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To cite this version:
Rémi Blieck, Luca Perego, Ilaria Ciofini, Laurence Grimaud, Marc Taillefer, et al.. Copper-Catalysed Hydroamination of N-Allenylsulfonamides: The Key Role of Ancillary Coordinating Groups. SYNTHESIS, Georg Thieme Verlag, 2019, 51 (05), pp.1225-1234. 10.1055/s-0037-1611673. hal-02075687

HAL Id: hal-02075687
https://hal.umontpellier.fr/hal-02075687
Submitted on 21 Mar 2019

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Copper-Catalysed Hydroamination of N-Allenylsulfonamides: The Key Role of Ancillary Coordinating Groups

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Published as part of the 50 Years SYNTHESIS – Golden Anniversary Issue

Received: 17.01.2019
Accepted: 18.01.2019
Published online: 13.02.2019

License terms:

Abstract

A copper-catalysed hydroamination reaction of N-Allenylsulfonamides with amines has been developed through a rational approach based on mechanistic studies. The reaction is promoted by a simple copper(I) catalyst and proceeds at room temperature with complete regioselectivity and excellent stereoselectivity towards linear (E)-N-(3-aminoprop-1-enyl)sulfonamides. Density Functional Theory (DFT) studies allow interpreting the key role of unsaturated substituents on nitrogen as ancillary coordinating moieties for the copper catalyst.

Key words: hydroamination, N-Allenylsulfonamide, copper(I) catalyst, N-(3-aminoprop-1-enyl)sulfonamide, mechanistic study, ancillary coordinating moiety

Hydroamination, namely the addition of the N-H moiety across a C=C double or triple bond, is a straightforward and atom-economical method to access amine derivatives from simple precursors.\textsuperscript{1} Moreover, the remarkable chemical and stereoselectivity of some hydroamination protocols allows their application to highly functionalized substrates, ultimately leading to molecular architectures that would be challenging to obtain otherwise. In 2016 we reported the first copper-catalysed intermolecular hydroamination of allenes (Scheme 1, a)\textsuperscript{2} and in-depth mechanistic studies\textsuperscript{3} revealed the key role of cationic Cu(I) as the catalytically active species. Mechanistic insight stimulated the extension of our protocol to allenamides\textsuperscript{3} and N-allenylazoles\textsuperscript{4} (Scheme 1, b) under exceptionally mild conditions, i.e. at room temperature and with a comparatively low 5 mol% catalyst loading.

Scheme 1 Copper-catalysed hydroamination of allenes

Only a handful of naturally occurring compounds contain the sulfonamide functional group.\textsuperscript{5} However, this moiety has played a central role in the development of biologically active molecules since the dawn of modern pharmacology with the discovery of the first synthetic antibacterials.\textsuperscript{6} Nowadays, more than 110 active pharma-
ecutical ingredients are on the market and 489 compounds that reached clinical trials contain a sulfonamide group. This moiety has been central in the development of several classes of drugs, including antimicrobials, anti-inflammatory agents, carbonic anhydrase inhibitors, hypoglycaemic agents, anticancers, and antivirals.

Considering the importance of the sulfonamide functional group, we wondered if our protocol for the copper-catalysed hydroamination of allenes could be extended to readily available N-allylsulfonamides (Scheme 1, c) to access the corresponding amino-substituted N-allylsulfonamides. We present here the results of our studies, which highlighted the fundamental role of strategically placed metal-coordinating unsaturated functions for the success of this reaction.

At the beginning of our study, we expected that N-allylsulfonamides would have a reactivity analogous to that of N-allylcarboxamides (allenamides), but this turned out not to be the case. As a first attempt, N-allyl-N-methyl-p-toluene sulfonamide (1a) was treated with morpholine under the standard conditions we optimized for other nitrogen-substituted allenes (Scheme 2). Unfortunately, no reaction took place at 25 °C. Heating at 40 °C for 72 hours accomplished complete conversion of the starting material, but the expected hydroamination product was detected by 1H NMR analysis in less than 10% yield, together with decomposition products of the allene (Scheme 2).

In our previous studies we observed that 1-allyl-1,2-azoles are especially reactive in copper catalysis (Scheme 1, b) because their affinity for the catalyst is enhanced by chelation through the pyridine-like nitrogen (Figure 1, b).

Similarly, one of the factors contributing to the excellent reactivity of allenamides (Scheme 1, b) is the coordination of the C=O moiety to the copper catalyst (Figure 1, a). Therefore, we turned our attention to N-allylsulfonamides having a structural element possibly acting as an innate metal-directing group. Taking into account the good affinity of cationic copper(I) for C=C unsaturations, we reasoned that introducing a strategically placed double bond could be enough to achieve the desired reactivity (Figure 1, c).

Indeed, N-allyl-N-allyl-p-toluene sulfonamide (1b) reacted with morpholine to give an excellent yield of the hydroamination product 2b at 25 °C with Cu(NCMe)4PF6 as the catalyst (Scheme 3). To reinforce the idea that this substantial enhancement of reactivity was not due to factors other than the terminal double bond, the behaviour of the analogous N-propyl derivative 1c was also assessed in the same experimental conditions. The corresponding hydroamination product 2c actually formed, but in only 20% NMR yield with complete conversion of the starting material 1c that appeared to be fully decomposed (Scheme 3). This observation, thus, confirmed our initial hypothesis.

The influence of the N-substituent of the sulfonamide on this reaction was then examined systematically by varying the nature of R in derivatives of general structure TsNR(CH＝CH2). Results are summarized in Scheme 4. The reaction of the substrate with R = trans-cinnamyl 1d was less efficient than that of 1b, but the expected hydroamination product 2d was still obtained in a satisfactory 56% yield. The yield was further reduced for R = trans-crotyl (2e). Interestingly, for R = Bn 1f, the hydroamination product 2f was obtained in fair yield as an 83:17 E/Z mixture. For all the other substrates, complete selectivity for the E alkene was observed, as the Z product could not be detected by 1H NMR analysis of the crude reaction mixture. Good reactivity was observed for R = Ph (2g). Both electron-donating (2h) and electron-withdrawing substituents (2i,j) are tolerated on the aromatic ring.

The scope of the reaction was then explored by varying the sulfonyl group and the amine coupling partner while keeping the N-allyl group constant (Scheme 5).
Different aromatic substituents can be accommodated in the sulfonyl moiety (2k–m). Notably, an iodo substituent, which in principle could be activated by the copper catalyst, survived the reaction. The dimeric product 2m could be obtained in a very good yield. A methanesulfonamide also reacted efficiently to give 2n. A variety of open chain (2o, p) and cyclic (2q–s) secondary aliphatic amines are suitable reaction partners, including sterically hindered ones (2t, u). No reaction was observed with primary aliphatic amines, as reported before. 3,4 However, both aniline and N-methylaniline gave good yields of the hydroamination products 2v, w, in contradistinction to what we observed for the reactions of allenamides and N-allylazoles.3,4

To shed more light on the reactivity trends we observed, DFT calculations have been performed. Computational details are reported in the Supporting Information. Consistently with our previous proposals regarding related transformations,3,4 the reaction takes place by a turnover-limiting nucleophilic attack of the amine to a cationic Cu(I)/allene complex I via transition state TS1 (Scheme 6). A Z-alkenylcopper II is obtained exclusively in this process, because the addition must take place anti with respect to copper. Stereospecific proto-demetallation with retention of the double bond configuration takes place through TS_PDM and delivers the E-alkene 2 (Scheme 6).

Scheme 4 Influence of N-substituents on the Cu-catalysed hydroamination of N-allenylsulfonamides. Isolated yields, if not specified otherwise. a Yield determined by 1H NMR. b Reaction performed at 40 °C.

Scheme 5 Scope of the Cu-catalysed hydroamination of N-allenyl-N-allylsulfonamides

Isolated yields.
Conformational analysis of TS1 is key to understanding the influence of the structure of the allene on reactivity. With N-allenyl-N-allyl-p-toluensulfonamide (1b) and morpholine (mp) as model substrates, six conformers of TS1 could be located (TS1a–f). Their 3D structures and schematic drawings are reported in Figure 2, together with computed free energies of formation (ΔG) with respect to non-interacting [Cu(mp)2]+, mp, and 1b. In TS1a and TS1b the double bond of the allyl chain coordinates the copper centre in an η² fashion. In TS1c and TS1d one of the O atoms of the sulfonamide moiety interacts with the metal, similarly to what happens for allenamides (Figure 1, a).3 TS1e and TS1f feature no secondary interaction of the substrate with the metal centre, but either the O (TS1e) or the N (TS1f) atom or the sulfonamide is hydrogen-bonded to one of the mp ligands, as it happens for allenyl ethers.3

In agreement with the crucial role played by the allyl chain to achieve good reactivity, the lowest-lying transition state features an η²-coordination of copper by the C=C bond (TS1a, ΔG = +14.2 kcal mol⁻¹), while the O-chelate TS1c is

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**Figure 2** Transition states for the Cu-catalysed hydroamination of N-allenyl-N-allyl-p-toluensulfonamide (1b). Computed Gibbs free energies at 298 K (ΔG) relative to noninteracting [Cu(mp)2]+, morpholine (mp), and 1b are reported. For clarity, the mp ligands are shown as thin wireframe in the structures of TS1a–d.
just above in energy (ΔG = +16.0 kcal mol⁻¹). All the other transition states, having no significant interaction of the allyl chain with the metal (TS1d–f), are more than 5 kcal mol⁻¹ higher in free energy than TS1a. The two transition states featuring π coordination by the double bond (TS1a,b) have a pseudo-tetrahedral arrangement of the four ligands (i.e., the allyl double bond, the allenyl moiety and the two molecules of mp) around the metal centre. In TS1a (refer to Figure 3 for structure and selected geometric parameters) the C(4)–Cu and C(5)–Cu distances are equal (2.20 Å) and indicative of a strong interaction. The complete computed energy profile for the formation of the alkenylcopper intermediate II is reported in the Supporting Information. Concerning the transition states featuring chelation through the sulfonamide oxygen atom TS1c,d, for compound 1b the Cu–O distances (2.50 Å and 2.72 Å, respectively), are longer than that observed for allenamides (2.22 Å), reflecting the weaker coordination ability of the S=O function than C=O.

A similar theoretical analysis was also performed for sulfonamide 1g, having an N-phenyl substituent, and for 1a, which features an N-methyl group (see the Supporting Information for a detailed discussion). In the case of 1g, the most stable conformation of the transition state for the addition of mp (TS2a, ΔG = +14.1 kcal mol⁻¹, Figure 3) is the one in which an n²-type interaction with copper is established by the ipso and ortho carbons of the phenyl ring, analogously to what we previously observed for the allyl chain in TS1a. In TS2a, the C(4)–Cu and C(5)–Cu distances are not equal (2.62 Å and 2.85 Å, respectively) and longer than the C–Cu distances in TS1a, suggesting a weaker chelation ability of 1g compared to 1b. The most energetically accessible transition state for 1a, which has no unsaturated moiety that can interact with copper, was found to be of the O-chelate type (TS3c, see the Supporting Information). Its formation is about 3 kcal mol⁻¹ more endergonic (ΔG = +17.2 kcal mol⁻¹) than that of the most stable transition states involving 1b and 1g, in agreement with the poor reactivity of 1a.

In summary, we disclosed efficient conditions for the copper-catalysed hydroamination of N-allenylsulfonamides at room temperature with complete regio- and stereoselectivity for the linear (E)-N-(3-aminoprop-1-yl)sulfonamide. We established that satisfactory reactivity could be achieved for substrates having N-allyl or N-aryl substituents. DFT calculations allowed understanding the role of these unsaturated moieties as metal-directing groups that chelate the cationic copper(I) catalyst by acting as π-type coordination sites.

Unless otherwise stated, commercially available materials were used as received from suppliers. THF and dioxane were distilled from Na and benzophenone under argon before use. All the air-free manipulations have been performed by standard Schlenk techniques. Pre-coated F₂₅₄ silica gel plates on aluminum foil (Fluka Analytical or Macherey-Nagel) were used for TLC analyses and visualized under UV light, with Dragendorff’s reagent for tertiary amines or with alkaline KMnO₄ solution, as appropriate. NMR chemical shifts were referenced to the residual solvent peak. Syntheses and characterisation of substrates 1 are given in the Supporting Information.

**Hydroamination of N-Allenylsulfonamides; General Procedure**

An NMR tube (5-mm diameter) or a Schlenk flask of appropriate size was charged with Cu(NCMe)₄PF₆ (0.05 equiv) and closed with a rubber septum. After evacuation and back-filling with argon repeatedly (3 ×), dry THF (1 ml per mmol of substrate), the required secondary amine (1.2 equiv), and the N-allenylsulfonamide (1.0 equiv) were sequentially added. The vessel was shaken until a completely homogeneous solution resulted and the mixture was left overnight at 25 °C (or for a longer time if specified otherwise). Complete conversion was checked by no-D ¹H NMR, taking into consideration the disappearance of the characteristic allene resonances. The vessel was opened to the air and the content poured into EtOAc (10 volumes) and parti-
tioned with sat. aq NaCl solution (3 volumes). The aqueous phase was back-extracted with EtOAc (3 × 3 volumes) and the combined organic phases were dried (Na₂SO₄). Volatiles were evaporated under reduced pressure and the residue was purified by flash chromatography (NaHCO₃-treated silica gel as detailed in the Supporting Information) to afford the required hydromination product.

(E)-N-Allyl-N-(3-morpholinoprop-1-enyl)-p-toluenesulfonamide (2b)
The reaction of N-allyl-N-allyl-p-toluenesulfonamide (1b; 125 mg, 0.50 mmol) with morpholine (52.5 μL, 0.60 mmol) according to the general procedure (flash chromatography: EtOAc) gave 2b (151 mg, 90%) as a pale brown oil.

IR (ATR): 3084, 3048, 2965, 2946, 2916, 2858, 2812, 1658, 1348, 1158, 90%) as a pale brown oil.


(E,E)-N-Cinnamyl-N-(3-morpholinoprop-1-enyl)-p-toluenesulfonamide (2d)
The reaction of (E)-N-allyl-N-cinnamyl-p-toluenesulfonamide (1d; 71.0 mg, 0.218 mmol) with morpholine (23.0 μL, 0.262 mmol, 1.2 equiv) according to the general procedure (reaction time: 48 h, flash chromatography: toluene/EtOAc 80:20) gave 2d (50.0 mg, 56%) as a yellow solid.

IR (ATR): 2964, 2919, 2851, 1656, 1598, 1451, 1162, 1113, 732 cm⁻¹.


(E,E)-N-(But-2-enyl)-N-(3-morpholinoprop-1-enyl)-p-toluenesulfonamide (2e)
The reaction of (E)-N-allyl-N-(but-2-enyl)-p-toluenesulfonamide (1e; 163 mg, 0.62 mmol) with morpholine (65 μL, 0.74 mmol, 1.2 equiv) according to the general procedure (reaction time: 72 h, flash chromatography: toluene/EtOAc 80:20) gave 2e (63.8 mg, 29%) as a pale yellow oil. NMR spectra of compound 2e (and of its precursor 1e) are complicated by the presence of at least two conformations in slow equilibrium on the timescale of NMR. Spectral data of the major conformer are given in the following data.

IR (ATR): 2971, 2920, 1597, 1445, 1354, 1161, 1093, 812, 662 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 7.63 (d, J = 8.2 Hz, 2 H), 7.27 (d, J = 8.2 Hz, 2 H), 6.74 (d, J = 14.2 Hz, 1 H), 5.70–5.45 (m, 1 H), 5.34–5.15 (m, 1 H), 4.80 (dt, J = 14.2, 7.1 Hz, 1 H), 3.92 (dt, J = 5.8, 1.6 Hz, 2 H), 3.68 (t, J = 4.7 Hz, 4 H), 2.95 (d, J = 7.1 Hz, 2 H), 2.46–2.32 (m, 4 H), 2.40 (s, 3 H), 1.58 (dd, J = 6.4, 1.6 Hz, 3 H).

13C NMR (75 MHz, CDCl₃): δ = 143.8, 136.4, 129.8, 129.6, 129.4, 127.0, 124.2, 120.5, 67.0, 59.3, 53.3, 47.6, 21.6, 17.6.

The reaction of N-allyl-N-(4-bromophenyl)-p-toluene-sulfonamide (1j; 181 mg, 0.5 mmol) with morpholine (52.5 µL, 0.6 mmol, 1.2 equiv) according to the general procedure (reaction time: 18 h, flash chromatography: pentane/EtOAc 20:80) gave 2j (101 mg, 45%) as an orange powder.

1H NMR (400 MHz, CDCl3): δ = 7.53 (d, J = 8.3 Hz, 2 H), 7.47 (d, J = 8.7 Hz, 2 H), 7.28 (d, J = 8.1 Hz, 2 H), 7.08 (d, J = 14.1 Hz, 1 H), 6.87–6.79 (m, 2 H), 4.39 (dt, J = 14.1, 7.2 Hz, 1 H), 3.72–3.61 (m, 4 H), 2.92 (dd, J = 7.2, 0.9 Hz, 2 H), 2.44 (s, 3 H), 2.35 (br s, 4 H).

13C NMR (101 MHz, CDCl3): δ = 144.4, 135.6, 133.0, 131.98, 131.95, 129.7, 126.6, 123.4, 107.4, 67.0, 58.8, 55.6, 21.8.


(E)-N-(4-Allyl-1-iodo-3-morpholinoprop-1-enyl)benzenesulfonamide (2k)
The reaction of N-allyl-N-allyl-iodo-1-iodobenzenesulfonamide (1k; 175 mg, 0.48 mmol) with morpholine (51 µL, 0.58 mmol, 1.2 equiv) according to the general procedure (reaction time: 72 h, no chromatographic purification needed) gave 2k (194 mg, 89%) as a brown solid.

IR (ATR): 2964, 2992, 2762, 1732, 1658, 1567, 1349, 1004, 729 cm⁻¹.

1H NMR (300 MHz, CDCl3): δ = 7.86 (d, J = 8.5 Hz, 2 H), 7.48 (d, J = 8.5 Hz, 2 H), 6.73 (d, J = 14.1 Hz, 1 H), 5.61 (ddt, J = 17.2, 10.4, 5.4 Hz, 1 H), 5.23–5.11 (m, 2 H), 4.85 (dt, J = 14.1, 7.1 Hz, 1 H), 4.01 (d, J = 5.3 Hz, 2 H), 3.69 (t, J = 4.7 Hz, 4 H), 2.96 (d, J = 7.1 Hz, 2 H), 2.42–2.32 (m, 4 H).

13C NMR (75 MHz, CDCl3): δ = 138.9, 138.6, 131.3, 128.7, 128.4, 118.4, 107.8, 100.6, 67.0, 59.2, 53.4, 48.3.

The reaction of N-allyl-N-allyl-p-toluenesulfonamide (1b; 125 mg, 0.50 mmol) with N-methylpiperazine (66 μL, 0.6 mmol, 1.2 equiv) according to the general procedure (reaction time: 18 h, flash chromatography: CH₂Cl₂/MeOH 98:2) gave 2p (153 mg, 89%) as an orange oil.


(E)-N-Allyl-N-[3-(2-methylpiperazin-1-yl)prop-1-enyl]-p-toluenesulfonamide (2s)
The reaction of N-allyl-N-allyl-p-toluenesulfonamide (1b; 125 mg, 0.50 mmol) with azepane (68 μL, 0.36 mmol, 1.2 equiv) according to the general procedure (reaction time: 18 h, flash chromatography: EtOAc gave 2o (79.3 mg, 82%) as a pale brown oil.

IR (ATR): 2928, 2856, 2791, 1654, 1598, 1356, 1164, 843, 813, 664 cm⁻¹.


(E)-N-Allyl-N-[3-(4-methylpiperazin-1-yl)prop-1-enyl]-p-toluenesulfonamide (2r)
The reaction of N-allyl-N-allyl-p-toluenesulfonamide (1b; 125 mg, 0.50 mmol) with N-methylpiperazine (66 μL, 0.6 mmol, 1.2 equiv) according to the general procedure (reaction time: 18 h, flash chromatography: CH₂Cl₂/MeOH 98:2) gave 2r (155 mg, 89%) as an orange oil.


Due to the limited stability of this compound in the analysis conditions, no meaningful HRMS data (either EI or ESI) could be obtained. However, comparison of spectral data with analogous compounds that could be fully characterized allowed establishing the structure beyond reasonable doubt.
The reaction of N-allyl-N-allyl-p-toluene sulfonamide (1b; 125 mg, 0.50 mmol) with aniline (55.0 mmol) in N-methylcyclohexylamine (72 µL, 0.6 mmol, 1.2 equiv) according to the general procedure (reaction time: 18 h, flash chromatography: petroleum ether/EtOAc gradient 10:90 to 0:100) gave 2u (138 mg, 76%) as a red oil.

1H NMR (400 MHz, CDCl3): δ = 7.66–7.61 (m, 2 H), 7.28–7.25 (m, 2 H), 6.75 (d, J = 14.2 Hz, 1 H), 5.60 (ddt, J = 17.2, 10.5, 5.3 Hz, 1 H), 5.19–5.09 (m, 2 H), 4.79 (dt, J = 14.2, 7.1 Hz, 1 H), 3.97 (d, J = 5.3 Hz, 2 H), 3.08 (dd, J = 7.1, 0.7 Hz, 2 H), 2.40–2.32 (m, 4 H), 2.16 (s, 3 H), 1.75 (br d, J = 8.0 Hz, 4 H), 1.60 (br d, J = 12.0 Hz, 1 H), 1.27–0.97 (m, 5 H).

13C NMR (101 MHz, CDCl3): δ = 143.9, 136.2, 131.6, 129.9, 128.4, 127.0, 117.9, 108.6, 61.8, 54.2, 48.1, 37.0, 28.5, 26.3, 26.0, 21.6.


Acknowledgement

We thank Centre National de la Recherche Scientifique (CNRS), Ecole Normale Supérieure (ENS), Ecole Nationale Supérieure de Chimie de Paris (ENSCP - Chimie ParisTech), Ecole Nationale Supérieure de Chimie de Montpellier (ENSCM), Région Languedoc-Roussillon and the Agence Nationale de la Recherche (ANR) program CD2I (project CuFeCCBond) for financial support. F.M. also acknowledges the support of Institut Universitaire de France (IUF).

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611673.

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Bäckvall and co-workers have already observed a similar influence of pendant allyl groups in a copper-catalysed reaction. N-allyl and N-aryl secondary sulfonamides could be coupled with bromoallenes by the use of a copper catalyst giving N-allenyl-N-allylsulfonamides, but the reaction failed when saturated N-substituents were employed. Persson, A. K. Å.; Johnston, E. V.; Bäckvall, J.-E. Org. Lett. 2009, 11, 3814.