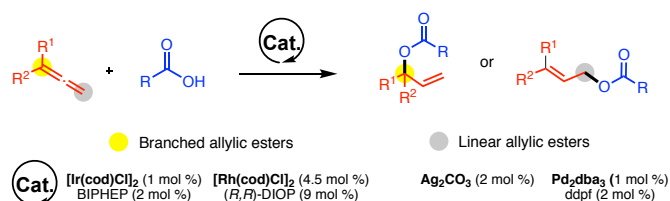# Copper-Catalyzed Hydrocarboxylation of Allenes

Rémi Blieck,[a] Marc Taillefer,[a]* and Florian Monnier[a,b]*

The addition of carboxylic acids to allenes was performed with copper catalysis. This hydrocarboxylation reaction, occuring on the terminal carbon of the allenes, is totally regio- and stereoselective. It represents the first copper-catalyzed example of intermolecular C-O bond formation by allene hydrofunctionalization. This ligand-free system, is based on the use of catalytic amounts of copper combined with a base (10 mol % of K_2CO_3).

The direct and simple metal-catalyzed substitution of allylic compounds bearing leaving groups is a powerful method to obtain various functionalized allylic compounds.[1] Despite an impressive efficiency, the Tsuji-Trost reaction suffered from an atom-economical point of view, as one equivalent of leaving group is lost from the starting molecule. Therefor alternatives appeared in the literature, and one of the most direct one is the hydrofunctionalization of allenes. For construction of C-N bonds, metal-catalyzed hydroamination of allenes were recently developed,[2] as for the formation of C-C bonds with various transition-metal-based catalysts.[3] In the case of addition of O-nucleophiles as alcohols or phenols, few results were published these recent years.[4] In the special case of the addition of carboxylic acids, few examples were reported with iridium-, rhodium-, silver- or palladium-catalysts.[5-8] Depending on the nature of the metal, regioselectivity of the addition of the nucleophile varies as mentioned in Scheme 1. Systems based on Ir[5] and on Rh[6] respectively developed by Krische and Breit gave the branched allylic esters. On the other hand, Ag[7] and Pd[8]-catalytic systems allow the selective formation of linear allyclic molecules with the selective formation of E double bond. Nevertheless these reported methodologies suffered from expensive and/or toxic catalytic systems.

Scheme 1 Metal-catalyzed addition of carboxylic acids to allenes

To pursue our studies on hydrofunctionalization of allenes catalysed by simple and cheap catalyst based on copper,[2g,3k,9] we engaged our efforts on the formation of C-O bonds, in the presence of copper salts playing the role of precatalyst, by the addition of carboxylic acids on terminal allenes.

Herein, we would like to report the first hydrocarboxylation of allenes catalyzed by a copper system. The latter leads to the selectively linear allylic esters in moderate to excellent yields (Scheme 2).

This work

16 examples
Regio- and Stereoselective
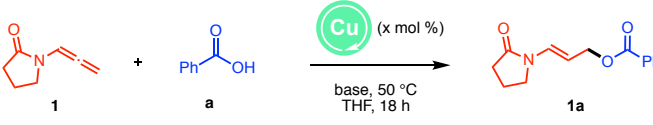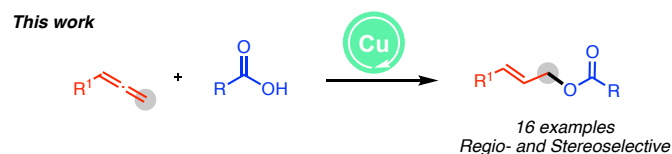
Scheme 2 Copper-catalyzed hydrocarboxylation of allenes

First, a set of experiments was performed using allenamide **1** and benzoic acid **a** as model substrates. We then tested catalytic system developed by our group[3k] for the addition of 1,3-dicarbonyl compounds on allenes (Table 1, entry 1). Only 13% of desired product **1a** was observed in the presence of 10% of $Cu(CH_3CN)_4PF_6$ and one equivalent of base Cs_2CO_3. As mentioned in literature,[5-7] base could be used in catalytic amount for the addition of carboxylic acid on allenes. Indeed when we reduced the amount of Cs_2CO_3 to 10% (Table 1, entry 2) we observed an impressive increase of the formation of **1a** to 64%. Decreasing temperature from 50 °C to 25 °C affords to a loose of reactivity with only 15% of **1a** formed (Table 1, entry 3). Blank experiments revealed that combination of copper precatalyst and base is absolutely needed for the reaction. (Table 1, entries 5-6). In a second set of experiments, we showed that K_2CO_3 is the most suitable base to perform the hydrocarboxylation (Table 1, entries 4, 7-9). It is also important to note that others copper (I) precatalysts (CuI, CuBr, Cu_2O) did not allow better reactivity than 10% mol of $Cu(CH_3CN)_4PF_6$ (Table 1, entries 10-13). Thus the most suitable conditions to perform the hydrocarboxylation of **1** are those of the entry 9: one equivalent of allene **1** reacts with 1.2 equivalent of benzoic acid **a** in 1.5 mL of THF during 18 h at 50 °C in the presence of 10% of $Cu(CH_3CN)_4PF_6$ and 10% of K_2CO_3 acting as a base. These smooth conditions allow the regio- and stereoselective formation of **1a** in 90% NMR yield.
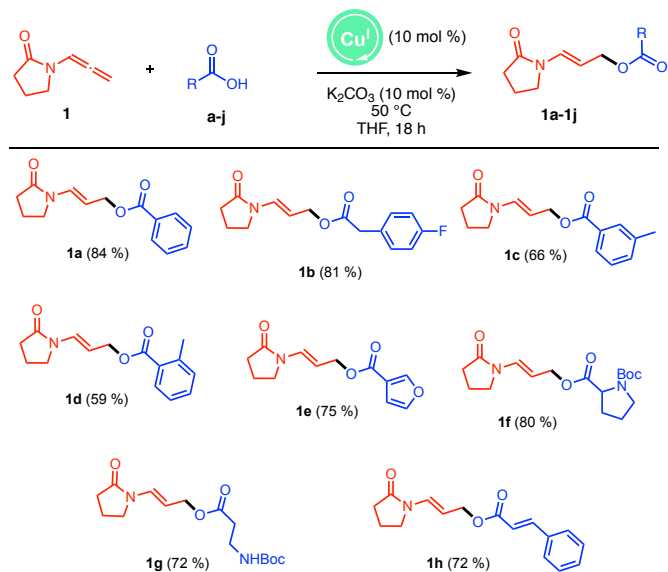
Table 1 Hydrocarboxylation of **1** with benzoic acid **a**. Selected data for reaction development.[a]

| entry	[Cu] (x mol %)	Base (y eq.)	THF (mL)	Yield[b] (%)
1	Cu(CH₃CN)₄PF₆ (10)	Cs₂CO₃ (1)	2.5	13
2	Cu(CH₃CN)₄PF₆ (10)	Cs₂CO₃ (0.1)	2.5	64
3	Cu(CH₃CN)₄PF₆ (10)	Cs₂CO₃ (0.1)	2.5	15[c]
4	Cu(CH₃CN)₄PF₆ (10)	Cs₂CO₃ (0.1)	1.5	80
5	Cu(CH₃CN)₄PF₆ (10)	-	1.5	0
6	-	Cs₂CO₃ (0.1)	1.5	0
7	Cu(CH₃CN)₄PF₆ (10)	KOH (0.1)	1.5	85
8	Cu(CH₃CN)₄PF₆ (10)	NaOH (0.1)	1.5	82
9	Cu(CH₃CN)₄PF₆ (10)	K₂CO₃ (0.1)	1.5	90
10	CuI (10)	K₂CO₃ (0.1)	1.5	32
11	CuBr (10)	K₂CO₃ (0.1)	1.5	43
12	Cu₂O (10)	K₂CO₃ (0.1)	1.5	21
13	Cu(CH₃CN)₄PF₆ (5)	K₂CO₃ (0.1)	1.5	52

[a] Reaction conditions: **1** (0.5 mmol), **a** (0.6 mmol), base (0.05 to 0.5 mmol) and catalyst (0.025 to 0.05 mmol) were placed in a screw tube under argon in THF for 18 h at 50 °C. [b] NMR yields using 1,3,5-trimethoxybenzene as internal standard. [c] At 25 °C.

Scheme 3 Copper-catalyzed hydrocarboxylation of allene **1** with various carboxylic acids **a-h** (isolated yields).

Next, investigations on the scope and limitations of reaction were engaged. In a first set of experiments, we wanted to know if this selective reaction is tolerant toward various carboxylic acids (Scheme 3). Moderate to excellent yields were obtained when *N*-allenyl-2-pyrrolidinone **1** reacted with aromatic carboxylic acids such as benzoic acid **a**, 4-fluoro-phenylacetic acid **b**, *m*-methylbenzoic acid **c**, *o*-methylbenzoic acid **d** (Scheme 3). We also demonstrated that *N*-allenyl-2-pyrrolidinone **1** allowed the formation of the desired carboxylated product **1e** in 75% yield, when engaged with carboxylic acid bearing heterocycle as 2-furoic acid **e**. To our delight, we also engaged successfully *N*-protected amino acids as source of carboxylic acids. To this purpose, boc-proline **f** and boc-β-alanine **g** reacted with allene **1** under standard conditions to give desired allylic esters compounds **1f** and **1g** respectively in 80% and 72% yields. Finally cinnamic acid **h** with allene **1** gave the desired molecule **1h** in 72% yield. All products **1a-1h** were obtained in regio- and stereoselective manner without the generation of any other products or isomers.

In a following set of experiments, we showed that diverse allenamides could be suitable substrates for this selective reaction (Scheme 4). *N*-allenyloxazolidinone **2** reacted with benzoic acid **a** to give **2a** in 67% yield. Other important class of allenes such as *N*-allenyl-sulfonamide was engaged successfully, and under standard reaction conditions we were able to obtain **3a**, **4a** and **5a** respectively in 43%, 51% and 47% yield. Finally *N*-allenyl-azoles such as allenes bearing triazole **6** and benzotriazole **7** were also good candidates for this hydrofunctionalization reaction in the presence of benzoic acid **a**.
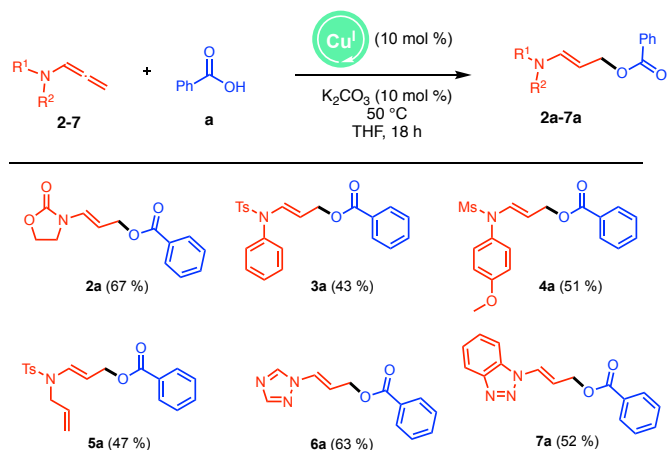
Scheme 4 Copper-catalyzed hydrocarboxylation of various allenes **2-7** with benzoic acid **a** (isolated yields).

Taking into account our previous reports on hydroamination of allenes catalysed by similar catalytic system,[9a-b] we propose a mechanism involving cationic copper species, which in a first

step could complex the allene to afford intermediate **A** (Scheme 5). The in-situ generated carboxylate anion $R^1CO_2^-$ could attack **A** in an antiperiplanar manner to afford a *Z* alkenylcopper intermediate **B**. Another equivalent of carboxylic acid could perform a protodemetallation through intermediate **C**, which could release the desired *E* allylic ester and regenerate carboxylate anion $R^1CO_2^-$. The latter could be re-engaged in the catalytic cycle, thus explaining the use of only catalytic amount of base in this reaction. Work is in progress to assess the soundness of this mechanistic proposal.
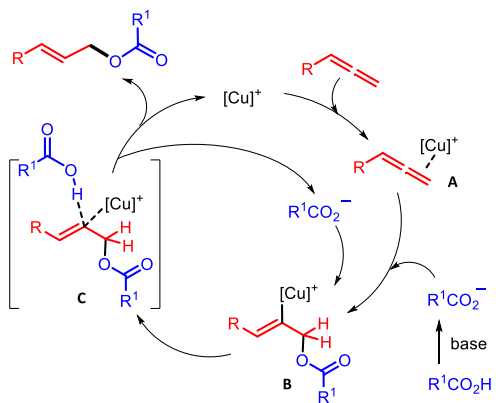
Scheme 5 Proposed mechanism for the hydrocarboxylation of allenes.

In conclusion we have reported the first copper-catalyzed C-O bond formation performed by hydrofunctionalization of allenes, giving an efficient and selective access to allylic moieties with a total atom economy. Under smooth conditions, using catalytic amount of base, we explored the powerfulness and the tolerance of this novel catalytic system for the regio- and stereoselective generation of allylic esters starting from simple substrates, and we demonstrated the high flexibility of copper-based catalytic systems in the functionalization of allenes.

Conflicts of interest

"There are no conflicts to declare".

Acknowledgements

Notes and references

‡ Footnotes relating to the main text should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

1   For reviews on transition-metal-catalyzed allylic substitutions, see: (a) J. Qu and G. Helmchen *Acc. Chem. Res.,* 2017, **50**, 2539; (b) N. A. Butt and W. Zhang *Chem. Soc. Rev.,* 2015, **44**, 7929; (c) Z. Lu and S. Ma, *Angew. Chem., Int. Ed.,* 2008, **47**, 258; (d) B. M. Trost and M. L. Crawley, *Chem. Rev.,* 2003, **103**, 2921; (e) B. M. Trost and D. L. Van Vranken, *Chem. Rev.,* 1996, **96**, 395.

2   For recent reports respectively with Pd, Pt, Au, Rh, Ni , Ag and Cu, see: (a) H. Tafazolian, D. C. Samblanet and J. A. R. Schmidt, *Organometallics,* 2015, **34**, 1809; (b) K. L. Toups and R. A. Widenhoefer, *Chem. Commun.,* 2010, **46**, 1712; (c) X. Zeng, M. Soleilhavoup and G. Bertrand, *Org. Lett.,* 2009, **11**, 3166; (d) M. L. Cooke, K. Xu and B. Breit, *Angew. Chem., Int. Ed.,* 2012, **51**, 10876; (e) H. Tafazolian and J. A. R. Schmidt, *Chem. Eur. J.,* 2017, **23**, 1507; (f) T. Wei, M. S. Xie, G.-R. Qu, H.-Y. Niu and H.-M. Guo, *Org. Lett.,* 2014, **16**, 900; (g) R. Blieck, J. Bahri, M. Taillefer and F. Monnier, *Org. Lett.,* 2016, **18**, 1482.

3   (a) Y. Yamamoto, M. Al-Masum and N. Asao, *J. Am. Chem. Soc.,* 1994, **116**, 6019; (b) B. M. Trost and V. J. Gerusz, *J. Am. Chem. Soc.,* 1995, **117**, 5156; (c) L. Besson, J. Goré and B. Cazes, *Tetrahedron Lett.,* 1995, **36**, 3853; (d) T. Wei, M. S. Xie, G.-R. Qu, H.-Y. Niu and H.-M. Guo, *Org. Lett.,* 2014, **16**, 900; (e) Y. Yamamoto and M. Al-Masum, *Synlett,* 1995, 69; (f) Y. Yamamoto, M. Al-Masum and A. Takeda, *Chem. Commun.,* 1996, 831; (g) B. M. Trost, A. B. C. Simas, B. Plietker, C. Jäkel and J. Xie, *Chem. Eur. J.,* 2005, **11**, 7075; (h) H. Zhou, Y. Wang, L. Zhang, M. Cai and S. Luo, *J. Am. Chem. Soc.,* 2017, **139**, 3631; (i) C. Li and B. Breit, *J. Am. Chem. Soc.,* 2014, **136**, 862; (j) T. M. Beck and B. Breit, *Angew. Chem., Int. Ed.,* 2017, **56**, 1903; (k) R. Blieck, R. Abed Ali Abdine, M. Taillefer and F. Monnier, *Org. Lett.,* 2018, **20**, 2232.

4   For selected reports on hydroalkoxylation of allenes, see: (a) R. J. Harris, R. G. Carden, A. N. Duncan and R. A. Widenhoefer *ACS Catal.,* 2018, **8**, 8941; (b) S. Webster, D. R. Sutherland and A.-L. Lee *Chem. Eur. J.,* 2016, **22**, 18593; (c) Z. Liu and B. Breit, *Angew. Chem., Int. Ed.,* 2016, **55**, 8440; (d) L. Jiang, T. Jia, M. Wang, J. Liao and P. Cao *Org. Lett.,* 2015, **17**, 1070; (e) W. Lim, J. Kim and Y. H. Rhee *J. Am. Chem. Soc.* 2014, **136**, 13618; (f) Z. Zhang, S. D. Lee, A. S. Fisher and R. A. Widenhoefer *Tetrahedron*, 2009, **65**, 1794; (g) R. S. Paton and F. Maseras, *Org. Lett.,* 2009, **11**, 2237; (g) T. Kawamoto, S. Hirabayashi, X.-X. Guo, T. Nishimura and T. Hayashi *Chem. Commun.,* 2009, 3528; (h) N. Nishina and Y. Yamamoto *Tetrahedron Lett.,* 2008, **49**, 4908. For a general review, see : J. Le Bras and J. Muzart *Chem. Soc. Rev.,* 2014, **43**, 3003.

5   I. S. Kim and M. J. Krische *Org. Lett.,* 2008, **10**, 513.

6   (a) P. Koschker, A. Lumbroso and B. Breit *J. Am. Chem. Soc.,* 2011, **133**, 20746. For macrolactonisation via allene hydrocarboxylation, see : (b) S. Ganss and B. Breit *Angew. Chem. Int. Ed.,* 2015, **55**, 9738.

7   See ref 2f

8   (a) M. Al-Masum and Y. Yamamoto, *J. Am. Chem. Soc.,* 1998, **120**, 3809; (b) N. T. Patil, N. K. Pahadi and Y. Yamamoto *Can. J. Chem.,* 2005, **83**, 569.

9   (a) L. Perego, R. Blieck, A. Groué, F. Monnier, M. Taillefer, I. Ciofini and L. Grimaud, *ACS Catal.,* 2017, **7**, 4253; (b) L. A. Perego, R. Blieck, J. Michel, I. Ciofini, L. Grimaud, M. Taillefer and F. Monnier, *Adv. Synth. Catal.,* 2017, **359**, 4388. (c) R. Blieck, L. A. Perego, I. Ciofini, L. Grimaud, M. Taillefer and F. Monnier, *Synthesis,* 2019, **51**, 1225.