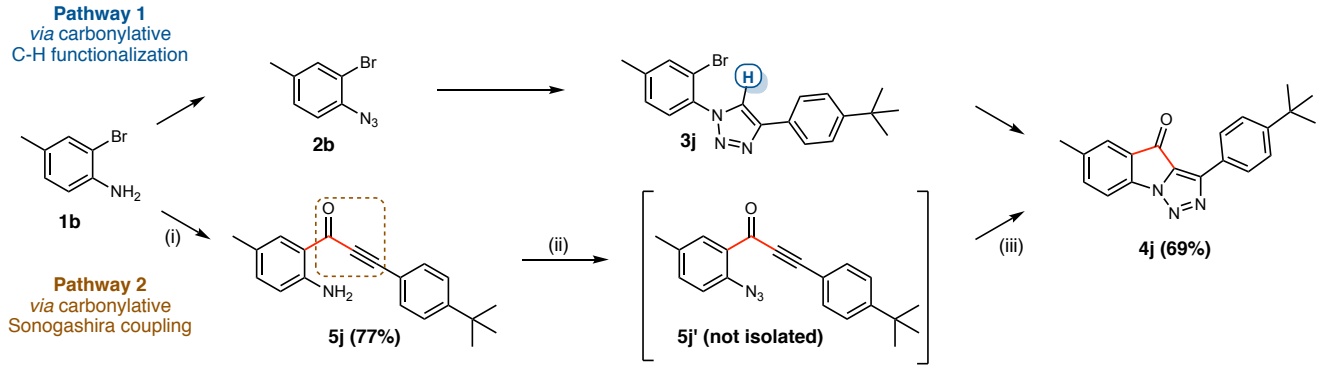
In order to enhance the accessibility of the new heterocyclic scaffold, we investigated an alternative pathway using the same reagents (Scheme 3). The viability of this approach was demonstrated with one example. First, intermediate **5j** was furnished in 77% *via* a palladium-catalyzed carbonylative Sonogashira coupling of 2-bromo-4-methyl aniline **2b** with *tert*-butylphenylacetylene.[20] Next, a two-step one pot procedure, in which the amine was converted into the azide followed by ruthenium-catalyzed cycloaddition, yielded the triazolo[1,5-*a*]indolone **4j** in 69%.[11,21]

In summary, we have presented a new and useful methodology to perform intramolecular ring closure of 1,2,3-triazoles *via* carbonylative C-H functionalization. This transformation gave direct access to an unprecedented triazolo[1,5-*a*]indolone. Next, ^{13}C-carbonyl labeling was performed to demonstrate the usefulness of late-stage installation of carbon isotopes. Moreover, only near-stoichiometric amounts of CO were required in the synthesis, attributing to the safety aspects of this method. The study was finalized by enhancing the accessibility towards this new scaffold *via* an alternative pathway, using the same starting materials. Further applications of this new carbonylation strategy on triazoles are currently in progress in our laboratory.

Experimental Section

General Procedure for the Intramolecular Carbonylative C-H Functionalization of Triazole (3) towards Triazolo[1,5-*a*]indolones (4).

Chamber A of a flame-dried two-chamber reactor (COware)[16] was filled with triazole **3** (0.4 mmol, 1.0 equiv.), palladium(II) acetate (3.6 mg, 0.016 mmol, 4 mol%), tricyclohexylphosphine (9.0 mg, 0.032 mmol, 8 mol%) and potassium carbonate (111 mg, 0.80 mmol, 2.0 equiv.). The reactor was brought under nitrogen atmosphere by two consecutive vacuum-nitrogen cycles. Next, chamber B was filled through a septum with 2 mL of



Scheme 3. An alternative pathway towards triazolo[1,5-*a*]indolones: (i) carbonylative Sonogashira coupling, (ii) functional group interconversion (iii) and Ru-catalyzed azide-alkyne [3+2] cycloaddition. [a]

[a] *Reaction conditions:* (i) 2-bromo-4-methylaniline (1.0 mmol), 4-*tert*-butylphenylacetylene (2.0 mmol), $PdCl_2$ (5 mol%), Xantphos (5 mol%), Et_3N (3.0 mmol) and CO (1.50 mmol) in 2 mL of dry degassed dioxane for 18 h at 100 °C (ii) compound **5j** (0.40 mmol), *t*-BuONO (0.60 mmol), $TMSN_3$ (0.48 mmol) in 5 mL of acetonitrile for 30 min. at room temperature (iii) intermediate **5j'** (0.40 mmol) and $Cp^*RuCl(PPh_3)_2$ (2 mol%) in 8 mL of dry degassed dioxane for 18 h at 60 °C.

dry degassed toluene, 23 µL formic acid (0.60 mmol, 1.5 equiv.) and 47 µL mesyl chloride (0.60 mmol, 1.5 equiv.). In chamber A, 2 of dry degassed toluene was added. Finally, 167 µL triethylamine (1.2 mmol, 3.0 equiv.) was added by injection through the septum in chamber B and instant gas formation was observed. After 2 minutes, the reactor was immersed in an oil-bath at 120 °C. After 18 hours, the reactor was brought to room temperature and the residual pressure was released carefully by removing one of the caps. As carbon monoxide is a highly toxic gas, the reaction was stirred at room temperature for another 15 minutes to ensure that all carbon monoxide gas was extracted out of the fume hood. Next, the content of chamber A was transferred to a 100 mL round-bottomed flask. Chamber A was rinsed five times with 2 mL of ethyl acetate and these fractions were added to the same flask. After the addition of 1 gram Celite®535, the solvent was removed under reduced pressure. The crude product was purified by solid-phase flash column chromatography on silica gel.

Note: In case triazole **3** was a viscous oil (compound **3o** and **3p**), it was first dissolved in 1 mL of dry degassed toluene and was added to chamber A right before the triethylamine was added to chamber B to generate the carbon monoxide.
Note: ^{13}C-carbonyl labeling was performed by using 23 µL of ^{13}C-HCOOH (95 wt% in H_2O).

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