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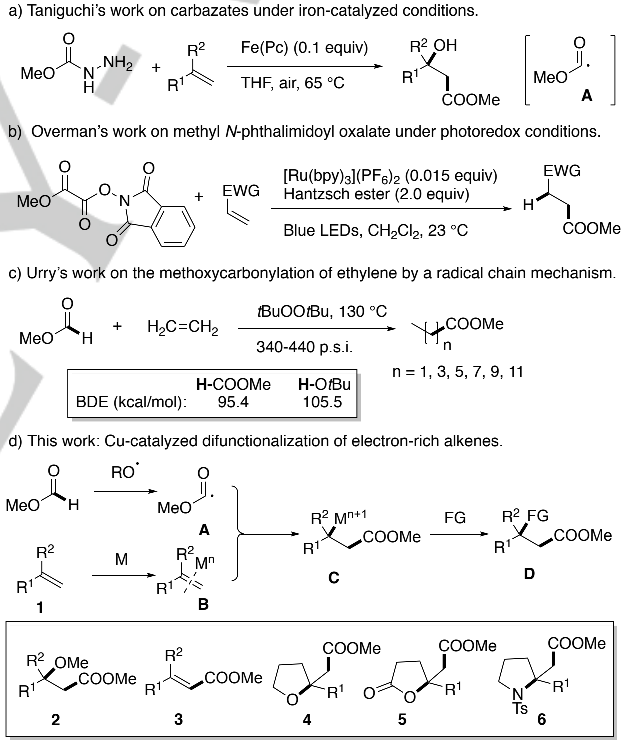
Copper-Catalyzed 1,2-Methoxy Methoxycarbonylation of Alkenes with Methyl Formate

Balázs Budai, Alexandre Leclair, Qian Wang, Jieping Zhu*

Abstract: *Here we report a copper-catalyzed 1,2-methoxy methoxycarbonylation of alkenes by an unprecedented use of methyl formate as a source of both the methoxy and the methoxycarbonyl groups. This reaction transforms styrene and its derivatives to value-added β-methoxy alkanoates, cinnamates as well as medicinally important five-membered heterocycles such as functionalized tetrahydrofurans, γ-lactones and pyrrolidines. A ternary β-diketiminato-Cu(I)-styrene complex, fully characterized by NMR spectroscopy and X-ray crystallographic analysis, is capable of catalyzing the same transformation. Our finding suggests that pre-coordination of electron-rich alkenes to copper might play an important role in accelerating the addition of nucleophilic radicals to electron-rich alkenes and could have general implications in the design of novel radical-based transformations.*

Intramolecular addition of alkoxycarbonyl radicals, generated *in situ* by reduction of carbonic acid derivatives (ROCOX, X = Cl, SePh, TePh), onto tethered alkenes is known for years[1] and has been successfully used in the total synthesis of complex natural products.[2] Intermolecular Minisci-type alkoxycarbonylation of electron-poor heteroaromatics has also been developed.[3] On the other hand, examples on the difunctionalization of alkenes initiated by intermolecular addition of alkoxycarbonyl radicals remained rare. In this regard, Taniguchi and coworkers reported the first examples of iron-catalyzed oxidative 1,2-hydroxy methoxycarbonylation of electron-rich alkenes using carbazates as precursors of methoxycarbonyl radical **A** (Scheme 1a).[4] Overman and Slutskyy demonstrated that **A**, generated from methyl *N*-phthalimidoyl oxalate under visible light photoredox conditions, reacted only with electron-poor Michael acceptors to afford 1,4-dicarbonyl compounds and defined **A** as nucleophilic,[5] rather than ambiphilic radical proposed previously based on computational studies (Scheme 1b).[6-9] Other potentially explosive, toxic and corrosive chemicals[3,10-14] have also been developed for the generation of methoxycarbonyl radical **A**. However, these earlier investigations focused primarily on the generation, rather than the synthetic application of **A**.

As an abundant commodity chemical produced over 770,000 metric tons a year, methyl formate would be an ideal precursor of methoxycarbonyl radical **A** from the viewpoint of synthetic efficiency and sustainability. From the bond dissociation energy (BDE) of MeOC(O)-H (95.4 kcal/mol)[15] and *t*BuO-H (105.5 kcal/mol, Scheme 1), it is reasonable to expect that *t*-butoxy radical would be able to abstract the hydrogen from methyl formate to generate **A**. Indeed, Urry *et al.* in their seminal work demonstrated that heating a mixture of methyl formate with di-*t*-butylperoxide in an autoclave (130 °C, ethylene, 340-440 p.s.i.) afforded a mixture of homologated alkanoates (Scheme 1c).[16] The result indicated that both *t*-BuO· and the alkyl radical RCH_2· are capable of abstracting a hydrogen from methyl formate. However, the competing oligomerization processes rendered this chain process synthetically insignificant.


a) Taniguchi's work on carbazates under iron-catalyzed conditions.

b) Overman's work on methyl *N*-phthalimidoyl oxalate under photoredox conditions.

c) Urry's work on the methoxycarbonylation of ethylene by a radical chain mechanism.

d) This work: Cu-catalyzed difunctionalization of electron-rich alkenes.

Scheme 1. Methoxycarbonyl radical: Generation and synthetic application.

To address the aforementioned challenges, we sought to develop a non-chain difunctionalization process combining the radical addition reaction with the metal-catalyzed transformation. Assuming that the presence of iron salt in Taniguchi's protocol might be responsible for the apparent contradictory results of Taniguchi and Overman regarding the electronic properties of radical **A**, a working hypothesis was advanced as shown in Scheme 1d. Coordination of electron-rich alkenes to a metal would afford metal-π complex **B** with decreased LUMO energy of the double bond,[17] facilitating therefore the addition of nucleophilic methoxycarbonyl radical **A**.[18] Functionalization of the carbon-metal bond would then furnish the β-functionalized

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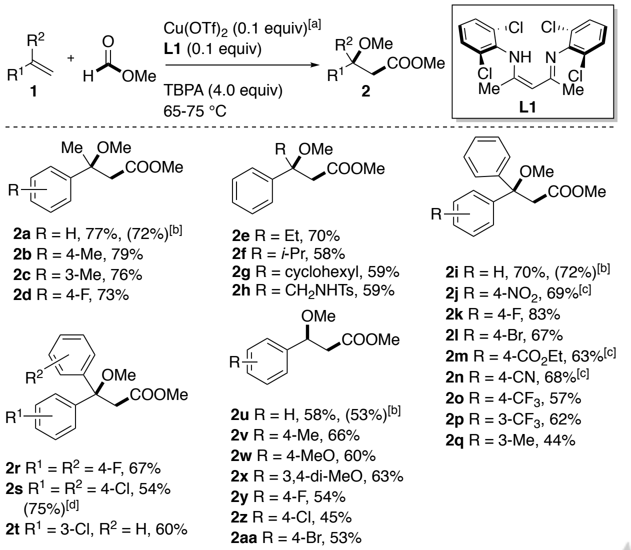
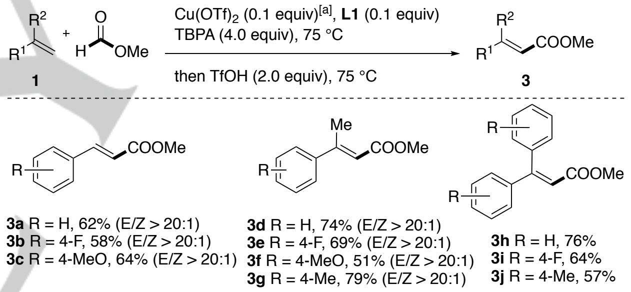
alkanoate **D** with concurrent regeneration of the catalytic species. We report herein the realization of this unprecedented transformation that converts unactivated alkenes **1** to β-methoxy alkanoates **2** (FG = OMe) under copper catalysis.[19] The versatility of the process is illustrated by the ready access to other important structural motifs such as cinnamates **3**, tetrahydrofurans **4**, γ-lactones **5** and pyrrolidines **6** by slightly modifying the work-up procedure and the nature of the substituents of the starting materials **1**.



Scheme 2. Cu-catalyzed reaction of electron-rich alkenes with methyl formate: Synthesis of β-methoxy alkanoates. [a] Reaction was performed at 0.25 mmol scale in methyl formate (*c* 0.1 M). [b] Gram-scale experiment. [c] The reaction was performed at 85 °C. [d] Yield based on conversion.

α-Methyl styrene (**1a**, R^1 = Ph, R^2 = Me, Scheme 2) was chosen as a test substrate. In our initial experiments, the β-methoxy alkanoate **2a** was indeed isolated, albeit with a very low yield. Efforts were therefore dedicated to optimize this novel 1,2-methoxy methoxycarbonylation process by varying systematically the copper salts, the ligands, the peroxide and the reaction temperature (see SI for details). The key observation was summarized as follows: a) Cu(OTf)$_2$ turned out to be the catalyst of choice and *tert*-butyl peroxyacetate (TBPA) was the best source of the alkoxy radical; b) diketimines stood out as a ligand of choice from those screened (phenanthrolines, bisquinolines, bipyridines, Pybox, bisoxazolines, salens) and **L1** derived from pentane-2,4-dione and 2,6-dichloroaniline outperformed other differently substituted diketimines; c) the reaction outcome was very sensitive to the reaction temperature. At the optimum temperature of 75 °C, the reaction proceeded quickly and the product **2a** remained stable for hours under the reaction conditions. At higher temperatures (85 °C), partial degradation of **2a** occurred as the reaction proceeded. Overall, performing the reaction of **1a** in methyl formate (*c* 0.1 M) in the presence of *tert*-butyl peroxyacetate (TBPA), a catalytic amount of Cu(OTf)$_2$ and ligand **L1** (0.1 equiv) at 75 °C under nitrogen atmosphere afforded **2a** in 77% isolated yield. Of mechanistic importance, the efficiency of this transformation decreased significantly when MeOH was used as co-solvent (HCOOMe/MeOH = 2:1, 22% NMR yield), in sharp contrast to other Cu-catalyzed carboetherification of alkenes developed previously in this laboratory.[20]

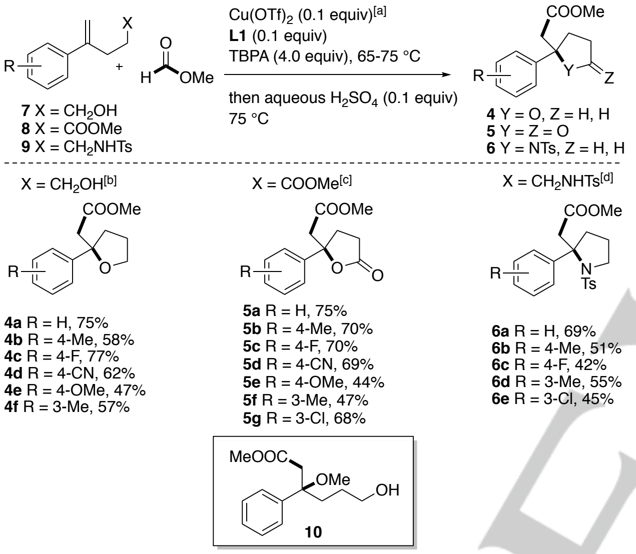
The scope of this transformation was next explored (Scheme 2). The terminal alkenes bearing an alkyl and an aryl substituent were converted to the corresponding β-methoxy alkanoates (**2a**-**2h**) regardless of the steric and stereoelectronic effect of the substituents. The 1,1-diaryl substituted ethylenes participated in the reaction without event (**2i**-**2t**). More importantly, styrenes, known to be highly prone to polymerization in radical processes, were transformed to 3-methoxy-3-arylpropanoates **2u**-**2aa** in good yields. The presence of strong electron-donating group (OMe) and strong electron-withdrawing group (NO$_2$) were tolerated in this transformation. A broad range of functional groups such as halides (F, Cl, Br), ester, sulfonamide and cyano were compatible with the reaction conditions, providing therefore handles for further functionalization. Simple aliphatic alkenes were however not suitable substrates for this transformation, probably due to the competitive H-abstraction of the allylic CH (BDE of allylic CH in propene: 88 kcal/mol). Ethoxy ethoxycarbonylation of **1a** under standard conditions afforded the desired product in low yield. Finally, the scalability of the reaction was also examined with three classes of substrates. To our delight, compounds **2a**, **2i**, **2u** were all formed in comparable yields in gram-scale experiments.



Scheme 3. Conversion of styrenes to cinnamate derivatives. [a] Reaction was performed at 0.25 mmol scale in methyl formate (*c* 0.1 M).

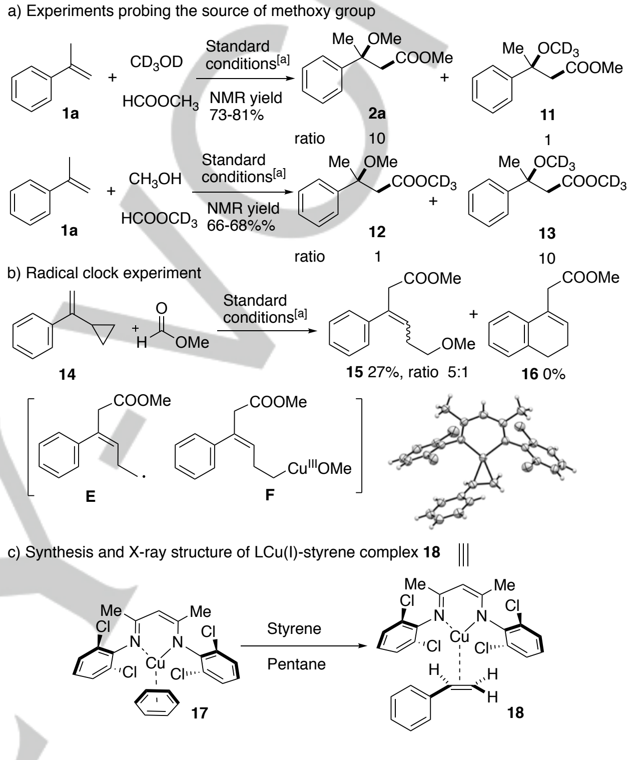
Conversion of terminal alkenes to α,β-unsaturated esters is a transformation of high importance in the synthesis of complex bioactive compounds. The cross-metathesis and a more classic two-step sequence involving ozonolysis of the double bond followed by the Wittig reaction of the resulting carbonyl compound are two of the most frequently used reactions for this purpose. We therefore set out to investigate the one-pot conversion of terminal alkenes **1** to α,β-unsaturated esters **3** taking advantage of the intermediacy of compound **2**.[21] A wide range of bases, Lewis and Brønsted acids were examined in order to promote the *in situ* β-elimination of the β-methoxy alkanoates and triflic acid (TfOH) stood out from this screening (See SI for details). Under optimized conditions, the α,β-unsaturated ester **3a** was isolated in good yield with excellent *E/Z* selectivity (Scheme 3). α-Methyl styrene and its derivatives with different electronic properties were converted to the corresponding β,β-disubstituted α,β-unsaturated esters (**3d**-**3g**) with high synthetic efficiency. 1,1-Diaryl substituted ethylenes were similarly transformed to the homologated esters (**3h**-**3j**).

To further extend the application scope of this protocol, methoxycarbonylative cycloetherification, lactonization and cycloamination were examined (Scheme 4). Gratifyingly, heating a methyl formate solution of 4-phenylpent-4-en-1-ol (**7a**) under standard conditions provided the 2,2-disubstituted tetrahydrofuran **4a** together with a small amount of ester **10**. However, adding a catalytic amount of sulfuric acid (0.1 equiv) before aqueous work-up afforded cleanly **4a** in 72% yield. The methyl 4-phenylpent-4-enoate (**8a**, X = COOMe) and *N*-(4-phenylpent-4-en-1-yl)tolylsulfonamide (**9a**, X = CH_2NHTs) were transformed into the corresponding lactone **5a** and pyrrolidine **6a**, respectively, in similar yields. As it is illustrated in Scheme 3, substrates with different electronic properties were converted to the corresponding heterocycles. However, the presence of OMe group led in general to the corresponding products with reduced yields due mainly to the instability of the resulting heterocycles.



Scheme 4. Cu-catalyzed reaction of methyl formate with alkenes bearing an internal nucleophile. [a] Reaction was performed at 0.25 mmol scale in methyl formate (*c* 0.1 M). [b] Synthesis of tetrahydrofurans; [c] Synthesis of γ-lactones; [d] Synthesis of pyrrolidines.

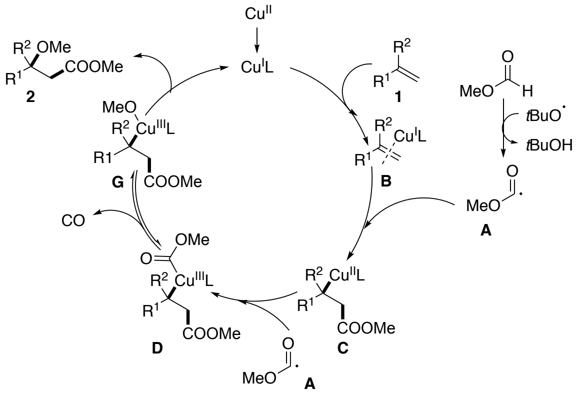
To gain insight into the reaction mechanism, a series of control experiments were carried out. As it would be expected, the reaction did not proceed in the absence of copper catalyst. Performing the methoxy methoxycarbonylation of **1a** in the presence of CD_3OD (2.0 equiv) under otherwise standard conditions afforded compounds **2a** and **11** in a 10 to 1 ratio. Conversely, performing the same reaction in $HCOOCD_3$ in the presence of MeOH (2.0 equiv) afforded **12** and **13** in a ratio of 1 to 10 (Scheme 5a). The results of these two crossover experiments suggested that both methoxycarbonyl and methoxy groups came from methyl formate and that the formation of C-O bond did not go through a cationic intermediate. In addition, reaction of **2a** with $HCOOCD_3$ under standard conditions led also to the formation of a small amount of **11** via most probably the ionization of **2a** to carbocation followed by nucleophilic trapping. We hypothesized that this pathway could also account for the formation of the minor products **11** and **12** in the crossover experiments. Submitting 1-(1-cyclopropylvinyl)benzene (**14**) to the standard conditions afforded homoallylic alcohol **15** in 27% yield (Scheme 5b). Should the radical intermediate **E** be involved, the formation of 1,2-dihydronaphthalene **16** would be expected. The fact that **16** was not detected suggested that the reaction might proceed through an organometallic species **F** rather than the radical intermediate **E**. Although intermediate **F** could in principle undergo homolytic cleavage to afford homoallylic radical **E** and Cu(II) species,[22] the reductive elimination of **F** was apparently kinetically faster to provide methyl ether **15** instead.



Scheme 5. Control experiments and X-ray structure of LCu(I)-styrene complex **18**. [a] **1a** or **14** (0.25 mmol), in $HCOOCH_3$ or $HCOOCD_3$ (*c* 0.1 M), Cu(OTf)$_2$ (0.1 equiv), **L1** (0.1 equiv), TBPA (4.0 equiv), 75 °C.

Since fragmentation of the cyclopropyl methyl radical was a kinetically fast process, the aforementioned results implied that the alkene-Cu complex might be formed before radical addition. Gratifyingly, stirring a pentane solution of styrene and the β-diketiminato Cu(I) (μ-benzene) complex **17**, synthesized according to Warren,[23] afforded a new complex **18** whose structure was fully established by spectroscopic and X-ray single crystal structure analysis (Scheme 5c).[24,25] In the presence of an equal amount of Cu(OTf)$_2$ or TfOH, both **17** and **18** were competent catalysts for the methoxy methoxycarbonylation of **1a** under otherwise standard conditions.

On the basis of the results of these control experiments, a possible reaction pathway is depicted in Scheme 6. Reduction of *tert*-butyl peroxyacetate (TBPA) by Cu(I) would generate the *tert*-butoxy radical which would abstract hydrogen from methyl formate to afford the nucleophilic methoxycarbonyl radical **A**.[26] On the other hand, coordination of LCu(I) to electron-rich alkenes **1** would afford Cu(I)-π complex **B** that would react with **A** to furnish **C**. Radical rebound of adduct **C** with **A** would produce the Cu(III) intermediate **D** which might be in equilibrium with methoxy complex **G**. Reductive elimination of the latter would then furnish the β-methoxy alkanoate **2** with concurrent regeneration of the Cu(I) species.[27] In line with this mechanistic hypothesis, the yield of **2a** was reduced to 28% when the reaction was performed under CO atmosphere under otherwise identical conditions. An experimental protocol was designed that allowed us to detect the generated CO under the reaction conditions (See SI).



Scheme 6. Possible reaction pathway.

We have also carried out kinetic studies on the initial rate of the methoxy methoxycarbonylation of styrene and its 4-substituted derivatives (4-Cl, 4-F, 4-Me, 4-OMe) and found that the rate of formation followed the following order: **2w** (R = OMe) >> **2v** (R = 4-Me) ~ **2u** (R = H) > **2z** (R = 4-Cl) > **2y** (R = 4-F, see SI). Considering that the radical **A** is nucleophilic, this observation could be tentatively accounted for by the fact that the electron rich alkene **1v** (R = 4-Me) is more prone to form the alkene-Cu complex **B**, accelerating therefore the subsequent radical addition reaction.

In summary, methyl formate was successfully exploited for the first time in a synthetically useful Cu-catalyzed difunctionalization of alkenes. Acting as a donor of both methoxycarbonyl and methoxy groups,[28] methyl formate transforms styrene and its derivatives to value-added β-methoxy alkanoates, cinnamates as well as medicinally important five-membered heterocycles. It was believed that "the reaction of alkyl radicals is synthetically significant only when the olefinic double bond is conjugated with electron-withdrawing groups owing to the nucleophilic character of the alkyl radical".[29] While the statement is correct in absolute sense, the landscape is changing and the transition metal-catalyzed difunctionalization of electron-rich alkenes involving addition of nucleophilic alkyl radical is seen in the recent literature.[30] We surmised that pre-coordination of electron rich double bond to metal might play an important role and it could have general implications in designing novel radical-based transformations.

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Keywords: Alkene difunctionalization; methoxycarbonyl radical; homogeneous catalysis; heterocycle; methyl formate

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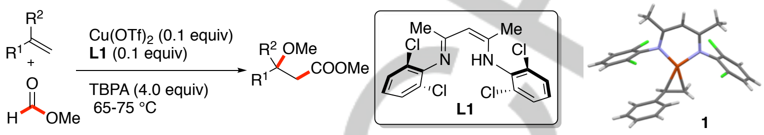
Layout 1:

Synthetic Method

*Balázs Budai, Alexandre Leclair, Qian Wang, and Jieping Zhu**___________ ***Page – Page***

Copper-Catalyzed 1,2-Methoxy Methoxycarbonylation of Alkenes with Methyl Formate



Generous donor. *Methyl formate acts as a donor of both methoxycarbonyl and methoxy groups in the above Cu-catalyzed alkene difunctionalization process. Formation of diketiminato-Cu(I)-styrene ternary complex* ***1***, *fully characterized, was proposed to accelerate the addition of nucleophilic methoxycarbonyl radical.*