COMMUNICATIONS doi.org/10.1002/adsc.202100432 Advanced Synthesis & Catalysis

Copper(I)-Catalyzed Intramolecular Cyclization of *o*-Propargyloxy Diketopiperazines to Access Diverse Diazabicyclic and Spiro-Diketopiperazinochromanes

Bita Manavi,[a] Hossein Zahedian Tejeneki,[a] Frank Rominger,[b] Mahsa Armaghan,[c] Walter Frank,[c] Hamid Reza Bijanzadeh,[d] and Saeed Balalaie[a, e,*]

[a] Peptide Chemistry Research Institute, K. N. Toosi University of Technology, P. O. Box 15875-4416, Tehran, Iran,
Tel: +98-21-23064226
Fax: +98-21-22889403
E-mail: balalaie@kntu.ac.ir
[b] Organisch-Chemisches Institut der Universität Heidelberg, Im Neuenheimer Feld 270, D-69120 Heidelberg
[c] Institut für Anorganische Chemie und Strukturchemie, Heinrich-Heine-Universität Düsseldorf, Universitätsstraße 1, 40225 Düsseldorf, Germany
[d] Department of Environmental Sciences, Faculty of Natural Resources and Marine Sciences, Tarbiat Modares University, Tehran, Iran
[e] Medical Biology Research Center, Kermanshah University of Medical Sciences, Kermanshah, Iran

Manuscript received: April 6, 2021; Revised manuscript received: June 26, 2021;
Version of record online: ■■, ■■

Supporting information for this article is available on the WWW under https://doi.org/10.1002/adsc.202100432

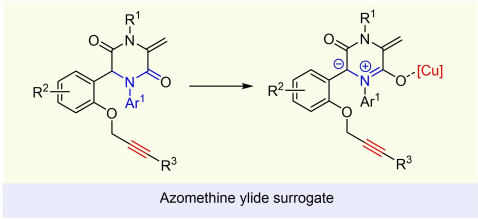
Abstract: In this report, two distinctive intramolecular cyclizations of *o*-propargyloxy diketopiperazines (achieved from a one-pot Ugi post-transformation) is achieved *via* a copper(I)-catalyzed intramolecular reaction of azomethine ylide and alkyne moiety. The presence of internal alkyne in the starting materials directed the reaction towards through [3+2]-cycloaddition, while terminal alkyne led to a spirocyclization reaction between azomethine ylide and terminal unsaturated C–C bond. This method offering an opportunity for the synthesis of challenging Diazabicyclics and Spiro-Diketopiperazinochromanes in high yields with exclusive diastereoselectivity.

Keywords: Copper; Cyclization; Cycloaddition; Heterocycles; Homogeneous catalyst; Multicomponent reactions

Over the past decades, there has been significant progress in the Lewis acid-catalyzed cycloaddition reaction and it has become the method of choice for the rapid synthesis of complex structural building blocks using simple raw materials with high atom economy in a single step.[1] One of the most important factors in these formations is the selection of a proper metal catalyst. Nowadays, earth-abundant metals are preferred in many cases based on their unique advantages including that they are readily available, cost-effective, and the fact that they have low toxicity.[2] In this context, metal-catalyzed cycloaddition reactions of unsaturated C–C bonds with dipolar species in general, and azomethine ylides in particular, have been developed into striking and integral transformations for the synthesis of complex *N*-heterocycles, especially when they are performed in an intramolecular setting.[3]

Considering the significance of azomethine ylides, there are a variety of methods for *in situ* preparation of these intermediates. However, the formation of these dipolar species is mostly limited to the carboxylative condensation of aldehydes with amino acids or amino esters. Moreover, most of the cycloaddition reactions of azomethine ylides and dienophiles involve substrates encompassing electron-withdrawing groups (EWGs) to the unsaturated C–C bond.[3] In this project, we successfully present a new generation of azomethine ylide surrogates (Scheme 1). These intermediates were subsequently incorporated in an intramolecular

[3+2]-cycloaddition reaction with an inactive triple C–C bond. Recently, Ugi post-transformation reactions have proved to be a powerful synthetic method for the synthesis of a wide range of carbocycles, heterocycles, and bridge rings that are not easily accessible by traditional synthetic routes through careful selection starting materials.[4] Inspired by prior reports, we envisaged that an intramolecular [3+2]-cycloaddition



Scheme 1. Generation of azomethine ylide from 2,5- diketopiperazine.

reaction can be a viable Ugi post-transformation strategy to provide a capable method to access diazabicyclic skeletons.[5,6]

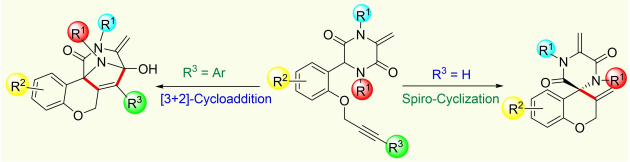
Bridged heterocycles have always been of paramount importance in the field of medicinal chemistry since they have been used as key structures in routes to access a variety of pharmaceutical agents.[7] Drug targets containing bridged heterocycles and their unbridged counterparts often have similar physiochemical properties, while the rigid bridged structures can cause additional potency and target selectivity.[8] Diazabicyclics are a well-known class of bridged heterocycles that have the subject of interest among bioactive compounds including antibiotics, antitumor agents, antibacterial agents, and some other critical biologically active compounds.[9] As a result, there is an increasing demand for the development of more convenient and operationally simple processes for the synthesis of compounds containing fused diazabicyclic scaffolds (Scheme 2).

Herein, we introduce an efficient strategy for *in situ* formations of azomethine ylide from C(sp^3)–H of α-amide in 2,5- diketopiperazines. The mentioned diketopiperazines are synthesized *via* Ugi post-transformation reaction.

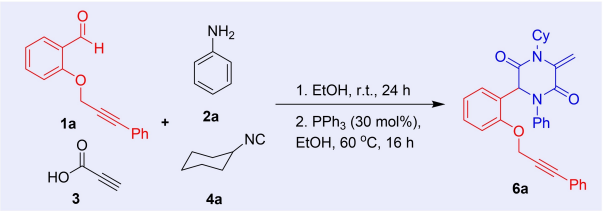
Afterwards, the [3+2]-cycloaddition reaction of these azomethine ylide intermediates with an internal alkyne residue results in the diastereoselective synthesis of 3,8-diazabicyclo[3.2.1] oct-6-en-2-ones. Additionally, we demonstrate that the presence of terminal alkyne moiety on the *o*-propargyloxy diketopiperazines would direct the reaction toward a regioselective spirocyclization to afford a series of spiro-diketopiperazinochromanes. Both reactions happen in a single step with 100% atom utilization.

Initially, the screening studies were focus on synthesis of the *o*-propargyloxy diketopiperazine **6 a**. We focused on the preparation of bifunctional precursor **1 a** using the synthetic procedure for the formation of *o*-propargyloxybenzaldehyde mentioned in supporting information.[10] As outlined in Scheme 3, subjecting *o*-propargyloxy benzaldehyde **1 a**, aniline **2 a**, propiolic acid **3**, and cyclohexyl isocyanide **4 a** to stirring in ethanol for 24 h at room temperature produced the desired Ugi product with 87% yield after workup. Next, with this Ugi adduct in hand, we conducted the reaction for the generation of *o*-propargyloxy diketopiperazine **6 a** in the presence of PPh_3 as the catalyst in ethanol as solvent at 60 °C for 16 h, and the product was obtained in 55% isolated yield.[5b,e] Afterwards, we attempted a one-pot procedure for the synthesis of diketopiperazine without the isolation of the Ugi product. We carried out the reaction without evaporating and changing the solvent of the Ugi reaction. The one-pot procedure worked perfectly and improved the overall yield to 89%.

Furthermore, we used the *o*-propargyloxy diketopiperazine **6 a** as a model substrate in different conditions for further transformations. We began by probing the possible reactions by using different catalysts and bases. We achieved neither products in the absence of base nor catalyst, thus we realized that the presence of both of them is crucial for the development of further transformations. Treating **6 a** with a variety of Lewis acid catalysts and bases revealed that applying CuBr and a base partner such as **KO*t*Bu** (2 eq.) in acetonitrile results in diazabicyclic compound **7 a** (Table 1, entry 1). Screening the reaction in different temperatures, revealed that the optimum temperature for this step was 60 °C within 30 min (Table 1, entries 2–7). In the next stage, the reaction was subjected to several solvents for further optimization. It was observed that only toluene rendered the product in a yield higher than that of acetonitrile (Table 1, entry 8). Moreover, while using other catalysts such as $InCl_3$, $AgNO_3$, AgOTf, Cu_2O, $Cu(OAc)_2$, $Pd(OAc)_2$, $PdCl_2(PPh_3)_2$, and $PdCl_2$ did not form the desired product **7 a**, $In(OTf)_3$ and CuI successfully produced

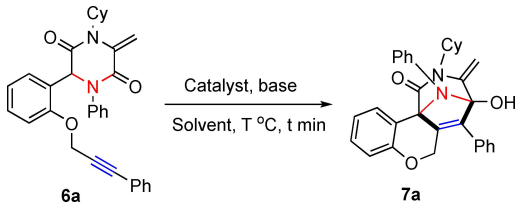


Scheme 2. Selective synthesis of azabicyclic and spiro compounds.



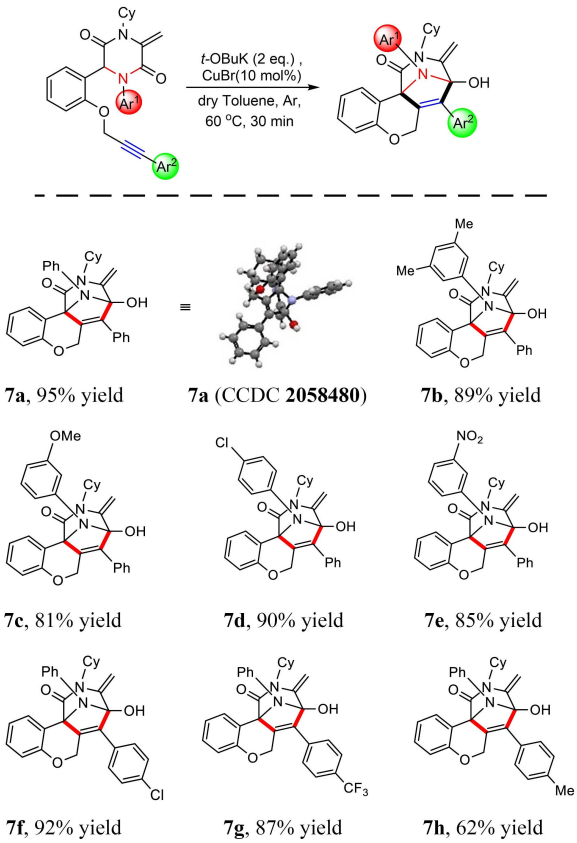
Scheme 3. One-pot synthesis of *o*-propargyloxy diketopiperazine.

Table 1. Optimization of the reaction conditions.



Entry[a]	Cat. (mol%)	Solvent	T (°C)	Base	Yield
1	CuBr (20)	MeCN	80	KO*t*Bu	29
2[b]	CuBr (20)	MeCN	r.t.	KO*t*Bu	55
3	CuBr (20)	MeCN	70	KO*t*Bu	39
4	CuBr (20)	MeCN	60	KO*t*Bu	59
5	CuBr (20)	MeCN	50	KO*t*Bu	48
6[c]	CuBr (20)	MeCN	60	KO*t*Bu	53
7[d]	CuBr (20)	MeCN	60	KO*t*Bu	47
8	CuBr (20)	Toluene	60	KO*t*Bu	89
9	$In(OTf)_3$ (10)	Toluene	60	KO*t*Bu	47
10	CuI (20)	Toluene	60	KO*t*Bu	38
11	**CuBr (10)**	**Toluene**	**60**	**KO*t*Bu**	**95**
12	CuBr (5)	Toluene	60	KO*t*Bu	48
13	CuBr (20)	Toluene	60	NaH	24

[a] The model reaction set up with 0.2 mmol of **6a** in the presence of 2 eq. base.
[b] The reaction carried out for 24 h.
[c] The reaction carried out for 20 min.
[d] The reaction carried out for 40 min.



Scheme 4. Substrates scope for synthesis of 3,8-diazabicyclo [3.2.1] oct-6-en-2-ones **7a**–**h**.

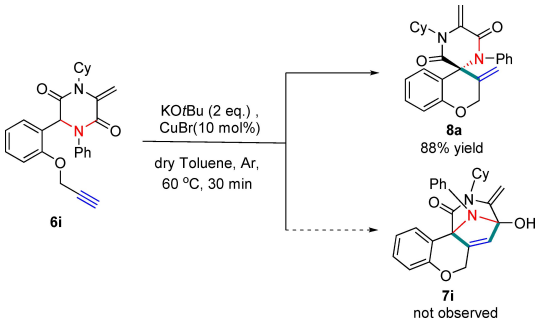
the expected product **7a**; however, these catalysts failed to further enhance the yield of the reaction in comparison to CuBr (Table 1, entries 9 and 10). Consequently, CuBr was chosen as the best catalyst for the model reaction. Carrying out the reaction using 10 mol% of CuBr at 60 °C in toluene as solvent, improved the reaction yield to 95% (Table 1, entry 11) but in the presence of 5 mol% of CuBr, the reaction yield was decreased to 48% (Table 1, entry 13). Screening different organic and inorganic bases such as Et_3N, DBU, NaOAc, and Cs_2CO_3 failed to provide any results, and the only other base partner that proved to be successful was indeed NaH; however, NaH also failed to improve the yield of the reaction in comparison to **KO*t*Bu** (Table 1, entry 13). Finally, based on these pieces of information, the best result (95% yield) was achieved in the presence of CuBr (10 mol%) as the catalyst, **KO*t*Bu** (2 eq.) as the base, and toluene as the solvent at 60 °C in a period of 30 min.

With the optimal conditions in hand, we then explored this *in situ* copper-catalyzed [3 + 2]-cycloaddition and representative results shown below (Scheme 4). All of the products were obtained in good to excellent yields in a completely diastereoselective manner. This reaction showed generality and functional group tolerance. The protocol was found to be efficient to both electron-withdrawing and electron-donating substituents in both aromatic rings Ar^1 and Ar^2. All products were characterized by ^1H NMR, ^{13}C NMR, and HRMS spectral analysis. In addition, X-ray diffraction analysis of the product **7a** has confirmed the structure of these compounds.

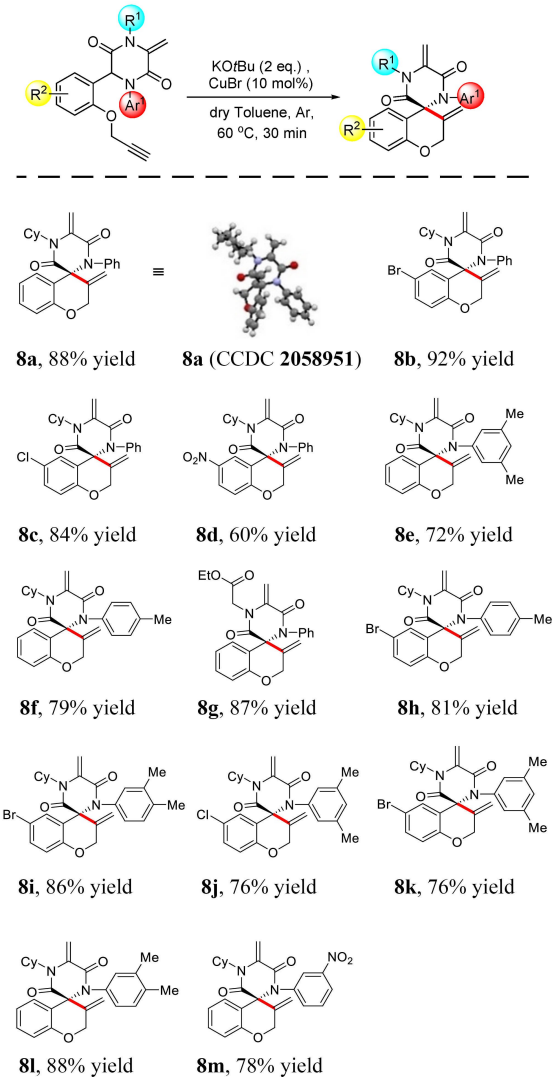
To our surprise, removing the Ar^2 aromatic ring in compound **6i** caused the emerging of a serendipitous reaction in the standard reaction condition. We realized that using a terminal alkyne containing compound **6i**, failed to produce the expected structure **7i**, and structure **8a** was detected as the sole product in 88% isolated yield with exclusive chemoselectivity. The spiro-diketopiperazinochromanes **8a** was identified based on ^1H NMR, ^{13}C NMR, HRMS spectral analysis, and

X-ray diffraction analysis. In this case, the reaction proceeds through selective 6-*exo*-*dig* spirocyclization (Scheme 5), and spiro-diketopiperazinochromane **8a** was synthesized without any specific side product.

Resting on these observations, the substrate scope of the copper-catalyzed cyclization of terminal alkyne containing *ortho*-propargyloxy diketopiperazines for the synthesis of new spiro-diketopiperazinochromanes was explored and representative results are shown in Scheme 6. All of the products were obtained in good



Scheme 5. Cu(I)-Catalyzed serendipitous spirocyclization.



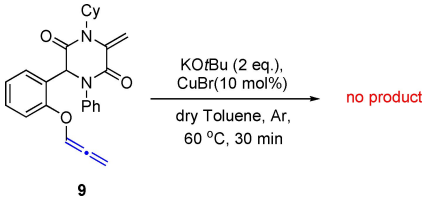
Scheme 6. Substrates scope for the synthesis of spiro-diketopiperazinochromanes.

to excellent yields with exclusive regioselective spirocyclization. This reaction was successful in tolerating various functional groups. Electron-withdrawing substitutions on the aryl group of aldehydes were all compatible under the standard condition. Moreover, both electron-donating and electron-withdrawing substitutions on the aryl group of amines worked quite well. By using aliphatic amine in the synthesis of starting materials, the reaction became a complex mixture of products. Notably, in addition to the cyclohexyl group in R^1 position, CH_2CO_2Et also worked very well. But in the presence of the *t*-butyl group in the R^1 position, the rection does not lead to the desired product.

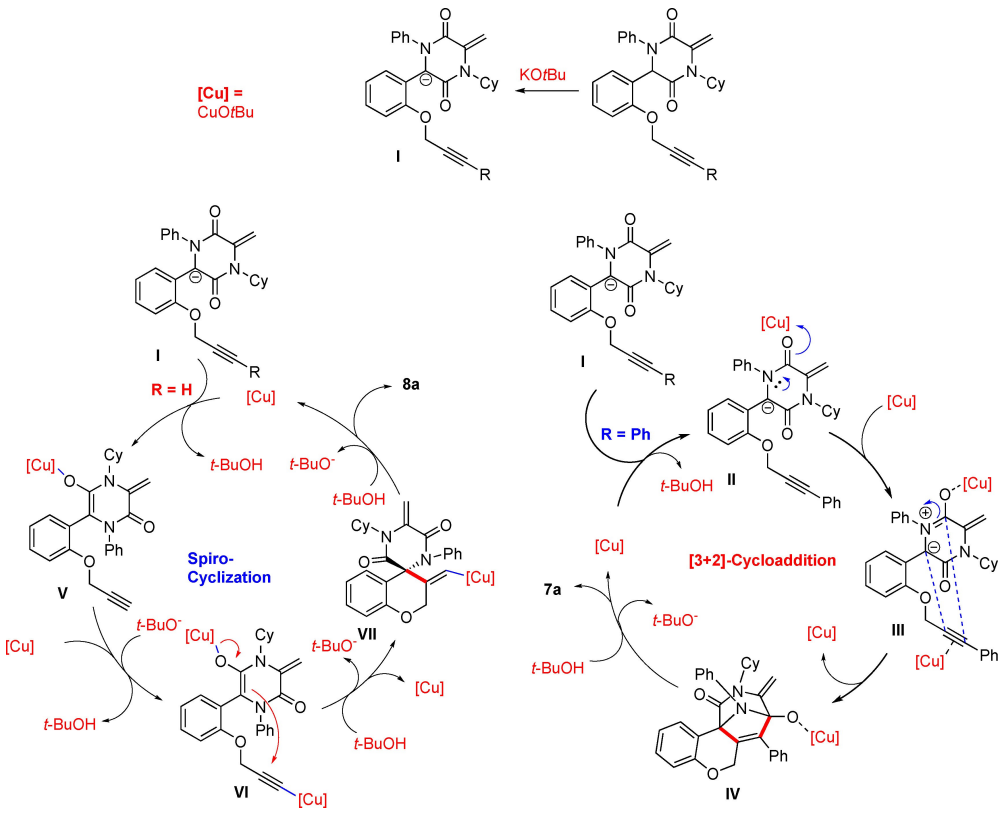
To gain a deeper insight into the mechanism of this spiro-cyclization for the synthesis of **8a** product, *ortho*-allenoxy benzaldehyde was synthesized[11] and subjected to Ugi reaction. The corresponding Ugi adduct was then incorporated in cyclization reaction in the presence of PPh_3 to provide compound **9**. Finally, this structure was subjected to the standard reaction condition, but no product was detected (Scheme 7). This experiment revealed that the reaction does not proceed through the allenoxy intermediate **9**.

Based on the mentioned results and previous works, a plausible pathway for these reactions is shown in Scheme 8. In the presence of **KO*t*Bu**, CuBr converted to KBr (not soluble in toluene) and *t*-BuOCu which acted as the catalysis of the reaction.[12] Initially, after deprotonation of the acidic proton by KO*t*Bu, the carbanion intermediate **I** is generated. Afterwards, two separate pathways can be possible depending on the R group. On one hand, if R=Ar, the reaction proceeds through the formation of azomethine ylide. The generated azomethine ylide **III** can undergo [3+2]-cycloaddition with the π bond of alkyne (through the **II** intermediate) to generate intermediate **IV**. Finally, after protodemetalation of this intermediate, the desired diazabicyclic product is performed. On the other hand, the spiro compound is synthesized through a spiro-cyclization. If R=H, the enol type intermediate **V** is formed. Then, the triple bond is activated, and followed by the nucleophilic addition of carbon chiral center to alkyne bond, that would result in the intermediate **VII**. Finally, after hydrogen abstraction of this intermediate, the spiro-diketopiperazinochromane compound is achieved as the product (Scheme 8).

To demonstrate the synthetic potential of our products, compounds **8a** and **8e** were treated with phenylboronic acid for oxidative Heck reaction of



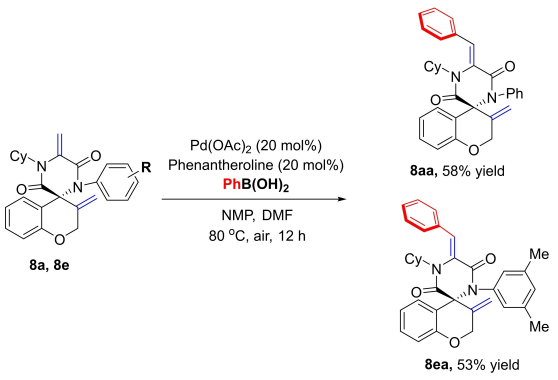
Scheme 7. Control experiment of the spiro cyclization by using *o*-allenoxy diketopiperazine **9**.



Scheme 8. Proposed reaction mechanism for the synthesis of **7a** and **8a**.

geminal hydrogens of two *exo*-double bonds (Scheme 9).[5b] Among four geminal hydrogens in this compound, only one of them participated in the oxidative Heck reaction, and just 1 eq. phenyl group was coupled in a completely chemo- and stereoselective manner.

In conclusion, we have reported an efficient route to achieve functionalized diazabicyclic compounds, *via* copper-catalyzed intramolecular [3+2]-cycloaddition reaction of *o*-propargyloxy diketopiperazines in high yields with exclusive diastereoselectivity. The starting materials for this cycloaddition reaction were synthesized in two steps by PPh_3-mediated Ugi post-transformation reaction. Furthermore, using different starting materials with the terminal triple bonds, we were able to synthesis functionalized spiro-diketopiperazino-chromanes in the standard reaction condition. This spiro-cyclization reaction occurs completely regioselective.



Scheme 9. Selective oxidative Heck reaction of geminal hydrogen of compound **8a** and **8e**.

Experimental Section

General procedure for the synthesis of final products

A 10 ml Schlenk tube was flame-dried under vacuum, backfilled with argon and cooled to room temperature using a standard Schlenk line apparatus. The Schlenk tube was charged with CuBr (2.8 mg, 10 mol%), *t*-BuOK (45 mg, 0.4 mmol, 2 eq.). The Schlenk tube was put under vacuum and backfilled with argon. Afterwards dry toluene (2 mL) was added by syringe under a flow of argon. *O*-propargyloxy diketopiperazine (0.2 mmol, 1 eq.) was added. The Schlenk tube was sealed by a screw cap and the resulting mixture was stirred for 30 min at 60 °C. The crude reaction mixture was evaporated under reduced pressure. The residue was purified via column chromatography on silica gel (eluent: EtOAc/ *n*-Hexane = 1/7) to afford the corresponding product after drying under vacuum.

CCDC-2058480 and CCDC-2058951 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgements

We thank the Alexander von Humboldt Foundation for the Linkage Research Group Program.

References

[1] Selected reviews on cycloaddition reactions: a) W. C. Herndon, *Chem. Rev.* **1972**, *72*, 157–179; b) A. Padwa, *1,3-Dipolar Cycloaddition Chemistry, Vol. 1;* Wiley: New York, N. Y., 1984; c) A. Padwa, *Ed. 1,3-Dipolar Cycloaddition Chemistry, Vol. 2*; Wiley: New York, N. Y., **1984**; d) H. W. Frühauf, *Chem. Rev.* **1997**, *97*, 523–596; e) A. Padwa, W. H. Pearson, *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products*; Wiley: Chichester, U. K., **2002**; Vol. 59; f) G. W. Goodall, W. Hayes, *Chem. Soc. Rev.* **2006**, *35*, 280–312; g) L. M. Stanley, M. P. Sibi, *Chem. Rev.* **2008**, *108*, 2887–2902; h) F. Amblard, J. H. Cho, R. F. Schinazi, *Chem. Rev.* **2009**, *109*, 4207–4220; i) K. E. O. Ylijoki, J. M. Stryker, *Chem. Rev.* **2013**, *113*, 2244–2266; j) L. Min, Y. J. Hu, J. H. Fan, W. Zhang, C. C. S. Li, *Chem. Soc. Rev.* **2020**, *49*, 7015–7043.

[2] Selected reviews on earth-ebundant metal catalyzed reactions: a) A. Fürstner, C. C. Stimson, *Angew. Chem. Int. Ed.* **2007**, *46*, 8845–8849; *Angew. Chem.* **2007**, *119*, 9001–9005; b) S. Kobayashi, Y. Yamashita, *Acc. Chem. Res.* **2011**, *44*, 58–71; c) M. Albrecht, R. Bedford, B. Plietker, *Organometallics* **2014**, *33*, 5619–5621; d) P. Chirik, R. Morris, *Acc. Chem. Res.* **2015**, *48*, 2495; e) S. L. Shi, S. L. Buchwald, *Nat. Chem.* **2015**, *7*, 38–44; f) L. L. Schafer, P. Mountford, W. E. Piers, *Dalton Trans.* **2015**, *44*, 12027–12028; g) D. Wang, D. Astruc, *Chem. Soc. Rev.* **2017**, *46*, 816–854; h) O. S. Wenger, *J. Am. Chem. Soc.* **2018**, *140*, 13522–13533; i) F. Romiti, J. Del Pozo, P. H. S. Paioti, S. A. Gonsales, X. Li, F. W. W. Hartrampf, A. H. Hoveyda, *J. Am. Chem. Soc.* **2019**, *141*, 17952–17961; j) J. Loup, U. Dhawa, F. Pesciaioli, J. Wencel-Delord, L. Ackermann, *Angew. Chem. Int. Ed.* **2019**, *58*, 12803–12818; *Angew. Chem.* **2019**, *131*, 12934–12949; k) A. H. Hoveyda, Y. Zhou, Y. Shi, M. K. Brown, H. Wu, S. Torker, *Angew. Chem. Int. Ed.* **2020**, *59*, 21304–21359; *Angew. Chem.* **2020**, *132*, 21488–21543.

[3] Selected reviews and examples on azomethine ylides: a) C. Najera, J. M. Sansano, *Curr. Org. Chem.* **2003**, *7*, 1105–1150; b) I. Coldham, R. Hufton, *Chem. Rev.* **2005**, *105*, 2765–2810; c) G. Pandey, P. Banerjee, S. R. Gadre, *Chem. Rev.* **2006**, *106*, 4484–4517; d) S. Su, J. A. Porco, *J. Am. Chem. Soc.* **2007**, *129*, 7744–7745; e) T. Hashimoto, K. Maruoka, *Chem. Rev.* **2015**, *115*, 5366–5412; f) K. A. P. Payne, M. D. White, K. Fisher, B. Khara, S. S. Bailey, D. Parker, N. J. W. Rattray, D. K. Trivedi, R. Goodacre, R. Beveridge, P. Barran, S. E. J. Rigby, N. S. Scrutton, S. Hay, D. Leys, *Nature* **2015**, *522*, 497–501; g) A. Pascual-Escudero, A. de Cózar, F. P. Cossío, J. Adrio, J. C. Carretero, *Angew. Chem. Int. Ed.* **2016**, *55*, 15334–15338; *Angew. Chem.* **2016**, *128*, 15560–15564; h) S. Chen, V. Bacauanu, T. Knecht, B. Q. Mercado, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2016**, *138*, 12664–12670; i) S. Tang, X. Zhang, J. Sun, D. Niu, J. J. Chruma, *Chem. Rev.* **2018**, *118*, 10393–10457; j) X. Fang, C. J. Wang, *Org. Biomol. Chem.* **2018**, *16*, 2591–2601; k) L. Wei, Q. Zhu, L. Xiao, H. Y. Tao, C. J. Wang, *Nat. Commun.* **2019**, *10*, 1–12.

[4] Selected reviews related to Ugi post-transformation: a) A. Dömling, I. Ugi, *Angew. Chem. Int. Ed.* **2000**, *39*, 3168–3210; *Angew. Chem.* **2000**, *112*, 3300–3344; b) J. Zhu, B. Hugues, *eds. Multicomponent reactions*; Wiley-VCH, Weinheim, 2005; c) E. Ruijter, R. Scheffelaar, R. V. A. Orru, *Angew. Chem. Int. Ed.* **2011**, *50*, 6234–6246; *Angew. Chem.* **2011**, *123*, 6358–6371; d) A. Dömling, W. Wang, K. Wang, *Chem. Rev.* **2012**, *112*, 3083–3135; e) R. C. Cioc, E. Ruijter, R. V. A. Orru, *Green Chem.* **2014**, *16*, 2958–2975; f) U. K. Sharma, N. Sharma, D. D. Vachhani, E. V. Van Der Eycken, *Chem. Soc. Rev.* **2015**, *44*, 1836–1860; g) J. Bariwal, R. Kaur, L. G. Voskressensky, E. V. Van der Eycken, *Front. Chem.* **2018**, *6*, 1–21; h) R. O. Rocha, M. O. Rodrigues, B. A. D. Neto, *ACS Omega* **2020**, *5*, 972–979; i) M. A. Fouad, H. Abdel-hamid, M. S. Ayoup, *RSC Adv.* **2020**, *10*, 42644–42681.

[5] a) S. Balalaie, M. Shamakli, A. Nikbakht, N. S. Alavijeh, F. Rominger, S. Rostamizadeh, H. R. Bijanzadeh, *Org. Biomol. Chem.* **2017**, *15*, 5737–5742; b) S. Balalaie, R. Ramezani Kejani, E. Ghabraie, F. Darvish, F. Rominger, F. Hamdan, H. R. Bijanzadeh, *J. Org. Chem.* **2017**, *82*, 12141–12152; c) S. Balalaie, S. Mirzaie, A. Nikbakht, F. Hamdan, F. Rominger, R. Navari, H. R. Bijanzadeh, *Org. Lett.* **2017**, *19*, 6124–6127; d) H. Janatian Ghazvini, T. J. J. Müller, F. Rominger, S. Balalaie, *J. Org. Chem.* **2019**, *84*, 10740–10748; e) H. Zahedian Tejeneki, A. Nikbakht, S. Balalaie, F. Rominger, *J. Org. Chem.* **2020**, *85*, 8544–8552.

[6] Selected Ugi post-transformations: a) S. Santra, P. R. Andreana, *Angew. Chem. Int. Ed.* **2011**, *50*, 9418–9422; *Angew. Chem.* **2011**, *123*, 9590–9594; b) S. G. Modha, A. Kumar, D. D. Vachhani, J. Jacobs, S. K. Sharma, V. S. Parmar, L. Van Meervelt, E. V. Van Der Eycken, *Angew. Chem. Int. Ed.* **2012**, *51*, 9572–9575; *Angew. Chem.* **2012**, *124*, 9710–9713; c) Z. Xu, F. De Moliner, A. P. Cappelli, C. Hulme, *Angew. Chem. Int. Ed.* **2012**, *51*, 8037–8040; *Angew. Chem.* **2012**, *124*, 8161–8164; d) A. Kumar, D. D. Vachhani, S. G. Modha, S. K. Sharma, V. S. Parmar, E. V. Van Der Eycken, *Beilstein J. Org. Chem.* **2013**, *9*, 2097–2102; e) N. Sharma, Z. Li, U. K. Sharma, E. V. Van Der Eycken, *Org. Lett.* **2014**, *16*, 3884–3887; f) Z. Li, N. Sharma, U. K. Sharma, J. Jacobs, L. Van Meervelt, E. V. Van Der Eycken, *Chem. Commun.*

2016, *52*, 5516–5519; g) Y. He, Z. Li, G. Tian, L. Song, L. Van Meervelt, E. V. Van Der Eycken, *Chem. Commun.* **2017**, *53*, 6413–6416; h) Z. Li, L. Song, L. Van Meervelt, G. Tian, E. V. Van Der Eycken, *ACS Catal.* **2018**, *8*, 6388–6393; i) V. Srinivasulu, S. M. N. Sieburth, R. El-Awady, N. M. Kariem, H. Tarazi, M. J. O'Connor, T. H. Al-Tel, *Org. Lett.* **2018**, *20*, 836–839; j) Y. He, D. Wu, Z. Li, K. Robeyns, L. Van Meervelt, E. V. Van Der Eycken, *Org. Biomol. Chem.* **2019**, *17*, 6284–6292; k) Y. He, Z. Liu, D. Wu, Z. Li, K. Robeyns, L. Van Meervelt, E. V. Van Der Eycken, *Org. Lett.* **2019**, *21*, 4469–4474; l) P. Pertejo, I. Carreira-Barral, P. Peña-Calleja, R. Quesada, M. García-Valverde, *J. Org. Chem.* **2020**, *85*, 2291–2302.

[7] a) A. Zask, J. Kaplan, J. C. Verheijean, D. J. Richard, K. Curran, N. Brooijmans, E. M. Bennett, L. Toral-Barza, I. Hollander, S. Ayral-Kaloustian, K. Yu, *J. Med. Chem.* **2009**, *52*, 7942–7945; b) K. J. Curran, J. C. Verheijean, J. Kaplan, D. J. Richard, L. Toral-Barza, I. Hollander, J. Lucas, S. Ayral-Kaloustian, K. Yu, A. Zask, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1440–1444; c) H. Li, R. Xu, D. Cole, J. W. Clader, W. J. Greenlee, A. A. Nomeir, L. Song, L. Zhang, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6606–6609.

[8] a) A. Kilonda, E. Dequeker, F. Compernolle, P. Delbeke, S. Toppet, B. Bila, G. J. Hoornaert, *Tetrahedron* **1995**, *51*, 849–858; b) C. E. Neipp, S. F. Martin, *J. Org. Chem.* **2003**, *68*, 8867–8878; c) A. Zask, J. C. Verheijen, D. J. Richard, J. Kaplan, K. Curran, L. Toral-Barza, J. Lucas, I. Hollander, K. Yu, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2644–2647; d) Z. Chen, A. M. Venkatesan, O. Dos Santos, E. Delos Santos, C. M. Dehnhardt, S. Ayral-Kaloustian, J. Ashcroft, L. A. McDonald, T. M. Mansour, *J. Org. Chem.* **2010**, *75*, 1643–1651; e) D. G. Wishka, P. Beagley, J. Lyon, K. A. Farley, D. P. Walker, *Synthesis* **2011**, 2619–2624.

[9] a) E. P. Fuerst, G. L. Lamoureux, W. H. Ahrens, *Pestic. Biochem. Physiol.* **1991**, *39*, 138–148; b) D. E. Moreland, F. T. Corbin, J. E. Mcfarland, *Pestic. Biochem. Physiol.* **1993**, *45*, 43–53; c) S. Villa, D. Barlocco, G. Cignarella, G. J. Papp, B. Baláti, J. Takács, A. Varró, A. Borosy, K. Keserû, P. Mátyus, *Eur. J. Med. Chem.* **2001**, *36*, 495–506; d) G. H. C. Woo, S. H. Kim, P. Wipf, *Tetrahedron* **2006**, *62*, 10507–10517; e) R. Filosa, A. Peduto, P. de Caprariis, C. Saturnino, M. Festa, A. Petrella, A. Pau, G. A. Pinna, P. La Colla, B. Busonera, R. S. Loddo, *Eur. J. Med. Chem.* **2007**, *42*, 293–306; f) R. Holl, D. Schepmann, P. J. Bednarski, R. Grünert, B. Wünsch, *Bioorg. Med. Chem.* **2009**, *17*, 1445–1455; g) X. Xu, Y. Li, Y. Zhang, L. Zhang, L. Pan, Q. Liu, *Adv. Synth. Catal.* **2011**, *353*, 1218–1222; h) L. Huck, J. F. González, E. De La Cuesta, J. C. Menéndez, C. Avendaño, *Org. Biomol. Chem.* **2011**, *9*, 6271–6277.

[10] a) J. Panteleev, R. Y. Huang, E. K. J. Lui, M. Lautens, *Org. Lett.* **2011**, *13*, 5314–5317; b) X. F. Xia, X. R. Song, X. Y. Liu, Y. M. Liang, *Chem. Asian J.* **2012**, *7*, 1538–1541; c) P. Martín-Acosta, G. Feresin, A. Tapia, A. Estévez-Braun, *J. Org. Chem.* **2016**, *81*, 9738–9756; d) M. Karuppasamy, B. S. Vachan, P. Vinoth, I. Muthukrishnan, S. Nagarajan, L. Ielo, V. Pace, S. Banik, C. U. Maheswari, V. Sridharan, *Org. Lett.* **2019**, *21*, 5784–5788; e) C. A. Dimirjian, M. Castiñeira Reis, E. I. Balmond, N. C. Turman, E. P. Rodriguez, M. J. Di Maso, J. C. Fettinger, D. J. Tantillo, J. T. Shaw, *Org. Lett.* **2019**, *21*, 7209–7212.

[11] B. Alcaide, P. Almendros, I. Fernández, T. M. Del Campo, T. Naranjo, *Chem. Eur. J.* **2015**, *21*, 1533–1541.

[12] a) T. Tsuda, T. Hashimoto, T. Saegusa, *J. Am. Chem. Soc.* **1972**, *94*, 658–659; b) C. Shu, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2004**, *116*, 4898–4901; c) R. Motoki, M. Kanai, M. Shibasaki, *Org. Lett.* **2007**, *9*, 2997–3000; d) Y. Huang, M. J. Ajitha, K. W. Huang, Z. Zhang, Z. Weng, *Dalton Trans.* **2016**,*45*, 8468–8474.

COMMUNICATIONS

Copper(I)-Catalyzed Intramolecular Cyclization of *o*-Propargyloxy Diketopiperazines to Access Diverse Diazabicyclic and Spiro-Diketopiperazinochromanes

Adv. Synth. Catal. **2021**, *363*, 1 – 8

B. Manavi, H. Z. Tejeneki, F. Rominger, M. Armaghan, W. Frank, H. R. Bijanzadeh, S. Balalaie*