Peptide Macrocyclization via Cu-catalyzed 1,3-Dipolar Cycloaddition of Azomethine Ylides

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ABSTRACT: Cyclic peptides are highly valued synthetic targets in organic and medicinal chemistry. The development of new synthetic methodologies for peptide macrocyclization, different from classical lactamization, is essential for the progress of the field. Herein, we report an efficient diastereoselective macrocyclization strategy for the synthesis of cyclic peptides using 1,3-dipolar cycloaddition of azomethine ylides. Linear precursors of different length and bearing diverse amino acids have shown to be compatible with this method (26 examples), giving good yields and almost complete diastereoselectivity. The DFT calculations suggest a stepwise mechanism in which Cu plays a key role in reagents preorganization.

Cyclic peptides are intriguing molecules widely present in nature with applications ranging from drug development to nanomaterials or food additives.[1] Compared to their linear counterparts, cyclic peptides provide a more versatile platform for exploring chemical space enabled by the possibility of adjusting the conformation using the appropriate technique for their chemical synthesis. Therefore, expanding the toolkit for peptide cyclization is highly demanding for discovering new macrocycles endowed with unique properties.[2,3]

Nonetheless, cyclization of linear peptides remains a challenge since the activated peptide must adopt an entropically disfavoured pre-cyclization conformation before the desired intramolecular reaction can occur. Traditional methods for peptide cyclization rely on the intramolecular formation of ester, amide or disulphide bonds.[4] Alternatively, more recently, new approaches based on the use of Mannich,[5] Ugi,[6] Horner-Wadsworth-Emmons,[7] transition metal catalyzed processes,[8] and photocatalyzed transformations[9] have been developed.

Toward the generation of new engineered cyclic peptides, the introduction of non-peptide units in the cyclic structure has been used as a strategy for enhancing conformational rigidity and metabolic stability.[1d] For instance, several research groups have demonstrated that the incorporation of heterocyclic moieties into cyclic peptides has a positive influence on reaching the required binding conformation for biological interactions.[10] However, this type of cyclic peptides can be challenging to prepare using classical approaches. Therefore, methodologies that simultaneously cyclize and introduce one or more non-canonical backbone structures are highly appealing.

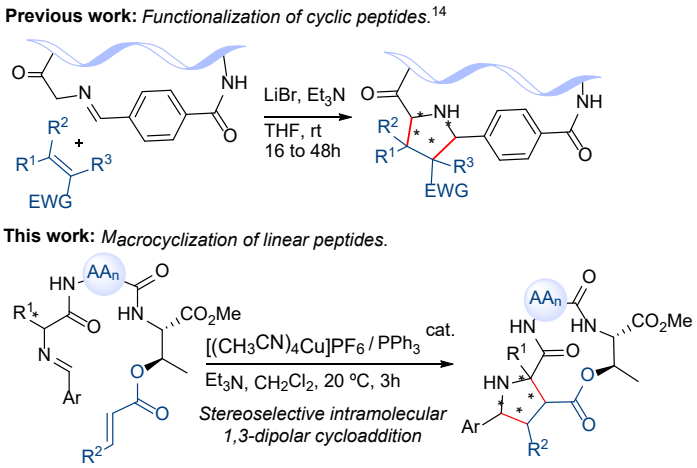
In this context, 1,3-dipolar cycloaddition, one of the most attractive synthetic routes to five membered heterocycles, displays a unique potential for the preparation of cyclic peptides containing heterocyclic scaffolds. However, as far as we are aware, only azide-alkyne 1,3-dipolar cycloaddition has been broadly used as a tool for peptide cyclization.[11]

Azomethine ylides have received particular attention as 1,3-dipoles because of the significance of the pyrrolidine ring which constitute the central structure of the proline amino acid and it is present in a plethora of natural products and catalysts.[12] Specifically, the metal catalyzed intramolecular 1,3-dipolar cycloaddition of azomethine ylide has emerged as a valuable tool for the preparation of pyrrolidine containing polycyclic natural products.[13]

In 2020 Guéret and Waldmann[14] developed an efficient methodology for the preparation of natural product-inspired cyclic peptide- hybrids on solid support by macrocyclization of the peptide chain via imine formation. The subsequent 1,3-dipolar cycloaddition in the presence of lithium bromide and Et_3N efficiently delivered the corresponding adducts (Scheme 1).

On these grounds, building on the previous experience of our research group in 1,3-dipolar cycloadditions,[15] we set out the development of a new methodology for accessing to modified cyclic peptides based on a metal-catalyzed azomethine ylide intramolecular 1,3-dipolar cycloaddition process.

Scheme 1. Late-stage functionalization of peptides via a 1,3-dipolar cycloaddition process

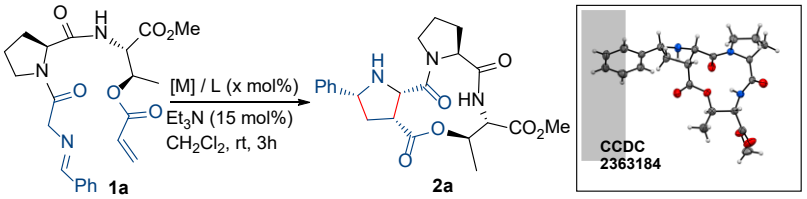


To attain this goal, we were aware that two challenges needed to be addressed: (a) The effective coordination of the metal to the imino amide precursor of the azomethine ylide in the presence of numerous basic centres existing in the linear counterpart. (b) Achieved precise asymmetric control dictated by the stereogenic centres present in the peptide chain.

To reach our goal, we chose as model substrate the linear tripeptide **1a** decorated with an activated double bond at the side chain of the *C*-terminus and an azomethine ylide precursor at *N*-terminus.[16] Initially, we tested several of the most common conditions for 1,3-dipolar cycloadditions of azomethine ylide precursors (Table 1).[17] In these initial experiments, we were delighted to find that in the presence AgOAc as catalyst, 1,1′-bis(diphenylphosphino)ferrocene (dppf) as ligand and Et_3N as base in CH_2Cl_2 (0,06 M), the 11-membered-cyclopeptide **2a** was obtained in 51% isolated yield (entry 1). Remarkably, the reaction proceeded with excellent regio and stereocontrol since only the peptide **2a** with 2,3,5-*cis* configuration in the resulting pyrrolidine unit was obtained. In addition, the unreacted linear peptide was recovered unaltered and no oligomerisation

product was detected in the analysis of the reaction crude. Although result was slightly improved in the presence the monodentate ligand PPh_3 (61%, entry 2), the most significant increase in reactivity was observed using $[(CH_3CN)_4Cu]PF_6$ as the metal source (90%, entry 3). Similar results were obtained using KO^{t}Bu as base (entry 4), but other bases or solvents gave poorer results.[18] Control experiments showed that ligand, base, and copper source were necessary to obtain high conversions (entries 5-7).

Table 1. Optimization studies



Entry	Metal	L	T (ºC)	Yield (%)[a]
1	AgOAc	dppf	rt	51
2	AgOAc	PPh_3	rt	61
3	$[(CH_3CN)_4Cu]PF_6$	PPh_3	rt	90
4[b]	$[(CH_3CN)_4Cu]PF_6$	PPh_3	rt	88
5	$[(CH_3CN)_4Cu]PF_6$	--	rt	33
6[c]	$[(CH_3CN)_4Cu]PF_6$	PPh_3	rt	30
7	--	PPh_3	rt	0
8	--	PPh_3	80	0
9[d]	$[(CH_3CN)_4Cu]PF_6$	PPh_3	rt	85

[a] Isolated yield after chromatographic purification. [b] KO^{t}Bu as base. [c] No base. [d] 5 mol% of catalyst. dppf = 1,1'-bis(diphenylphosphino)ferrocene.

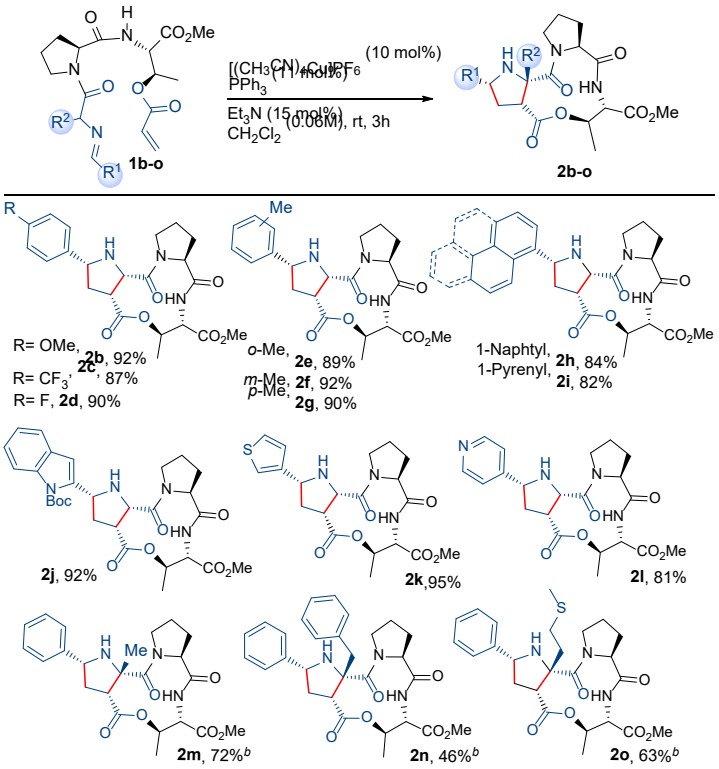
No reactivity was observed even when the reaction was carried out at higher temperature (80 ºC) in the absence of the copper catalyst (entry 7). A slight drop in the yield was observed when the catalyst loading was reduced to 5 mol% (85%, entry 8). The configuration of cyclopeptide **2a** was unequivocally stablished by X-ray crystallographic analysis.[19]

With the optimized reaction conditions in hands, we next explored the generality of this intramolecular cycloaddition process regarding the substitution at the azomethine ylide precursor. A wide range of imino amides derived from aromatic aldehydes were examined (Scheme 2). The cycloaddition afforded selectively the corresponding cyclopeptides **2b-d** with good yields (87-92%) using imino amides either with electron-donating or electron-withdrawing substituents at the aromatic ring. Aromatic azomethine ylide precursors **1e-g** with *ortho*-, *meta*- or *para*- substituents provided similar results (cycloadducts **2e-g**). Substrates incorporating polycyclic aromatic hydrocarbons such as naphtyl **1h** and pyrenyl **1i** were found to by compatible in the cycloaddition process.

Notably, the fluorescence exhibit by the resulting polyaromatic-cyclopeptides highlight their potential utility as structural probes.[20]

The cycloaddition was equally effective with heteroaromatic-substituted imino amides such as indenyl **1j**, thienyl **1k**, and pyridyl **1l** (cycloadducts **2j-l**). Remarkably, cyclopeptides decorated with pyrrolidines containing a quaternary stereocenter in position 2 can also be prepared using this methodology. Thus, cycloadducts bearing proline derivatives with either methyl (**2m**), benzyl (**2n**) or (methylthio)ethyl (**2o**) substituents at *C*-2 were isolated with high yield and diastereoselectivity.

Scheme 2. Scope regarding azomethine ylide precursor[a]

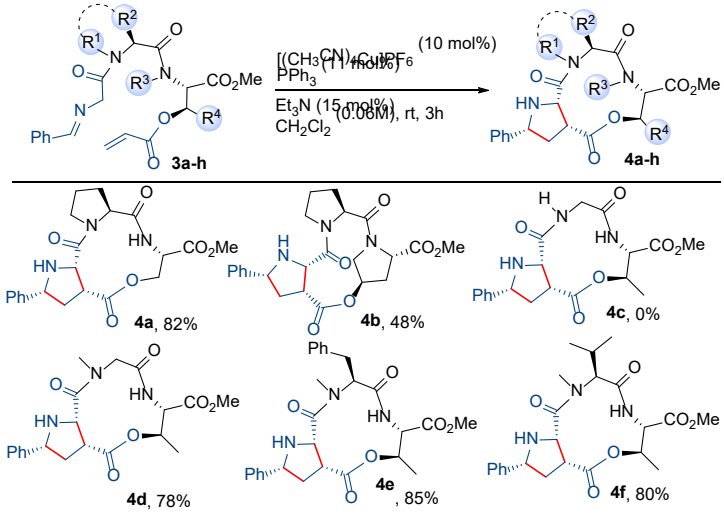


[a] Isolated yield after chromatographic purification. [b] KO^{t}Bu instead of Et_3N.

Next, we turned our attention to establish the scope of the methodology regarding the peptide chain. As shown in Scheme 3, the switch of threonine for serine results in excellent reaction efficacy and diastereoselectivity (cyclopeptide **4a**, 82%). Likewise, its switch for 4-hydroxyproline smoothly led to the cyclic peptide **4b** containing three proline units, although with lower yield (48%).

The presence of turn-induce elements such as proline in the peptide chain is usually critical for preorganized peptides for the cyclization. In fact, the reaction of linear peptide **3d** with a glycine instead of proline did not afford the macrocyclization product (**4c**). However, we were pleased to find that when the sarcosine was used instead of glycine the reaction took place with excellent yield (**4d**, 78%). The use of substrates containing Phe and Val residues resulted in efficient macrocyclization [**4e** (85%) and **4f** (80%)].

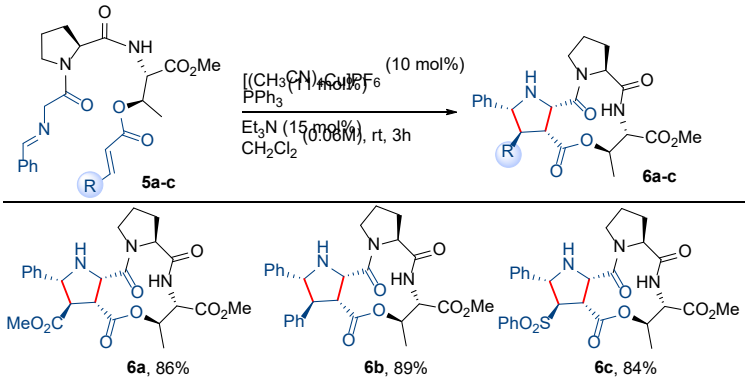
Scheme 3. Scope regarding the peptide chain[a]



[a] Isolated yield after chromatographic purification.

Next, we studied the compatibility of the procedure regarding other dipolarophiles (Scheme 4). The use of a linear peptide precursor with a *trans* diactivated olefin derived from fumarate (**5a**) provided the corresponding macrocycle **6a** in 86% yield. The reaction also showed compatibility with a phenyl group in the β-position of the α,β-unsaturated ester (**6b**, 89% yield). Additionally, the sulfonyl precursor **5c** proved to be an excellent substrate, affording the corresponding adduct with almost complete diastereoselectivity and an excellent yield (**6c**, 84%).

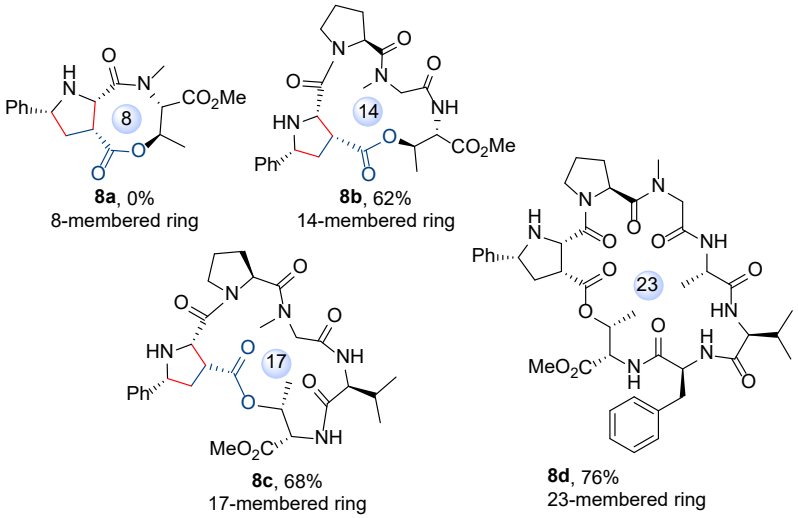
Scheme 4. Scope with respect to the dipolarophile[a]



Finally, we explored the range of different ring size that could be assembled using this methodology (Scheme 5). We found that this methodology is not suitable for the cyclization of shorter peptide chains (8 atoms) (Scheme 5, **8a**) which aligns with the inherent stability of the amide *trans*-conformation. However, in addition to the 11-membered cycles shown in Schemes 2-4, peptides sequences containing 14, 17 and 23

atoms (**7b-d**, respectively) effectively underwent the cycloaddition reaction using the optimized reaction conditions [**8b** (62%), **8c** (68%), and **8d** (76%)].

Scheme 5. Scope regarding peptide macrocycle ring size[a]



[a] Isolated yield after chromatographic purification.

To elucidate the mechanistic details of the cyclization step, DFT calculations were performed by employing the linear tripeptide **1a** and the ligand PPh_3 to model the possible reaction intermediates by coordination to a Cu^I atom from the catalyst (Figure 1). Most likely, the bidentate coordination (through N and O1) of **1a** to the Cu(I) would favor the *in situ* generation of the azomethine ylide leading to complex **I**. In this complex, due to the simultaneous coordination of PPh_3, that generates both steric and π-stacking interactions with the tripeptide, the linear structure adopts an optimal conformation allowing the coordination of the carbonyl group (through O2) at the sidechain of the *C*-terminus to the Cu^I center, fixing the *endo* approach (distances around Cu atom remain almost constant throughout the process, see SI for details). This preorganization would arrange the dipolarophile moiety at an angle and a distance appropriate for the 1,3-dipolar reaction to proceed efficiently. Thus, the formation of the C1–C2 bond between the benzylic position of the ylide part and the alkene unit *via* **TS-I-II** (12.8 kcal·mol^{-1}) would lead to the formation of the zwitterionic intermediate **II** (6.9 kcal·mol^{-1}), followed by subsequent cyclization [the second C3–C4 bond formed *via* **TS II-III** (7.9 kcal·mol^{-1})] to afford the cycloaddition product **III** (-5.6 kcal·mol^{-1}). Therefore, according to these computational studies, the cyclization should proceed through a stepwise mechanism. The low activation barriers and the structure of complexes account for the relatively fast reaction and complete *endo*-diastereoselectivity experimentally observed.

In summary, we present an efficient and selective methodology for cyclizing peptides via intramolecular Cu-catalyzed (3+2) cycloaddition of azomethine ylides. This approach allows the incorporation of proline moieties with up to four new chiral centers into the macrocycle, achieving excellent yields and complete diastereocontrol. The cycloaddition is compatible with a range of natural amino acids, various macrocyclic sizes, and different dipolarophiles.

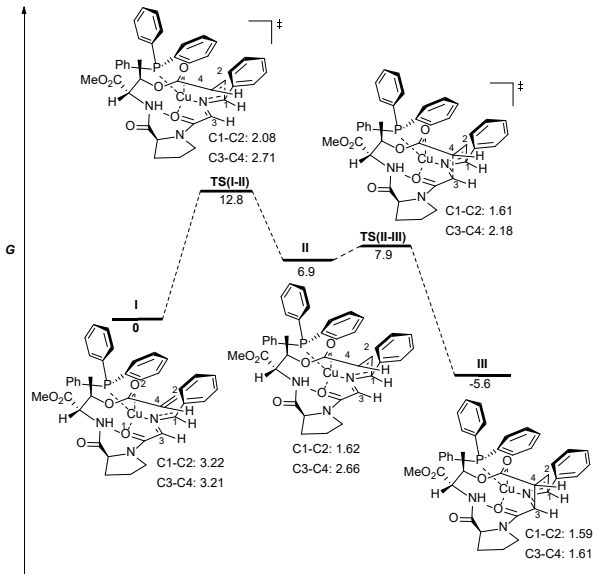


Figure 1. Free energy profile for the Cu-catalyzed 1,3-dipolar cycloaddition of 1a. (M06/6-311++G(d,p) (C,H,N,O,P), LANL2TZ(f) (Cu)/SMD(CH_2Cl_2)///B3LYP-D3/6-31G(d) (C,H,N,O,P), LANL2DZ(f) (Cu)). Relative G values at 298 K (kcal·mol^{-1}) and representative distances (Å) are indicated.

ASSOCIATED CONTENT

The Supporting Information is available free of charge at https://pubs.acs.org.

Supplementary figures and tables; detailed materials and methods; full experimental procedures and analytical data for all the listed reactants and products; and computational data (PDF).

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The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript.

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Notes

The authors declare no competing financial interest.

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