A Metal-Catching Linker

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An Engineered Linker Capable of Promoting On-Resin Reactions for Microwave-Assisted Solid-Phase Organic Synthesis**

*Li-Ping Sun and Wei-Min Dai**

Solid-phase organic synthesis (SPOS)[1] has emerged as one of the key tools in combinatorial chemistry[2] for generating libraries of small organic molecules. In order to transfer the versatile reaction types established in solution to solid-phase synthesis, numerous classes of linkers[1–3] have been developed, including traceless and multifunctional linkers.[4] The latter enable the generation of diversity in the end products upon cleavage (R in Figure 1A). If a linker possesses elements of chirality, reactions occurring on the tethered scaffold are induced to form chiral molecules.

In a different approach from the resin-bound chiral auxiliaries,[5] the immobilization of chiral ligands and metal complexes has been advanced in recent years, to allow easy recovery of resin-bound chiral catalysts from the reaction solution (Figure 1B).[6] In such heterogeneous catalysis, the substrate is not loaded onto the resin and conventional purification is required for product separation. Despite the fact that many metal-catalyzed reactions have been carried out on resin-bound scaffolds,[1d] there is virtually no example of a solid-phase reaction promoted by a metal species that is covalently bound in close proximity to the scaffold. We report herein an engineered linker (cat·linker) with the dual functions of a normal linker for attachment of a scaffold and a promoter for facilitating the reaction occurring on the tethered scaffold (Figure 1C). It has been proven essential for performing Cu^{II}-mediated heteroannulation on a cat·linker-conjugated scaffold under microwave irradiation.[7]

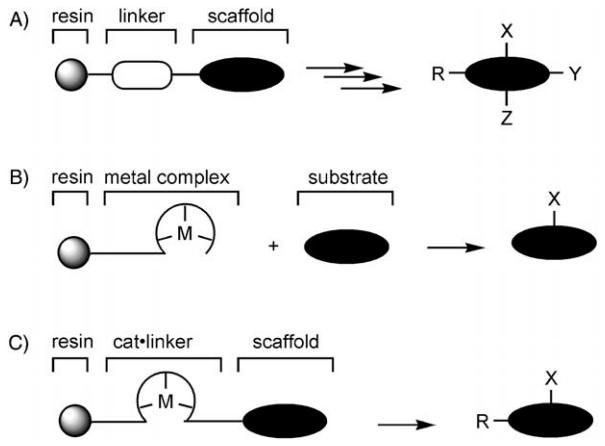
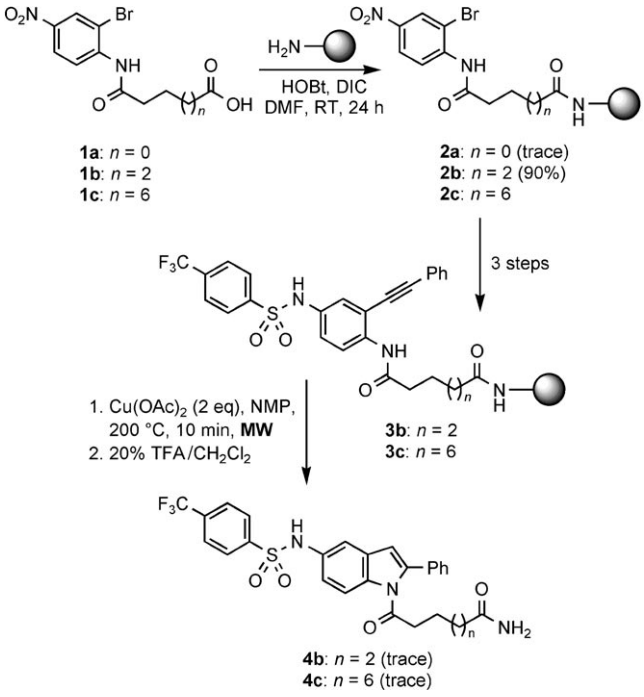


Figure 1. Schematic representations of A) solid-phase synthesis, B) solution synthesis by using supported metal complexes, and C) solid-phase synthesis with a novel linker capable of on-resin activation. M = metal ion, cat·linker = a linker capable of catching metal ions and promoting on-resin reactions.

In connection with our previous solid-phase synthesis of an indole library[8] through Pd^{II}-[9] or Cu^{II}-catalyzed[10] intramolecular heteroannulation under controlled microwave heating,[11] we designed the solid-phase synthesis of 2,5-disubstituted indoles **4** by anchoring 2-bromo-4-nitroaniline onto Rink amide resin through a diacid spacer (Scheme 1).



Scheme 1. Initial attempts to form 1-acyl indoles **4** by using diacid-modified linkers. DIC = *N*,*N*-diisopropylcarbodiimide, DMF = *N*,*N*-dimethylformamide, HOBt = *N*-hydroxybenzotriazole, **MW** = microwave, NMP = *N*-methylpyrrolidinone, TFA = trifluoroacetic acid.

This approach differed from our reported solid-phase synthesis employing resin-bound 1-alkynes.[8] We envisaged that the *N*-acyl chains in **4** could be easily removed during postcleavage modification upon exposure to a base,[12] which would result in an indirect traceless synthesis.[4]

We found that the diacid chain length influenced the solid-phase reactions at different stages. First, the succinic acid derived **1a** failed[13] to couple with the Rink amide resin while

[*] Dr. L.-P. Sun, Prof. W.-M. Dai
Department of Chemistry
The Hong Kong University of Science and Technology
Clear Water Bay, Kowloon, Hong Kong SAR (P.R. China)
Fax: (+852) 2358-1594
E-mail: chdai@ust.hk
Homepage: http://ihome.ust.hk/~chdai/index.html

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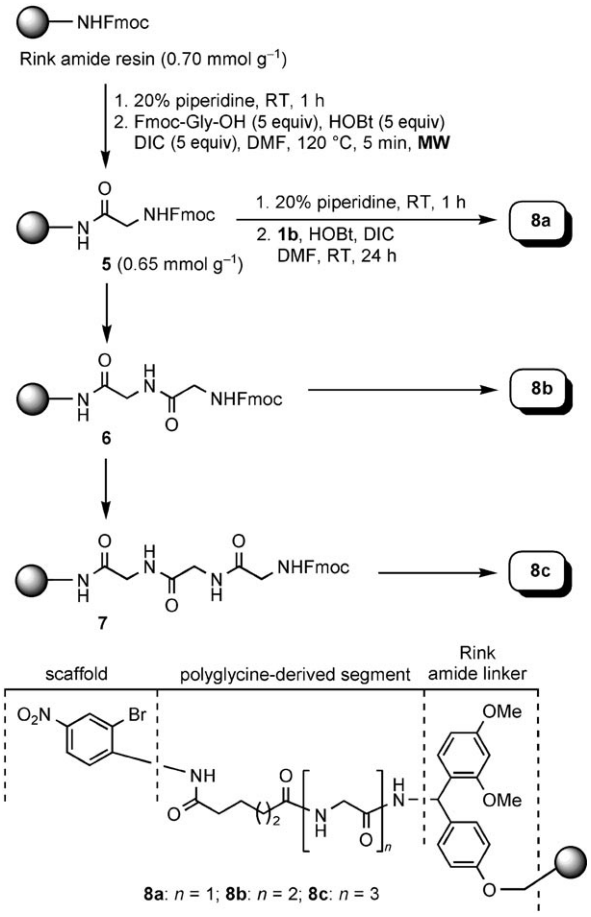
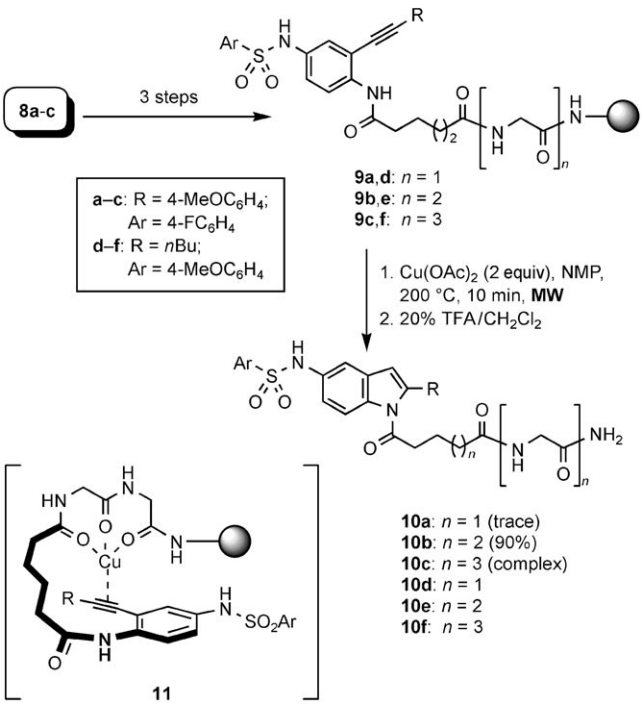
1b and **1c**, with their longer chains, could be successfully loaded onto the resin. For example, cleavage of **2b** supplied the resin-free product in 90% yield. From **2b** and **2c**, the resin-bound 2-alkynyl anilides **3b** and **3c** were prepared in good purities and yields by following our established procedures.[8] To our surprise, the Cu^{II}-mediated cyclization under controlled microwave heating at 200 °C[8] did not produce indoles **4b** and **4c**, as confirmed by cleavage of the materials from the resin. We reasoned that the failure in the cyclization might result from an inferior contact of Cu^{II} with the resin-bound alkynes.

In order to enhance the efficiency of solid-phase reactions by running them in a more "solution-like" environment, poly(ethylene glycol) (PEG) grafted polystyrene supports and other resins have been introduced.[1a] We took a different approach to improve the heterogeneous reaction profiles by building a metal-capture unit onto the linker in close proximity to the scaffold. Scheme 2 illustrates our design and the fabrication of the polyglycine-derived engineered linkers. We built the polyglycine chains on the Rink amide resin (0.70 mmol g^{-1}) through microwave-assisted polypeptide synthesis.[14] A 93% yield was estimated for **5** based on a loading of 0.65 mmol g^{-1}. By iterative peptide synthesis, the glycine-modified resins **6** and **7** were prepared. Removal of Fmoc in **5**–**7** followed by coupling with the acid **1b** furnished **8a**–**c** in excellent overall yields.



Scheme 2. Design and synthesis of three examples of the new system cat·linker (polyglycine-derived segment + Rink amide linker). Fmoc = (9-fluorenylmethyloxy)carbonyl.

With **8a**–**c** in hand, we synthesized the resin derivatives **9a**–**c** by a) Sonogashira cross-coupling, b) nitro reduction, and c) sulfonamide formation (Scheme 3).[8] Upon exposure



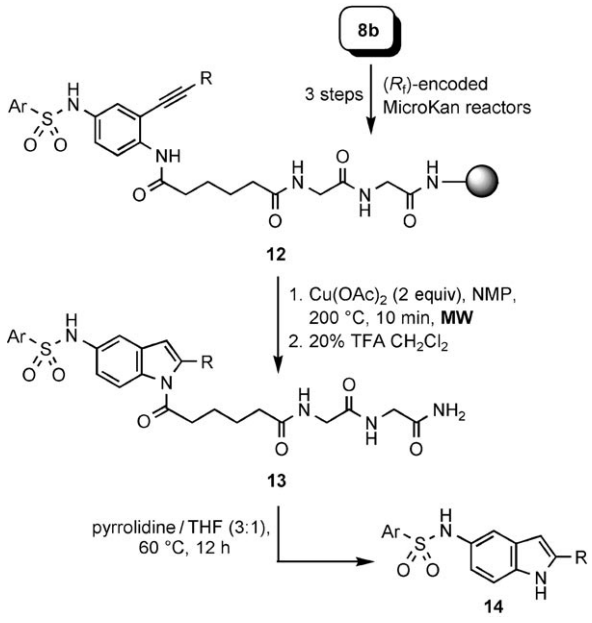
Scheme 3. Effect of glycine units on cat·linker performance.

of **9a**–**c** to $Cu(OAc)_2$ in NMP under controlled microwave heating at 200 °C for 10 min, the desired product **10b** was obtained in 90% yield after cleavage from the resin. By contrast, compound **10a** was hardly detected in the resin cleavage mixture and **10c** was a trace component of a complex mixture. The remarkable effect of the built-in glycine units on the heteroannulation might be explained by a metal-catching and activation mechanism. That is, the dipeptide moiety in **9a** was not efficient for fishing Cu^{II} from the solution onto the resin, while the coordination sites of Cu^{II} were mostly occupied by the tetrapeptide in the case of **9c**, thereby rendering activation of the alkyne difficult.[15] As depicted in the structure of **11**, the tripeptide unit of **9b** may form a Cu^{II} complex through the amide carbonyl oxygen donors[16] and the Cu ion also chelates with the neighboring alkyne to promote the heteroannulation. It should be emphasized that the formation of stable Cu^{II} complexes is not necessary for activating the alkyne moiety toward heteroannulation because excess Cu^{II} was used for the solid-phase reaction. Instead, any factor, such as diffusion, which improves transfer of Cu^{II} onto the resin is beneficial to the heterogeneous reaction.

In order to gain support for the above assumption, we carried out control experiments with the resin-bound alkynes **9d**–**f**, prepared from **8a**–**c**. First, **9d**–**f** were subjected to microwave heating in NMP at 200 °C for 10 min *in the absence of* $Cu(OAc)_2$. After cleavage, the resin-free alkynes were

essentially recovered, as confirmed by ^{1}H NMR spectroscopy (see S37–S39 in the Supporting Information). In a separate set of experiments, the resin-bound alkynes **9d–f** were sopped in an NMP solution of $Cu(OAc)_2$ at room temperature for 24 h, thereby allowing Cu^{II} to diffuse onto the resin. After washing and drying, the Cu^{II}-treated alkynes were subjected to the same microwave heating in NMP at 200 °C for 10 min *without additional Cu(OAc)$_2$*. Formation of indole **10e** was clearly demonstrated by ^{1}H NMR analysis of the crude reaction mixture. Indoles **10d** and **10f** were also formed but to a much lesser extent (see S35–S36 in the Supporting Information). On the basis of these findings, we can conclude that: a) a combination of microwave heating and Cu^{II} is essential for the heteroannulation,[8,10] b) once Cu^{II} is sopped up onto the resin, heteroannulation takes place upon heating, and c) the diglycine-derived cat·linker in **8b** is superior for promoting on-resin heteroannulation, although the exact mode of Cu intake may be subject to further discussion.

As an application of the cat·linker, we synthesized a 16-member library of indoles **14** from the scaffold **8b** by using 4 terminal alkynes and 4 arylsulfonyl chlorides. The results are summarized in Scheme 4 and Table 1. The solid-phase synthesis of **12** was carried out by using the IRORI radio frequency (R_f)-encoded MicroKan reactors.[8] Then, an individual library member **12** was transferred from the MicroKan reactor along with the R_f tag to a 10-mL pressurized process vial for the Cu^{II}-mediated heteroannulation, heated with a technical microwave reactor. Attempts to directly release indole **14** from the resin-bound product were not successful. Therefore, **13** was cleaved from the support at the site of the Rink amide linker and was converted into **14** by treatment with a mixed pyrrolidine/THF solution at 60 °C for 12 h. The peptide residue could be easily removed from the product by filtration through a short silica gel plug. The overall yields of indoles **14** are 38–60%, as calculated from the loading of **5** (0.65 mmol g^{-1}). To our delight, the purities of **14** are excellent (89–100%), as determined by LC–MS analysis (Table 1).[17]



Scheme 4. Synthesis of a library of indoles **14** (see Table 1).

Table 1: Synthesis of a 16-member indole library.

14: R; Ar	Yield [%][a]	Purity [%][b]
a: 4-MeC_6H_4; 4-FC_6H_4	49	93[c]
b: 4-MeC_6H_4; 4-MeOC_6H_4	38	98
c: 4-MeC_6H_4; 4-*i*PrC_6H_4	45	97
d: 4-MeC_6H_4; 2-thienyl	45	93
e: 4-MeOC_6H_4; 4-FC_6H_4	48	90[c]
f: 4-MeOC_6H_4; 4-MeOC_6H_4	60	96
g: 4-MeOC_6H_4; 4-*i*PrC_6H_4	53	97
h: 4-MeOC_6H_4; 2-thienyl	43	98
i: Ph; 4-FC_6H_4	51	95[c]
j: Ph; 4-MeOC_6H_4	44	89
k: Ph; 4-*i*PrC_6H_4	56	97
l: Ph; 2-thienyl	46	98
m: *n*Bu; 4-FC_6H_4	47	96[c]
n: *n*Bu; 4-MeOC_6H_4	51	100
o: *n*Bu; 4-*i*PrC_6H_4	43	99
p: *n*Bu; 2-thienyl	59	99

[a] Calculated based on the loading of **5** (0.65 mmol g^{-1}). [b] Determined by HPLC. The structures were characterized by ^{1}H NMR spectroscopy and MS. [c] The fluorine atom was replaced by pyrrolidine.

In summary, we have developed an engineered linker with dual functions for anchoring the scaffold onto a solid support and for promoting a metal-mediated reaction at an appropriate stage of the solid-phase synthesis. Incorporation of the Cu^{II}-capturing tripeptide segment into the so-called cat·linker proves essential for the microwave-assisted indole synthesis through heteroannulation. We consider that diffusion of Cu^{II} from the solution onto the support may be a main path, but distribution of Cu^{II} on the resin surface is influenced by the linker structure. Only Cu^{II} species located close to the attached scaffold and capable of complexation with the alkyne can promote the heteroannulation. In addition to easy on-resin fabrication, the cat·linker has no influence on the Pd^0–Cu^I-catalyzed Sonogashira cross-coupling reaction or the $SnCl_2{\cdot}H_2O$ reduction of NO_2. The cat·linker-modified polystyrene support retains the same resin profile and can be used, as in the current study, for IRORI MicroKan reactor-based R_f-encoded split-pool combinatorial synthesis.

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[17] The LC–MS charts can be found in the Supporting Information.

