Visible Light Promoted β-C-H Alkylation of β-Ketocarbonyls *via* a β-Enaminyl Radical Intermediate

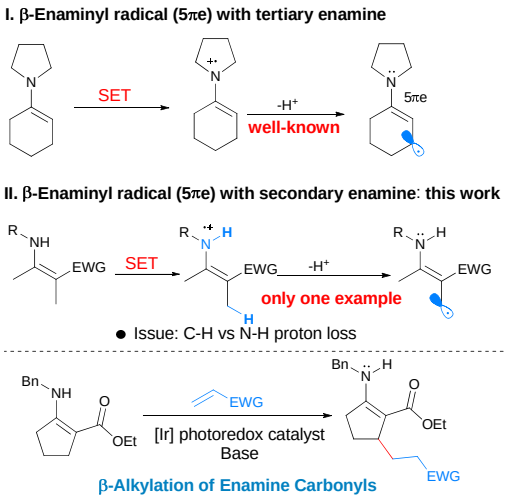
Dehong Wang,[a] Long Zhang [ab] and Sanzhong Luo*[ab]

ABSTRACT A 5πe carbonyl activation mode is reported on the basis of photo-induced SET oxidation of a secondary enamine. The resulted β-enaminyl radical intermediate was trapped by a wide range of Michael acceptors, producing β-alkylation products of β-ketocarbonyls in a highly efficient manner.
KEYWORDS secondary enamine, β-enaminyl radical, C-H alkylation, photoredox catalysis, β-ketocarbonyls

Introduction

As electron rich species, enamine is also redox-labile and can be readily oxidized to radical cation upon single electron transfer.[1,2] MacMillan and others have successfully demonstrated the application of enamine cation radical in asymmetric catalysis, termed as SOMO catalysis.[3] Recently, the same group introduced a unique 5πe carbonyl activation mode *via* β-enaminyl radical intermediate, generated upon SET (single-electron-transfer) with enamine and a subsequent proton loss.[4] Stoichiometric amount of base such as 1, 4-diazabicyclo [2.2.2] octane (DABCO), was required in these cases to facilitate the generation of β-enaminyl radical and the resulted β-functionalizations. On the other hand, 5πe carbonyl activation mode with secondary enamine, derived from the equally prevalent primary amine, has surprisingly remained underdeveloped (Scheme 1).[4d] One easily conceived issue would be the competitive C-H cleavage *vs* N-H cleavage, while only the former proton loss would be productive for β-enaminyl radical process.

Scheme 1. Direct β-alkylation of secondary enamine carbonyls



The β-alkylation of saturated ketones or aldehydes typically requires the use of unsaturated carbonyl substrates and stoichiometric organometallic reagents,[5] and the strategy of direct β-alkylation developed by MacMillan is restricted to aldehydes[4b]. Based on our previous works on secondary enamine carbonyls,[6] we have explored 5πe carbonyl activation with preformed secondary enamine carbonyls under photoredox catalysis[7]. The expected transient β-enaminyl radical intermediate, formed *via* an enamine oxidation/C-H deprotonation sequence, could be intercepted by a Michael acceptor, thus generating the direct β-alkylation products of β-ketocarbonyls .

Results and Discussion

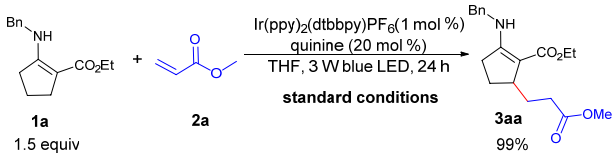
Results

To substantiate our hypothesis, enamine **1a** was synthesized beforehand. Indeed, with appropriate choice of photocatalyst and base, the expected β-alkylation is feasible. Methyl acrylate was initially selected as the electrophilic coupling partner. To our delight, we obtained the desired β-alkylation in nearly quantitative yield (table 1, entry 1), when employing $Ir(ppy)_2(dtbbpy)PF_6$ as photocatalyst and a catalytic amount of quinine as base. Among the photocatalysts screened, only $Ir[(dFCF_3(ppy)_2)]dtbbpy$ could promote the coupling reaction efficiently (entries 5-7). Without the photocatalyst or light, no products were observed (entries 2-3), highlighting the photoresponsive nature of this reaction. Catalytic amount of quinine was suffice to effectively promote the reaction and the reaction even worked to give the desired alkyaltion product in 34% yield without any added base (entry 4). Likely, the enamine itself may serve as a base to assist in proton abstraction. The use of other organic bases such as DABCO, quinulcidine, pyridine, 2, 6-lutidine led to diminished productivity (entries 11-14). On the other hand, the use of ethyl protected quinine resulted in comparable results, indicating the catalysis was mainly related to the tertiary amine moiety, but not the free OH group (entry 15). The reaction generally worked well in aprotic polar solvent and THF was identified as the optimal solvent (entries 8-10)

[a] Key Laboratory of Molecular Recognition and Function, Institute of Chemistry, Chinese Academy of Sciences, Beijing, 100190 (China); College of Chemistry and Chemical Engineering, University of Chinese Academy of Sciences, Beijing, 100490
[b] Collaborative Innovation Center of Chemical Science and Engineering (Tianjin), Tianjin, 300071 (China).
E-mail: luosz@iccas.ac.cn

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/cjoc.201700785

Table 1 Screening and Optimization[a]

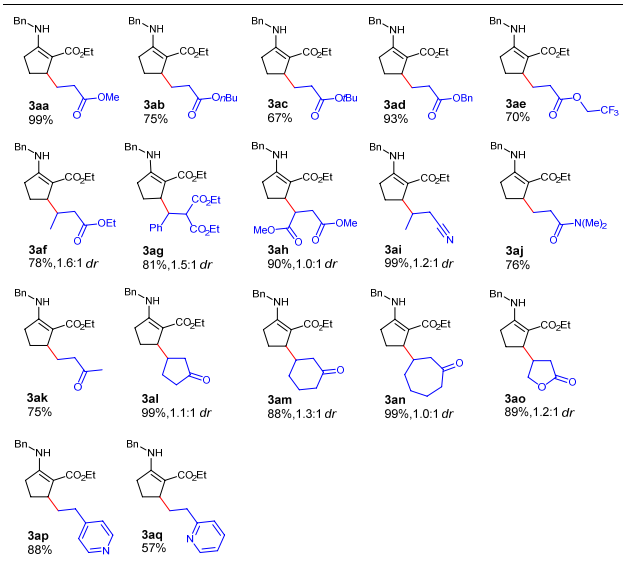


Entry	variation from standard conditions	Yield(%)[b]
1	none	99
2	no $Ir(ppy)_2(dtbbpy)PF_6$	0
3	no light	0
4	no quinine	34
5	$Ru(bpy)_3Cl_2$	0
6	Eosin Y	0
7	$Ir[(dFCF_3(ppy)_2)](dtbbpy)PF_6$	90
8	CH_3CN	95
9	DMF	92
10	CH_2Cl_2	61
11	DABCO[c]	64
12	quinuclidine	72
13	pyridine	45
14	2,6-lutidine	26
15	*O*-Et-quinine	90

[a]Reactions were performed at room temperature in 0.5 mL THF with 1a (0.15 mmol), 2a (0.10 mmol), quinine (20 mol %), photocatalysts (1 mol %) under Ar with 3 W blue LEDs irradiation for 24 h, unless otherwise noted. [b]Isolated yield. [c]When conducted with 1 equiv of DABCO, the yield was 61%

Having identified optimal conditions for this photoredox catalyzed β-alkylation reaction, we first investigated the scope of Michael acceptors (table 2). A broad range of electrophilic olefin acceptors were identified as effective alkylation partners for this protocol. Unsubstituted acrylates with different ester groups were generally tolerated in this direct β-alkylationreaction (**3aa-3ae**). Delightfully, ethyl (E)-crotonate also performed well (**3af**) with 1.6:1 *dr*. When the alkene became more electron-deficient, the reaction worked well with good yields, but low diastereoselectivity (**3ag-3ah**). Notably, both crotononitrile and N, N-dimethylacrylamide were proved to be highly effective acceptors (**3ai-3aj**). Among other electron deficient alkenes, cyclic and acyclic enones, 2-buten-4-olide also worked well to give the alkylation adducts. Unfortunately, the diastereoselectivity was poor in these cases (**3ak-3ao**). 4-Ethenylpyridine and 2-ethenylpyridine have also been examined in the reaction showing good activity (**3ap-3aq**).

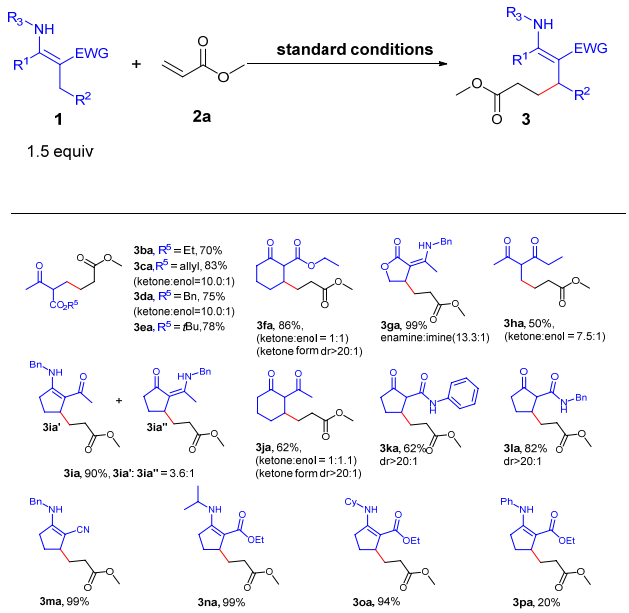
Table 2. Scope of the Michael Acceptors[a]



[a]Reactions were performed at room temperature in 0.5 mL THF with **1a** (0.15 mmol), **2a** (0.10 mmol), quinine (20 mol %), $Ir(ppy)_2(dtbbpy)PF_6$ (1 mol %) under Ar with 3 W blue LEDs irradiation for 24 h, unless otherwise noted. Yields shown were of isolated products. Diastereomeric ratios were determined by ^1H NMR analysis.

We next focused our attention on the scope of the secondary enamine carbonyls coupling partner (table 3). In cases where partial hydrolysis of enamine observed, the product mixture was first worked up with 1 M HCl to give β-alkylation product of β-ketocarbonyl compounds in one port manner. Enamines with different ester moieties including those with sterically bulky tert-butyl ester, benzyl, and allyl groups, afforded the desired alkylation adducts in good yields (**3ba-3ea**). The current catalysis worked well with cyclic enamine esters to give the desired products with high yields. The relatively unstable α-acetybutyrolactone was also amenable to the mild catalytic conditions, furnishing **3ga** in 99% yield. Most delightfully, both cyclic and acyclic 1, 3-diketones were workable substrates under the current conditions (**3ha-3ia**). The enamine **1i** was prepared as a mixture of regioisomers, and the corresponding β-alkylation product was obtained with regioselectivity of 3.6/1. Enamine amides with either N-phenyl or N-benzyl amides were also viable substrates for this reaction (**3ka-3la**). Additionally, enamine **1m** derived from cyclopentanone-2-carbonitrile can also be incorporated in the alkylation reaction to give the desired alkylation adduct **3ma** in a quantitative yield. When other types of enamines derived from isopropylamine, cyclohexylamine and aniline were employed to the coupling reaction, the results were also satisfactory, though the yield of 3pa is relatively low (**3na-pa**). These results set basis for the development of a catalytic asymmetric version using chiral primary amine catalysts.

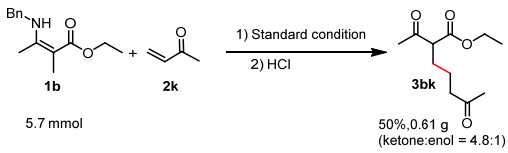
Table 3. Scope of the enamines [a]



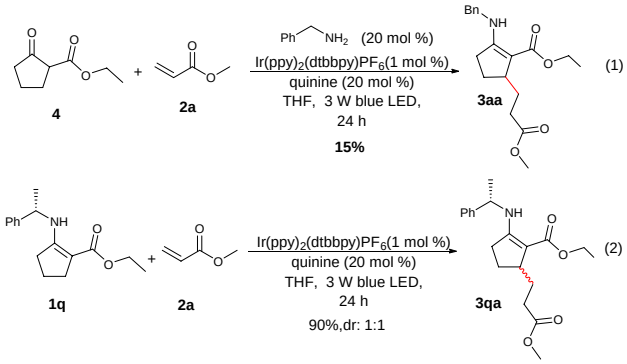
[a]Reactions were performed at room temperature in 0.5 mL THF with **1a** (0.15 mmol), **2a** (0.10 mmol), quinine (20 mol %), $Ir(ppy)_2(dtbbpy)PF_6$ (1 mol %) under Ar with 3 W blue LEDs irradiation for 24 h, unless otherwise noted. Yields shown were of isolated products. Diastereomeric ratios were determined by ^1H NMR analysis. Compounds **3ba-ea**, **3fa**, **3ha** and **3ja-la** were isolated after working up with 1 M HCl and R^3 = Bn

To probe the utility of our method in preparative synthesis, a subgram-scale reaction of enamine **1b** with methyl vinyl ketone **2k** was performed, delivering the alkylation product **3bk** in 50% yield after hydrolysis (Scheme 2). We also examined the direct alkylation of β-ketoester **4** in the presence of catalytic amount of benzyl amine (20 mol %). Enamine ester product **3aa** was obtained in only 15% yield, and it seemed turnover of the enamine intermediate was an issue under the basic conditions (Scheme 3, eq 1). A chiral enamine **1q** was employed to induce chirality at β position, with unfortunately 1:1 *dr* for product **3qa** (Scheme 3, eq 2).

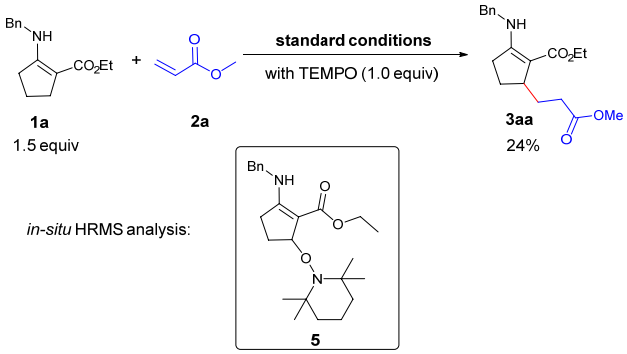
Scheme 2 Subgram-scale and conversion reactions



Scheme 3 Catalytic and asymmetric version



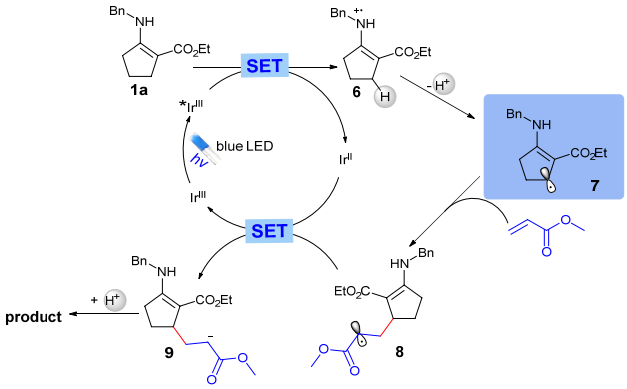
Scheme 4 Control experiments



To shed light on the mechanism, a radical quenching experiment was conducted. The yield of alkylation product was decreased dramatically in the presence of TEMPO (scheme 4). HRMS analysis of the quenched reaction mixture clearly indicated radical trapped adducts **5** from TEMPO. This observation provided direct support to the radical mechanism and the existence of β-enaminyl radical.

A plausible mechanism for this coupling reaction is proposed in Scheme 5. With the irradiation of blue LED, the photoexcited $*Ir^{III}$ acts as a strong oxidant ($E^{1/2*III/II}$ = 0.70 V *vs* Ag/AgCl in CH_3CN) in a single SET event with **1a**, generating radical cation **6** and the reduced photocatalyst Ir^{II}. Stern-Volmer fluorescence quenching experiments (see the Supporting Information for details) indicated that enamine **1a** could quench photoexcited $*Ir^{III}$ efficiently. It is known that SET oxidation could significantly increase X-H acidity[8]. Initial DFT calculation indicated β-C-H (pKa = 0.47) would be more acidic than N-H (pKa = 5.96)[9], deprotonation of the β-C-H of the radical cation **6** would be favored, resulting in the formation of β-enaminyl radical intermediate **7** under the present conditions. The transiently generated species **7** could be rapidly intercepted by an electrophilic Michael acceptor, forging the desired C–C bond while delivering the α-carbonyl radical adduct **8**. Ir^{III} is regenerated upon the oxidation of Ir^{II} by **8**, completing the photoredox catalytic cycle. Finally, the alkylation product is obtained by the protonation of the enolate **9**. The measured quantum yield of the model reaction was Φ=0.35, indicating that a radical chain process may not be involved in the reaction.

Scheme 5. Proposed Mechanism of the β-Alkylation reaction



Conclusions

In conclusion, we have developed a 5πe β-enaminyl activation platform based on secondary enamine, which enabled the direct β-alkylation of β-ketocarbonyls. This method was further demonstrated to be a general approach for direct β-functionalization of β-ketocarbonyls. Mechanistic studies provided direct evidence for the existence of enaminyl radical. Further explorations on developing a catalytic asymmetric variant are currently underway.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2018xxxxx.

Acknowledgement

We thank the Natural Science Foundation of China (21390400, 21521002, 21572232 and 21672217) and the Chinese Academy of Science (QYZDJ-SSW-SLH023) for financial support. S. L. is supported by National Program of Top-notch Young Professionals.

References

[1] For recent reviews on asymmetric aminocatalysis, see: (a) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev*. **2009**, *38*, 2178-2189 (b) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138-6171. (c) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed*. **2008**, *47*, 4638-4660. (d) Barbas, C. F. *Angew. Chem., Int. Ed*. **2008**, *47*, 42-47. (e) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev*. **2007**, *107*, 5471-5569 (f) Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev*. **2007**, *107*, 5416-5470. (g) Marigo, M.; Jørgensen, K. A. *Chem. Commun*. **2006**, 2001-2011. (h) Lelais, G.; MacMillan, D. W. C. *Aldrichimica Acta*, **2006**, *39*, 79-87. (i) List, B. *Chem. Commun.* **2006**, 819-824. (j) Notz, W.; Tanaka, F.; Barbas, C. F. *Acc. Chem. Res*. **2004**, *37*, 580-591.

[2] (a) Schoeller, W. W.; Niemann, J.; Rademacher, P. *J. Chem. Soc., Perkin Trans. 2*. **1988**, 369-373. (b) Renaud, P.; Schubert, S. *Angem Chem. Int. Ed.* **1990**, *29*, 433-434. (c) Shono, T.; Matsumura, Y.; Hamaguchi, H.; Imanishi, T.; Yoshida, K. *Bull. Chem. Soc. Jpn*. **1978**, *51*, 2179-2180. (d) Chiba, T.; Okimoto, M.; Nagai, H.; Takata, Y. *J. Org. Chem*. **1979**, 44, 3519-3523. (e) Audebert, P.; Bekolo, H.; Cossy, J.; Bouzide, A. *J. Electroanaly. Chem*. **1995**, *389*, 215-218. (f) Eilenberg, W.; Schäfer, H. J. *Tetrahedron Lett*. **1984**, *25*, 5023-5026. (g) Narasaka, K.; Okauchi, T.; Tanaka, K.; Murakami, M. *Chem. Lett*. **1992**, *10*, 2099-2102.

[3] (a) Comito, R. J.; Finelli, F. G.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2013**, *135*, 9358–9361. (b) Jui, N. T.; Garber, J. A.; Finelli, F. G.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2012**, *134*, 11400-11403. (c) Pham, P. V.; Ashton, K.; MacMillan, D. W. C. *Chem. Sci*. **2011**, *2*, 1470-1473. (d) Mastracchio, A.; Warkentin, A. A.; Walji, A. M.; MacMillan, D. W. C. *Proc. Nat. Acad. Sci. USA*, **2010**, *107*, 20648-20651. (e) Devery, J. J.; Conrad, J. C.; MacMillan, D. W. C.; Flowers, R. A. *Angew. Chem. Int. Ed*. **2010**, *49*, 6106-6110. (f) Jui, N. T.; Lee, E. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 10015-10017. (g) Van Humbeck, J. F.; Simonovich, S. P.; Knowles, R. R.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2010**, *132*, 10012-10014. (h) Um, J. M.; Gutierrez, O.; Schoenebeck, F.; Houk, K. N.; MacMillan, D. W.C. *J. Am. Chem. Soc*. **2010**, *132*, 6001–6005. (i) Rendler, S.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2010**, *132*, 5027-5029. (j) Wilson, J. E.; Casarez, A. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 11332-11334. (k) Conrad, J. C.; Kong, J.; Laforteza, B. N.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2009**, *131*, 11640-11641. (l) Amatore, M.; Beeson, T. D.; Brown, S. P.; MacMillan, D. W. C. *Angew. Chem. Int. Ed.* **2009**, *48*, 5121-5124. (m) Graham, T. H.; Jones, C. M.; Jui, N. T.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2008**, *130*, 16494-16495. (n) Kim, H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2008**, *130*, 398-399. (o) Jang, H. Y.; Hong, J. B.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2007**, *129*, 7004-7005. p) Beeson, T. D.; Mastracchio, A.; Hong, J. B.; Ashton, K.; MacMillan, D. W. C. *Science*, **2007**, *316*, 582-585.

[4] (a) Jeffrey, J. L.; Petronijević, F. R.; MacMillan, D. W.C. *J. Am. Chem. Soc*. **2015**, *137*, 8404–8407.(b) Terrett, J. A.; Clift, M. D.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2014**, *136*, 6858–6861.(c) Petronijević, F. R.; Nappi, M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2013**, *135*, 18323−18326. (d) Pirnot, M. T.; Rankic, D. A.; Martin, D. B.; MacMillan, D. W. C. *F*.

[5] (a) Rossiter, B. E.; Swingle, N. E. *Chem. Rev*. **1992**, *92*, 771-806. (b) Sibi, M. P.; Manyem, S. Tetrahedron 2000, 56, 8033-8061.

[6] Zhang, L.; Fu, N.; Luo, S. *Acc. Chem. Res*. **2015**, *48*, 986-997.

[7] For recent review on photocatalysis, see: (a) Chen, J.-R.; Hu, X.-Q.; Lu, L.-Q.; Xiao, W.-J. *Acc. Chem. Res*. **2016**, *49*, 1911–1923. (b) Skubi, K. L.; Blum, T. R.; Yoon, T. P. *Chem. Rev*. **2016**, *116*, 10035–10074. (c) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322–5363. For selected examples, see: (a) Liu, Y.; Dong, W. *Chin. J. Chem.* **2017**, *35*, 1491-1500. (b) Wu, J.; Li, J.; Li, H.; Zhu, C. *Chin. J. Org. Chem*. **2017**, *37*, 2203-2210. (c) Zhang, W.-Q.; Li, Q.-Y.; Yang, X.; Ma, Z.; Wang, H.; Wang, X.-J. *Acta Chim. Sinica*. **2017**, *75*, 80-85.(d) Liu, W.; Zheng, X.; Zeng, J.; Cheng, P. *Chin. J. Org. Chem*. **2017**, *37*, 1-19. (e) Wang, D.; Zhang, L.; Luo, S. *Acta Chim. Sinica*. **2017**, *75*, 22-33. (f) Yang, Z.; Li, S.; Luo, S. *Acta Chim. Sinica*. **2017**, *75*, 351-354. (g)Wu, Z.; Wang, J. *Acta Chim. Sinica*. **2016**, *75*, 74-79. (h) Zhou, Q.; Liu, D.; Xiao, W.-J.; Lu, L. *Acta Chim. Sinica*. **2016**, *75*, 110-114. (i) Sun, X.; Yu, S. *Chin. J. Org. Chem.* **2016**, *36*, 239-247.

[8] (a) Qin, Y.; Zhu, L.; Luo, S. *Chem. Rev*. **2017**, **117**, 9433–9520. (b) For an internet bond-energy database: http://ibond.chem.tsinghua.edu.cn.

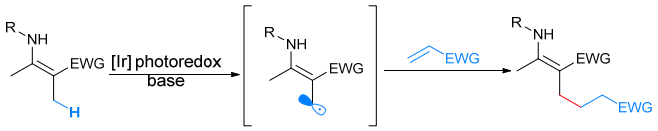
[9] A model enamine ester derived from iso-propylamine was used for DFT calculation.

(The following will be filled in by the editorial staff)
Manuscript received: XXXX, 2017
Revised manuscript received: XXXX, 2017
Accepted manuscript online: XXXX, 2017

Version of record online: XXXX, 2017

Entry for the Table of Contents

Table of contents



β-Alkylation of Enamine Carbonyls

an unprecedented 5πe β-enaminyl activation platform based on secondary enamine, which enabled the direct β-alkylation of β-ketocarbonyls has been established.