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Copper-Catalyzed Oxidative Alkenylation of C (sp^3)–H Bonds *via* Benzyl or Alkyl Radical Addition to β-Nitrostyrenes

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A new method for the preparation of (*E*)-β-alkylstyrene derivatives has been developed *via* the addition of benzyl or alkyl radical to β-nitrostyrenes using *di*-tert-butyl peroxide (DTBP) as oxidant in the presence of Cu powder catalyst. The C-H bond in various toluene derivatives, ethers, alkanes and alcohols were successfully converted into C-C bond to yield the (*E*)-β-alkylstyrene derivatives in moderate to good yields.

Introduction

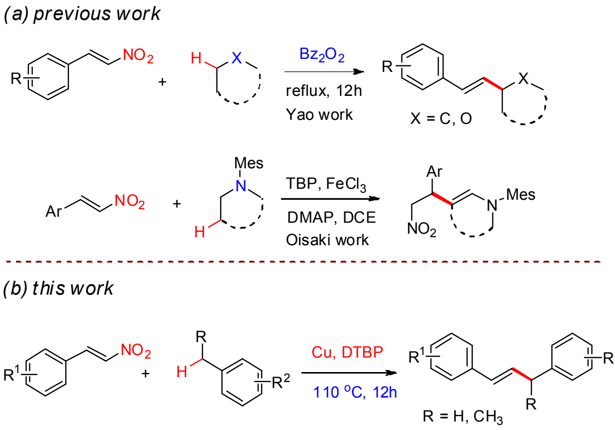
The direct oxidative C(sp^3)-H functionalization *via* radical pathway has been extensively exploited for the formation of C–X (X=C, O, S et al) bond in recent years.[1] Among the direct C(sp^3)-H functionalization methods, the C(sp^3)–H adjacent to heteroatom such as O and N atom attracts great attention via radical process. [2] The oxidative C–H bond of benzylic substrates also achieved much progress and various benzylic hydrocarbons have been used as benzyl radical coupling partners.[3]

β-nitrostyrenes are a kind of flexible intermediates used in many classes of reactions.[4] It has been shown that nitro olefins could undergo free-radical addition to generate (*E*)-β-alkylstyrenes.[5] In 2003, Yao group described a radical addition-elimination reaction of β-nitrostyrenes with the C(sp^3)-H bond adjacent to O atom in cylic ethers.[5a] Recently, Kanai discovered a Fe-catalyzed direct dehydrogenative functionalization of tertiary amines *via* activation of the unactivated C (sp^3)-H bond (Scheme 1, *a*). [5e]

Inspired by recent reports on the oxidative benzyl radical coupling reaction [3] and continue to our oxidative radical coupling research.[2h-2j] We envisioned an oxidative alkenylation coupling reaction between toluene derivatives and β-nitrostyrenes is possible *via* activation of the benzylic C-H bonds through radical pathway.[6] In view of this, we herein, for the first time, present a facile copper-catalyzed benzylation reaction of β-nitrostyrenes with no prefunctionalized toluene derivatives as benzylation reagents (Scheme 1, *b*).

Results and discussion

Initially, the reaction of β-nitrostyrene (1a) and toluene (2a) was selected as the model to optimize the reaction conditions with different catalysts and oxidants (table 1). Interestingly, β-nitrostyrene (1a) could react with toluene (2a) using 1 mol% $Pd(OAc)_2$ as the catalyst in the presence of 2 equiv DTBP, providing the product of 3aa in 45% yield (entry 1). Encouraged by this result, other commercially available transition metal catalysts were investigated. Lower yields were obtained when using $PdCl_2$, $(CH_3CN)_2PdCl_2$, CuBr, CuI and CuO as catalyst (entry 2-6), Cu_2O and $Cu(OAc)_2$ afforded good yields (entries 7-8). Surprisingly, the inexpensive copper powder achieved the best yield (entry 9).

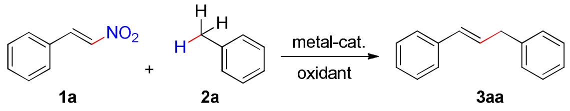


Scheme 1. Scope of Application of β-nitrostyrenes

Other oxidants or radical initiators such as TBHP (*tert*-butyl hydroperoxide), BPO (benzoyl peroxide), $PhI(OAc)_2$ and $(NH_4)_2S_2O_8$, were tested. It was found the TBHP and BPO were less efficient than DTBP (entries 10-11) and no reaction occurred when $PhI(OAc)_2$ and $(NH_4)_2S_2O_8$ were used (entries 12-13). It was worth noting that the reaction proceeded poorly in the absence of copper powder or oxidant (entries 14-15). Among the reaction temperatures examined, it turned out that the reaction at 110 °C gave the best result (entries 16-17). Prolonging the reaction time to 24h, the amount of catalyst could be reduced to 0.2 mol % and still lead to good yield (entry 18).

With the optimized condition in hand, the scope of the reaction with a variety of β-nitrostyrenes was investigated (Table 2). From the result of table 2, we could found that β-nitrostyrenes with electron-donating substituent gave moderate to good yields of the products (entries 1-4). However, the di-methyl or methoxy substituted β-nitrostyrenes showed relatively lower efficiency (entries 5-6). β-nitrostyrenes with electron-withdrawing groups such as chlorine, fluorine and trifluoromethyl groups on the aromatic ring showed good efficiency and the products **3ah**, **3ai** and **3aj** were observed in 85 %, 88 %, 86 % yields, respectively (entries 8-10). Additionally, the bulky (*E*)-1-(2-nitrovinyl) naphthalene was also a good substrate for this coupling reaction with 82% yield obtained (entry 7). It is noteworthy that heteroaryl *β*-nitrostyrenes could also be used as the denitrylative coupling partners with toluene to produce the desired (*E*)-*β*-alkylstyrenes in moderate yields (entries 11-12). *Ortho*- and *meta*- positions substituted *β*-nitrostyrene also afforded the corresponding products in good yields (entries 13-16). It is very interesting that the same product of **3aa** was obtained in 80% yield when the isomer of (*Z*)-*β*-nitrostyrene (**1a'**) was used (entry 1[c]) and the (*Z*)-product was not observed from the GC-MS and ^{1}H NMR spectra.

Table 1. Optimization of the reaction conditions [a]



entry	Catalyst	Oxidant	yield (%) [b]
1	Pd(OAc)$_2$	DTBP	45
2	PdCl$_2$	DTBP	32
3	(CH$_3$CN)$_2$PdCl$_2$	DTBP	40
4	CuBr	DTBP	48
5	CuI	DTBP	42
6	CuO	DTBP	51
7	Cu$_2$O	DTBP	80
8	Cu(OAc)$_2$	DTBP	81
9	Cu	DTBP	**84**
10	Cu	TBHP	76
11	Cu	BPO	77
12	Cu	PhI(OAc)$_2$	N.R. [c]
13	Cu	(NH$_4$)$_2$S$_2$O$_8$	N.R. [c]
14	Cu	-	N.R. [c]
15	-	DTBP	12
16	Cu	DTBP	45[d]
17	Cu	DTBP	81[e]
18	Cu	DTBP	80[f]

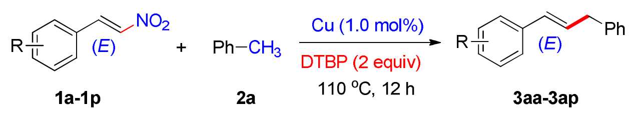
[a] Catalytic conditions: *β*-nitrostyrene (0.5 mmol), toluene (3.0 mL), catalyst (1.0 mol%), oxidant (2.0 equiv.) at 110 °C under an argon atmosphere for 12 h. [b] Isolated yield. [c] Not detected by GC-MS. [d] At 90 °C. [e] At 120 °C. [f] copper (0.1mol%) for 24h.

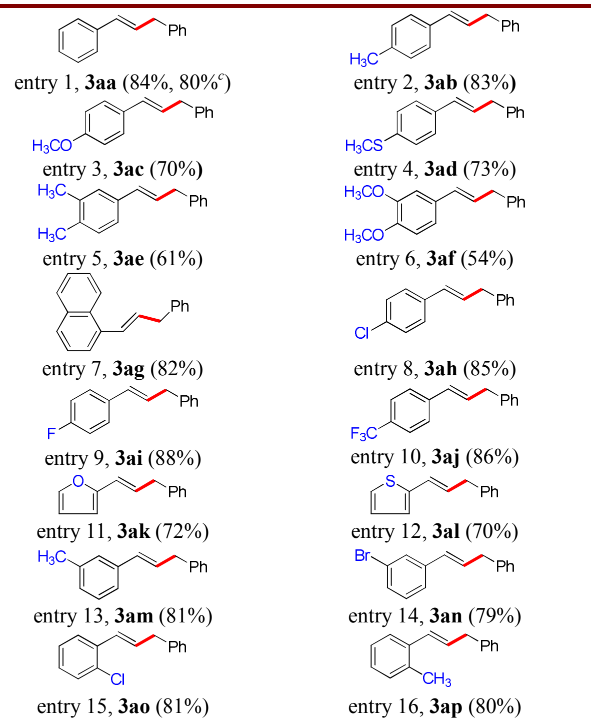
Subsequently, the scope of different C–H bond in benzylic hydrocarbons were also investigated (Table 3). Toluene derivatives such as *p*-xylene, *m*-xylene, *o*-xylene, ethylbenzene and mesitylene all worked well and were effectively converted into the corresponding (*E*)-*β*-alkylstyrenes in moderate to good yields. Interestingly, the reaction of different xylenes and mesitylene with (*E*)-*β*-nitrostyrenes only yielded its mono-coupling products without affecting the other methyl group.

From the results of table 3, it can also be seen that the reaction of (*E*)-*β*-nitrostyrenes containing an electron-withdrawing group with toluene derivatives are more efficient with good yield (enties 3, 8, 13, 20) than that of *β*-nitrostyrenes containing an electron-donating group which only led to a moderate yield (enties 1-2, 5-7,10-12, 14-17, 19). On the other hand, it was observed that the reaction activity of toluene derivatives especially the mesitylene is better than toluene with shorter time and good yield, which is probably due to the higher activity of the intermediate radical under the oxidative conditions. Only moderate yields were obtained when heteroaromatic and *di*-methyl groups were introduced into the aromatic ring of (*E*)-*β*-nitrostyrenes (enties 4, 9, 18, 21). It should be noted that this system shows poor functional group tolerance for toluene derivatives and no desired product was obtained when those substituents such as X (F, Cl, Br, I), CH$_3$O, CH$_3$CO, CH$_3$COO, CN and NO$_2$ are on the aromatic ring of toluene derivatives under the reaction conditions (entry 22).

A number of other compounds containing C(sp^3)–H bonds such as alkanes, ethers and alcohols could also be directly functionalized by (*E*)-*β*-nitrostyrenes under the optimized conditions (Table 4). This radical-addition nitro-elimination reaction of (*E*)-*β*-nitrostyrenes with hydrocarbons such as cyclopentane, cyclohexane, cyclooctane, norbornane and adamantane produced the corresponding products in 81%, 83%, 85%, 78% and 84% yields, respectively (entries 1-5). Moreover, ethers such as tetrahydrofuran and 1,4-dioxane could also act as the effective substrates in the coupling reactions with (*E*)-*β*-nitrostyrenes (entries 6-7). It was noteworthy that the α-C-H bonds in simple alcohol could also be activated, giving hydroxyl-containing products in good yield (entries 8-9).

Table 2. Reaction of *β*-nitrostyrenes with Toluene [a,b]



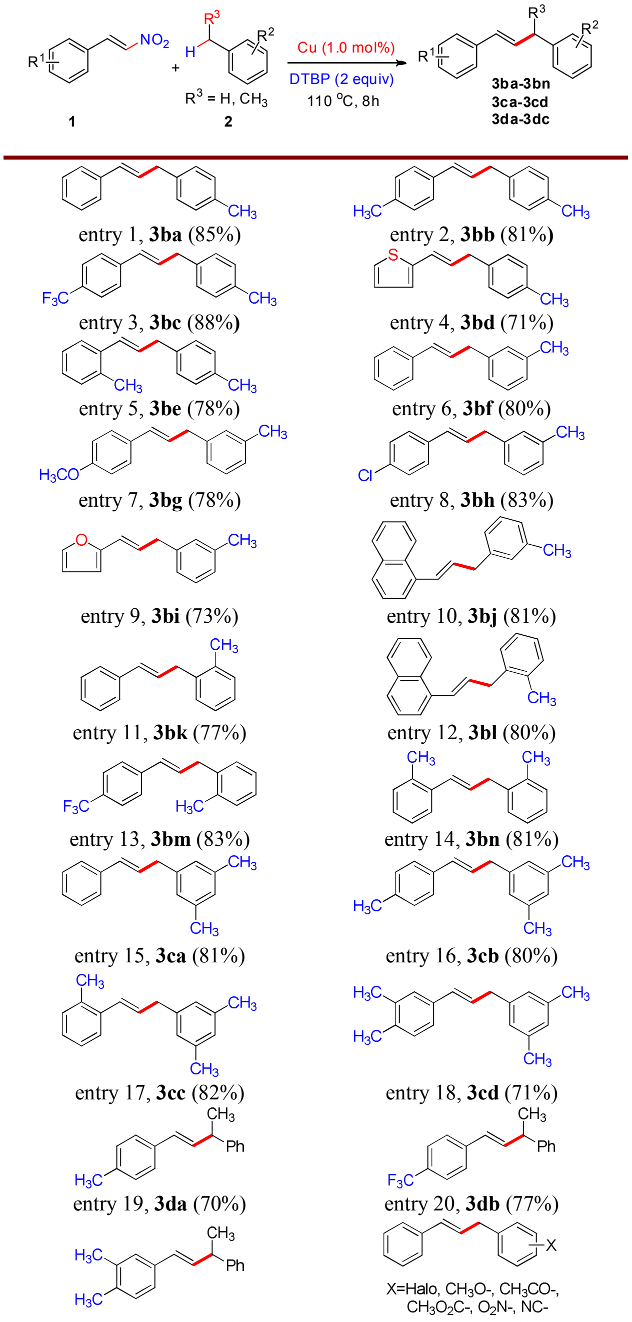


entry 1, **3aa** (84%, 80%[c])
entry 2, **3ab** (83%)
entry 3, **3ac** (70%)
entry 4, **3ad** (73%)
entry 5, **3ae** (61%)
entry 6, **3af** (54%)
entry 7, **3ag** (82%)
entry 8, **3ah** (85%)
entry 9, **3ai** (88%)
entry 10, **3aj** (86%)
entry 11, **3ak** (72%)
entry 12, **3al** (70%)
entry 13, **3am** (81%)
entry 14, **3an** (79%)
entry 15, **3ao** (81%)
entry 16, **3ap** (80%)

[a] Reaction conditions: [a] Catalytic conditions: *β*-nitrostyrene (0.5 mmol), toluene (3.0 mL), Cu powder (1.0 mol%), oxidant (2.0 equiv.) at 110 °C under an argon atmosphere for 12 h. [b] Isolated yield.[c]

To investigate the details of the mechanism for this new reaction, we performed some additional experiments. In the absence of toluene, only denitro-methylation product was obtained (Scheme ***2a***). Adding the radical scavengers such as TEMPO or BHT (2,4-di-tert-butyl-4-methylphenol) into the reaction system, no product obtained (Scheme **2b**). In addition, an intermolecular competing kinetic isotope effect (KIE) experiment was carried out and it was observed with the $k_H/k_D = 5.6$ (*Scheme* **2c**).[3a-3c] Those two experiments indicate that the hydrogen abstraction of the sp^3 C–H bond should be involved in this procedure.

Table 3. Coupling of β-Nitrostyrenes with Arenes [a, b]

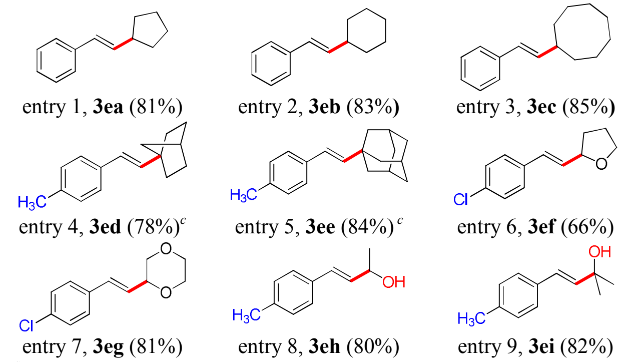


entry 1, **3ba** (85%)	entry 2, **3bb** (81%)
entry 3, **3bc** (88%)	entry 4, **3bd** (71%)
entry 5, **3be** (78%)	entry 6, **3bf** (80%)
entry 7, **3bg** (78%)	entry 8, **3bh** (83%)
entry 9, **3bi** (73%)	entry 10, **3bj** (81%)
entry 11, **3bk** (77%)	entry 12, **3bl** (80%)
entry 13, **3bm** (83%)	entry 14, **3bn** (81%)
entry 15, **3ca** (81%)	entry 16, **3cb** (80%)
entry 17, **3cc** (82%)	entry 18, **3cd** (71%)
entry 19, **3da** (70%)	entry 20, **3db** (77%)
entry 21, **3dc** (56%)	entry 22, (0%)

[a] Reaction conditions: β-nitrostyrene (0.5 mmol), arenes (10 equiv), DCE (1.0 mL), Cu powder (1.0 mol%), oxidant (2.0 equiv.) at 110 °C under an argon atmosphere for 8 h. [b] Isolated yield.

Based on previous observations and similar literature reports,[2, 4] a possible mechanism was proposed as shown in Scheme 3. Firstly, DTBP decomposes to the *tert*-butoxyl radical, methyl radical and ketone in the presence of copper. Next hydrogen is extracted from the C-H bond of methyl in toluene, giving the benzyl radical. Then addition of benzyl radical to the β-position of carbon–carbon double bond in β-nitrostyrenes generates a radical intermediate. Finally, the radical intermediate formed the product *via* an elimination of $\cdot NO_2$ free radical.[5] Unfortunately, the exact role of copper salts and how do it catalyze this transformation is still unclear, but it should be noted that the reaction did not work well in absence of metal-catalyst.

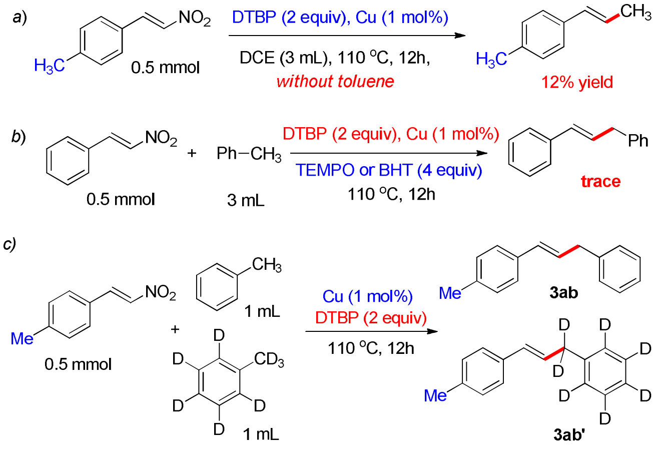
Table 4. Copper-Catalyzed Denitro-Coupling Reaction of β-Nitrostyrenes with Alkanes, Ethers and Alcohols[a,b]



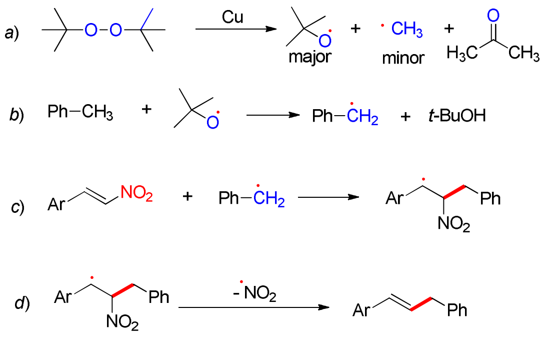
entry 1, **3ea** (81%)	entry 2, **3eb** (83%)	entry 3, **3ec** (85%)
entry 4, **3ed** (78%)[c]	entry 5, **3ee** (84%)[c]	entry 6, **3ef** (66%)
entry 7, **3eg** (81%)	entry 8, **3eh** (80%)	entry 9, **3ei** (82%)

[a] Reaction conditions: β-nitrostyrene (0.5 mmol), alkanes (or alcohols, 10 equiv), DCE (2.0 mL), Cu (1.0 mol%), DTBP (2.0 equiv.) at 110 °C under argon atmosphere for 8 h. [b] Isolated yield. [c] alkanes (3.0 equiv).

Scheme 2. Investigation into the Reaction Mechanism



Scheme 3. A Proposed Mechanism



Conclusions

In summary, this work demonstrates a novel Cu promoted approach for the stereospecific synthesis of (*E*)-*β*-alkylstyrenes through the denitro-coupling reaction of *β*-nitrostyrenes with benzylic hydrocarbons, ethers, alkanes and alcohols. Various substituted *β*-nitrostyrenes could be ready to proceed *via* the radical addition and denitro-elimination mechanism. In addition, compared with the traditional method to synthesis of the (*E*)-*β*-alkylstyrenes and its derivatives, the direct C-C bond construction *via* activation of the sp^{3} C-H bond in this work might be novel and attractive in radical chemistry. Further investigation of this procedure including extension of the substrate scope and disadvantage is underway in our laboratory.

Experimental

General information

Column chromatography was generally performed on silica gel (100-200 mesh) and reactions were monitored by thin layer chromatography (TLC) using UV light (254 nm) to visualize the course of the reactions. The ^{1}H (300 MHz and ^{13}C NMR (75 MHz) data were recorded on Bruker AV300 spectrometers using $CDCl_3$ as solvent. The chemical shifts (δ) are reported in ppm and coupling constants (J) in Hz. ^{1}H NMR spectra was recorded with tetramethylsilane (δ = 0.00 ppm) as internal reference; ^{13}C NMR spectra was recorded with $CDCl_3$ (δ = 77.500 ppm) as internal reference.

2. Typical Experimental Procedure:

An oven-dried Schlenk tube (15 mL) was charged with *β*-nitrostyrenes (0.5 mmol, 1.0 equiv) and Cu powder (1.0 mol %). The tube was evacuated and backfilled with argon (three times). DTBP (1 mmol, 2.0 equiv) and the benzylic hydrocarbon (3.0 mL) were added by syringe. The tube was then sealed and the mixture was stirred for 8-12h at 110 ^{o}C. Upon completion of the reaction, the mixture was diluted with EtOAc. The solvent was then removed under vacuum. The residue was purified with column chromatography on silica gel (eluent gradient of EtOAc/hexane, 1:40 to 1:5) to give the corresponding products **3** in the yields listed in Tables **2, 3, 4**.

Acknowledgements

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Notes and references

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

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Copper-Catalyzed Oxidative Alkenylation of C (sp^3)–H Bonds *via* Benzyl Radical or Alkyl Addition to *β*-Nitrostyrenes

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A new method for the preparation of (*E*)-*β*-alkylstyrene derivatives has been developed *via* the addition of benzyl or alkyl radical to *β*-nitrostyrenes using *di*-tert-butyl peroxide (DTBP) as oxidant in the presence of Cu powder catalyst. The C-H bond in various toluene derivatives, ethers, alkanes and alcohols were successfully converted into C-C bond to yield the corresponding (*E*)-*β*-alkylstyrene derivatives in moderate to good yields.