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## Introduction

The design of a novel C–C bond forming reaction that relies on naturally occurring functional groups and/or chemical feedstocks as coupling fragments instead of organometallics is an ongoing effort in the synthetic community.<sup>1</sup> One strategy that could be used to satisfy this demand would be the cross-electrophile reaction.<sup>2</sup> This strategy has enabled construction of C–C bonds directly from electrophiles, demonstrating excellent functional group compatibility, and unique selectivity orthogonal to the classic cross-couplings.<sup>3</sup> Over the past years, there have been great achievements in the development of reactions using organic halides (Scheme 1(1)).<sup>2</sup> However, the reactions of C–O electrophiles have been less studied,<sup>4</sup> and there are only isolated examples that have shown the cross-coupling between two C–O electrophiles.<sup>5</sup> The development of such reactions would help expand the applicability of this method, and take advantage of the abundant C–O bonds in natural and artificial products. In this manuscript, we report the coupling reactions between vinyl/aryl and alkyl C–O electrophiles, which enable synthesis of cycloalkenes from ketones and alcohols (Scheme 1(2a)), and selective modification of tyrosine in peptides (Scheme 1(2b)).

Considering the development of reactions between C–O electrophiles, we became interested in the synthesis of

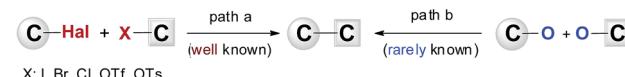
## Ni-catalyzed cross-electrophile coupling between vinyl/aryl and alkyl sulfonates: synthesis of cycloalkenes and modification of peptides†

Jicheng Duan, Yun-Fei Du, Xiaobo Pang and Xing-Zhong Shu  \*

We report here the coupling reactions between vinyl/aryl and alkyl C–O electrophiles that can be derived from chemical feedstocks and naturally occurring functional groups. This method provides an efficient approach to the synthesis of a wide range of functionalized, and/or secondary alkyl substituted cycloalkenes. These compounds are difficult to produce by conventional methods. The reaction proceeds with broad substrate scope, and tolerates various functional groups such as alcohol, aldehyde, ketone, ester, amide, alkene, alkyne, heterocycles, organotin and organosilicon compounds. The synthetic utility of this method has been demonstrated by providing facile access to important building blocks. We also demonstrated the possibility to apply this method for late-stage modification of peptides. A broad range of functionalized alkyl groups could be selectively introduced into tyrosine in peptides via C–C bond formation, which has been a challenge to the existing procedures.

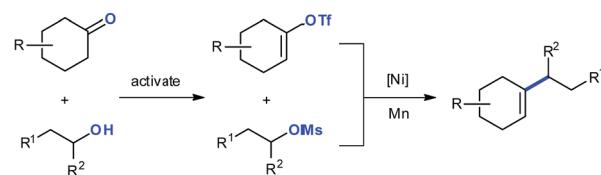
cycloalkenes. Cycloalkenes represent key structural elements in a variety of natural products, pharmaceuticals, and functional materials, and they constitute the foundation for numerous important reactions.<sup>6</sup> Unlike the many synthetic approaches to acyclic alkenes, the synthesis of cycloalkenes is much less advanced and highly relies on chemistry developed decades ago.<sup>7</sup> One of the most reliable methods is the metal-catalyzed cross-coupling reaction using well-defined vinyl species, which circumvents the regio- and stereoselectivity problems associated with conventional alkylation–elimination processes.<sup>8</sup> To

### (1) The cross-electrophile reactions



### (2) This work: The cross-coupling of C–O electrophiles

(a) Synthesis of aliphatic cycloalkenes from ketones and alcohols



(b) Modification of tyrosine in peptides



Scheme 1 The cross-coupling of electrophiles.

State Key Laboratory of Applied Organic Chemistry (SKLAC), College of Chemistry and Chemical Engineering, Lanzhou University, 222 South Tianshui Road, Lanzhou, 730000, China. E-mail: shuxingzh@lzu.edu.cn

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date, this method has received considerable attention,<sup>9</sup> and numerous applications in the field of total synthesis of biologically relevant targets have been found.<sup>10</sup> Despite the impressive advances, much remains to be improved. For instance, the synthesis of highly functionalized and/or secondary alkyl substituted cycloalkenes remains difficult,<sup>7,11</sup> and the requirement for cyclic vinyl metals and alkyl metals is still less than ideal because of their limited availability, and high reactivity profiles.<sup>12</sup>

Encouraged by recent progress in reductive vinylation reactions using organic halides,<sup>13</sup> we wondered about the possibility of constructing aliphatic cycloalkenes from ketones and alcohols through the coupling of their derivatives, vinyl triflates<sup>14</sup> and alkyl mesylates<sup>15</sup> (Scheme 1(2a)). Whereas the former are highly reactive towards oxidative addition to low valent metals (vinyl-OTf  $\gg$  vinyl-Br  $>$  PhBr),<sup>16</sup> unactivated alkyl mesylates remain one of the most challenging substrates in the cross-coupling arena.<sup>17</sup> Such highly mismatched reactivity of two electrophiles means that control of selectivity in the formation of the cross-product would be difficult.<sup>18</sup>

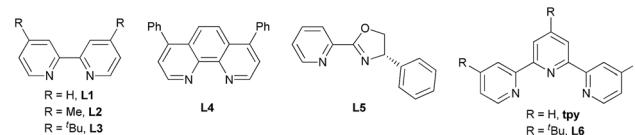
## Results and discussion

With these challenges in hand, we started our investigation by focusing on the reaction of triflate **1a** with **2a** and screening a range of conditions (Table 1, also see Table S1 in the ESI<sup>†</sup>). As expected, our initial studies revealed that, in most cases, vinyl triflate was converted into the protonated and dimerized byproducts, while alkyl mesylate remained intact. Further studies established that performing the reaction with NiI<sub>2</sub> (10 mol%), tpy (15 mol%), and Mn (3.0 equiv.) in DMA at 100 °C gave the best result, affording **3a** with 81% isolated yield (entry 1). The use of NiCl<sub>2</sub> or NiBr<sub>2</sub> gave either trace amounts or a low yield of the desired product, with most of the **2a** recovered, indicating the importance of the catalytic amount of iodide for the activation of alkyl mesylate (entries 2 and 3).<sup>19</sup> This is also consistent with the observation that the use of NaI (0.5 equiv.) improved the reactivity of **2a** under NiBr<sub>2</sub> catalysis, affording **3a** with 63% yield along with a large amount of alkyl-alkyl dimers (entry 3 vs. 4). Most of the **2a** was converted into the alkyl-alkyl dimer when NaI (0.5 equiv.) was used under the standard conditions (entry 1 vs. 5). The bipyridine ligands **L1–L3** and bathophenanthroline **L4**, which proved effective in the vinylation of alkyl halides<sup>13c,h</sup> and arylation of alkyl tosylates,<sup>4f,5</sup> gave **3a** with low yields (entries 6–9). Further studies revealed that the tridentate ligand afforded the best result (entries 1 and 11). The use of Zn instead of Mn gave a trace amount of **3a** (entry 12). The use of TDAE instead of Mn afforded **3a** in 8% yield, suggesting that Mn might act as a reductant in this process (entry 13). No desired product was observed in the absence of either Ni or Mn (entry 14).

With the optimized reaction conditions in hand, we then studied the scope of the reaction with respect to vinyl triflates (Table 2). Cyclic vinyl triflates ranging from five- to eight-membered rings coupled with **2a** to give target products with moderate to good yields (**3a–d**). Nonaromatic heterocycles are prevalent in pharmaceuticals, but their introduction through

Table 1 Nickel-catalyzed reductive coupling of **1a** with **2a**<sup>a</sup>

<b>1a</b>	<b>2a</b> (1.8 equiv.)	10 mol% NiI <sub>2</sub> , 15 mol% tpy Mn (3.0 equiv.), DMA 100 °C, 12 h	<b>3a</b>
Entry		Change of conditions	<b>3a</b> (%)
1	None		87 (81) <sup>b</sup>
2	NiCl <sub>2</sub> instead of NiI <sub>2</sub>		Trace
3	NiBr <sub>2</sub> instead of NiI <sub>2</sub>		15
4	NiBr <sub>2</sub> with NaI (0.5 equiv.)		63
5	NiI <sub>2</sub> with NaI (0.5 equiv.)		38
6	<b>L1</b> instead of tpy		26
7	<b>L2</b> instead of tpy		34
8	<b>L3</b> instead of tpy		28
9	<b>L4</b> (BPhen) instead of tpy		37
10	<b>L5</b> instead of tpy		21
11	<b>L6</b> instead of tpy		77
12	Zn instead of Mn		4
13	TDAE <sup>c</sup> instead of Mn		8
14	No Ni or Mn		0



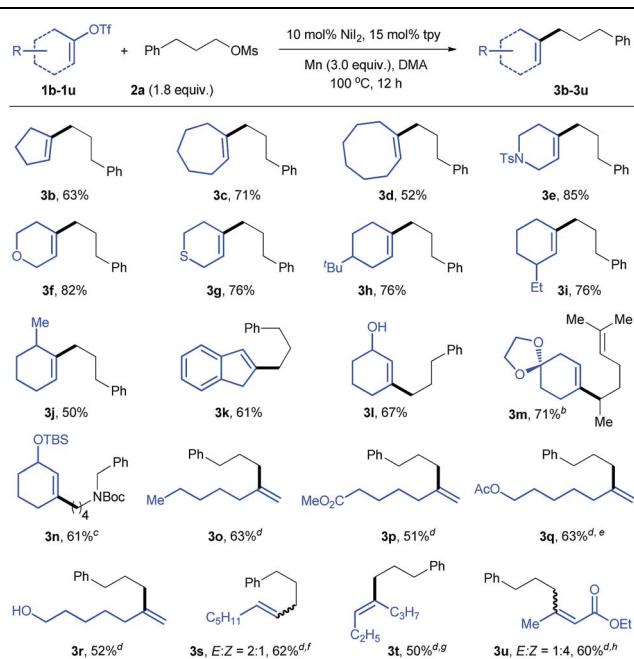
<sup>a</sup> **1a** (0.2 mmol) was used and reacted for 12 h; the yields were determined by GC analysis with dodecane as the internal standard.

<sup>b</sup> Isolated yield. <sup>c</sup> TDAE: tetrakis(dimethylamino)ethylene.

C–C bonds represents a challenge.<sup>20</sup> Under our conditions, various heterocycles such as 3-piperideine (**3e**), 3,6-dihydro-2*H*-pyran (**3f**), and 3,6-dihydro-2*H*-thiopyran (**3g**) were efficiently incorporated into the alkyl chain. Vinyl triflate with a <sup>t</sup>Bu substituent on the ring performed well (**3h**). Unlike vinyl halides, 3- and 6-substituted vinyl triflates were readily available from unsymmetrical ketones and converted into products **3i** and **3j** smoothly. A moderate yield of **3k** was obtained when indenyl triflate was used. Incorporation of functionalized vinyl groups is important to increase the diversity of molecules. In this respect, the reactions of vinyl triflates derived from dicarbonyl compounds gave **3l**, **3m**, and **3n** with moderate yields. The last two compounds are key building blocks in natural product synthesis.<sup>21</sup> Reactions of acyclic vinyl electrophiles were also effective when more reactive alkyl tosylates were employed, affording the desired products with useful yields (**3o–u**).<sup>4f,i,5</sup> The presence of ester and alcohol groups was tolerated (**3p–r**). While the reaction of terminal vinyl triflate **1s** (*E* : *Z* = 1 : 9) afforded **3s** with a ratio of *E* : *Z* is 2 : 1, only the *E*-product was obtained when internal substrate **1t** (*E* : *Z* = 3 : 1) was used (**3t**). On the other hand, the reaction of *Z*-**1u** afforded **3u** in 60% yield with a ratio of *E* : *Z* = 1 : 4, whereas only a trace of **3u** was observed when *E*-**1u** was used. Presently, the reaction of fully substituted vinyl triflates has not been successful.

A wide range of sulfonated alcohols coupled efficiently with vinyl triflate **1e** under the standard conditions (Table 3). The reaction of the  $\beta$ -substituted alkyl electrophile afforded product



Table 2 Scope of vinyl triflates<sup>a</sup>

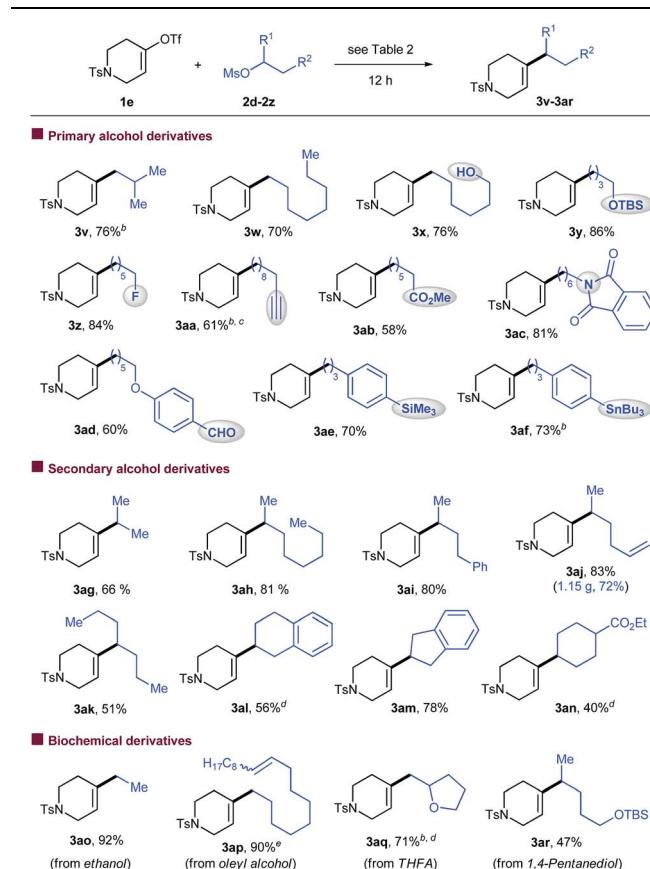
<sup>a</sup> Isolated yields. <sup>b</sup> 6-Methylhept-5-en-2-yl mesylate (2b) was used, NaI (0.5 equiv.),  $80^\circ\text{C}$ . <sup>c</sup> Bn-N(Boc)(CH<sub>2</sub>)<sub>4</sub>-OTs (2c) was used, NaI (0.5 equiv.). <sup>d</sup> Ph(CH<sub>2</sub>)<sub>3</sub>-OTs (2a') was used, NaI (0.5 equiv.),  $60^\circ\text{C}$ . <sup>e</sup> NMR yield. <sup>f</sup> Vinyl triflate 1s (E:Z = 1:9, 3 equiv.) was used. <sup>g</sup> Vinyl triflate 1t (E:Z = 3:1, 3 equiv.) was used. <sup>h</sup> Vinyl triflate Z-1u (only Z isomer) was used.

3v with good yield. A simple long-chain alkyl substrate was converted into 3w smoothly. The reactions were highly chemoselective for the vinylation of alkyl mesylate, leaving a gamut of functionalities such as alcohol (3x), silyl ether (3y), alkyl fluoride (3z), alkyne (3aa), ester (3ab), amide (3ac), and aldehyde (3ad) intact. Both organosilicon (3ae) and organotin (3af) were also tolerated.

Incorporation of secondary alkyl groups at the alkene position remains a significant challenge. Under our conditions, a number of secondary alkyl mesylates coupled with vinyl triflate efficiently (3ag-an). The use of NaI (0.5 equiv.) was necessary to improve the reaction efficiency. Terminal alkene (3aj) and ester groups (3an) were compatible, and substrates derived from cyclic alcohols were also successfully employed (3al-an). The reaction could be scaled up to the gram scale and produced 3aj with 72% yield.

The abundance of alcohols in nature prompted us to investigate vinylation of substrates derived from biochemicals. Mesylates derived from ethanol (3ao) and oleyl alcohol (3ap) were found to be suitable for this transformation, affording the desired products with high yields. The reaction of a substrate derived from tetrahydrofurfuryl alcohol (THFA) gave 3aq with 71% yield. When the 1,4-pentanediol derivative was used, the reaction was highly selective for vinylation of the secondary C-OMs bond over the primary C-OTBS bond (3ar).

Enyne 5 exemplifies the inefficiency of previous approaches to prepare the functionalized aliphatic cycloalkene (Scheme 2a).

Table 3 Scope of alkyl electrophiles<sup>a</sup>

<sup>a</sup> Isolated yields. NaI (0.5 equiv.) was used for secondary alkyl mesylates.

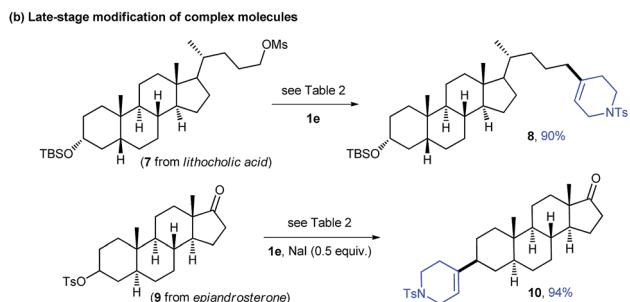
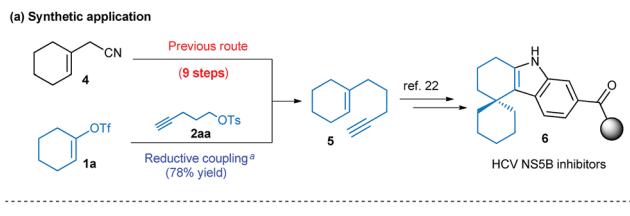
<sup>b</sup> NaI (0.5 equiv.). <sup>c</sup> Alkyl-OTs,  $40^\circ\text{C}$ . <sup>d</sup> Alkyl-OTs. <sup>e</sup> E/Z isomers (4:1).

This compound is an important building block in the synthesis of a number of HCV NS5B inhibitors, and has been prepared in nine steps from nitrile 4.<sup>22</sup> With reductive cross-coupling, a simpler starting material, 1a, can be used and the desired product 5 was accessed in a single step with 78% yield.

The late-stage modification of complex molecules represents a promising approach to alter the pharmacological profiles of natural products. To further demonstrate the utility of our method, we then investigated the vinylation reactions of several biologically active compounds (Scheme 2b). Substrates derived from lithocholic acid and epiandrosterone reacted with 1e efficiently, affording the vinylated products 8 and 10 with 90 and 94% yields, respectively.

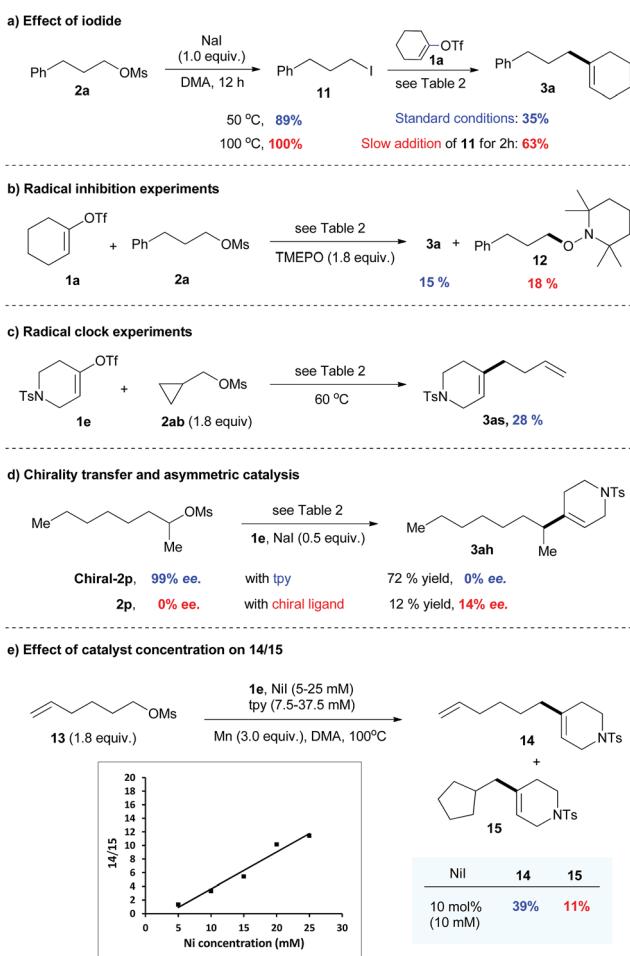
The control experiments shown in Table 1 indicate the importance of the catalytic amount of iodide for the activation of alkyl mesylate (entries 1–5). The observation by GC-MS analysis of tiny amounts of alkyl iodide during the reaction suggests that alkyl mesylate might be activated through mesylate-iodide exchange *in situ*.<sup>19</sup> This prompted us to study the reaction of mesylate 2a with NaI (1.0 equiv.), and it was found that 2a was fully converted into iodide 11 at  $100^\circ\text{C}$  after 12 h (Scheme 3a). While alkyl iodide 11 was too reactive to give good selectivity for the cross-product, the yield of 3a was





**Scheme 2** Synthetic application and late-stage modification of biologically active molecules. <sup>a</sup>Conditions as for Table 2, but NaI (0.5 equiv.), 40 °C was used, reaction for 24 h.

significantly improved by slow addition of **11**. These results indicate that catalytic mesylate/iodide exchange *in situ* is important for the success of this reaction.



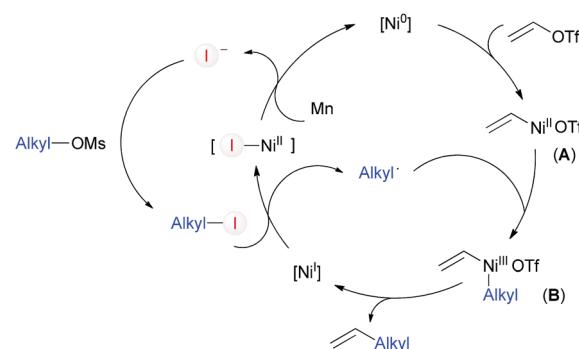
**Scheme 3** Mechanistic studies.

The reaction of **1a** with **2a** was significantly inhibited in the presence of a radical scavenger such as TEMPO (Scheme 3b). The radical trapping product **12** was obtained with 18% yield. The reaction of **1e** with cyclopropyl substrate **2ab** resulted in a ring opening product **3as** with 28% yield (Scheme 3c). The use of the optically pure alkyl mesylate chiral-**2p** gave **3ah** with no enantiomeric excess (ee) under the standard conditions (Scheme 3d). Furthermore, the reaction of racemic **2p** afforded **3ah** with 14% ee when the chiral ligand was used. These results suggest a potential radical mechanism.

To verify a potential radical chain mechanism,<sup>23</sup> we then studied the effect of catalyst concentration on the products of reaction **13** with **1e** (Scheme 3e). Given that the C-centered radical is more easily trapped by the catalyst before cyclization under high catalyst concentration, we expected that, if a radical chain mechanism was followed, the ratio of **14/15** would increase with increasing catalyst concentration. Our results, presented in Scheme 3e, were consistent with this expectation, indicating that a radical chain mechanism may be involved.

Based on the above results and on reports presented by other investigators, we tentatively proposed a catalytic cycle for the coupling between vinyl and alkyl C–O electrophiles as shown in Scheme 4. The oxidative addition of vinyl triflate to Ni(0) would give vinyl-Ni(II) (**A**), which may be trapped by the alkyl radical and undergo reductive elimination to afford the desired product. The alkyl radical may be generated by reaction of alkyl-I with [Ni<sup>I</sup>].<sup>23a</sup> Alkyl-I can be catalytically formed through mesylate/iodide exchange,<sup>19</sup> and iodide will be regenerated during the cycle.

Phenols are common and important structural motifs in natural products like tyrosine. To further illustrate the potential synthetic application of the cross-coupling between C–O electrophiles, we then studied the modification of tyrosine-containing peptides *via* reductive alkylation of the sulfonated phenol group.<sup>24</sup> Late-stage modification of peptides has emerged as a significant task of current interest.<sup>25</sup> The construction of covalent bonds to peptides provides a means of accessing non-natural peptides, which are of key relevance for numerous applied research areas such as asymmetric synthesis, drug delivery, proteomics and diagnosis.<sup>26</sup> Tyrosine is a natural amino acid found in almost all proteins. While various cross-coupling methods have been developed for diversification of



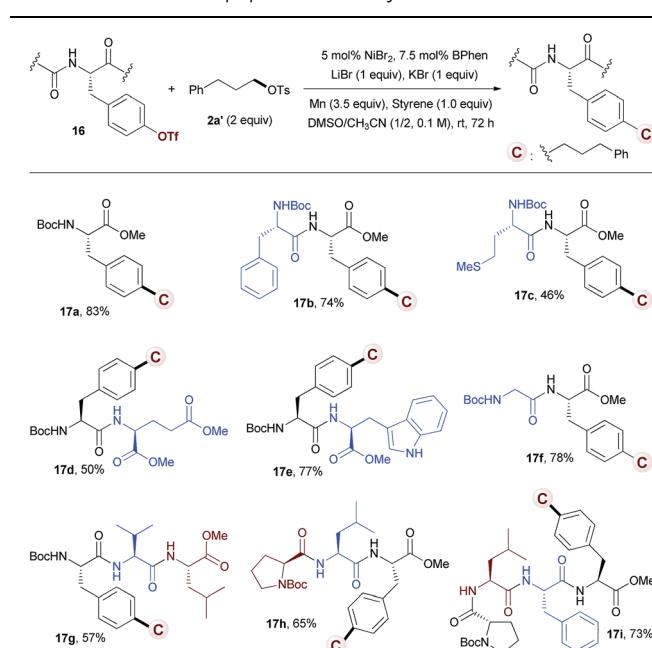
**Scheme 4** Proposed mechanism.

tyrosine in peptides,<sup>27</sup> the introduction of an alkyl group *via* C–C bond formation remains largely unexplored. Moreover, unlike the conventional cross-coupling method that has been widely applied in this area,<sup>27,28</sup> the potential of the cross-electrophile reaction for peptide modification is still waiting to be disclosed.<sup>29</sup>

With these considerations in mind, we started our investigation by studying the reaction of tyrosine **16a** with tosylate **2a'**. However, under the standard conditions for reductive alkylation of vinyl triflates, no desired product **17a** was observed (Scheme S1a†). The use of Hosoya's conditions<sup>13h</sup> that are effective for reductive alkylation of aryl-OTf with alkyl iodide gave a trace of **17a** (Scheme S1b†). Further optimization of the reaction conditions revealed that the use of  $\text{NiBr}_2/\text{BPhen}$  (5/7.5 mol%) as a catalyst,  $\text{LiBr}/\text{KBr}$  (1.0/1.0 equiv.)<sup>30</sup> and styrene (1.0 equiv.) as additives, and  $\text{DMSO}/\text{CH}_3\text{CN}$  as a solvent afforded **17a** in 83% yield (see Tables S3 and S4 in the ESI† for details). Although the role of styrene is presently unclear, the use of styrene (1.0 equiv.) has totally inhibited the protonation of **16a**. The reaction of dipeptide **16b** with alkyl tosylate **2a'** afforded the desired product in 74% yield (Table 4, **17b**). No racemization at the stereogenic centers of the product was observed.<sup>31</sup> A wide range of amino acids, including phenylalanine (**17b**), methionine (**17c**), glutamate (**17d**), tryptophan (**17e**), glycine (**17f**), valine (**17g**), leucine (**17g**), and proline (**17h**), embedded in the peptides are compatible with the reductive conditions. Tyrosines in tripeptides (**17g**, **17h**) and tetrapeptide (**17i**) were alkylated selectively with moderate to good yields.

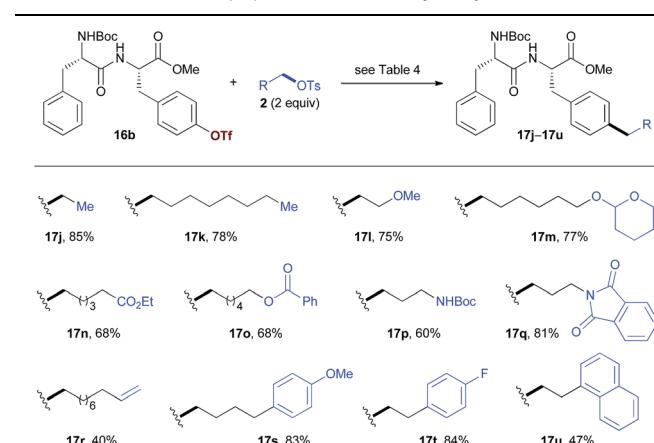
We then studied the scope of the reaction with respect to alkyl tosylates (Table 5). The reactions of **16b** with non-

Table 4 Reactions of peptides with alkyl-OTs **2a'**<sup>a</sup>



<sup>a</sup> Peptide **16** (0.1 mmol) was used, isolated yields.

Table 5 Reactions of peptide **16b** with alkyl tosylates<sup>a</sup>



<sup>a</sup> Peptide **16b** (0.1 mmol) was used, isolated yields.

functionalized alkyl tosylates afforded the products with high yields (**17j**, **17k**). The introduction of functional groups into the peptides can provide the opportunity for further diversification. Alkyl tosylates that bear functional groups such as the methoxy group (**17l**), THP- or benzoyl-protected alcohol (**17m**, **17o**), ester (**17n**), amides (**17p**, **17q**), and alkene (**17r**) coupled with **16b** efficiently. The use of aryl substituted alkyl electrophiles resulted in the products with moderate to high yields (**17s-u**). Unfortunately, in the current stage, attempts to introduce secondary alkyl groups have been unsuccessful.

## Conclusions

In summary, we have demonstrated a coupling reaction between vinyl/aryl and alkyl C–O electrophiles. This reaction enables facile access to a wide range of important, highly functionalized, and secondary alkyl substituted cycloalkenes that are difficult to obtain by conventional methods. This work established a framework for constructing aliphatic cycloalkenes from ketones and alcohols. It also provides an efficient approach for diversification of tyrosine in peptides. It thus expands the number of synthetic options that can be included in retrosynthetic analysis and allows facile modification of biochemicals. The synthetic application of this method, expanding the scope of cross-coupling between C–O electrophiles, and the asymmetric functionalization of C–O bonds are ongoing in our laboratory.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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