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# Copper catalyzed direct alkenylation of simple alkanes with styrenes†

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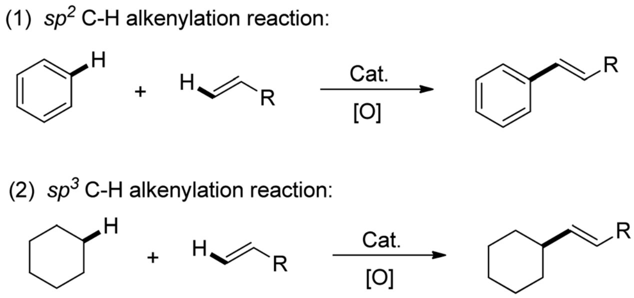
A novel Cu-catalyzed direct alkenylation of simple alkanes with styrenes was described. In the presence of a catalytic amount of $Cu(OTf)_2$, a diverse range of alkenes undergo coupling with cycloalkanes to produce (*E*)-alkyl alkenes. This transformation is proposed to proceed *via* a radical process.

Transition metal catalyzed C–H alkenylation reactions have attracted much attention and emerged as a tremendous challenge in recent years.[1] These transformations provide atom economical methods for replacing simple C–H bonds with readily derivatizable alkene functional groups. As early as 1967, Fujiwara and Moritani reported the first example of Pd-mediated C–H alkenylation of benzene (Scheme 1, eqn (1)).[2] Since then, significant advances have been made in the alkenylation of aromatic C–H bonds through C–H activation catalyzed by a variety of different metals (for example, Pd, Cu, Ni, Co, Rh and Ru).[3] In contrast, the similar process at unactivated alkyl C–H sites remains extremely rare. As far as we know, only two examples of unactivated $sp^3$ C–H olefination were disclosed by the groups of Yu[4] and Sanford[5] using a palladium catalyst and employing *N*-arylamide or pyridine as a neighboring directing group by means of metal insertion. The direct C–H alkenylation of simple alkane substrates (lacking directing or activating groups) is still a great challenge (Scheme 1, eqn (2)).

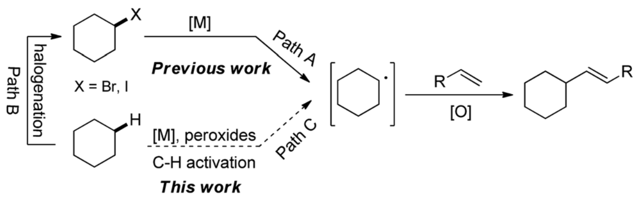
Recently, great achievements have been made in transition metal catalyzed Heck-type reactions of alkyl halides.[6] Different from traditional Heck reactions, mechanistically, the reactions were believed to involve a radical process: firstly, alkyl halides obtained a single electron from the transition metal to generate an alkyl radical, which then undergoes radical addition and oxidation to generate the desired products (Scheme 2, Path A). Usually, alkyl halides are obtained by the halogenation reaction of alkanes[7] (Scheme 2, Path B). The fact that alkanes could be easily converted into the corresponding alkyl radicals in the presence of peroxides[8] inspired us to try the directly coupling of alkanes with alkenes in a novel C–H alkenylation reaction in the presence of peroxides and appropriate metal catalysts. As our preliminary results, herein, we report a novel Cu-catalyzed direct alkenylation of simple alkanes with styrenes (Scheme 2, Path C).

The reaction of 4-chlorostyrene and cyclohexane was chosen as a model reaction to screen the catalysts and conditions.

The results are listed in Table 1. Firstly, various Cu precursors were screened for the reaction at 100 °C in the presence of di-*tert*-butyl peroxide (TBP). No reaction occurred with common Cu(I) salts or a common complex as the catalyst (Table 1, entries 1–4). However, the reaction did proceed when CuOTf or $CuCl_2$ was used and afforded the coupling product in 16% and 12% yield, respectively (Table 1, entries 5–6). To our delight, upon switching the catalyst to $Cu(OTf)_2$, the yield of **3a** was increased to 55% (Table 1, entry 8). Note that no product **3a** could be observed in the absence of any catalyst (Table 1, entry 19). The efficiency of this transformation was dramatically affected by the choice of oxidant. When other oxidants, such as $K_2S_2O_8$, *tert*-butyl hydroperoxide (TBHP), benzoyl peroxide (BPO) and $O_2$



Scheme 1 Transition metal catalyzed C–H alkenylation reactions.



Scheme 2 Coupling reactions of alkenes with alkyl halides or alkanes.

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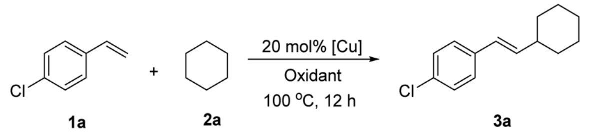
Table 1 Screening of reaction conditions[a]



| Entry | [Cu] | Oxidant | CyH (mL) | Yield[b] (%) |
|---|---|---|---|---|
| 1 | CuI | TBP | 3 | <5 |
| 2 | CuBr | TBP | 3 | <5 |
| 3 | CuCl | TBP | 3 | <5 |
| 4 | $Cu(MeCN)_4PF_6$ | TBP | 3 | <5 |
| 5 | CuOTf[e] | TBP | 3 | 16 |
| 6 | $CuCl_2$ | TBP | 3 | 12 |
| 7 | $Cu(OAc)_2$ | TBP | 3 | <5 |
| 8 | $Cu(OTf)_2$ | TBP | 3 | 55 |
| 9 | $Cu(acac)_2$ | TBP | 3 | <5 |
| 10 | $Cu(OTf)_2$ | $K_2S_2O_8$ | 3 | 0 |
| 11 | $Cu(OTf)_2$ | TBHP | 3 | 0 |
| 12 | $Cu(OTf)_2$ | BPO | 3 | 0 |
| 13 | $Cu(OTf)_2$ | $O_2$ | 3 | 0 |
| 14 | $Cu(OTf)_2$ | TBP | 2 | 51 |
| 15 | $Cu(OTf)_2$ | TBP | 4 | 82 |
| 16 | $Cu(OTf)_2$ | TBP | 5 | 83 |
| 17 | $Cu(OTf)_2$ | TBP | 4 | 61[c] |
| 18 | $Cu(OTf)_2$ | TBP | 4 | 65[d] |
| 19 | — | TBP | 4 | 0 |

[a] Reaction conditions: $Cu(OTf)_2$ (0.1 mmol), 4-chlorostyrene (0.5 mmol), TBP (1.5 mmol) at 100 °C for 12 h. [b] Isolated yield. [c] Temperature was 80 °C. [d] 10 mmol% $Cu(OTf)_2$ was used. [e] $(CuOTf)_2 \cdot C_6H_6$ was used as the source of CuOTf.

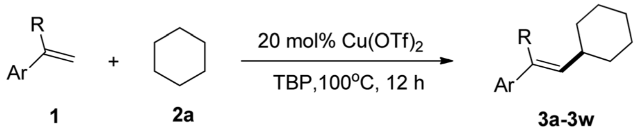
were used instead of TBP, no desired product was detected (Table 1, entries 10–13). The effects of temperature and the amount of cyclohexane on the reaction were also investigated, and the best yield could be obtained when the reaction was performed in the presence of 4 mL cyclohexane for 0.5 mmol alkene at 100 °C (Table 1, entry 14). Therefore, the optimized reaction conditions are: $Cu(OTf)_2$ (20 mol%), TBP (3 equiv.), at 100 °C for 12 h in the presence of 4 mL cyclohexane for 0.5 mmol alkene (for more details, see ESI†).

With the above optimized conditions in hand, the scope of the double C–H coupling of cyclohexane with other styrene derivatives was tested and the results were listed in Table 2. On the whole, the reaction was aided by electron donating groups and hindered by electron withdrawing groups attached to the styrene aromatic ring. Styrene bearing electron donating groups and weak electron withdrawing groups reacted smoothly under the optimized conditions to form the corresponding esters in good yields (**3a–f**, **3h–i**). With strong electron withdrawing groups, the yield of the product decreased remarkably (**3j**). In the extreme, substrates bearing highly electron-withdrawing groups, such as *p*-nitrostyrene, were completely unreactive (**3g**). It was evident that the steric properties of the substituents had no effect on the yield of the desired product. For example, a sterically demanding substrate such as 2,4,6-trimethylstyrene also worked well in this catalytic system and afforded the corresponding product in 75% yield (**3k**). Additionally, naphthalenyl groups were also employed (**3o** and **3p**). Specifically, all these reactions exclusively formed the (*E*)-alkyl product.

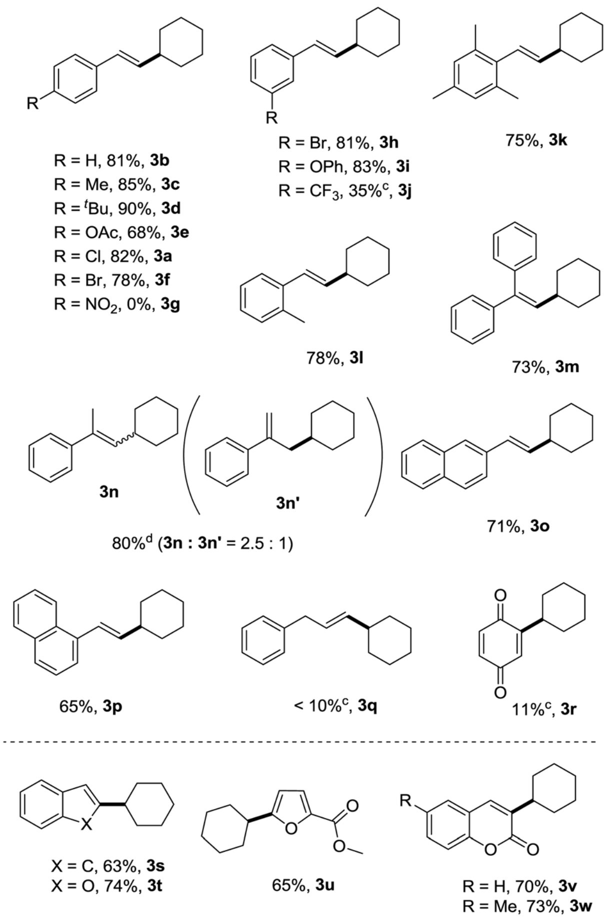
Substituents on the α-position of the styrene (**3m** and **3n**) had little or no effect on the yield; however, a 2.5 : 1 olefin isomerization mixture was obtained for **3n**. The protocol was ineffective for aliphatic olefins; when allyl benzene and quinone were used in the catalytic system, only trace amounts of product were detected by $^1H$ NMR (**3q** and **r**).

This protocol is also compatible with a range of cyclic olefins and heterocyclic aromatics such as indenes, furans and coumarins (**3s–w**). It is worth pointing out that our Cu-catalyzed oxidative coupling process only gave single isomers for these substrates, which contrasts sharply with the typical outcome of

Table 2 Generality of substrates[a]



Yield of products **3a-3w** (%)[b]



R = H, 81%, **3b**
R = Me, 85%, **3c**
R = $^tBu$, 90%, **3d**
R = OAc, 68%, **3e**
R = Cl, 82%, **3a**
R = Br, 78%, **3f**
R = $NO_2$, 0%, **3g**

R = Br, 81%, **3h**
R = OPh, 83%, **3i**
R = $CF_3$, 35%[c], **3j**

75%, **3k**

78%, **3l**

73%, **3m**

**3n** **3n'**
80%[d] (**3n** : **3n'** = 2.5 : 1)

71%, **3o**

65%, **3p**

< 10%[c], **3q**

11%[c], **3r**

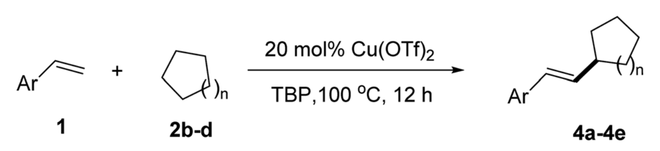
X = C, 63%, **3s**
X = O, 74%, **3t**

65%, **3u**

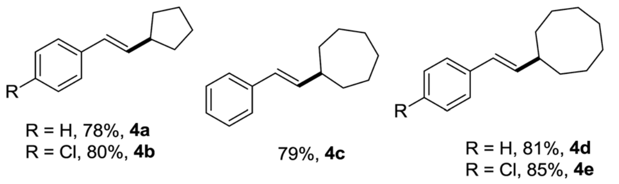
R = H, 70%, **3v**
R = Me, 73%, **3w**

[a] Reaction conditions: $Cu(OTf)_2$ (0.1 mmol), alkene (0.5 mmol), cyclohexane (4 mL) and TBP (1.5 mmol) at 100 °C for 12 h. [b] Isolated yield. [c] Yield determined by $^1H$ NMR. [d] *E*/*Z* was 3 : 1.

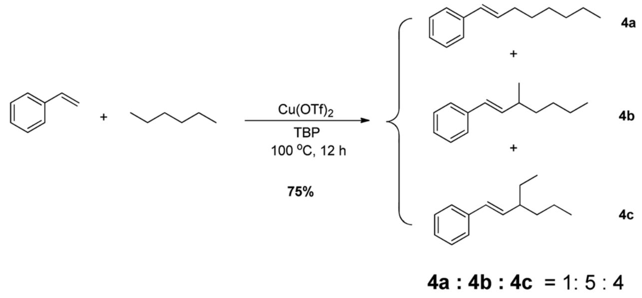
Table 3 Generality of substrates[a]



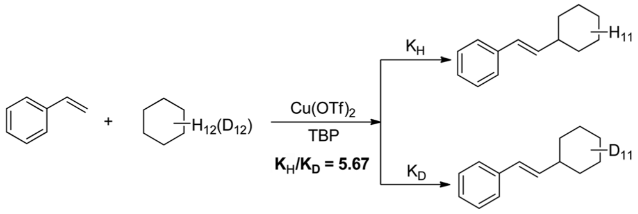
Yield of products **4a-4e** (%)[b]



[a] Reaction conditions: $Cu(OTf)_2$ (0.1 mmol), alkene (0.5 mmol), cycloalkanes (4 mL) and TBP (1.5 mmol) at 100 °C for 12 h. [b] Isolated yield.



Scheme 3 Reaction of styrene and hexane.

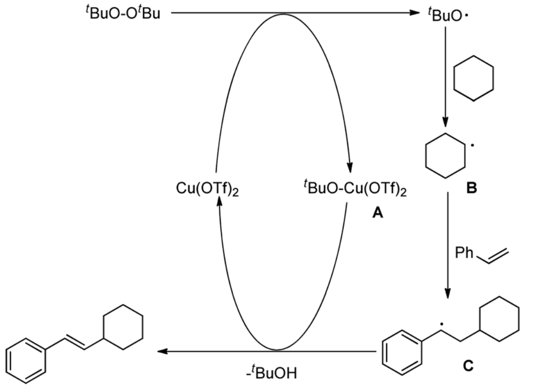


Scheme 4 Kinetic isotope effect experiment.

Heck reactions on these substrates. Usually, Heck reactions on indenes and furans afford mixtures of positional isomers.[9]

In an endeavor to expand the scope of the methodology, the catalytic system was applied to other alkanes. We were pleased to find that other cycloalkanes such as cyclopentane, cycloheptane and cyclooctane also worked well and all gave the desired products in good yields (Table 3, **4a–e**). However, when hexane was used in the catalytic system, mixed products were obtained due to the existence of three different C–H bonds in hexane (Scheme 3, see ESI†).

To gain insight into the catalytic pathway of this Cu-catalyzed C–H alkenylation reaction, we conducted some control experiments under the standard reaction conditions. Radical scavengers, such as TEMPO and BHT, were employed in the standard reaction, and no desired coupling product was detected. This result suggested that a single electron transfer process (SET) was involved in the present oxidative Heck reaction. Further, a kinetic isotope effect was determined by comparing the product ratio of **3b** with **3b–D$_{11}$** under the standard conditions (Scheme 4, see ESI†). The observed significant primary isotopic effects ($k_H/k_D = 5.67$) indicated that the sp$^3$ C–H bond cleavage step was involved in the rate-limiting step of this transformation.



Scheme 5 Proposed reaction mechanism.

Although the mechanistic details of this transformation are not clear at the moment, on the basis of the above results and previous reports,[10] a plausible mechanism for the present process can be proposed as shown in Scheme 5. First, $Cu(OTf)_2$ donates an electron to TBP to generate Cu(III) species **A** and the *tert*-butoxy radical, which then abstracts a hydrogen atom from the alkane to generate the alkyl radical **B**. The radical addition of **B** to the alkene gives the benzylic radical **C**, which is believed to undergo direct oxidation by deprotonation to release the final product. Meanwhile, the $Cu(OTf)_2$ is regenerated to continue the catalytic cycle.

## Conclusions

In summary, a first example of intermolecular Cu-catalyzed double C–H coupling of styrenes with unfunctionalized hydrocarbons was reported. This process constitutes a user-friendly and operationally simple reaction for preparing (*E*)-alkyl substituted alkenes under mild reaction conditions. Studies of the detailed mechanistic aspects and applications of this C–H bond functionalization strategy in other C–H functionalization reactions are currently in progress in our lab.

## Acknowledgements

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