EurJOC
European Journal of Organic Chemistry

Chemistry Europe
European Chemical Societies Publishing

Accepted Article

Title: Hydroarylation of Allenyl Derivatives Catalyzed by Copper

Authors: Racha Abed Ali Abdine, Lucas Pages, Marc Taillefer, and Florian Monnier

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.202001333

Link to VoR: https://doi.org/10.1002/ejoc.202001333

WILEY-VCH

FULL PAPER

DOI: 10.1002/adsc.202((will be filled in by the editorial staff))

Hydroarylation of *N*-Allenyl Derivatives Catalyzed by Copper

Racha Abed Ali Abdine,[#,a] Lucas Pagès,[#,a] Marc Taillefer,[a,*] and Florian Monnier[a, b,*]

[a] Ecole Nationale Supérieure de Chimie de Montpellier, Institut Charles Gerhardt Montpellier UMR 5253, Univ. Montpellier, CNRS, ENSCM, 8 rue de l'Ecole Normale, Montpellier 34296 Cedex 5, France.
E-mail : marc.taillefer@enscm.fr; florian.monnier@enscm.fr
[b] Institut Universitaire de France, IUF, 1 rue Descartes, Paris 75231 Cedex 5, France.
[#] These two authors contributed equally to this work.

Received: ((will be filled in by the editorial staff))

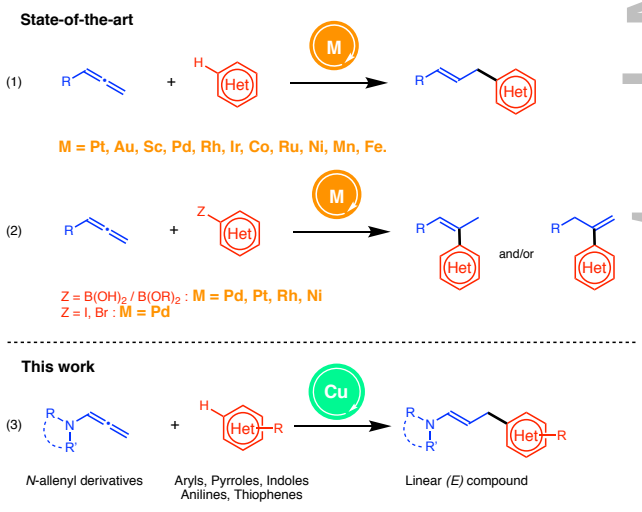
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

Abstract. A additive-free copper catalytic system was used to perform the addition of (hetero)aryl nucleophiles to *N*-allenyl derivatives. This intermolecular C-C bond formation occurs with both complete regio- and stereoselectivity to afford the linear (*E*) allylic product with moderate to excellent yields. This atom economical method is the first example of hydroarylation of allenes catalyzed by copper.

Keywords: allenes; copper; hydroarylation; allylic compounds, arenes, homogeneous catalysis

Allylic or vinylic molecules are highly valuable intermediates[1] which are easy-to-prepare through transition metal-catalyzed hydrofunctionalization of monosubstituted allenes.[2–4] This atom economical strategy usually occurs without any prefunctionalization and with very high chemo-, regio- and stereospecificity. Hydrofunctionalization of allenes mainly allowed the selective formation of C-N, C-O and C-C bond.[2,3,5–8] The latter being performed through the addition of pronucleophiles such as malonates,[9–12] nitriles,[13–16] alkynes,[17–19] alkenes[20–22] and aryl derivatives. The reaction of aromatic compounds with allenes, known as hydroarylation reaction, consists in adding an aryl moiety to a C-C double bond, and constitutes a powerful tool to form a Csp^3-Csp^2 bond in regio- and stereoselective manner.

The first example of hydroarylation of allenes with ArH catalyzed by a transition metal was described by the group of Panunzi with a platinum(II) catalyst.[23] Since then, a lot of different transition metals (Sc,[24,25] Pd,[26] Rh,[27–30] Ir,[31] Co,[32] Ru,[33] Ni,[34] Mn[35,36] and Fe[37]) have also been used to perform hydroarylation of allenes with aryl nucleophiles (Scheme 1), especially from cationic gold(I) catalysts that are well known as π-acid complexes.[38–43] Most of these hydroarylation methods are limited to electron-rich aryl nucleophiles and afford the linear product *i.e.* the anti-Markovnikov product (Scheme 1, equation 1). Other groups reported hydroarylation reactions with various nucleophilic partners such as aryl boronic acids $ArB(OH)_2$,[44] aryl boronic esters $ArB(OR)_2$[45] or aryl halides ArX[46] allowing an *ipso*-arylation. These methods allowed the addition of a wide scope of aryl partners selectively on the central carbon of the allene, affording then either the *endo*- or the *exo*-olefinic product (Scheme 1, equation 2). These two regio-divergent pathways are providing interesting products that could be further functionalized through either the C-C double bond or the (hetero)aryl group.



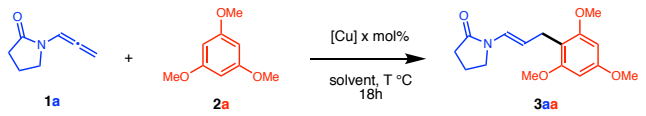
Scheme 1. Metal-catalyzed hydroarylation of allenes: known methods and pathway described herein with Cu catalysis

Herein, we report an unprecedented copper-catalyzed hydroarylation of allenes illustrated by the addition of aryl and heteroaryl derivatives on *N*-allenyl compounds. Based on our previous works on copper-catalyzed hydrofunctionalization of allenamides,[47–55] we began to study the model reaction between *N*-

10.1002/ejoc.202001333

allenyl-2-pyrrolidinone **1a** with 1,3,5-trimethoxybenzene **2a** under various experimental conditions (Table 1).

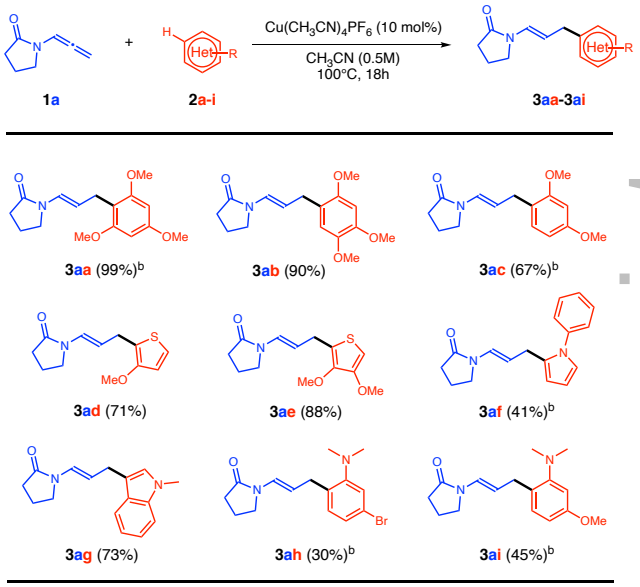
Table 1. Hydroarylation of **1a** with **2a**: Selected data for reaction parametric study.[a]



	solvent (0.5M)	T (°C)	[Cu]	x	yield (%)[b]
1	1,4-dioxane	25	CuI	20	0
2	THF	25	CuI	20	10
3	DMF	25	CuI	20	17
4	CH_3CN	25	CuI	20	23
5	CH_3CN	25	-	0	0
6	CH_3CN	25	CuOAc	20	13
7	CH_3CN	25	$Cu(OTf)_2$	20	16
8	CH_3CN	25	$Cu(OTf)_2.PhH$	10	41
9	CH_3CN	25	$Cu(CH_3CN)_4PF_6$	20	51
10	CH_3CN	80	$Cu(CH_3CN)_4PF_6$	20	76
11	CH_3CN	100	$Cu(CH_3CN)_4PF_6$	20	90
12	CH_3CN	100	$Cu(CH_3CN)_4PF_6$	10	88
13	CH_3CN	100	$Cu(CH_3CN)_4PF_6$	5	49
14	CH_3CN	100	$Cu(CH_3CN)_4PF_6$	10	57[c]
15	CH_3CN	100	$Cu(CH_3CN)_4PF_6$	10	>99[d]

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.2 equiv, 0.6 mmol) and catalyst (0.025 to 0.1 mmol) were placed in a screw tube under argon in 1 mL of solvent for 18h at 25 to 100°C. [b] NMR yields using 4-iodoanisole as internal standard. [c] The mixture was reacted for 10 hours. [d] Reaction performed with 1 mmol, 2 equiv of **2a**.

We initially tested the reaction at 25 °C with 20 mol% of CuI as a catalyst in various solvents: 1,4-dioxane, THF, DMF and acetonitrile (entries 1-4, table 1). The latter was then considered as our reference solvent as it gave the desired product **3aa** in 23% yield. A control experiment was conducted to prove that no reaction is occurring without any copper salts (entry 5, table 1). Different copper sources were then investigated, and $Cu(CH_3CN)_4PF_6$ allowed the best rate of formation of **3aa** (entries 6-9, table 1). We observed that the higher the temperature, the better the yield up to 100°C (entries 9-11, table 1). We then reduced the catalyst loading, and observed at this temperature no major difference between 10 or 20 mol% of $Cu(CH_3CN)_4PF_6$ while the yield significantly decreased with only 5 mol% of copper (entries 12-13, table 1). Tests performed at 100 °C with 10 mol% of $Cu(CH_3CN)_4PF_6$ showed that the reaction is not complete after 10 hours (entry 14, table 1). Finally, adding 2 equiv instead of 1.2 equiv of aryl reagent **2a** allowed us to further increase the yield of **3aa** (entry 15, table 1). The reaction was found to be totally stereo- (only the *(E)* product was obtained) and regioselective as the addition occurred only on the terminal carbon of the allene. With these optimized conditions (entry 12 and 14, table 1) in hand, we first explored the scope of the method for the hydroarylation of allenamide **1a** with various readily available (hetero)aryl compounds **2a-i** (Scheme 2). Noteworthy that obtained compounds are enamide-type molecules which constitute a versatile building block for medicinal chemistry and for total synthesis of natural products.[56]

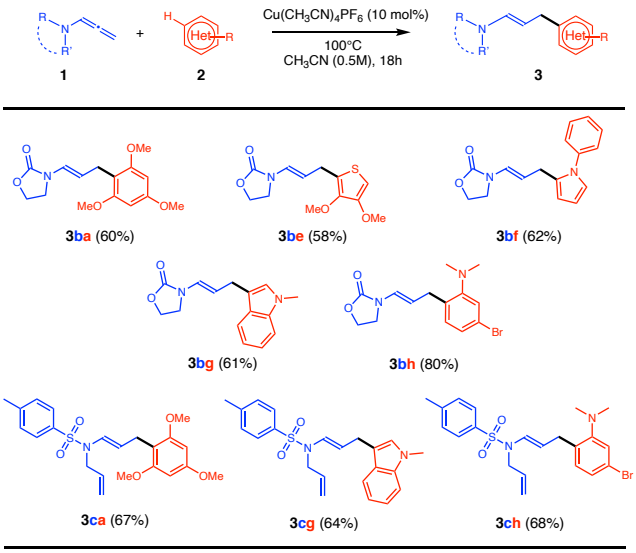


[a] Reaction conditions: **1a** (0.5 mmol), **2a-i** (1.2 equiv, 0.6 mmol, unless otherwise notified), $Cu(CH_3CN)_4PF_6$ (10 mol%, 0.05 mmol), CH_3CN (0.5M, 1mL), argon, 100°C, 18h. Isolated yields. [b] Reaction performed with 2 equiv, 1 mmol of aryl partner **2**.

Scheme 2. $Cu(CH_3CN)_4PF_6$-catalyzed hydroarylation of various (hetero)aryl compounds 2a-i with allene 1a.[a]

The reaction of both 1,3,5-trimethoxybenzene **2a** and 1,2,4-trimethoxybenzene **2b** with **1a** gave the formation of **3aa** and **3ab**, respectively in quantitative (>99%) and in 90% isolated yields. Whereas 1,3-dimethoxybenzene **2c** afforded **3ac** with a lower yield of 67%, 1,4-dimethoxybenzene and anisole did not yield the desired product. Different types of N- (pyrrole, indole) or S-containing (thiophenes) heteroaromatic compounds were also successfully engaged in the reaction with **1a**, affording products **3ad** to **3ag** in medium to excellent yields. Othe heteroaromatic substrates did not provided any product under these conditions, such as substituted pyridines, toluene and 1,3,5-trimethylbenzene. The *meta*-substituted *N,N*-dimethylanilines **2h** and **2i** afforded the corresponding products **3ah** and **3ai** in moderate yields. It is interesting to notice that **3ah** could be potentially involved in further cross-coupling reaction through its aryl bromide moiety. Noteworthy that analysis of ^1H NMR spectra clearly showed the exclusive formation of one product with the (*E*)

configuration of the double bond (see supporting information).

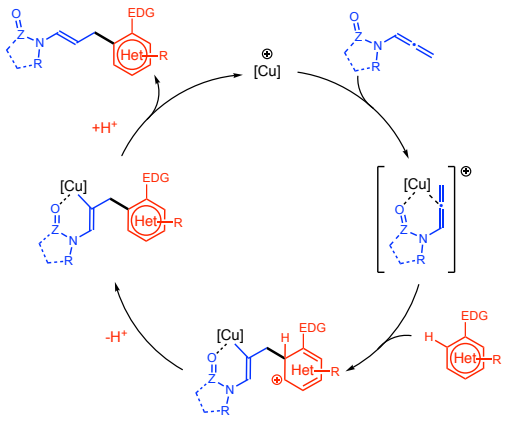


[a] Reaction conditions: **1** (0.5 mmol), **2** (2 equiv, 1 mmol), $Cu(CH_3CN)_4PF_6$ (10 mol%, 0.05 mmol), CH_3CN (0.5M, 1mL), argon, 100°C, 18h. Isolated yields.

Scheme 3. Extension to other *N*-allenyl derivatives and cross reactivity.[a]

Other *N*-allenyl derivatives bearing either a carbamate **1b** or a sulfonamide moiety **1c** were then successfully engaged in this copper-catalyzed hydroarylation, affording the corresponding products in good to high yields (Scheme 3). These substrates **1b** and **1c** afforded the corresponding linear *(E)* products with electron-rich arene (**3ba**, **3ca**), thiophene derivatives (**3be**), *N*-phenyl pyrrole (**3bf**), indole derivatives (**3bg**, **3cg**) and aniline derivatives (**3bh**, **3ch**) in moderate to good yields with a total control of regio- and stereoselectivity.

Based on our previous studies[49,51] and mechanisms described in the literature,[38,43,57] we suggest as the first step of the process the coordination of the copper to the *N*-allenyl derivative through the assisting group and the central carbon of the allene. We assume that the electron rich aryl is then reacting as a nucleophile on the terminal position of the allene. This electrophilic aromatic substitution (S_EAr) leads to the formation of a plausible Wheland intermediate, which undergoes into protodecupration to afford selectively the *(E)*-product. The need of electron donating groups in adequate positions on the (hetero)aryl substrate is consistent with this mechanism proposal (Scheme 4).



Scheme 4. Plausible mechanism for the copper-catalyzed hydroarylation of *N*-allenyl derivatives.

In summary, we reported an unprecedented copper-catalyzed hydroarylation of allenes illustrated by the addition of (hetero)aryl nucleophiles on *N*-allenyl derivatives which afford selectively *(E)*-allylic compounds with medium to excellent yields in a total atom economical fashion. Various readily available aromatic compounds were successfully engaged in the reaction with allene substrates, showing the good tolerance of the methodology. Nevertheless, we noticed that electron-rich substrates are required for the reaction to proceed, which is consistent with the literature and S_EAr-type mechanism. Further investigations on the potential of copper-catalyzed systems for hydrofunctionalization of allenes will be reported in due course.

Experimental Section

Detailed experimental procedures and characterization data for all new compounds are provided (PDF).

General procedure for hydroarylation of *N*-allenyl derivatives: An oven-dried Schlenk flask of appropriate size equipped with a magnetic stirring bar is placed under vacuum then back-filled with argon. This procedure is repeated three times. Under a stream of argon, Tetrakis(acetonitrile)copper(I) hexafluorophosphate $Cu(CH_3CN)_4PF_6$ (10 mol%) is added, followed by the (hetero)aryl nucleophile (1.2 equiv or 2 equiv as mentionned in main text), acetonitrile (0.5M, 1 mL) and the allene (0.5 mmol, 1 equiv). The Schlenk flask is then sealed under a positive pressure of argon, stirred and heated at 100°C for 18h. After allowing the reaction to cool down to room temperature, either 1,3,5-trimethoxybenzene (0.33 equiv, 0.165 mmol, 27.8 mg) or 4-iodoanisole (0.33 equiv, 0.165

mmol, 38.6 mg) is added as internal standard. The reaction mixture is then diluted in *ca.* 3 mL of dichloromethane and extracted with water. The organic layer is dried over anhydrous magnesium sulfate $MgSO_4$ and the solvent is removed under vacuum. The residue is then purified by triethylamine NEt_3 treated silica gel column chromatography.

Acknowledgements

Financial support provided by École Nationale Supérieure de Chimie de Montpellier (ENSCM, PhD fellowship for RA and LP), Institut Universitaire de France (IUF, FM) and Centre National de la Recherche Scientifique (CNRS) are warmly acknowledged with thanks.

References

[1] S. Ma, *Chem. Rev.* **2005**, *105*, 2829–2871.

[2] M. P. Muñoz, *Chem. Soc. Rev.* **2014**, *43*, 3164–3183.

[3] J. M. Alonso, M. T. Quirós, M. P. Muñoz, *Org. Chem. Front.* **2016**, *3*, 1186–1204.

[4] P. Koschker, B. Breit, *Acc. Chem. Res.* **2016**, *49*, 1524–1536.

[5] R. Zimmer, C. U. Dinesh, E. Nandanan, F. A. Khan, *Chem. Rev.* **2000**, *100*, 3067–3125.

[6] M. P. Muñoz, *Org. Biomol. Chem.* **2012**, *10*, 3584–3594.

[7] J. Le Bras, J. Muzart, *Chem. Soc. Rev.* **2014**, *43*, 3003–3040.

[8] G. Li, X. Huo, X. Jiang, W. Zhang, *Chem. Soc. Rev.* **2020**, *49*, 2060–2118.

[9] L. J. Hilpert, B. Breit, *Angew. Chem. Int. Ed.* **2019**, *58*, 9939–9943.

[10] R. Blieck, R. Abed Ali Abdine, M. Taillefer, F. Monnier, *Org. Lett.* **2018**, *20*, 2232–2235.

[11] H. Zhou, Y. Wang, L. Zhang, M. Cai, S. Luo, *J. Am. Chem. Soc.* **2017**, *139*, 3631–3634.

[12] B. M. Trost, A. B. C. Simas, B. Plietker, C. Jäkel, J. Xie, *Chem. Eur. J.* **2005**, *11*, 7075–7082.

[13] S. Arai, Y. Amako, X. Yang, A. Nishida, *Angew. Chem. Int. Ed.* **2013**, *52*, 8147–8150.

[14] H. Hori, S. Arai, A. Nishida, *Adv. Synth. Catal.* **2017**, *359*, 1170–1176.

[15] K. Matsumoto, S. Arai, A. Nishida, *Tetrahedron* **2018**, *74*, 2865–2870.

[16] J. Long, J. Gao, X. Fang, *Org. Lett.* **2020**, *22*, 376–380.

[17] B. M. Trost, G. Kottirsch, *J. Am. Chem. Soc.* **1990**, *112*, 2816–2818.

[18] C. P. Grugel, B. Breit, *Org. Lett.* **2018**, *20*, 1066–1069.

[19] L. Jeanne-Julien, G. Masson, R. Kouoi, A. Regazzetti, G. Genta-Jouve, V. Gandon, E. Roulland, *Org. Lett.* **2019**, *21*, 3136–3141.

[20] W. Li, N. Chen, J. Montgomery, *Angew. Chem. Int. Ed.* **2010**, *49*, 8712–8716.

[21] S. Parisotto, L. Palagi, C. Prandi, A. Deagostino, *Chem. Eur. J.* **2018**, *24*, 5484–5488.

[22] G. Xu, B. Fu, H. Zhao, Y. Li, G. Zhang, Y. Wang, T. Xiong, Q. Zhang, *Chem. Sci.* **2019**, *10*, 1802–1806.

[23] D. Renzi, A. Panunzi, A. Saporito, A. Vitagliano, *J. Chem. Soc. Perkin Trans* **1983**, *2*, 993–996.

[24] S. Ma, S. Yu, *Org. Lett.* **2005**, *7*, 5063–5065.

[25] G. Song, B. Wang, M. Nishiura, Z. Hou, *Chem. Eur. J.* **2015**, *21*, 8394–8398.

[26] Z. Fang, C. Fu, S. Ma, *Chem. Eur. J.* **2010**, *16*, 3910–3913.

[27] R. Zeng, C. Fu, S. Ma, *J. Am. Chem. Soc.* **2012**, *134*, 9597–9600.

[28] B. Ye, N. Cramer, *J. Am. Chem. Soc.* **2013**, *135*, 636–639.

[29] Z.-J. Jia, C. Merten, R. Gontla, C. G. Daniliuc, A. P. Antonchick, H. Waldmann, *Angew. Chem. Int. Ed.* **2017**, *129*, 2469–2474.

[30] C. Ghosh, P. J. Nagtilak, M. Kapur, *Org. Lett.* **2019**, *21*, 3237–3241.

[31] Y. J. Zhang, E. Skucas, M. J. Krische, *Org. Lett.* **2009**, *11*, 4248–4250.

[32] S. Nakanowatari, R. Mei, M. Feldt, L. Ackermann, *ACS Catal.* **2017**, *7*, 2511–2515.

[33] S. Nakanowatari, L. Ackermann, *Chem. Eur. J.* **2015**, *21*, 16246–16251.

[34] S. Nakanowatari, T. Müller, J. C. A. Oliveira, L. Ackermann, *Angew. Chem. Int. Ed.* **2017**, *56*, 15891–15895.

[35] C. Wang, A. Wang, M. Rueping, *Angew. Chem. Int. Ed.* **2017**, *129*, 10067–10070.

[36] S. Y. Chen, Q. Li, H. Wang, *J. Org. Chem.* **2017**, *82*, 11173–11181.

[37] A. M. Messinis, L. H. Finger, L. Hu, L. Ackermann, *J. Am. Chem. Soc.* **n.d.**, *0*, null.

[38] R. Skouta, C. J. Li, *Can. J. Chem.* **2008**, *86*, 616–620.

[39] K. L. Toups, G. T. Liu, R. A. Widenhoefer, *J. Organomet. Chem.* **2009**, *694*, 571–575.

[40] C. N. Kona, M. H. Shinde, C. V Ramana, *Org. Biomol. Chem.* **2015**, *13*, 5358–5362.

[41] M. Z. Wang, C. Y. Zhou, Z. Guo, E. L. M. Wong,

M. K. Wong, C. M. Che, *Chem. Asian J.* **2011**, *6*, 812–824.

[42] D. R. Sutherland, L. Kinsman, S. M. Angiolini, G. M. Rosair, A. L. Lee, *Chem. Eur. J.* **2018**, *24*, 7002–7009.

[43] M. C. Kimber, *Org. Lett.* **2010**, *12*, 1128–1131.

[44] S. Ma, N. Jiao, L. Ye, *Chem. Eur. J.* **2003**, *9*, 6049–6056.

[45] G. Takahashi, E. Shirakawa, T. Tsuchimoto, Y. Kawakami, *Adv. Synth. Catal.* **2006**, *348*, 837–840.

[46] I. Shimizu, T. Sugiura, J. Tsuji, *J. Org. Chem.* **1985**, *50*, 537–539.

[47] R. Blieck, R. Abed Ali Abdine, M. Taillefer, F. Monnier, *Org. Lett.* **2018**, *20*, 2232–2235.

[48] R. Blieck, S. Lemouzy, M. Taillefer, F. Monnier, **2020**, DOI 10.26434/chemrxiv.11830935.v3.

[49] L. A. Perego, R. Blieck, A. Groué, F. Monnier, M. Taillefer, I. Ciofini, L. Grimaud, *ACS Catal.* **2017**, *7*, 4253–4264.

[50] R. Blieck, J. Bahri, M. Taillefer, F. Monnier, *Org. Lett.* **2016**, *18*, 1482–1485.

[51] L. A. Perego, R. Blieck, J. Michel, I. Ciofini, L. Grimaud, M. Taillefer, F. Monnier, *Adv. Synth. Catal.* **2017**, *359*, 4388–4392.

[52] R. Blieck, L. Perego, I. Ciofini, L. Grimaud, M. Taillefer, F. Monnier, *Synthesis* **2019**, *51*, 1225–1234.

[53] R. Blieck, R. Abed Ali Abdine, M. Taillefer, F. Monnier, *Org. Lett.* **2018**, *20*, 2232–2235.

[54] R. Blieck, M. Taillefer, F. Monnier, *J. Org. Chem.* **2019**, *84*, 11247–11252.

[55] A. N. Philippova, D. V Vorobyeva, F. Monnier, S. N. Osipov, *Org. Biomol. Chem.* **2020**, *18*, 3274–3280.

[56] T. Courant, G. Dagousset, G. Masson, *Synthesis* **2015**, *47*, 1799–1826.

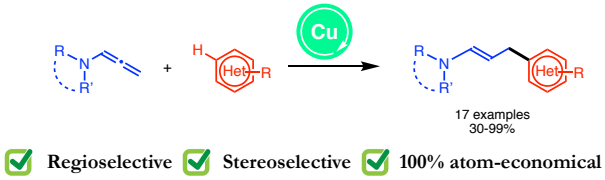
[57] K. L. Toups, G. T. Liu, R. A. Widenhoefer, *J. Organomet. Chem.* **2009**, *694*, 571–575.

10.1002/ejoc.202001333

FULL PAPER

Hydroarylation of *N*-Allenyl Derivatives Catalyzed by Copper

The regio- and stereoselective addition of (hetero)aryl nucleophiles to *N*-allenyl derivatives is described under copper catalysis. represents the first example of hydroarylation of allenes catalyzed by copper.



KEYTOPIC: Allene hydroarylation

Racha Abed Ali Abdine, Lucas Pagès, Marc Taillefer,* and Florian Monnier*