


 Cite this: *RSC Adv.*, 2020, **10**, 25947

 Received 29th May 2020
 Accepted 25th June 2020

DOI: 10.1039/d0ra04729e

rsc.li/rsc-advances

Visible-light promoted three-component tandem reaction to synthesize difluoromethylated oxazolidin-2-imine†

 Kun Bao,^{‡ab} Jun Wei,^{‡a} Huihui Yan^{ab} and Rong Sheng^{ab*}

An effective synthetic method to achieve difluoromethylated oxazolidin-2-imine has been developed via visible-light promoted three-component tandem reaction of aryl allylamines, 2-BTSo2CF2H (BT = Benzothiazole) and isocyanates. This method features mild reaction conditions and good functional group tolerance, and the reaction mechanism was confirmed by experiments and interpreted by quantum chemical calculations.

Difluoromethyl containing compounds have been widely used in the fields of pharmaceuticals and agrochemistry because of their unique physical, chemical, and biological properties.¹ Generally, the –CF₂ moiety can act as a bioisostere of the –CH₂ or –CO group and the CF₂H is isopolar to the –OH and –SH group, which can be used as a lipophilic hydrogen bond donor.^{2,3} In recent years, much attention has been focused on the synthesis of difluoromethylated molecules.⁴ FDA approved medicine Gemcitabine and Lubiprostone both contain difluoromethyl group (Fig. 1a).

The oxazolidin-2-imine skeleton exists in many biologically active compounds. For example, compound **I** is a novel nitric oxide synthase inhibitor with an EC₅₀ value of 41 nM,⁵ and compound **II** acts as a very potent selective androgen receptor modulator (SARM) with a sub-nanomolar EC₅₀ value (Fig. 1b).⁶ In addition, substituted oxazolidin-2-imines are critical synthetic intermediates that can be transformed into a variety of other structures, and represent a useful chiral auxiliary for the asymmetric alkylations.⁷ The high value of oxazolidin-2-imine in medicinal chemistry and organic chemistry has driven successive efforts to develop effective synthetic methods. Shinichi Saito's group reported the cycloaddition of aziridines with isocyanates catalyzed by NiI₂ to furnish oxazolidin-2-imines in good yields (Scheme 1a).⁸ Beifuss's group revealed intermolecular 1,2-addition/intramolecular *N*-vinylation of 2-bromo-2-propen-1-ols and dicyclohexyl carbodiimide for the synthesis of oxazolidin-2-imines (Scheme 1b).⁹ Recently, Bu₂SnI₂–InCl₃

catalysed cycloaddition of propylene oxide with diphenyl carbodiimide was reported by Ikuya Shibata's group¹⁰ (Scheme 1c).

Radical-triggered cascade multi-component reactions serve as an ideal strategy in the synthesis of heterocyclic scaffolds, owing to forming multiple bonds under a single set of reaction conditions.¹¹ Particularly, the visible-light promoted radical addition-cyclization has demonstrated its synthetic utility in the construction of compounds with various scaffold,¹² including 2-oxazolidinones,¹³ coumarin,¹⁴ phenanthridines,¹⁵ and so on. We envisioned that the combination of difluoromethyl moiety with oxazolidin-2-imine scaffold may exert potential use in medicinal chemistry and other related fields. As part of our work on the visible-light mediated radical difluoromethylation,¹⁵ we try to explore a novel and convenient method to construct HCF₂-containing oxazolidin-2-imines via visible-light promoted three-component tandem reaction (Scheme 1d).

We began our investigation by using *N*-benzyl-2-phenylprop-2-en-1-amine **1a**, 1-isocyanato-4-methylbenzene **3a** as the model

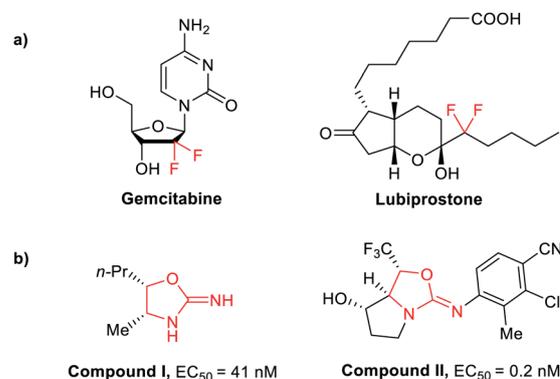


Fig. 1 (a) Structure of Gemcitabine and Lubiprostone (b) selected bioactive oxazolidin-2-imine derivatives.

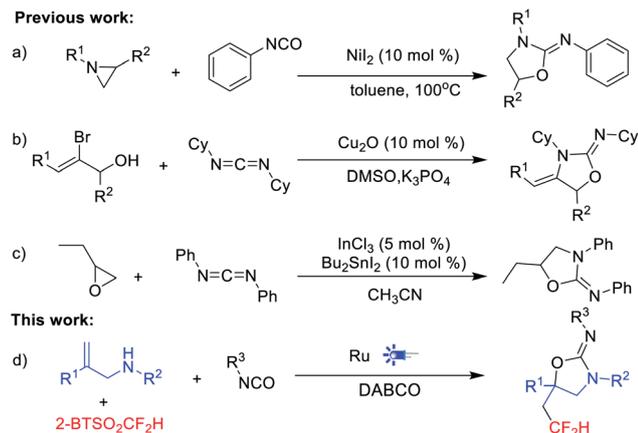
*College of Pharmaceutical Sciences, Zhejiang University, Hangzhou, 310058, People's Republic of China. E-mail: shengr@zju.edu.cn

^bCollaborative Innovation Center of Yangtze River Delta Region Green Pharmaceuticals, Zhejiang University of Technology, Hangzhou, 310014, P. R. China

† Electronic supplementary information (ESI) available. CCDC 1998157. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0ra04729e

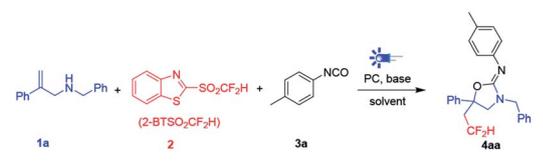
‡ These authors contributed equally to this paper.





Scheme 1 Different protocols for the synthesis of oxazolidin-2-imine.

substrate and 2-BTSO₂CF₂H (Hu's reagent) **2** as the difluoromethylation reagent. Initially, DABCO was used as base and target compound **4aa** can be produced in 29% yield using Ru(bpy)₃Cl₂·6H₂O as photocatalyst (Table 1, entry 1). Further screening of various bases, including Na₂CO₃, TMEDA, DBN, TEA and DIPEA, cannot get the **4aa**, indicating the DABCO was the optimal base for this reaction (Table 1, entries 2–6). Then, a series of solvents, including DMF, acetonitrile, NMP, acetone and toluene were screened, and the results showed that DMF

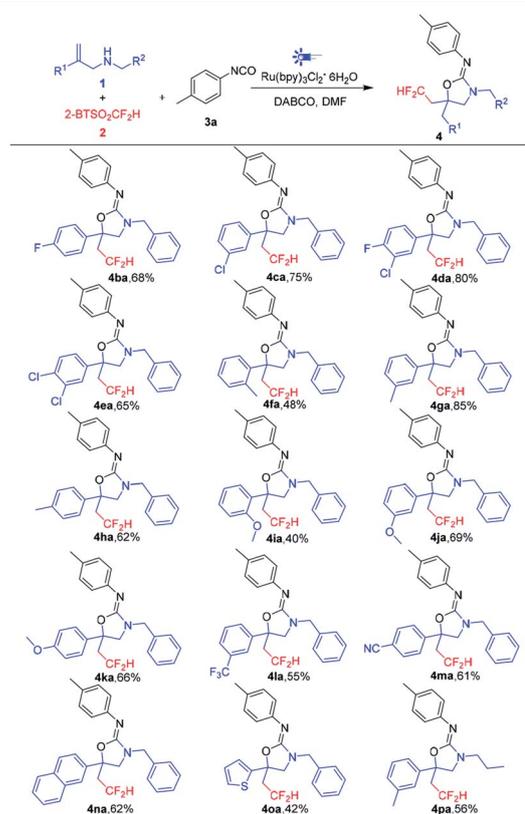
Table 1 Optimization of reaction conditions^a


Entry	Base	Solvent	3a/equiv.	Yield ^b (%)
1	DABCO	DMSO	1.2	29
2	Na ₂ CO ₃	DMSO	1.2	0
3	TMEDA	DMSO	1.2	0
4	DBN	DMSO	1.2	Trace
5	TEA	DMSO	1.2	Trace
6	DIPEA	DMSO	1.2	Trace
7	DABCO	DMF	1.2	35
8	DABCO	CH ₃ CN	1.2	26
9	DABCO	NMP	1.2	15
10	DABCO	Acetone	1.2	25
11	DABCO	Toluene	1.2	Trace
12 ^c	DABCO	DMF	1.2	28
13 ^d	DABCO	DMF	1.2	43
14 ^d	DABCO	DMF	1.8	61
15 ^d	DABCO	DMF	2.5	75
16 ^d	DABCO	DMF	3.0	74

^a Reaction condition: **1a** (0.5 mmol, 1.0 equiv.), **2** (0.6 mmol, 1.2 equiv.), PC (0.025 mmol, 5 mol%), base (1 mmol, 2.0 equiv.), solvent (2.0 mL), irradiated with a 6 W blue LED for 10 h at room temperature under N₂ atmosphere. ^b Isolated yields. ^c *fac*-Ir(ppy)₃ instead of Ru(bpy)₃Cl₂·6H₂O. ^d In the ice bath (8–10 °C) for 16 h.

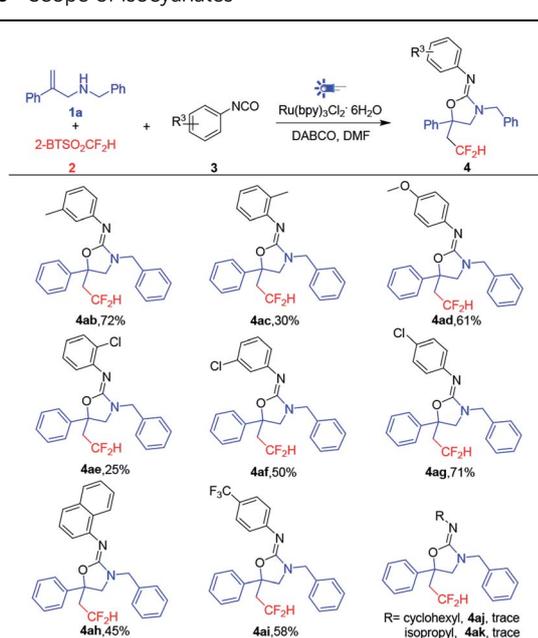
was more suitable for this reaction than others (Table 1, entries 7–11). In addition, the replacement of catalyst Ru(bpy)₃Cl₂·6H₂O with *fac*-Ir(ppy)₃ decreased the yield slightly (28%) (Table 1, entry 12). Interestingly, the decrease of temperature and increase the equivalence of **3a** can improve the yields of **4aa** obviously (entries 13 and 14). Therefore, the best result was obtained with a combination of **2** with **3a** (2.5 equiv.), DABCO (1 mmol, 2.0 equiv.), Ru(bpy)₃Cl₂·6H₂O (5 mol%) in DMF (2.0 mL) were irradiated with a 6 W blue LED for 16 h at 8–10 °C to furnish **4aa** in 75% yield (entry 15).

With the optimized reaction conditions in hand, the substrate scope of aryl allylamines **1** was extensively investigated. As shown in Table 2, the reaction tolerates various substituents on the phenyl ring, including halogen and alkyl (4ba~4ha). Substrates containing both electron-donating (–OCH₃) and electron-withdrawing (–CF₃, –CN) groups on phenyl can proceed this reaction smoothly and give CF₂H-containing oxazolidin-2-imines in good yields (4ja, 4la). In addition, 2-naphthyl allylamine **1n** and 2-thienyl allylamine **1o** also can produce the corresponding CF₂H-containing compounds **4na** and **4oa** in moderate to good yields. The

Table 2 Scope of aryl allylamines^{a,b}

^a Reaction conditions: **1** (0.5 mmol, 1.0 equiv.), **2** (0.6 mmol, 1.2 equiv.), **3a** (1.25 mmol, 2.5 equiv.), [Ru(bpy)₃]Cl₂·6H₂O (0.025 mmol 5 mol%), and DABCO (1 mmol, 2.0 equiv.) in DMF (2.0 mL) were irradiated with a 6 W blue LED for 16 h at 8–10 °C under N₂ atmosphere. ^b Yields isolated.

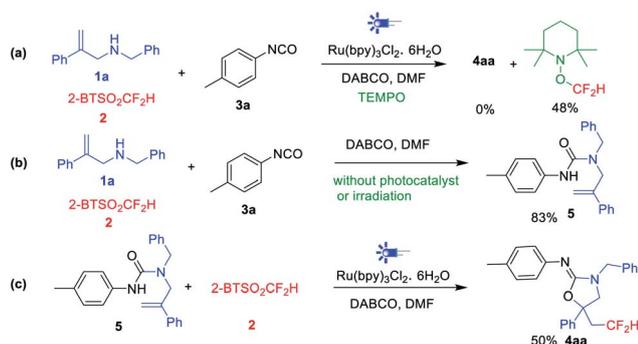


Table 3 Scope of isocyanates^{a,b}

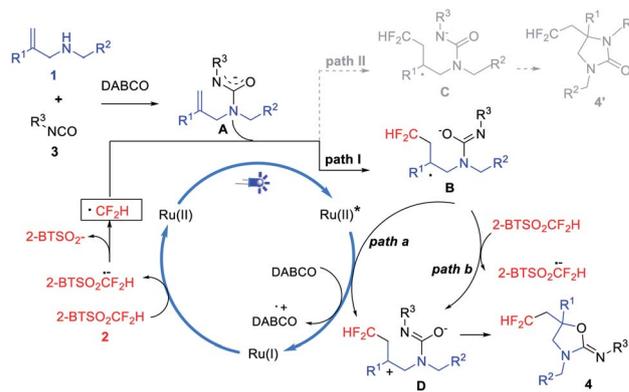
^a Reaction conditions: **1a** (0.5 mmol, 1 equiv.), **2** (0.6 mmol, 1.2 equiv.), **3** (1.25 mmol, 2.5 equiv.), $[Ru(bpy)_3]Cl_2 \cdot 6H_2O$ (0.025 mmol, 5 mol%), DABCO (1 mmol, 2.0 equiv.), in 2.0 mL DMF for 16 h at 8–10 °C under N_2 atmosphere. ^b Isolated yields.

relative low yields of **4fa** (48%) and **4ia** (40%) indicated the obvious steric effect in this reaction. More interestingly, the success of approaching **4pa** in moderate yield with **1p** (*N*-allyl-2-phenylprop-2-en-1-amine) showed the good tolerance for various substituents on amine in this reaction.

Subsequently, the substrate scope of isocyanates was also investigated (Table 3). The substituents on the phenyl ring were first evaluated, and the results showed that both electron-donating (Me, OMe) and electron-withdrawing groups (Cl, CF_3) on *para* or *meta* position were tolerated with good yields of corresponding products (50–72%). While similar to aryl allyl-amines **1**, the steric hindrance of substituent affects the yields of products obviously, for example, the *ortho*-methyl phenyl isocyanate **3c** and *ortho*-chloro phenyl isocyanate **3e** only gave



Scheme 2 The reaction mechanism study.



Scheme 3 A possible reaction mechanism.

poor yields of **4ac** (30%) and **4ae** (25%), respectively. The 1-naphthyl isocyanate **3h** also can produce the corresponding CF_2H -containing compound **4ah** in 45% yield. However, the cyclohexyl-isocyanate **3j** and isopropyl-isocyanate **3k** cannot get target compounds in this reaction, which indicates the alkyl isocyanates are not suitable for this transformation.

To confirm the reaction mechanism, a radical inhibition experiment was conducted. In the presence of the radical scavenger 2,2,6,6-tetramethyl-1-piperidinyl-oxy (TEMPO), the transformation was absolutely inhibited, and the TEMPO- CF_2H adduct product was detected by ^{19}F NMR spectroscopy analysis in 48% yield (Scheme 2a), which indicating a free radical pathway might be involved in this reaction. Then, condition-control experiments showed that both irradiation and photocatalyst are indispensable for this transformation (Scheme 2b). Moreover, when **1a**, **2**, **3a** and DABCO were mixed in DMF without photocatalyst and irradiation, the urea **5** was achieved in 83% yield, and further reaction of urea **5** with **2** in the standard conditions gave 50% yield of difluoromethylated oxazolidin-2-imine **4aa** (Scheme 2c). This result further confirmed that urea **5** is the key intermediate for this type of transformation. Finally, Stern–Volmer luminescence studies demonstrated that the excited state $*[Ru]^{2+}$ was quenched by DABCO ($E_{ox}^D = +0.69$ V vs. SCE, $E[Ru(II)^*/Ru(I)] = +0.77$ V) instead of allyl-amines **1a**, or 2-BTSA₂CF₂H **2**, or isocyanates **3a**, and the quenching effect of DABCO increased with its concentration (see the ESI for details†).

According to above studies, a plausible reaction mechanism is proposed in Scheme 3. The excited state $*[Ru]^{2+}$ is formed by visible light irradiation and reduced by DABCO to get $[Ru]^+$, which triggers 2-BTSA₂CF₂H to generate HCF₂ radical. Then, the addition of HCF₂ radical to **A** (formed by the condensation of **1** and **3** *in situ*) produces benzylic radical **B**, which is further oxidized by excited Ru(II) species to form carbocation **D** accompanying with concurrent regeneration of $[Ru]^+$ (**Path a**). It is also possible that **B** reacts with 2-BTSA₂CF₂H through a SET process to generate carbocation **D** (**Path b**). Subsequent cyclization of **D** to achieve difluoromethylated product **4**.

During the mechanism analysis, we found that the intermediate **A** and HCF₂ radical may experience two cyclization pathways to achieve difluoromethylated oxazolidin-2-imine (**4**) or



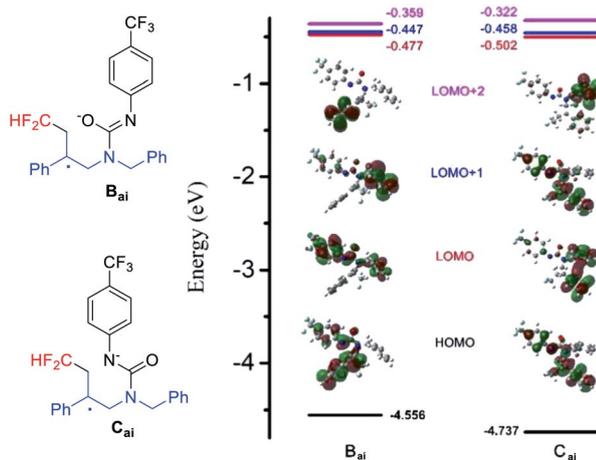


Fig. 2 Molecular Frontier orbital energy of intermediate B_{ai} and C_{ai} .

difluoromethylated imidazolinone ($4'$), respectively (Scheme 3). The good selectivity of this transformation prompts us to carry out quantum chemical calculations to explain the inner mechanism.¹⁶ $4ai$, with a single crystal structure (see the ESI for details[†]), was employed as the model substrate and state-of-the-art computational methods SMD-B3LYP-D3(BJ)/BS1//B3LYP/BS1 was used for calculation. As it shown in Fig. 2, the transition energies of B_{ai} and C_{ai} in different molecular orbitals, HOMO, LUMO, LUMO+1 and LUMO+2 were calculated. The values of intermediate B_{ai} were -4.556 eV, -0.477 eV, -0.447 eV and -0.359 eV, respectively. And which for intermediate C_{ai} were -4.737 eV, -0.502 eV, -0.458 eV and -0.322 eV, respectively (Fig. 2).

In photocatalytic process, it is well known that the lower energy level gap (HOMOs–LUMOs), the easier molecular will be excited.¹⁷ Therein, the energy level gaps between LUMO+2/LUMO+1/LUMO and HOMO of intermediate B_{ai} was 4.197 eV, 4.109 eV, 4.079 eV, respectively, which were lower than that of intermediate C_{ai} (4.415 eV, 4.279 eV, 4.235 eV, respectively). In addition, this can also be explained by a reaction between the hardest oxygen nucleophilic center with the hard carbocationic center.¹⁸ These results indicating that **Path I** is more favorable than **Path II**.

Conclusions

Overall, the one-pot synthesis of difluoromethylated oxazolidin-2-imine has been achieved by visible-light promoted three-component tandem reaction using aryl allylamines, 2-BT SO_2 -CF $_2$ H, and isocyanates. With regard to the widely available materials, mild conditions, good tolerance of substituents on allylamines and isocyanates, this new method demonstrated potential application in medicinal chemistry, agricultural chemistry and other related fields. The quantum chemical calculations also explained the inner mechanism of this transformation.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (21672187), Zhejiang Natural Science Foundation (LZ17H300002).

Notes and references

- (a) H. Jiang, M. Xu, W. Lu, W. Tian, W. Wan, Y. Chen, H. Deng, S. Wu and J. Hao, Direct Gem-Difluoromethylation of sp^3 -Hybridized Carbon Center Through Copper-mediated Radical/Radical Cross-Coupling for the Construction of a CH_2 - CF_2 Linkage, *Chem. Commun.*, 2015, **51**, 15756; (b) H. Xu, D. Wang, Y. Chen, W. Wan, H. Deng, K. Ma, S. Wu, J. Hao and H. Jiang, Copper-Catalyzed Gem-Difluoromethylation of C (sp^2)-H Bonds of Alkenes, *Org. Chem. Front.*, 2017, **4**, 1239; (c) J. Hu, T. J. Pu, Z. W. Xu, W. Y. Xu and Y. S. Feng, Cadmium Sulfide Quantum-Dot-Photocatalyzed Cascade Cyclization of Functionalized Difluoromethyl Chlorides with Unactivated Olefins, *Adv. Synth. Catal.*, 2019, **361**, 708.
- (a) C. Ni, L. Zhu and J. Hu, Advances in Transition-Metal-Mediated Di- and Monofluoroalkylations, *Acta Chim. Sin.*, 2015, **73**, 90; (b) N. A. Meanwell, Synopsis of Some Recent Tactical Application of Bioisosteres in Drug Design, *J. Med. Chem.*, 2011, **54**, 2529.
- F. Scheidt, J. Neufeld, M. Schafer, C. Thiehoff and R. Gilmour, Catalytic Geminal Difluorination of Styrenes for the Construction of Fluorine-rich Bioisosteres, *Org. Lett.*, 2018, **20**, 8073.
- (a) X. J. Tang and W. R. Dolbier, Efficient Cu-catalyzed atom transfer radical addition reactions of fluoroalkylsulfonyl chlorides with electron-deficient alkenes induced by visible light, *Angew. Chem., Int. Ed.*, 2015, **54**, 4246; (b) N. Noto, T. Koike and M. Akita, Metal-free di- and trifluoromethylation of alkenes realized by visible-light-induced perylene photoredox catalysis, *Chem. Sci.*, 2017, **8**, 6375; (c) P. Xu, S. Guo, L. Wang and P. P. Tang, Silver-catalyzed oxidative activation of benzylic C-H bonds for the synthesis of difluoromethylated arenes, *Angew. Chem., Int. Ed.*, 2014, **53**, 5955; (d) F. Pan, G. B. Boursalian and T. Ritter, Palladium-catalyzed decarbonylative difluoromethylation of acid chlorides at room temperature, *Angew. Chem., Int. Ed.*, 2018, **57**, 16871.
- S. Ueda, H. Terauchi, A. Yano, M. Ido, M. Matsumoto and M. Kawasaki, 4,5-Disubstituted-1,3-oxazolidin-2-imine Derivatives: A New Class of Orally Bioavailable Nitric Oxide Synthase Inhibitor, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 313.
- A. A. Nirschl, Y. Zou, S. R. Krystek, J. C. Sutton, L. M. Simpkins, J. A. Lupisella, J. E. Kuhns, R. Seethala, R. Golla, P. G. Slep, B. C. Beehler, G. J. Grover, D. Egan, A. Fura, V. P. Vyas, Y. X. Li, J. S. Sack, K. F. Kish, Y. An, J. A. Bryson, J. Z. Gougoutas, J. DiMarco, R. Zahler, J. Ostrowski and L. G. Hamann, N-Aryl-oxazolidin-2-imine Muscle Selective Androgen Receptor Modulators Enhance Potency through Pharmacophore Reorientation, *J. Med. Chem.*, 2009, **52**, 2794.



- 7 T. N. Le, Q. P. B. Nguyen, J. N. Kim and T. H. Kim, 5,5-Dimethyl-2-phenylamino-2-oxazoline as an Effective Chiral Auxiliary for Asymmetric Alkylations, *Tetrahedron Lett.*, 2007, **48**, 7834.
- 8 M. Takeshi, A. Isao, K. Takako, M. Hyuma and S. Shinichi, [3 + 2] Cross-Coupling Reactions of Aziridines with Isocyanates Catalyzed by Nickel(II) Iodide, *Org. Lett.*, 2006, **8**, 379.
- 9 H. Weischedel, D. Schmidt, J. Conrad and U. Beifuss, Formation of Substituted 2-Iminooxazolidines via Intermolecular 1,2-Addition/Intramolecular N-vinylation Using 3-Substituted-2-Bromo-2-Propen-1-ols as Substrates, *Tetrahedron*, 2018, **74**, 6426.
- 10 I. Suzuki, A. Imakuni, A. Baba and I. Shibata, Catalytic Annulation of Epoxides with Heterocumulenes by the Indium-Tin System, *Molecules*, 2018, **23**, 782.
- 11 (a) R. C. Cioc, E. Ruijter and R. V. A. Orru, Multicomponent reactions: advanced tools for sustainable organic synthesis, *Green Chem.*, 2014, **16**, 2958; (b) G. Bosica, R. Abdilla and K. Demanuele, Revisiting the Betti Synthesis: Using a Cheap, Readily Available, Recyclable Clay Catalyst under Solventless Conditions, *Eur. J. Org. Chem.*, 2018, **44**, 6127.
- 12 (a) X. Ren and Z. Lu, Visible light promoted difunctionalization reactions of alkynes, *Chin. J. Catal.*, 2019, **40**, 1003; (b) T. Koike and M. Akita, A versatile strategy for difunctionalization of carbon-carbon multiple bonds by photoredox catalysis, *Org. Chem. Front.*, 2016, **3**, 1345.
- 13 Z. Yin, J. Ye, W. Zhou, Y. Zhang, L. Ding, Y. Gui, S. Yan, J. Li and D. G. Yu, Oxy-Difluoroalkylation of Allylamines with CO₂ via Visible-Light Photoredox Catalysis, *Org. Lett.*, 2018, **20**, 190.
- 14 W. Fu, M. Zhu, G. Zou, C. Xu, Z. Wang and B. Ji, Visible-Light-Mediated Radical Aryldifluoroacetylation of Alkynes with Ethyl Bromodifluoroacetate for the Synthesis of 3-Difluoroacetylated Coumarins, *J. Org. Chem.*, 2015, **80**, 4766.
- 15 (a) J. Wei, D. Gu, S. Wang, J. Hu, X. Dong and R. Sheng, Visible-Light-Mediated Radical Arylthiodifluoromethylation of Isocyanides with Fluorinated 2-Pyridyl Sulfones, *Org. Chem. Front.*, 2018, **5**, 2568; (b) J. Rong, L. Deng, P. Tan, C. Ni, Y. Gu and J. Hu, Radical Fluoroalkylation of Isocyanides with Fluorinated Sulfones by Visible-Light Photoredox Catalysis, *Angew. Chem., Int. Ed.*, 2016, **55**, 2743.
- 16 (a) T. Kleine, R. Frohlich, B. Wibbeling and E. U. Wurthwein, Cyclization Reactions of 3,4-Diazaheptatrienyl Metal Compounds. Pyridines from an Anionic Analogue of the Fischer Indole Synthesis: Experiment and Theory, *J. Org. Chem.*, 2011, **76**, 4591; (b) Y. Li, Y. Zhao, Y. Yang, W. Shi and X. Fan, Revelation solvent effects: excited state hydrogen bond and proton transfer of 2-(benzo[d]thiazol-2-yl)-3-methoxynaphthalen-1-ol, *Org. Chem. Front.*, 2019, **6**, 2780.
- 17 H. Shahroosvand and M. Eskandari, Ultrafast Interfacial Charge Transfer from LUMO+1 in Ruthenium(II) Polypyridyl Quinoxaline-Sensitized Solar Cells, *Dalton Trans.*, 2017, **47**, 561.
- 18 W. j. Fu, X. Han, M. Zhu, C. Xu, Z. Q. Wang, B. M. Ji, X. Q. Hao and M. P. Song, Visible-light-mediated radical oxydifluoromethylation of olefinic amides for the synthesis of CF₂H-containing heterocycles, *Chem. Commun.*, 2016, **52**, 13413.

