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KI/TBHP-mediated oxidative cross-coupling of enamines and carboxylic acids under metal-free conditions: a facile access to functionalized 2*H*-azirines

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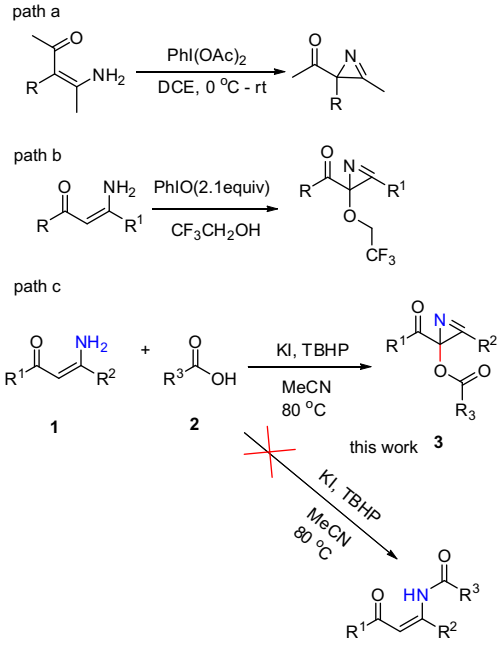
ABSTRACT

KI/TBHP-mediated oxidative cross coupling of enamines with carboxylic acids has been realized for the synthesis of functionalized 2*H*-azirines through the azirination of enamine intermediates. The metal-free strategy has several notable features, including the formation of C–O and C–N bonds in a one-pot procedure, broad functional group tolerance, good reaction yields, short reaction time, and high atom economy. It is the first example for direct formation of functionalized 2*H*-azirines via KI/TBHP-mediated intermolecular cross-coupling of enamines and carboxylic acids.

Heterocycles have drawn extensive and enduring attention for their wide occurrence in natural products, broad range of biological activities, and significant pharmaceutical potentials.[1] The strategy for the rapid synthesis and diversification of novel heterocycles has attracted wide-spread attention from the pharmaceutical industry.[2] Among the various heterocycle compounds, 2*H*-azirines have recently attracted attention in the field of synthetic chemistry and medicinal chemistry because of their manifold reactions, structural characteristics,[3] and unique biological properties.[4] Additionally, 2*H*-azirines are very useful building blocks because of their feasibility of being converted to pyridine,[5a–c] indole,[4a,6] pyrroles,[7] and oxazoles,[8] as well as their applications in the synthesis of other useful intermediate.[9] Therefore, much effort has been devoted to the construction of 2*H*-azirines,[3,4] including the Neber reaction, thermolysis and photolysis of vinyl azides and isoxazoles, elimination or oxidation of aziridine derivatives, intramolecular reactions of *N*-functionalized isoxazoles and oxazaphospholes, and intermolecular coupling reactions between nitriles and carbenes or nitrenes and acetylenes.

Although there are a versatile of diverse strategies for 2*H*-azirine synthesis ranging over numerous reaction types and starting



Scheme 1. Existing methods for construction of α-substituted 2*H*-azirines from enamines.

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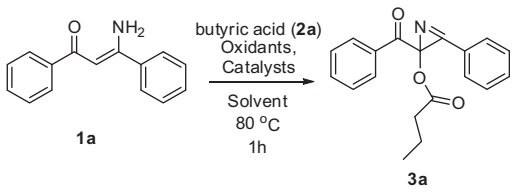
Table 1
Optimization of reaction conditions[a]



Entry	Catalysts (equiv)	Oxidants (equiv)	Solvent	Yield[b] (%)
1[c]	None	PhIO (2.2)	DCM	30
2	TBAI (2)	TBHP (4)	CH_3CN	nd
3	TBAB (2)	TBHP (4)	CH_3CN	nd
4	NBS (2)	TBHP (4)	CH_3CN	Trace
5	NIS (2)	TBHP (4)	CH_3CN	Trace
6	NH_4I (2)	TBHP (4)	CH_3CN	Trace
7	I_2 (2)	TBHP (4)	CH_3CN	nd
8[d]	KI (2)	TBHP (4)	CH_3CN	49
9	**KI (2)**	**TBHP (6)**	**CH_3CN**	**94**
10	KI (2)	TBHP (6)	DMF	0
11	KI (2)	TBHP (6)	THF	40
12	KI (2)	TBHP (6)	1,4-Dioxane	20
13	KI (2)	TBHP (6)	Toluene	67
14	KI (2)		CH_3CN	0
15		TBHP (6)	CH_3CN	0
16	KI (2)	DTBP (6)	CH_3CN	0
17	KI (2)	H_2O_2 (6)	CH_3CN	0
18	KI (2)	m-CPBA(6)	CH_3CN	0

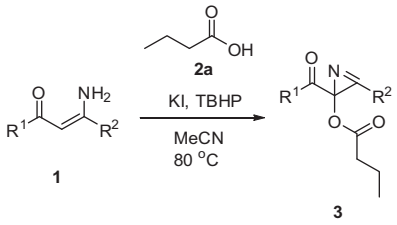
The bold values represent the optimal conditions.
[a] Reaction conditions: the substrates **1a** (1 mmol) was reacted with butyric acid (1 mmol), catalysts and oxidants in solvent (10 mL) for 30 min unless otherwise stated.
[b] Isolated yields.
[c] The reaction was carried out by mixing PhIO (2.2 mmol) and butyric acid (1 mmol) in DCM (10 mL) at rt for 15 min and then adding **1a** (1 mmol in 1 mL of DCM) dropwise at rt.
[d] Incomplete conversions were observed by ^1H NMR analysis.

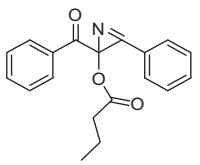
materials, azirination of substituted enamine compounds has been considered as a unique and attractive approach to access this biologically important class of heterocycles (Scheme 1, path a and b).[4] However, compared with the extensive studies on accustomed method for the construction of this useful heterocycles, construction of substituted 2*H*-azirines via metal-free oxidative cross coupling between enamine compounds and nucleophiles has received much less scrutiny. To our knowledge, there are few reports describing direct oxidative functionalization and azirination of enamines under metal-free conditions. A literature search shows that the only existing one example involves a hypervalent iodine-mediated oxidative trifluoroethoxylation and a subsequent azirination of the α-trifluoroethoxylated enamine intermediates[4b] (Scheme 1, path b). Although this strategy based on PhIO-mediated coupling of enamines with trifluoroethanol have achieved important progress,[4b] coupling partner of enamines only limit to trifluoroethanol. Herein, we present the synthesis of acyloxylated 2*H*-azirines via KI/TBHP-mediated cross coupling of enamine and carboxylic acids. Compared with Du's work,[4b] our protocol enables coupling of a wide range of acids with enamines (Scheme 1, path c). To date, there is no precedence of KI/TBHP-mediated methodology with enamines and carboxylic acids as precursors for the synthesis of substituted 2*H*-azirines via a cross coupling approach.

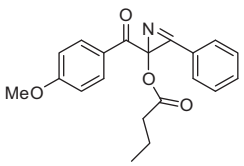
In this Letter, we disclosed an unprecedented cross-coupling reaction between enamines and carboxylic acids through KI/TBHP-mediated oxidative C–O bond and C–N bond formation (Scheme 1, path c). The significance of the present finding is threefold: (1) the atom and step economical synthesis of substituted 2*H*-azirines from simple precursors via direct C–H bond functionalization; (2) inexpensive and metal-free reagents, mild conditions, and avoidance of toxic byproducts; and (3) high reaction selectivity. Our method only provides substituted 2*H*-azirines, instead of an enamide product.[10]

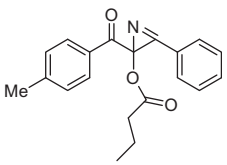
We began our investigation on reaction between (*Z*)-3-amino-1, 3-diphenylprop-2-en-1-one (**1a**) and butyric acid (**2a**) as the model substrate with PhIO (2.2 equiv) in DCM at room temperature, and the desired product **3a** was obtained in 30% yield. Next, the feasibility of reaction was tested with various catalysts and TBHP

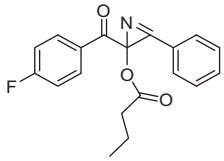
Table 2
Oxidative cross coupling of different enamines with butyric acid **2a**[a]

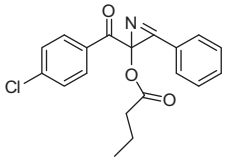


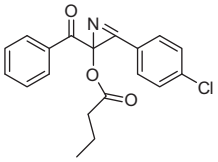

3a, 94%


3b, 63%

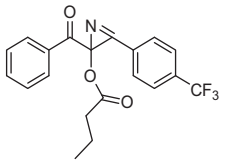

3c, 77%


3d, 69%

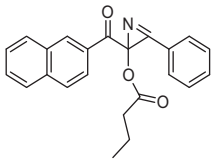

3e, 58%


3f, 56%

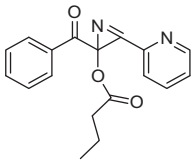
(*continued on next page*)



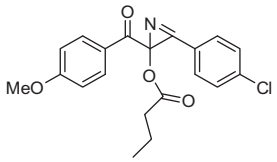
3g, 32%



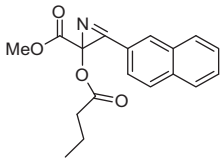
3h, 62%



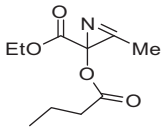
3i, trace



3j, 81%



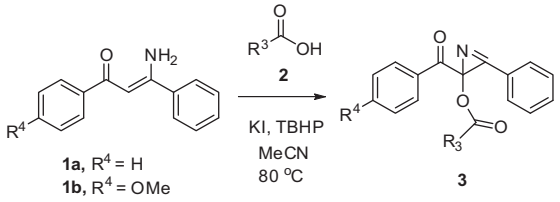
3k, 0%



3l, 0%

[a] Reaction conditions: enamines (1 mmol), butyric acid **2a** (1 mmol) KI (2 mmol), TBHP (6 mmol) in CH_3CN at 80 °C for 30 min under air.

Table 3
Scope of the reaction with enamine and different acids[a]

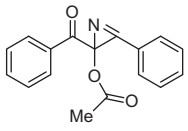


1a, R^4 = H
1b, R^4 = OMe

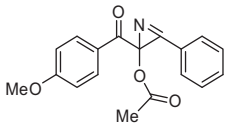
2

KI, TBHP
MeCN
80 °C

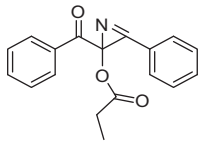
3



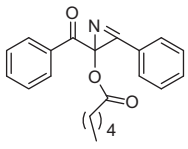
3m, 61%



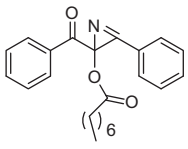
3n, 45%



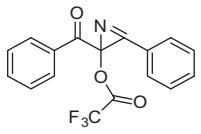
3o, 76%



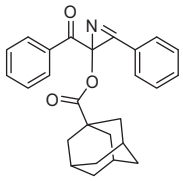
3p, 70%



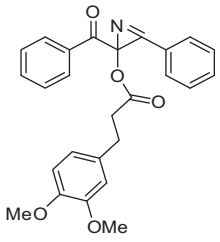
3q, 84%



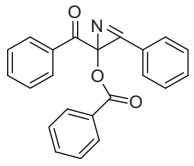
3r,0%



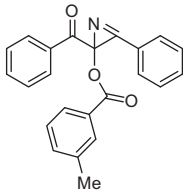
3s, 46%



3t, 65%



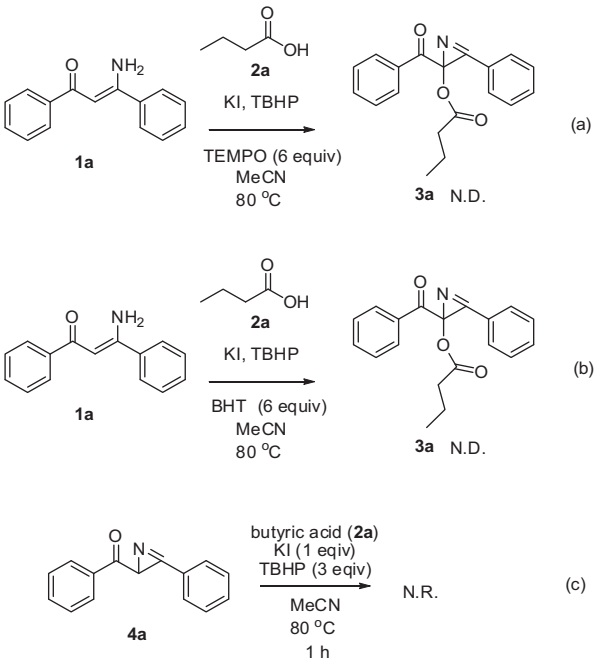
3u, 42%



3v, 30%

[a] Reaction conditions: enamines (1 mmol), acids (1 mmol) KI (2 mmol), TBHP (6 mmol) in CH_3CN at 80 °C for 30 min under air.

(4 equiv) (Table 1, entries 2–8). To our surprise, the desired compound **3a** was achieved in 49% with the recovery of **1a** in 16% yield using KI as catalyst (Table 1, entry 8). Increasing the dosage of the TBHP showed a positive result, with the starting material consumed completely in a short time and the yield improved to 94% (Table 1, entry 9). The solvent study revealed CH_3CN (Table 1, entry

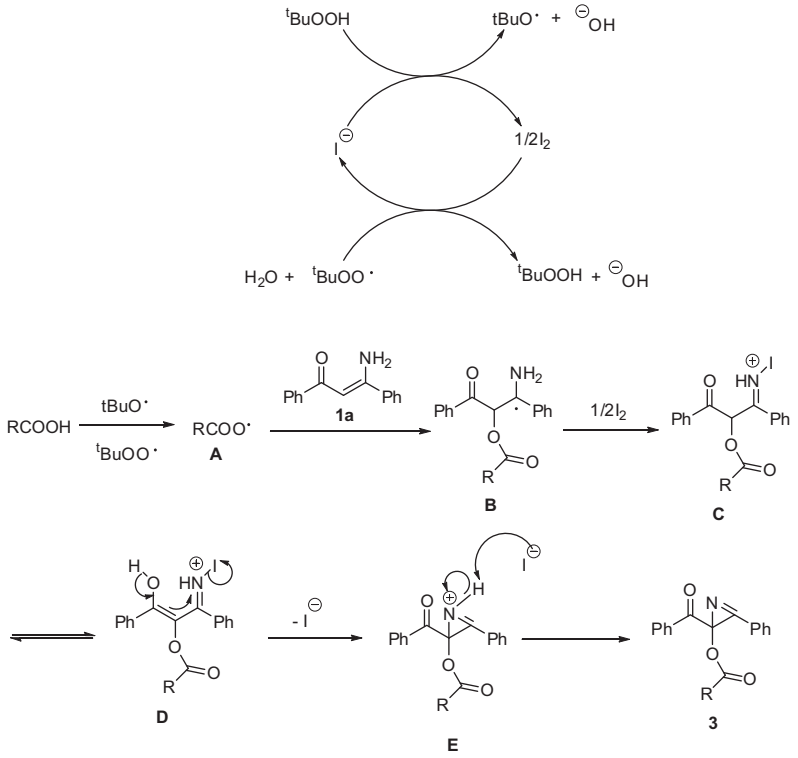


Scheme 2. Several control experiments.

9) as the best solvent (Table 1, entries 10–13). The reaction failed to proceed in the absence of KI or TBHP (Table 1, entries 14 and 15), suggesting that both KI and TBHP are very crucial for the formation of compound **3a**. Unfortunately, with the use of other oxidants such as DTBP, H_2O_2, or m-CPBA, no desired product was detected. Thus, the reaction parameters given in Table 1, entry 9, were the optimal reaction conditions.

With these optimized reaction conditions in hand, we first investigated the scope of enamine compounds (Table 2). Our experiments show that when R^2 is a phenyl group, the reactions allowed installing electron-donating benzene rings having methyl or methoxyl substituents to provide the corresponding product (**3b–3c**) in good yields. Halide substituents such as F, and Cl were also compatible in this transformation (**3d–e**). When R^1 is a phenyl group, the reactions allowed installing electron-withdrawing benzene rings having chloro or trifluoromethyl substituents to provide the corresponding product (**3f** and **3g**) in yields of 56% and 32%, respectively. For the substance containing naphthyl group, the reaction also conveniently afforded the desired product **3h** in a moderate yield (62%). However, for substrates containing heterocyclic ring in place of the phenyl ring, that is, pyridine ring, the reaction cannot afford the desired product **3i**. When R^1 is the *p*-MeO phenyl group and R^2 is the *p*-Cl phenyl group, the reaction also gave the desired product **3j** in 81% yield. The structure of enamine significantly influenced the reaction yield. The reaction did not give any product (**3l** or **3k**) when enamines contained an ester group. On the whole, the reaction was benefited by enamine moiety with aryl group (R^1, R^2 = aryl group, Table 2), hindered by enamine substrates with alkyl and alkoxyl group (R^1 = OMe, OEt, alkyl; R^2 = Me, see Supporting information, Table S1).

To further explore the potential of our methodology, a variety of acids were investigated (Table 3). Generally, aliphatic acids reacted well with enamine **1a** or **1b** to afford **3m–q** in moderate to excellent yields (45–84%). However, the coupling with the trifluoroacetic acid, could not occur to yield the desired product **3r**. In this case, it only afforded 1,3-diphenylpropane-1,3-dione in 27% yield, which is obviously the product from the hydrolysis of substrate **1a**. Notably, the sterically hindered acid did not hinder the reaction, providing the corresponding azirination product in a moderate yield (**3s**, 46%). 3-(3,4-Dimethoxyphenyl)propanoic acids are also suitable reaction substrates, which delivered the desired azirination product **3t** in a moderate yield (65%). The utility of



Scheme 3. Proposed mechanistic pathways.

the protocol was further extended to the reaction of aromatic acids (Table 3, **3u**–**3v**). These substrates exhibited lower reactivity compared to that of the aliphatic acid.

To gain insight into the reaction mechanism, several control experiments were performed. Since peroxides are the most common source of spontaneously induced free radicals, it was supposed that a free-radical process might be involved in the reaction. To ascertain this, 6 equiv of 2,6-di-tert-butyl-4-methylphenol (BHT) and 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) were respectively added as the radical scavenger in the reactions of **1a** and **2a** (Scheme 2, path a and b). Neither of the reactions afforded the corresponding product **3a**. Next, the second query that arose was whether the oxidative cross coupling reaction of enamines and acids occurs first followed by the construction of 2*H*-azirines ring or a reverse sequence operates. In the presence of KI (1 equiv)/TBHP (3 equiv) in CH_3CN, the treatment of intermediate **4a** with **2a** failed to give the desired product **3a** (Scheme 2, path c). This result supports the oxidative cross coupling reaction of enamines and acids occurs first.

Based on previous reports[4,8] and the above results, a possible mechanism was proposed using enamine (**1a**) and butyric acid (**2a**) as an example (Scheme 3). Initially, the *tert*-butoxyl and *tert*-butylperoxy radicals were generated in the catalytic system,[11] and they could abstract a hydrogen atom from acids to generate the radical **A**, which reacted with enamine to give the radical anion **B**, followed by a SET process with iodine to give a species **C**.[11c,d] The intermediate **C** tautomerizes into its enol isomer **D**, which would nucleophilically attack the nitrogen center, with the concomitant release of iodide anion, to produce intermediate **E**.[4a] Finally, the positively charged nitrogen atom in intermediate **E** was deprotonated by the iodide anion and gave the title 2*H*-azirine compound **3**.

In conclusion, we have reported a novel method for the synthesis of the acyloxylated 2*H*-azirines through oxidative cross coupling reaction between the enamines and acids in CH_3CN. The features of the present method include the ready availability of the starting materials, the mild and metal-free reaction conditions, and most significantly, its economic application to the synthesis of a wide range of functionalized 2*H*-azirines. Further studies on the application of this method to other more valuable compounds and detailed investigations of the reaction mechanism are in progress.

Acknowledgments

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Supplementary data

Supplementary data (list of new compounds along with their yield and copies of ^1H NMR and ^{13}C NMR spectra are included) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.02.060. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

1. For selected examples: (a) Payne, P. R.; Garcia, P.; Eisenberger, P.; Yim, J. C.-H.; Schafer, L. L. *Org. Lett.* **2013**, *15*, 4098; (b) Perry, M. A.; Hill, R. R.; Rychnovsky, S. D. *Org. Lett.* **2013**, *15*, 2226; (c) Vidal-Albalat, A.; Rodríguez, S.; González, F. V. *Org. Lett.* **2014**, *16*, 1752; (d) Le, P. Q.; Nguyen, T. S.; May, J. A. *Org. Lett.* **2012**, *14*, 6104.
2. Liu, Y.-J.; Xu, H.; Kong, W.-J.; Shang, M.; Dai, H.-X.; Yu, J.-Q. *Science* **2014**, *515*, 389.
3. (a) Katritzky, A. R.; Wang, M.; Wilkerson, C. R.; Yang, H. *J. Org. Chem.* **2003**, *68*, 9105; (b) Alonso-Cruz, C. R.; Kennedy, A. R.; Rodríguez, M. S.; Suárez, E. *J. Org. Chem.* **2008**, *73*, 4116; (c) Alonso-Cruz, C. R.; Kennedy, A. R.; Rodríguez, M. S.; Suárez, E. *Org. Lett.* **2003**, *5*, 3729; (d) Knoll, W.; Mieusset, J.-L.; Arion, V. B.; Brecker, L.; Brinker, U. H. *Org. Lett.* **2010**, *12*, 2366; (e) Davis, F. A.; Reddy, G. V.; Liu, H. *J. Am. Chem. Soc.* **1995**, *117*, 3651; (f) Moerdyk, J. P.; Bielawski, C. W. *J. Am. Chem. Soc.* **2012**, *134*, 6116.
4. (a) Li, X.; Du, Y.; Liang, Z.; Li, X.; Pan, Y.; Zhao, K. *Org. Lett.* **2009**, *11*, 2643; (b) Sun, X.; Lyu, Y.; Zhang-Negrerie, D.; Du, Y.; Zhao, K. *Org. Lett.* **2013**, *15*, 6222.
5. (a) Jin, L.; Wu, Y.; Zhao, X. *J. Org. Chem.* **2015**, *80*, 3547; (b) Loy, N. S. Y.; Singh, A.; Xu, X.; Park, C.-M. *Angew. Chem., Int. Ed.* **2013**, *52*, 2212; (c) Prechter, A.; Henrion, G.; Bel, P. F.; Gagosz, F. *Angew. Chem., Int. Ed.* **2014**, *53*, 4959.
6. (a) Candito, D. A.; Lautens, M. *Org. Lett.* **2010**, *12*, 3312; (b) Jana, S.; Clements, M. D.; Sharp, B. K.; Zheng, N. *Org. Lett.* **2010**, *12*, 3736.
7. Zhu, Lei; Yu, Y.; Mao, Z.; Huang, X. *Org. Lett.* **2015**, *17*, 30.
8. Liu, X.; Cheng, R.; Zhao, F.; Zhang-Negrerie, D.; Du, Y.; Zhao, K. *Org. Lett.* **2012**, *14*, 5480.
9. Loy, N. S. Y.; Kim, S.; Park, C.-M. *Org. Lett.* **2015**, *17*, 395.
10. Dash, J.; Reissig, H.-U. *Chem. Eur. J.* **2009**, *15*, 6811.
11. (a) Zhao, J.; Li, P.; Xia, C.; Li, F. *Chem. Commun.* **2014**, 4751; (b) Gao, Y.; Song, Q.; Cheng, G.; Cui, X. *Org. Biomol. Chem.* **2014**, *12*, 1044; (c) Majji, G.; Rajamanickam, S.; Khatun, N.; Santra, S. K.; Patel, B. K. *J. Org. Chem.* **2015**, *80*, 3440; (d) Lao, Z.-Q.; Zhong, W.-H.; Lou, Q.-H.; Li, Z.-J.; Meng, X.-B. *Org. Biomol. Chem.* **2012**, *10*, 7869.