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Copper-catalyzed [3 + 1] cyclization of cyclopropenes/diazo compounds and bromodifluoroacetamides: facile synthesis of α,α-difluoro-β-lactam derivatives†

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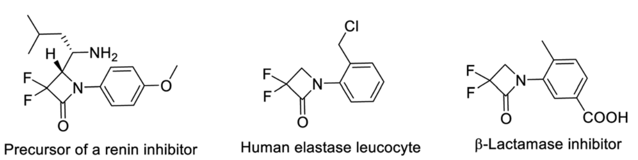
We have developed a novel copper-catalyzed cyclization of cyclopropenes/diazo compounds and bromodifluoroacetamides, efficiently synthesizing a series of α,α-difluoro-β-lactams in moderate to excellent yields under mild reaction conditions. This reaction represents the first example of [3 + 1] cyclization for the synthesis of β-lactams utilizing a metal carbene intermediate as the C1 synthon.

Introduction

Metal carbenes nowadays have been recognized as important active intermediates for many organic reactions, such as cyclopropanations, X–H (X = C, Si, O, S, N, *etc.*) insertions, 1,2-migrations, Buchner reactions, [2,3]-sigmatropic rearrangements, ylide formations and others.[1] In these reactions, a metal carbene can be used as a C1 synthon to form diverse carbon- and hetero-ring compounds.[2] However, it is very rare to utilize a metal carbene intermediate as a C1 synthon to construct four-membered cyclic compounds *via* a [3 + 1] cyclization process. In 2009, Barluenga and co-workers reported the first example of [3 + 1] cyclization by using a copper carbene intermediate derived from simple diazo compounds, vinyldiazo esters as the C1 synthon to synthesize cyclobutene derivatives.[3] Recently, Schomaker *et al.* successfully developed a [3 + 1] cyclization of rhodium carbene with bicyclic methylene aziridines to produce highly substituted methylene azetidines with excellent stereo- and regio-selectivity.[3b,c] To the best of our knowledge, using *in situ* generated metal carbene as the C1 synthon to form β-lactams *via* the [3 + 1] cyclization reaction has never been reported.

β-Lactams have been recognized as one of the most acclaimed classes of aza-ring compounds since the structure elucidation of penicillin in 1945.[4] Diverse β-lactam derivatives have shown important antibacterial, antimicrobial, anticancer, antiviral, antihyperglycemic and other biological activities.[5] The incorporation of the difluoromethylene (CF_2) group into organic compounds can usually substantially alter the physical and biological properties of the compounds, resulting in useful biological and pharmacological effects.[6] In fact, α,α-difluoro-β-lactams have been disclosed to be effective in the inhibition of human leukocyte elastase (Scheme 1).[7] Several methods have been established to synthesize these compounds.[7–10] Among them, intramolecular ring closure of 3-functionalized-2,2-difluoroamides[8] (Scheme 2A) and [2 + 2] cyclization of halodifluoroacetates with imines[9] (Scheme 2B) were common methods. While the former often needs multistep synthesized substrates and excess sodium hydride or phosphine,[8] the latter requires excess zinc powder or organozinc reagent[9] and sometimes provides a mixture of the α,α-difluoro-β-amino ester and α,α-difluoro-β-lactam.[9b] Recently, our group realized copper-catalyzed [3 + 2] cyclization of α-bromodifluoroacetamides with alkenes/alkynes to synthesize α,α-difluoro-γ-lactam derivatives, where α-bromodifluoroacetamides might be recognized as a three-atom synthon and acted as both the difluoromethylene group (CF_2) and amido group source.[11] We envision that a [3 + 1] cyclization of α-bromodifluoroacetamides might be realized by choosing an appropriate C1 synthon. Herein, we report the first example of copper-catalyzed [3 + 1] cyclization of α-bromodifluoroacetamides with cyclopropenes for facile access to a series of α,α-difluoro-β-lactams (Scheme 2c).



Scheme 1 Some representative examples of α,α-difluoro-β-lactams.

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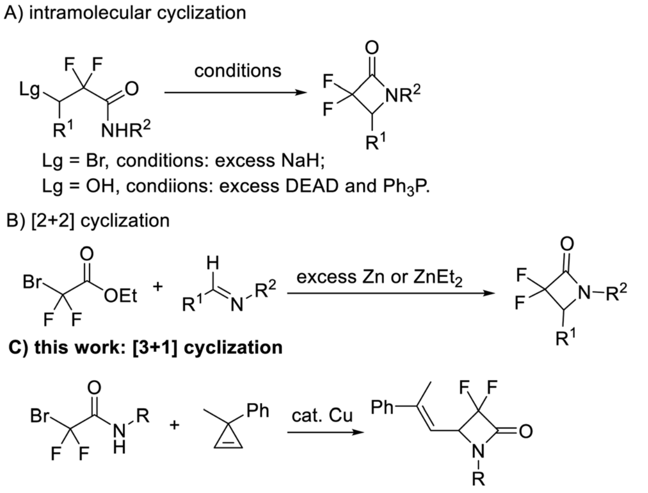


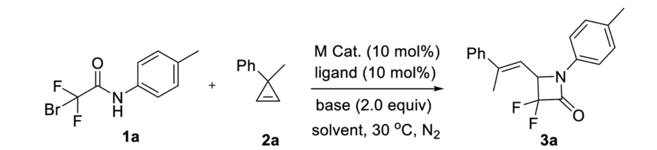
Scheme 2 The synthesis of α,α-difluoro-β-lactams.

Results and discussion

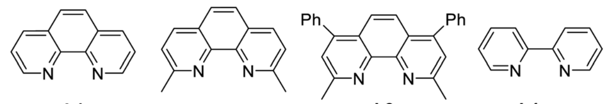
Given that cyclopropenes can usually serve as carbene precusors[12] and considering our recent work on the copper-catalyzed ring-opening coupling reaction of cyclopropene and phosphite *via* a possible copper vinyl carbene species,[13] we chose cyclopropene (**2a**) for the initial test of the [3 + 1] cyclization. The reaction of α-bromodifluoroacetamide **1a** (0.2 mmol) and **2a** (0.24 mmol, 1.2 equiv.) was performed in the presence of CuI (10 mol%), phen (**L1**, 10 mol%) and K_2CO_3 (2.0 equiv.) in CH_3CN (2 mL) under a nitrogen atmosphere at 30 °C. After 24 h, we were pleased to find that the expected [3 + 1] cyclization product α,α-difluoro-β-lactam **3a** was obtained in 60% yield (entry 1). When the ligand was absent, the yield of **3a** decreased to 51% (entry 2), which showed that the ligand played a minor role through the coordination with the active Cu species.[14] Without the catalyst or the base, no reaction occurred (entries 3 and 4). Other metal catalysts, such as Pd, Rh and Ag, which are usually used in the formation of metal carbenes, were ineffective for this [3 + 1] cyclization (for details, see ESI Table S2†). Further copper catalyst screening found that CuI was the superior choice (entries 5–7). Other ligands **L2–L4** did not improve the yield of **3a** (entries 8–10; for details, see ESI Table S1†). Scanning the base (entries 11 and 12; for details, see ESI Table S3†) showcased that K_2CO_3 was the best one. Other solvents were also tested (entries 13 and 14; for details, see ESI Table S4†), and no better results were obtained. When the reaction was performed at an elevated temperature (40 °C), the yield of **3a** was increased to 65% (entry 15). To our delight, **3a** was obtained in 86% yield when cyclopropene was added *via* a syringe[15] for 30 min (entry 16). Decreasing or increasing the amount of K_2CO_3 could not improve the yield of **3a** (entries 17 and 18). During these reactions, only *E*-α,α-difluoro-β-lactam **3a** was obtained and the corresponding *Z*-isomer was not observed.

With the optimized reaction conditions (Table 1, entry 16), we set to investigate the scope of α-bromodifluoroacetamides **1**

Table 1 The optimization of reaction conditions[a]



Entry	M cat.	Ligand	Base	Solvent	Yield (%)
1	CuI	**L1**	K_2CO_3	CH_3CN	60
2	CuI	None	K_2CO_3	CH_3CN	51
3	None	**L1**	K_2CO_3	CH_3CN	N.R.
4	CuI	**L1**	None	CH_3CN	N.R.
5	CuCl	**L1**	K_2CO_3	CH_3CN	3
6	CuBr	**L1**	K_2CO_3	CH_3CN	35
7	Cu cat.[b]	**L1**	K_2CO_3	CH_3CN	N.R.
8	CuI	**L2**	K_2CO_3	CH_3CN	59
9	CuI	**L3**	K_2CO_3	CH_3CN	60
10	CuI	**L4**	K_2CO_3	CH_3CN	45
11	CuI	**L1**	KO^tBu	CH_3CN	N.R.
12	CuI	**L1**	Cs_2CO_3	CH_3CN	Trace
13	CuI	**L1**	K_2CO_3	THF	28
14	CuI	**L1**	K_2CO_3	DCE	<20
15[c]	CuI	**L1**	K_2CO_3	CH_3CN	65
16[c,d]	CuI	**L1**	K_2CO_3	CH_3CN	86
17[c,d,e]	CuI	**L1**	K_2CO_3	CH_3CN	46
18[c,d,f]	CuI	**L1**	K_2CO_3	CH_3CN	57

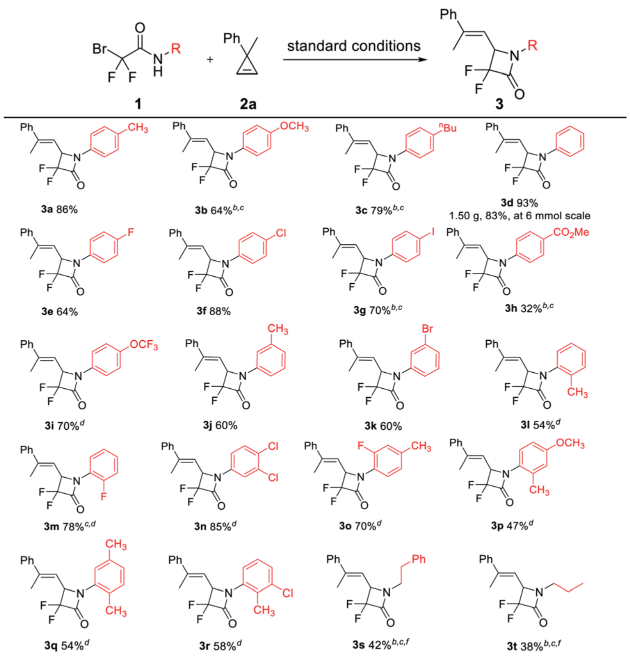


L1 L2 L3 L4

[a] Reaction conditions: **1a** (0.2 mmol, 1.0 equiv.), **2a** (0.24 mmol, 1.2 equiv.), solvent (2 mL), catalyst (10 mol%), ligand (10 mol%), base (2.0 equiv.), 24 h. Yields of isolated **3a** were given. N.R. = no reaction. [b] Cu cat. = $Cu(CH_3CN)_4PF_6$. [c] The reaction was performed at 40 °C. [d] The solution of **1a** in 2 mL CH_3CN was added *via* a syringe for 30 minutes. [e] 1 equiv. K_2CO_3 was used. [f] 3 equiv. K_2CO_3 was used.

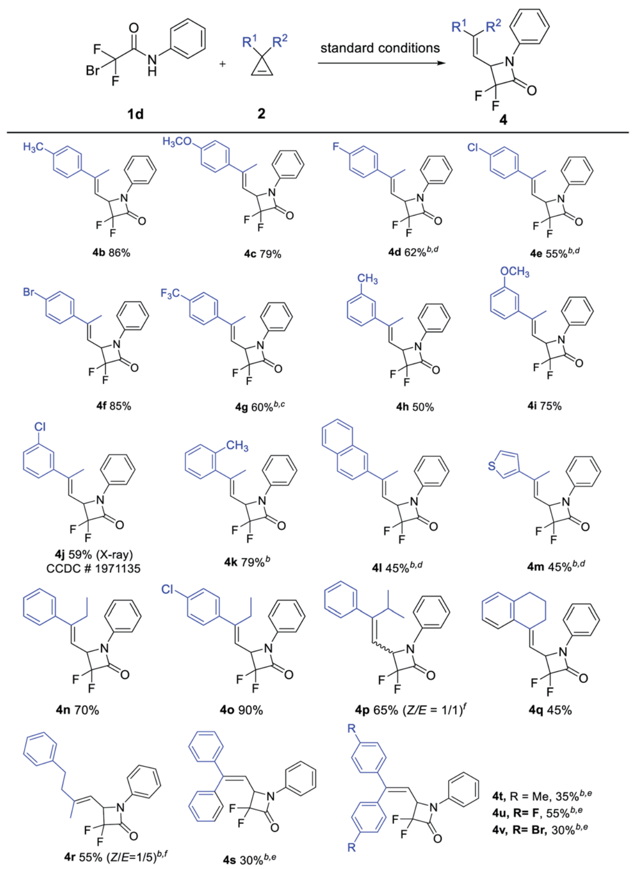
(Table 2). *N*-Aryl-α-bromodifluoroacetamides bearing either electron-donating or -withdrawing groups at the *para*/*meta*/*ortho* positions of the aromatic rings, such as **1a–1m**, worked well and afforded the desired α,α-difluoro-β-lactams **3a–3m** in moderate to excellent yields, but for the reaction of **1b**, **1c**, **1g**, **1h**, **1l** and **1m**, a relatively larger amount of **2a** or a higher temperature was required. Disubstituted *N*-aryl-α-bromodifluoroacetamides **1n–1r** also easily underwent the [3 + 1] cyclization, giving the desired products **3n–3r** in 47–85% yields. These results showed that the electronic effect was inconsequential during the transformation. Compared with other α-bromodifluoroacetamides **1**, *ortho*-substituted amides **1l**, **1m** and **1o–1r** gave the corresponding [3 + 1] cyclization products **3l**, **3m** and **3o–3r** in reasonable yields, which showed that the steric hindrance had no clear effect on the reactivity profile. *N*-Alkyl-α-bromodifluoroacetamides **1s** and **1t** were also examined and the corresponding α,α-difluoro-β-lactams **3s** and **3t** were obtained in acceptable yields. Furthermore, other amides instead of **1** were tested. The decomposition of α-bromo-α,α-difluoroacetamide was observed under the optimal conditions, without the formation of the desired product. No reaction

Table 2 Scope of α-bromodifluoroacetamides **1**[a]



[a] Reactions conditions: **1** (0.2 mmol, 1.0 equiv.), **2a** (0.24 mmol, 1.2 equiv.), CuI (10 mol%), **L1** (10 mol%), K_2CO_3 (2.0 equiv.), CH_3CN (4 mL), 40 °C, N_2, 24 h; isolated yields. [b] **2a** (0.40 mmol, 2.0 equiv.). [c] Performed at 50 °C. [d] **2a** (0.30 mmol, 1.5 equiv.). [e] Performed at 70 °C. [f] 1.0 equiv. K_2CO_3 was used.

Table 3 Scope of cyclopropenes **2**[a]

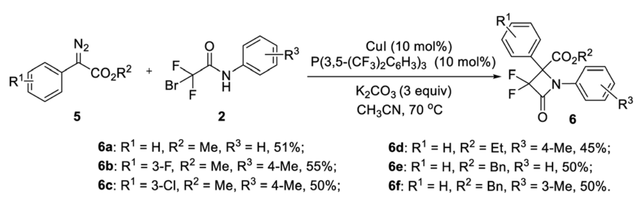


[a] Reactions conditions: **1a** (0.2 mmol, 1.0 equiv.), **2** (0.30 mmol, 1.5 equiv.), CuI (10 mol%), **L1** (10 mol%), K_2CO_3 (2.0 equiv.), CH_3CN (4 mL), 40 °C, N_2, 24 h; isolated yields. [b] **2** (0.40 mmol, 2.0 equiv.). [c] Performed at 50 °C. [d] Performed at 60 °C. [e] Performed at 70 °C. [f] *Z*/*E* ratio was determined by ^{1}H NMR spectroscopy.

occurred for α-bromo-*N*-phenylacetamide, and almost quantitative feedstock was recovered. Pleasingly, a gram-scale reaction (6 mmol of **1d**) can be readily implemented under the standard conditions with only slightly diminished reactivity (1.50 g, 83% yield).

Subsequently, we surveyed the scope of cyclopropenes **2** (Table 3). The aryl methyl cyclopropenes **2b–2k**, with either electron-donating or -withdrawing functional groups at the *para*, *meta*, or *ortho* positions on the aromatic rings could be efficiently converted into the desired α,α-difluoro-β-lactams **4b–4k** in moderate to good yields. The structure of the [3 + 1] cyclization product was further determined by a single-crystal diffraction experiment of **4j**. Naphthyl- or thienyl-containing cyclopropenes **2l** and **2m** could undergo the [3 + 1] cyclization smoothly, resulting in the corresponding products **4l** and **4m** in moderate yields. Next, other alkyl groups connected to cyclopropenes were examined. When ethyl group substituted aryl cyclopropenes **2n** and **2o** were used as the substrates, the desired [3 + 1] cyclization proceeded very smoothly and stereoselectively formed *E*-α,α-difluoro-β-lactams **4n** and **4o** in excellent yields. The reaction of *i*-propyl-substituted aryl cyclopropene **2p** could produce [3 + 1] cyclization product **4p** in a moderate yield (50% total yield), albeit with a low selectivity ($Z/E = 1/1$). For the tetrahydronaphthyl substituted substrate **2q**, *E*-α,α-difluoro-β-lactam **4q** could be generated in 45% yield with specific selectivity. Dialkyl cyclopropene **2r** and diaryl cyclopropenes **2s–2v** were also suitable substrates, and the desired products **4s–4v** were obtained in acceptable yields. Finally, a multisubstituted cyclopropene, namely 1,3-dimethyl-3-phenyl cyclopropene, was tested. Nevertheless, the reaction was very complicated and no desired product was observed.

In addition, diazoacetates, as the most commonly used metal carbene precursors,[1] were tested for the novel [3 + 1] cyclization (Scheme 3). Gratifyingly, under slightly modified conditions, diazoacetates could undergo the desired [3 + 1] cyclization. As shown in Scheme 3, methyl 2-diazo-2-



6a: R^1 = H, R^2 = Me, R^3 = H, 51%;
6b: R^1 = 3-F, R^2 = Me, R^3 = 4-Me, 55%;
6c: R^1 = 3-Cl, R^2 = Me, R^3 = 4-Me, 50%;
6d: R^1 = H, R^2 = Et, R^3 = 4-Me, 45%;
6e: R^1 = H, R^2 = Bn, R^3 = H, 50%;
6f: R^1 = H, R^2 = Bn, R^3 = 3-Me, 50%.

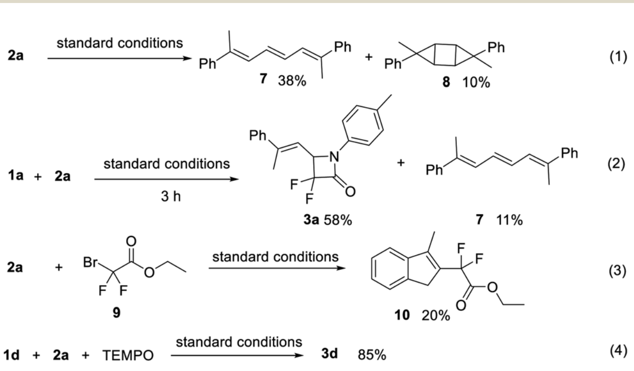
Reactions conditions: **5** (0.2 mmol, 1.0 equiv), **2** (0.6 mmol, 3.0 equiv), CuI (10 mol%), P(3,5-$(CF_3)_2C_6H_3)_3$ (10 mol%), K_2CO_3 (3.0 equiv), CH_3CN (2 mL), 70 °C, N_2, 24 h; isolated yields.

Scheme 3 [3 + 1] cyclization of diazoacetates **5** with α-bromodifluoroacetamides **2**.

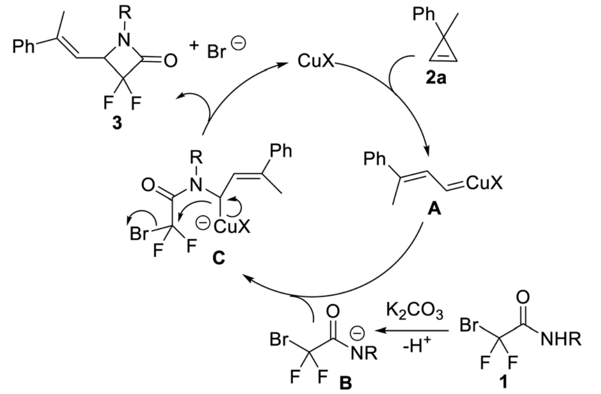
phenylacetates **5a–5c** afforded α,α-difluoro-β-lactams **6a–6c** in 51–55% isolated yields. Ethyl and benzylic diazos **5d** and **5e** were suitable carbene precursors for the reaction and gave α,α-difluoro-β-lactams **6d–6f** in acceptable yields. Nevertheless, the vinyldiazo compound, such as methyl (*E*)-2-diazopent-3-enoate, could not produce the desired lactam, only giving a complex mixture.

To gain insight into the mechanism of this novel [3 + 1] cyclization, some mechanistic experiments were carried out. In the absence of α-bromodifluoroacetamide **1**, cyclopropene **2a** could undergo dimerization to form conjugated triene **7** and cyclobutane **8** under standard conditions (Scheme 4, eqn (1)). Furthermore, when the model reaction was quenched after 3 h under standard conditions, **3a** and **7** were obtained in 58% and 11% yields, respectively (Scheme 4, eqn (2)). These results suggested that a copper vinyl carbene might be the reaction intermediate.[16] Additionally, given that α-bromo-α,α-difluoroacetamide **1** could produce a carbon radical in the presence of a copper catalyst,[11,17] α-Bromodifluoroacete **9**[17] instead of **1a**, was employed to react with cyclopropene **2a**. As a result, 20% of indene **10** was obtained (Scheme 4 eqn (3)),[18] which was not detected in the reaction of α-bromodifluoroacetamide **1a** and cyclopropene **2a**. Moreover, a radical inhibitor experiment was also performed. In the presence of 5.0 equivalents of TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)oxyl), the yield of **3d** slightly decreased to 85% (Scheme 4 eqn (4)). Collectively, these experimental results signified that radical species might not be involved in this [3 + 1] cyclization.

On the basis of the experimental results, as well as previous studies,[13,19,20] we proposed a possible reaction mechanism (Scheme 5). The Cu(I)-complex reacted with cyclopropene **2a** to form a ring-opened vinyl copper carbene intermediate **A**.[20] Compared with normally accepted copper carbene inserting into the N–H bond of aniline derivatives,[21] α-bromo-α,α-difluoroacetamide **1** with a relatively high acidity and low nucleophilicty[22] might be favoured to undergo a deprotonation in the presence of K_2CO_3 to form nitrogen anion species **B**. Subsequently, the nitrogen anion species **B** attacked the copper carbene **A**, generating Cu(I) species **C**, followed by an intramolecular nucleophilic substitution reaction to yield the expected product **3** and release the Cu(I) catalyst.[23] It should be noted that different from previous reports using a vinyl carbene intermediate as a C3 synthon,[19] herein the copper vinyl carbene species acted as an interesting C1 synthon.



Scheme 4 Control experiments.



Scheme 5 Proposed mechanism.

Conclusions

In conclusion, we have developed a facile and efficient copper-catalyzed [3 + 1] cyclization of cyclopropenes/diazo compounds and bromodifluoroacetamides and therefore furnished a straightforward and efficient method for synthesizing a wide range of valuable α,α-difluoro-β-lactams under mild conditions. This is the first example of employing an *in situ* generated metal carbene as the C1 synthon in [3 + 1] cyclization for the synthesis of α,α-difluoro-β-lactams. This novel methodology might provide a new pathway for the preparation of cyclic compounds by employing *in situ* generated metal carbenes.

Author contributions

M. Z., Y. L. and Q. Z. conceived the idea. M. Z. performed all experiments including condition optimizations, exploring the scope and investigating the mechanism. Y. L. and Q. Z. supervised the project. H. L. and J. Z. supported other authors to perform the project well. All the authors discussed the results and commented on the manuscript.

Conflicts of interest

The authors declare no competing financial interest.

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References

1 (*a*) Y. Xia, D. Qiu and J. Wang, *Chem. Rev.*, 2017, **117**, 13810–13889; (*b*) M. P. Doyle, M. A. McKervey and T. Ye, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*, Wiley, New York, 1998; (*c*) M. P. Doyle and D. C. Forbes, *Chem. Rev.*, 1998,

98, 911–935; (*d*) Z. Zhang and J. Wang, *Tetrahedron*, 2008, **64**, 6577–6605; (*e*) M. P. Doyle, R. Duffy, M. Ratnikov and L. Zhou, *Chem. Rev.*, 2010, **110**, 704–724; (*f*) A. Ford, H. Miel, A. Ring, C. N. Slattery, A. R. Maguire and M. A. McKervey, *Chem. Rev.*, 2015, **115**, 9981–10080.

2 (*a*) S. Chanthamath and S. Iwasa, *Acc. Chem. Res.*, 2016, **49**, 2080–2090; (*b*) J.-R. Chen, X.-Q. Hu, L.-Q. Lu and W.-J. Xiao, *Chem. Rev.*, 2015, **115**, 5301–5365.

3 (*a*) J. Barluenga, L. Riesgo, L. A. Lopez, E. Rubio and M. Tomas, *Angew. Chem., Int. Ed.*, 2009, **48**, 7569–7572; (*b*) S. C. Schmid, I. A. Guzei and J. M. Schomaker, *Angew. Chem., Int. Ed.*, 2017, **56**, 12229–12233; (*c*) S. C. Schmid, I. A. Guzei, I. Fernández and J. M. Schomaker, *ACS Catal.*, 2018, **8**, 7907–7914.

4 D. Crowfoot, C. W. Bunn, B. W. Rogers-Low and A. Turner-Jones, in, *Chemistry of Penicillin*, ed H. T. Clarke, J. R. Johnson and R. Robinson, Princeton University Press, Princeton, NJ, 1949.

5 For selected examples, see: (*a*) E. Ebrahimi, A. Jarrahpour, N. Heidari, V. Sinou, V. Sinou, J. M. Brunel, A. R. Zolghadr and E. Turos, *Med. Chem. Res.*, 2016, **25**, 247–262; (*b*) A. Jarrahpour, P. Shirvani, V. Sinou, C. Latour and J. M. Brunel, *Med. Chem. Res.*, 2016, **25**, 149–162; (*c*) M. W. Majewski, P. A. Miller, A. G. Oliver and M. J. Miller, *J. Org. Chem.*, 2017, **82**, 737–744; (*d*) K.-W. Yang, Y. Zhou, Y. Ge and Y. Zhang, *Chem. Commun.*, 2017, **53**, 8014–8017; (*e*) S. Thaisrivongs, H. J. Schostarez, D. T. Pals and S. R. Turner, *J. Med. Chem.*, 1987, **30**, 1837–1842; (*f*) J.-L. Maillard, C. Favreau, M. Reboud-Ravaux, R. Kobaiter, R. Joyeau and M. Wakselman, *Eur. J. Cell Biol.*, 1990, **52**, 213–218; (*g*) R. Joyeau, H. Molines, R. Labia and M. Wakselman, *J. Med. Chem.*, 1988, **31**, 370–374.

6 (*a*) E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly and N. A. Meanwell, *J. Med. Chem.*, 2015, **58**, 8315–8359; (*b*) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320–330; (*c*) W. K. Hagmann, *J. Med. Chem.*, 2008, **51**, 4359–4369.

7 R. Joyeau, A. Felk, S. Guilaume, M. Wakselman, I. Vergely, C. Doucet, N. Boggetto and M. Reboud-Ravaux, *J. Pharm. Pharmacol.*, 1996, **48**, 1218–1230.

8 (*a*) M. Bordeau, F. Frébault, M. Gobet and J.-P. Picard, *Eur. J. Org. Chem.*, 2006, 4147–4154; (*b*) A. Otaka, J. Watanabe, A. Yukimasa, Y. Sasaki, H. Watanabe, T. Kinoshita, S. Oishi, H. Tamamura and N. Fujii, *J. Org. Chem.*, 2004, **69**, 1634–1645; (*c*) A. Otaka, H. Watanabe, E. Mitsuyama, A. Yukimasa, H. Tamamura and N. Fujii, *Tetrahedron Lett.*, 2001, **42**, 285–287; (*d*) K. Nakayama, H. C. Kawato, H. Inagaki, R. Nakajima, A. Kitamura, K. Someya and T. Ohta, *Org. Lett.*, 2000, **2**, 977–980; (*e*) K. Uoto, S. Ohsuki, H. Takenoshita, T. Ishiyama, S. Iimura, Y. Hirota, I. Mrrsui, H. Terasawa and T. Soga, *Chem. Pharm. Bull.*, 1997, **45**, 1793–1804; (*f*) S. Thaisrivongs, H. J. Schostarez, D. T. Pals and S. R. Turner, *J. Med. Chem.*, 1987, **30**, 1837–1842.

9 (*a*) A. Tarui, T. Ikebata, K. Sato, M. Omote and A. Ando, *Org. Biomol. Chem.*, 2014, **12**, 6484–6489; (*b*) N. Boyer, P. Gloanec, G. De Nanteuil, P. Jubault and J.-C. Quirion, *Eur. J. Org. Chem.*, 2008, 4277–4295; (*c*) K. Sato, A. Tarui, S. Matsuda, M. Omote, A. Ando and I. Kumadaki, *Tetrahedron Lett.*, 2005, **46**, 7679–7681; (*d*) S. Marcotte, X. Pannecoucke, C. Feasson and J.-C. Quirion, *J. Org. Chem.*, 1999, **64**, 8461–8464; (*e*) M. R. Angelastro, P. Bey, S. Hehdi and N. P. Peet, *Bioorg. Med. Chem. Lett.*, 1992, **2**, 1235–1238; (*f*) J. E. Baldwin, G. P. Lynch and C. J. Schofield, *J. Chem. Soc., Chem. Commun.*, 1991, 736–738; (*g*) T. Taguchi, O. Kitagawa, Y. Suds, S. Ohkawa, A. Hashimoto, Y. Iitaka and Y. Kobayashi, *Tetrahedron Lett.*, 1988, **41**, 5291–5294.

10 (*a*) R. Joyeau, H. Molines, R. Labia and M. Wakselman, *J. Med. Chem.*, 1988, **31**, 370–374; (*b*) S. Fustero, B. Fernández, P. Bello, C. del Pozo, S. Arimitsu and G. B. Hammond, *Org. Lett.*, 2007, **9**, 4251–4253.

11 (*a*) Y. Lv, W. Pu, Q. Chen, Q. Wang, J. Niu and Q. Zhang, *J. Org. Chem.*, 2017, **82**, 8282–8289; (*b*) Y. Lv, W. Pu, Q. Wang, Q. Chen, J. Niu and Q. Zhang, *Adv. Synth. Catal.*, 2017, **359**, 3114–3119.

12 For a recent review, see: R. Vicente, *Chem. Rev.*, 2021, **121**, 162–226.

13 Z. Li, G. Peng, J. Zhao and Q. Zhang, *Org. Lett.*, 2016, **18**, 4840–4843.

14 (*a*) F. Hu and X. Lei, *ChemCatChem*, 2015, **7**, 1539–1542; (*b*) M. Ohashi, N. Ishida, K. Ando, Y. Hashimoto, A. Shigaki, K. Kikushima and S. Ogoshi, *Chem. Eur. J.*, 2018, **24**, 9794–9798.

15 Upon slowly syringing the solution of **1a**, **3a** was obtained in 86% yield, and only a trace amount of **5** was observed. While **1a** was added in one portion to the vial, **3a** and **5** were obtained in 65% and 15% yields, respectively. Slowly syringing **1a** might decease the concentration of vinyl carbene copper species, thus efficiently avoiding the formation of **5**.

16 Y. Zhou, B. G. Trewyn, R. J. Angelici and L. K. Woo, *J. Am. Chem. Soc.*, 2009, **131**, 11734–11743.

17 A. Prieto, R. Melot, D. Bouyssi and N. Monteiro, *ACS Catal.*, 2016, **6**, 1093–1096.

18 A radical pathway was favored for the formation of **10**. For details, see ESI Scheme S7.†

19 For a selected review, see: K. O. Marichev and M. P. Doyle, *Org. Biomol. Chem.*, 2019, **17**, 4183–4195.

20 (*a*) S. Chuprakov and V. Gevorgyan, *Org. Lett.*, 2007, **9**, 4463–4466; (*b*) J. Chen and S. Ma, *Chem.–Asian J.*, 2010, **5**, 2415–2421; (*c*) P.-H. Li, S. Yang, T.-G. Hao, Q. Xu and M. Shi, *Org. Lett.*, 2019, **21**, 3162–3166.

21 For selected reviews, see: (*a*) S.-F. Zhu and Q.-L. Zhou, *Acc. Chem. Res.*, 2012, **45**(8), 1365–1377; (*b*) X. Guo and W. Hu, *Acc. Chem. Res.*, 2013, **46**(11), 2427–2440.

22 The *gem*-difluoro unit endowed the amide compounds with a relatively low nucleophilicity and high acidity, see: (*a*) R. D. Trepka, J. W. Belisle and J. K. Harrington, *J.Org. Chem.*, 1974, **39**, 1094–1098; (*b*) C.-P. Zhang, Z.-L. Wang, Q.-Y. Chen, C.-T. Zhang, Y.-C. Gu and J.-C. Xiao, *J. Fluorine Chem.*, 2010, **131**, 761–766.

23 (*a*) S. Mori, E. Nakamura and K. Morokuma, *J. Am. Chem. Soc.*, 2000, **122**, 7294–7307; (*b*) N. Yoshikai and E. Nakamura, *Chem. Rev.*, 2012, **112**, 2339–2372.