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Audrey Beillard, Thomas-Xavier Métro, Xavier Bantreil, Jean Martinez, Frédéric Lamaty. A3-Coupling Reaction and [Ag(IPr)₂]PF₆: A Successful Couple. *European Journal of Organic Chemistry*, 2017, 2017 (31), pp.4642-4647. 10.1002/ejoc.201700985 . hal-02338923

HAL Id: hal-02338923

<https://hal.science/hal-02338923v1>

Submitted on 29 Jan 2021

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Silver Catalysis

A³-Coupling Reaction and [Ag(IPr)₂]PF₆: A Successful Couple

Audrey Beillard,^[a] Thomas-Xavier Métro,^{*[a]} Xavier Bantreil,^{*[a]} Jean Martinez,^[a] and Frédéric Lamaty^{*[a]}

Abstract: The recently described homoleptic cationic [Ag(IPr)₂]PF₆ [IPr = 1,3-bis(2,6-diisopropylphenyl)imidazolylidene] complex proved to be a versatile and highly efficient catalyst for the production of propargylamines by using the A³-coupling reaction. The reaction conditions were equally applicable to aliphatic and aromatic aldehydes and alkynes, including

highly hindered aromatic aldehydes. Propargylamines were prepared in short reaction times with low catalyst loadings by using MeOH as a low-toxicity solvent. In addition, the catalyst was stable enough to support continuous-flow conditions, which showed that the reaction conditions are scalable.

Introduction

Propargylamines are highly versatile building blocks that have been widely used for the construction of nitrogen-containing heterocycles, and they have found various applications ranging from ligands for catalysis to pharmaceuticals and agrochemicals.^[1] The discovery that metals could catalyze the reaction between an aldehyde, an amine, and an acetylene to form propargylamines, also known as the A³-coupling reaction, has led research groups to develop various strategies aimed at producing propargylamines and related heterocycles under efficient, direct, and mild experimental conditions.^[2] Many catalytic systems have been described, including copper,^[3] gold,^[4] silver,^[5] magnesium,^[6] indium,^[7] rhodium,^[8] iridium,^[9] iron,^[10] cobalt,^[11] and zinc.^[12] Whereas gold and copper appear to be the most frequently used catalysts for such transformations, silver presents some interesting advantages such as being greener and cheaper than gold, as well as generally requiring lower catalyst loadings and shorter reaction times than copper.^[2b,13] Since the group of Li reported AgI as an efficient catalyst for the A³-coupling reaction in water,^[5a] several studies described the catalytic activity of silver used in various forms, including salts,^[14] nanoparticles,^[15] nanocomposites,^[16] metal-organic frameworks,^[17] and polymeric^[18] as well as discrete organometallic complexes. Lately, ligands such as imidazoles,^[19] acridines,^[20] pyridines,^[5b,21] biarylylphosphanes,^[22] and N-heterocyclic carbenes (NHCs)^[23] have been studied, but to the best of our knowledge none of them were efficient for a wide range of substrates, including cyclic and linear secondary

amines, aliphatic and aromatic aldehydes, as well as alkynes presenting varied electronic and steric properties.

We recently described a general, rapid, user-friendly, and solvent-free synthesis of NHC–Ag^I complexes by using a ball mill.^[24] In particular, homoleptic and cationic silver(I) complexes bearing noncoordinating tetrafluoroborate or hexafluorophosphate counteranions could be isolated in high yields (Figure 1).^[24b]

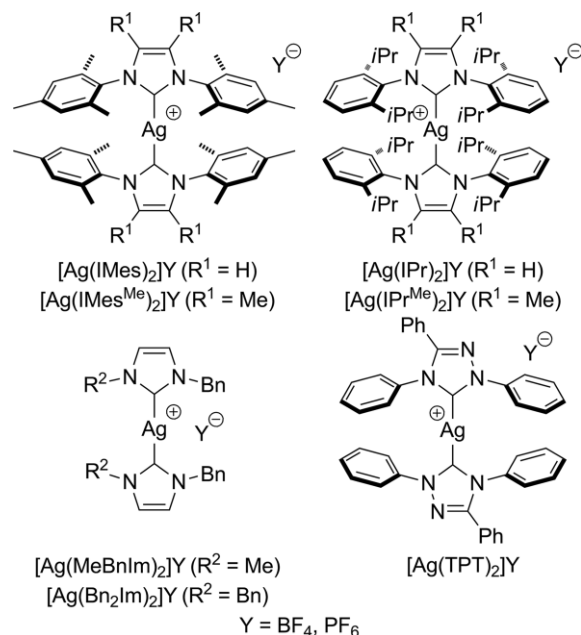


Figure 1. NHC–silver(I) complexes synthesized by ball milling and screened as catalysts in the A³-coupling reaction.

Such complexes were rarely described because of their difficult synthesis, and to date, solely three examples of their use as catalysts were reported, including only one with *N,N*-diaryl-NHCs.^[25]

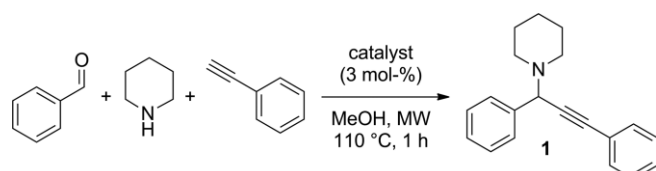
[a] Institut des Biomolécules Max Mousseron (IBMM), UMR 5247, CNRS, Université de Montpellier, ENSCM, Campus Triolet, Place Eugène Bataillon, 34095 Montpellier cedex 5, France
E-mail: thomas-xavier.metro@umontpellier.fr
xavier.bantreil@umontpellier.fr
frederic.lamaty@umontpellier.fr
http://www.greenchem.univ-montp2.fr

Hypothesizing that the high electrophilic nature of these cationic NHC–Ag^I complexes would favor efficient coordination of the alkyne on the catalyst and subsequent formation of the silver alkyne, we envisioned studying the efficiency of these cationic NHC–Ag^I complexes in catalyzing the A³-coupling reaction. Both the BF₄ and PF₆ salts of cationic silver complexes bearing the widely used IMes and IPr ligands [IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazolylidene; IPr = 1,3-bis(2,6-diisopropylphenyl)imidazolylidene], their sterically more hindered homologues IMes^{Me} and IPr^{Me} having methyl groups on the imidazole backbone [IMes^{Me} = [1,3-bis(2,4,6-trimethylphenyl)-4,5-dimethyl]imidazolylidene; IPr^{Me} = [1,3-bis(2,4,6-trimethylphenyl)-4,5-dimethyl]imidazolylidene], as well as MeBnlm (1-benzyl-3-methylimidazolylidene), Bn₂Im₂ (1,3-dibenzylimidazolylidene) and TPT (1,3,4-triphenyl-1,2,4-triazolylidene) were evaluated.

Results and Discussion

Thus, benzaldehyde (1.0 equiv.), piperidine (1.2 equiv.), and phenylacetylene (1.5 equiv.) were treated in the presence of 3 mol-% of each of these complexes in MeOH at 110 °C under microwave irradiation for 1 h. Although enabling good conversion of the substrates, complexes with *N,N*-dialkylimidazolylidene ligands furnished propargylamine **1** in low to moderate yields (Table 1, Entries 1–4). Ag^I complexes with the triazolylidene ligand did not lead to better results, supposedly as a result of an apparent low stability of the complex, as revealed by a relatively thick silver mirror observed on the reactor wall

Table 1. Catalyst screening for the A³-coupling reaction.^[a]



Entry	Catalyst	Yield [%] ^[b]
1	[Ag(MeBnlm) ₂]BF ₄	51
2	[Ag(MeBnlm) ₂]PF ₆	36
3	[Ag(Bn ₂ Im) ₂]BF ₄	11
4	[Ag(Bn ₂ Im) ₂]PF ₆	30
5	[Ag(TPT) ₂]BF ₄	8
6	[Ag(TPT) ₂]PF ₆	12
7	[Ag(IMes) ₂]BF ₄	66
8	[Ag(IMes) ₂]PF ₆	53
9	[Ag(IMes ^{Me}) ₂]BF ₄	52
10	[Ag(IMes ^{Me}) ₂]PF ₆	55
11	[Ag(IPr) ₂]BF ₄	24
12	[Ag(IPr) ₂]PF ₆	81 ^[c] (77) ^[d]
13	[Ag(IPr ^{Me}) ₂]BF ₄	14
14	[Ag(IPr ^{Me}) ₂]PF ₆	7

[a] Reaction conditions: benzaldehyde (1.0 mmol), piperidine (1.2 equiv.), phenylacetylene (1.5 equiv.), catalyst (3 mol-%), MeOH, microwave irradiation, 110 °C, 1 h. [b] Determined by HPLC analysis by using mesitylene as an internal standard. [c] Yield of isolated product. [d] Yield of isolated product upon using 1.1 equiv. of both piperidine and phenylacetylene along with 4 mol-% of [Ag(IPr)₂]PF₆.

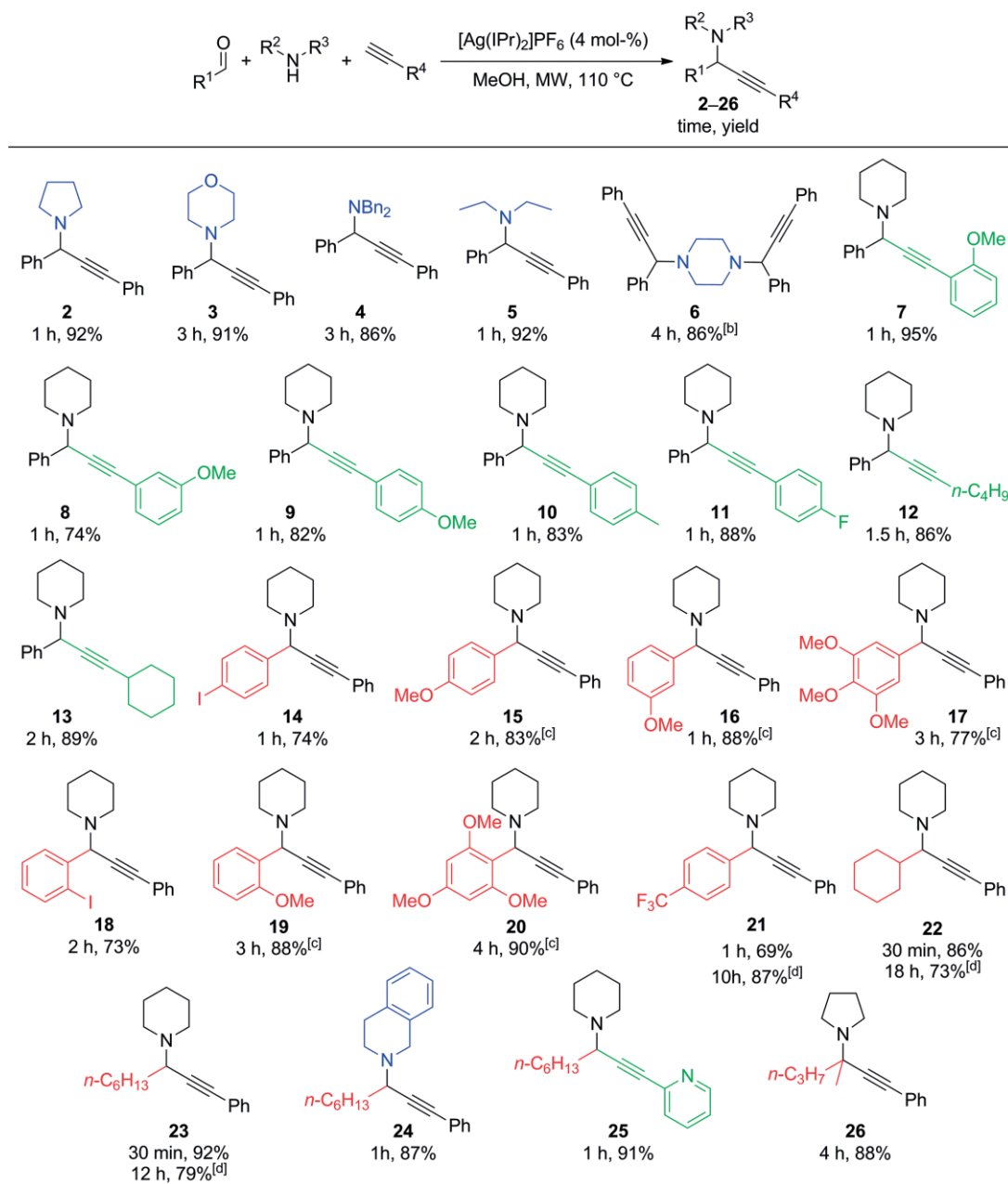
at the end of the reaction (Table 1, Entries 5 and 6). In contrast, Ag^I complexes bearing *N,N*-diarylimidazolylidene ligands furnished more satisfying results. [Ag(IMes)₂]BF₄ and [Ag(IMes)₂]PF₆ enabled the production of compound **1** in yields of 66 and 53 %, respectively (Table 1, Entries 7 and 8). The use of sterically more hindered IMes^{Me} ligands gave results similar to those obtained with the use of IMes ligands (Table 1, Entries 9 and 10). The best result was obtained with [Ag(IPr)₂]PF₆, which led to the formation of **1** in 81 % yield (Table 1, Entry 12). Gratifyingly, the amounts of both piperidine and phenylacetylene could be reduced to 1.1 equiv. without dramatically affecting the yield (77 %), provided that 4 mol-% of [Ag(IPr)₂]PF₆ was engaged in the reaction. Unlike for IMes, the use of IPr^{Me} instead of IPr was highly detrimental to the reaction, most probably because of the low solubility of [Ag(IPr^{Me})₂] salts in MeOH (Table 1, Entries 13 and 14). Despite the presence of the two highly hindered IPr ligands, the efficiency of [Ag(IPr)₂]PF₆ could be explained by the strong Lewis acid character of the cationic silver atom, which favors coordination of the alkyne and subsequent formation of the silver alkyne intermediate.

In view of these encouraging results, the efficacy of [Ag(IPr)₂]PF₆ was evaluated for the synthesis of a wide range of propargylamines. Given that aromatic aldehydes are less reactive than aliphatic ones in the silver-catalyzed A³-coupling reaction, benzaldehyde was kept to screen the amine and alkyne partners. Other cyclic amines such as pyrrolidine and morpholine as well as linear dialkylamines led to the corresponding propargylamines in excellent yields (Table 2; compounds **2–5**). Gratifyingly, dialkylated piperazine **6** was isolated in 86 % yield within 4 h upon using 0.55 equiv. of piperazine as the substrate (Table 2; compound **6**), whereas a 24 h reaction was necessary if a gold catalyst was used.^[4b]

These reaction conditions proved to be also highly tolerant to the terminal alkyne. Propargylamines were obtained in good to excellent yields whether the alkyne was substituted by phenyl groups bearing various substituents (Table 2; compounds **7–11**) or alkyl groups (Table 2; compounds **12–13**). These reaction conditions were also applicable with equal efficiency toward a set of benzaldehydes substituted by iodo or methoxy groups in the *para* and *meta* positions to furnish the corresponding propargylamines **14–17** in good to excellent yields. Even more hindered *ortho*-substituted benzaldehydes reacted efficiently under the silver/microwave conditions to furnish amines **18** and **19** in good yields.

Pleasingly, [Ag(IPr)₂]PF₆ was able to convert highly encumbered 2,4,6-trimethoxybenzaldehyde into propargylamine **20** (90 % yield). Similarly, propargylamine **21** could be isolated in a rather good yield of 69 % upon starting from highly electron-deficient 4-(trifluoromethyl)benzaldehyde. Of note, **21** could also be isolated in 87 % yield after 10 h at room temperature. A distinctive feature of this [Ag(IPr)₂]PF₆/microwave approach, if compared to most silver-catalyzed A³-coupling conditions,^[5b,19,20,22,23] is its efficiency towards both variously substituted aromatic and aliphatic aldehydes. Indeed, cyclohexanecarbaldehyde and heptanal could be easily transformed into propargylamines **22–25** (86–92 % yield). Interestingly, propargylamines **22** and **23** could be isolated either at 110 °C under

Table 2. Scope of [Ag(IPr)₂]PF₆ as a catalyst for the A³-coupling reaction.^[a]



[a] Reaction conditions: aldehyde (1.0 mmol), amine (1.1 equiv.), acetylene (1.1 equiv.), [Ag(IPr)₂]PF₆ (4 mol-%), MeOH (2 mL), microwave irradiation, 110 °C. [b] Piperazine (0.55 equiv.). [c] Aldehyde (1.0 mmol), piperidine (1.2 equiv.), phenylacetylene (1.5 equiv.). [d] Reaction was performed at room temperature.

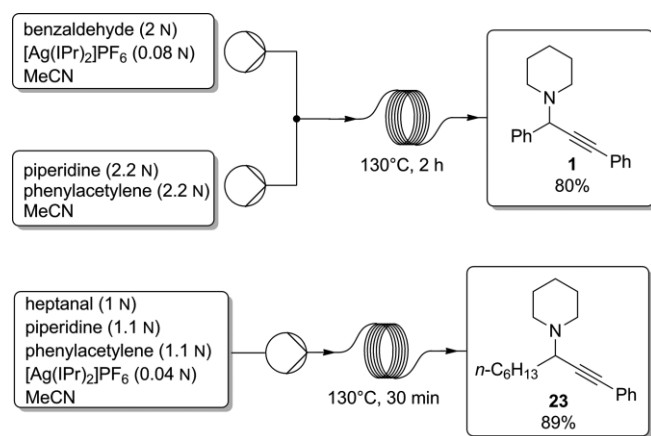
microwave irradiation within 30 min or at room temperature for longer reaction times.

The efficient synthesis of propargylamines **24** and **25** by treatment of heptanal with 1,2,3,4-tetrahydroisoquinoline/phenylacetylene and piperidine/2-ethynylpyridine, respectively, further extended the scope of this approach. Owing to their lower reactivity, ketones are less studied than aldehydes in the A³-coupling reaction. Delightfully, the [Ag(IPr)₂]PF₆/microwave reaction conditions were also applicable to ketones, as treatment of 2-pentanone with pyrrolidine and phenylacetylene in the presence of [Ag(IPr)₂]PF₆ furnished propargylamine **26** in 88% yield (Table 2). Of note, all of these propargylamines were

synthesized under ambient atmosphere by using technical-grade MeOH and without any purification of the reagents, giving additional ease to this user-friendly protocol.

To study the scalability of these reaction conditions, the synthesis of propargylamines **1** and **23** was tested under continuous flow.^[4d,26] Indeed, as both microwave and continuous-flow synthesis allow efficient heating/cooling and generation of a superheated solvent, high-temperature microwave synthesis should be easily transferred to continuous-flow synthesis.^[27] Thus, two separate solutions, one containing benzaldehyde (2 N) and [Ag(IPr)₂]PF₆ (0.08 N) in MeCN and the other containing piperidine (2.2 N) and phenylacetylene (2.2 N), were pumped

in a 20 mL polytetrafluoroethylene (PTFE) coil heated up to 130 °C at a flow rate of 0.17 mL min⁻¹ to ensure a 2 h residence time. An experimental setup with two pumps was necessary to avoid the fast formation and precipitation of the intermediate *N*-cyclohexylbenzaldimine. After classical workup and purification, propargylamine **1** was isolated in 80 % yield (Scheme 1), in the same range as that obtained for the reaction performed in MeOH at 110 °C under microwave irradiation (81 %; Table 1, Entry 12). On the other hand, pumping a single MeCN solution of heptanal (1 N), piperidine (1.1 N), phenylacetylene (1.1 N), and [Ag(IPr)₂]PF₆ (0.04 N) into a 10 mL PTFE coil heated up to 130 °C was possible and produced propargylamine **23** in 89 % yield (Scheme 1). Of note, MeCN was used instead of MeOH because of clogging and blockage of the system due to the poor solubility of [Ag(IPr)₂]PF₆ in MeOH. These results show that these reaction conditions are totally compatible with the production of propargylamines at a much higher scale.



Scheme 1. Continuous-flow synthesis of propargylamines **1** and **23**.

Conclusions

The homoleptic and cationic [Ag(IPr)₂]PF₆ complex was found to be a highly versatile and efficient catalyst for the production of a wide range of propargylamines under microwave irradiation or continuous flow. This represents one of the rare examples of successful catalysis involving homoleptic silver–NHC complexes. Propargylamines were synthesized in short reaction times with low catalyst loadings and by using low-toxic, technical-grade MeOH, all of which make the methodology easy and user-friendly. This approach is versatile and compatible with both aliphatic and aromatic aldehydes and alkynes, including highly hindered aromatic aldehydes, and less reactive ketones reacted efficiently. Finally, a continuous-flow approach was developed, which thus allowed a facilitated scale-up.

Experimental Section

General Information: All reagents were purchased from Aldrich Chemical Co., Fluka, and Alfa Aesar and were used without further purification. Reactions performed under microwave irradiation were performed with a Biotage® Initiator+ microwave synthesizer. The temperature was measured with an IR sensor on the outer surface

of the reaction vial. Continuous-flow experiments were performed by using Uniqsis Flowsyn Multi-X equipment. High-temperature PTFE coil reactors (10 or 20 mL) were set up. Flow rates were adapted to ensure an appropriate residence time in the reaction coil. The synthesis of the NHC–Ag^I catalysts was performed with a Retsch MM200 or MM400 vibrating ball mill (vbm) operated at 25–30 Hz or with a Retsch PM100 planetary mill (pbm) operated at 450 rpm, according to a previously reported procedure.^[24b] Analyses were performed at the “Plateforme Technologique Laboratoire de Mesures Physiques” (IBMM, Université de Montpellier). ¹H NMR spectra were recorded in CDCl₃ or [D₆]DMSO with a Bruker Avance I 300 MHz or a Bruker Avance III HD 400 MHz spectrometer. Chemical shifts are reported in ppm and are referenced to the residual protio solvent signal (CHCl₃ at δ = 7.26 ppm or DMSO at δ = 2.50 ppm). Data are reported as s = singlet, d = doublet, t = triplet, q = quadruplet, quint = quintuplet, sept = septuplet, m = multiplet; coupling constant in Hz; integration. ¹³C NMR spectra were recorded with a Bruker Avance I 75 MHz or a Bruker Avance III HD 101 MHz spectrometer. Chemical shifts are reported in ppm and are referenced to the solvent signal (CDCl₃ at δ = 77.2 ppm or [D₆]DMSO at δ = 39.5 ppm). ³¹P NMR spectra were recorded with a Bruker Avance III HD 162 MHz spectrometer and ¹⁹F NMR spectra with a Bruker Avance III HD 376 MHz instrument. HRMS analyses were performed with a UPLC Acquity H-Class from Waters hyphenated to a Synapt G2-S mass spectrometer with a dual ESI source from Waters.

[Ag(IPr)₂]PF₆: 1,3-Bis(2,6-diisopropylphenyl)imidazolium hexafluorophosphate (140.1 mg, 0.262 mmol, 1.00 equiv.), Ag₂O (30.3 mg, 0.131 mmol, 0.50 equiv.), and NaOH (11.5 mg, 0.288 mmol, 1.10 equiv.) were introduced into a 10 mL stainless-steel grinding bowl with one stainless-steel ball (10 mm diameter). The bowl was closed and subjected to grinding in the vibrating ball mill operated at 30 Hz for 3 h. The black powder was recovered with CH₂Cl₂, and the suspension was filtered through Celite. The filtrate was concentrated under vacuum. The white solid was dissolved in a minimum amount of CH₂Cl₂, washed with water (3 ×), and concentrated under vacuum. The solid was washed with water and Et₂O and dried under vacuum to afford bis[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]silver hexafluorophosphate (96.9 mg, 94.1 μmol, 72 %) as a white solid. ¹H NMR (400 MHz, [D₆]DMSO): δ = 7.77 (d, *J* = 0.9 Hz, 4 H), 7.51 (t, *J* = 7.8 Hz, 4 H), 7.18 (d, *J* = 7.8 Hz, 8 H), 2.20 (sept, *J* = 6.9 Hz, 8 H), 1.01 (d, *J* = 6.9 Hz, 24 H), 0.75 (d, *J* = 6.9 Hz, 24 H) ppm. ¹³C NMR (101 MHz, [D₆]DMSO): δ = 181.4 (dd, *J* = 201.6, 14.5 Hz), 144.6, 134.5, 130.3, 125.7, 125.6, 124.0, 28.1, 24.0, 23.7 ppm. ³¹P NMR (162 MHz, [D₆]DMSO): δ = -144.2 (sept, *J* = 711.3 Hz) ppm. ¹⁹F NMR (376 MHz, [D₆]DMSO): δ = -70.2 (d, *J* = 711.3 Hz) ppm.

***N*-(1,3-Diphenylprop-2-yn-1-yl)piperidine (1). By Microwave Irradiation:** Benzaldehyde (103 μL, 1.00 mmol, 1.00 equiv.), piperidine (109 μL, 1.10 mmol, 1.10 equiv.), phenylacetylene (116 μL, 1.10 mmol, 1.10 equiv.), [Ag(IPr)₂]PF₆ (41.4 mg, 0.04 mmol, 0.04 equiv.), and MeOH (2 mL) were introduced into a sealed reactor. The suspension was heated under microwave irradiation at 110 °C for 1 h. After cooling to room temperature, the mixture was filtered through Celite and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient cyclohexane/EtOAc) to afford *N*-(1,3-diphenyl-2-propynyl)piperidine (211 mg, 0.77 mmol, 77 %) as a yellow oil. **By Continuous Flow:** A solution of benzaldehyde (103 μL, 1.00 mmol, 1.00 equiv.), [Ag(IPr)₂]PF₆ (41.4 mg, 0.04 mmol, 0.04 equiv.), and MeCN (500 μL) was prepared and connected to pump A. Similarly, a solution of piperidine (109 μL, 1.10 mmol, 1.10 equiv.), phenylacetylene (116 μL, 1.10 mmol, 1.10 equiv.), and MeCN (500 μL) was prepared and connected to pump B. After setting the tempera-

ture to 130 °C, both valve positions were switched to place the mixture inline. Solutions A and B were pumped towards a T-shaped mixer, then into the 20 mL PTFE residence coil, and then through a back-pressure regulator (BPR) rated to 6.9 bar (100 psi) at a flow rate ensuring a 2 h residence time (0.17 mL min⁻¹). The mixture was recovered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient cyclohexane/EtOAc) to afford *N*-(1,3-diphenyl-2-propynyl)piperidine (220 mg, 0.80 mmol, 80 %) as a yellow oil. ¹H NMR (300 MHz, CDCl₃): δ = 7.65 (d, *J* = 7.2 Hz, 2 H), 7.53 (dd, *J* = 6.6, 3.0 Hz, 2 H), 7.40–7.30 (m, 6 H), 4.82 (s, 1 H), 2.58 (t, *J* = 5.1 Hz, 4 H), 1.66–1.57 (m, 4 H), 1.46 (q, *J* = 5.7 Hz, 2 H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ = 138.8, 131.9, 128.7, 128.4, 128.2, 127.6, 123.5, 88.0, 86.2, 62.5, 50.8, 26.3, 24.9 ppm.

***N*-[1-(2,4,6-Trimethoxyphenyl)-3-phenylprop-2-yn-1-yl]piperidine (20):** 2,4,6-Trimethoxybenzaldehyde (196 mg, 1.00 mmol, 1.0 equiv.), piperidine (119 μL, 1.20 mmol, 1.2 equiv.), phenylacetylene (158 μL, 1.50 mmol, 1.5 equiv.), [Ag(IPr)₂]PF₆ (41.4 mg, 0.04 mmol, 0.04 equiv.), and MeOH (2 mL) were introduced into a sealed reactor. The suspension was heated under microwave irradiation at 110 °C for 4 h. After cooling to room temperature, the mixture was filtered through Celite and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient cyclohexane/EtOAc) to afford *N*-[1-(2,4,6-trimethoxyphenyl)-3-phenylprop-2-yn-1-yl]piperidine (330 mg, 0.90 mmol, 90 %) as a yellow oil. ¹H NMR (300 MHz, CDCl₃): δ = 7.47–7.41 (m, 2 H), 7.27–7.24 (m, 3 H), 6.17 (s, 2 H), 5.24 (s, 1 H), 3.84 (s, 6 H), 3.82 (s, 3 H), 2.70–2.57 (m, 4 H), 1.63–1.55 (m, 4 H), 1.42–1.34 (m, 2 H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 160.9, 160.0, 131.8, 128.2, 127.5, 124.6, 124.4, 108.0, 91.8, 89.7, 56.3, 55.4, 51.6, 26.3, 24.5 ppm. HRMS: calcd. for C₂₃H₂₈NO₃ [M + H]⁺ 366.2069; found 366.2064.

***N*-[1-(2-Phenylethynyl)heptyl]piperidine (23). By Microwave Irradiation:** Heptanal (140 μL, 1.00 mmol, 1.0 equiv.), piperidine (109 μL, 1.10 mmol, 1.10 equiv.), phenylacetylene (116 μL, 1.10 mmol, 1.1 equiv.), [Ag(IPr)₂]PF₆ (41.4 mg, 0.04 mmol, 0.04 equiv.), and MeOH (2 mL) were introduced into a sealed reactor. The suspension was heated under microwave irradiation at 110 °C for 30 min. After cooling to room temperature, the mixture was filtered through Celite and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient cyclohexane/EtOAc) to afford *N*-[1-(2-phenylethynyl)heptyl]piperidine (261 mg, 0.92 mmol, 92 %) as a yellow oil. **By Agitation at Room Temperature:** Heptanal (140 μL, 1.00 mmol, 1.0 equiv.), piperidine (109 μL, 1.10 mmol, 1.10 equiv.), phenylacetylene (116 μL, 1.10 mmol, 1.1 equiv.), and [Ag(IPr)₂]PF₆ (41.4 mg, 0.04 mmol, 0.04 equiv.) were dissolved in MeOH (2 mL), and the mixture was agitated at room temperature for 12 h. The mixture was filtered through Celite and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient cyclohexane/EtOAc) to afford *N*-[1-(2-phenylethynyl)heptyl]piperidine (223 mg, 0.79 mmol, 79 %) as a yellow oil. **By Continuous Flow:** Heptanal (140 μL, 1.00 mmol, 1.00 equiv.), piperidine (109 μL, 1.10 mmol, 1.10 equiv.), phenylacetylene (116 μL, 1.10 mmol, 1.10 equiv.), and [Ag(IPr)₂]PF₆ (41.4 mg, 0.04 mmol, 0.04 equiv.) were dissolved in MeCN (1 mL) and placed in a vial. After setting the temperature to 130 °C, the valve position was switched to place the mixture inline. The mixture then flowed into the 10 mL PTFE residence coil and then through a back-pressure regulator (BPR) rated to 6.9 bar (100 psi) at a flow rate ensuring a 30 min residence time (0.33 mL min⁻¹). The mixture was then concentrated under reduced pressure and purified by flash column chromatography (gradient cyclohexane/EtOAc) to afford *N*-[1-(2-

phenylethynyl)heptyl]piperidine (252 mg, 0.89 mmol, 89 %). ¹H NMR (300 MHz, CDCl₃): δ = 7.48–7.45 (m, 2 H), 7.34–7.28 (m, 3 H), 3.48 (dd, *J* = 9.0, 5.8 Hz, 1 H), 2.77–2.62 (m, 2 H), 2.57–2.43 (m, 2 H), 1.77–1.69 (m, 3 H), 1.67–1.53 (m, 5 H), 1.51–1.42 (m, 3 H), 1.38–1.27 (m, 6 H), 0.94–0.86 (m, 3 H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 131.9, 128.3, 127.9, 123.8, 88.4, 85.7, 58.8, 50.7, 33.6, 31.9, 29.2, 27.0, 26.3, 24.7, 22.8, 14.2 ppm.

Acknowledgments

Université de Montpellier, Centre National de la Recherche Scientifique (CNRS), and French Ministry of Higher Education and Research (grant to A. B.) are acknowledged for funding.

Keywords: Alkynes · Amines · Carbenes · Silver · Multicomponent reactions · Continuous flow

- [1] a) E. Vessally, A. Hosseinian, L. Edjlali, A. Bekhradnia, M. D. Esrafil, *RSC Adv.* **2016**, *6*, 71662; b) E. Vessally, *RSC Adv.* **2016**, *6*, 18619; c) E. Vessally, A. Hosseinian, L. Edjlali, A. Bekhradnia, M. D. Esrafil, *RSC Adv.* **2016**, *6*, 99781; d) K. Pericherla, P. Kaswan, K. Pandey, A. Kumar, *Synthesis* **2015**, *47*, 887; e) Y. Liu, *ARKIVOC (Gainesville, FL, U.S.)* **2014**, 1.
- [2] a) G. Abbiati, E. Rossi, *Beilstein J. Org. Chem.* **2014**, *10*, 481; b) V. A. Peshkov, O. P. Pereshivko, E. V. Van der Eycken, *Chem. Soc. Rev.* **2012**, *41*, 3790; c) W.-J. Yoo, L. Zhao, C.-J. Li, *Aldrichim. Acta* **2011**, *44*, 43; d) C. Wei, Z. Li, C.-J. Li, *Synlett* **2004**, 1472.
- [3] a) T. T. T. Trang, D. S. Ermolat'ev, E. V. Van der Eycken, *RSC Adv.* **2015**, *5*, 28921; b) H.-B. Chen, Y. Zhao, Y. Liao, *RSC Adv.* **2015**, *5*, 37737; c) M. J. Albaladejo, F. Alonso, Y. Moglie, M. Yus, *Eur. J. Org. Chem.* **2012**, 3093; d) M. J. Aliaga, D. J. Ramon, M. Yus, *Org. Biomol. Chem.* **2010**, *8*, 43.
- [4] a) Q. Li, A. Das, S. Wang, Y. Chen, R. Jin, *Chem. Commun.* **2016**, *52*, 14298; b) G. A. Price, A. K. Brisdon, K. R. Flower, R. G. Pritchard, P. Quayle, *Tetrahedron Lett.* **2014**, *55*, 151; c) G. Villaverde, A. Corma, M. Iglesias, F. Sánchez, *ACS Catal.* **2012**, *2*, 399; d) L. Abahmane, J. M. Köhler, G. A. Groß, *Chem. Eur. J.* **2011**, *17*, 3005; e) C. Wei, C.-J. Li, *J. Am. Chem. Soc.* **2003**, *125*, 9584.
- [5] a) C. Wei, Z. Li, C.-J. Li, *Org. Lett.* **2003**, *5*, 4473; b) M. Trose, M. Dell'Acqua, T. Pedrazzini, V. Pirovano, E. Gallo, E. Rossi, A. Caselli, G. Abbiati, *J. Org. Chem.* **2014**, *79*, 7311.
- [6] X.-S. Tai, L.-L. Liu, *Open Mater. Sci. J.* **2015**, *9*, 1.
- [7] a) Y. Zhang, P. Li, M. Wang, L. Wang, *J. Org. Chem.* **2009**, *74*, 4364; b) H. N. K. Lam, N. B. Nguyen, G. H. Dang, T. Truong, N. T. S. Phan, *Catal. Lett.* **2016**, *146*, 2087.
- [8] L. Rubio-Pérez, M. Iglesias, J. Munárriz, V. Polo, J. J. Pérez-Torrente, L. A. Oro, *Chem. Eur. J.* **2015**, *21*, 17701.
- [9] S. Sakaguchi, T. Mizuta, M. Furuwan, T. Kubo, Y. Ishii, *Chem. Commun.* **2004**, 1638.
- [10] T. Zeng, W.-W. Chen, C. M. Cirtiu, A. Moores, G. Song, C.-J. Li, *Green Chem.* **2010**, *12*, 570.
- [11] W.-W. Chen, H.-P. Bi, C.-J. Li, *Synlett* **2010**, 475.
- [12] a) Z. Zarei, B. Akhlaghinia, *RSC Adv.* **2016**, *6*, 106473; b) B. Jiang, Y.-G. Si, *Tetrahedron Lett.* **2003**, *44*, 6767.
- [13] A. S. K. Hashmi in *Silver in Organic Chemistry* (Ed.: M. Harmata), Wiley, Hoboken, NJ, **2010**, pp. 357.
- [14] a) K. Mohan Reddy, N. Seshu Babu, I. Suryanarayana, P. S. Sai Prasad, N. Lingaiah, *Tetrahedron Lett.* **2006**, *47*, 7563; b) B. Huang, X. Yao, C.-J. Li, *Adv. Synth. Catal.* **2006**, *348*, 1528.
- [15] a) A. Elhampour, M. Malmir, E. Kowsari, F. Boorboor ajdari, F. Nemati, *RSC Adv.* **2016**, *6*, 96623; b) S. J. Borah, D. K. Das, *Catal. Lett.* **2016**, *146*, 656; c) S. Wang, X. He, L. Song, Z. Wang, *Synlett* **2009**, 447; d) A. Ghavami-Nejad, A. Kalantarifard, G. S. Yang, C. S. Kim, *Microporous Mesoporous Mater.* **2016**, *225*, 296.
- [16] N. Salam, A. Sinha, A. S. Roy, P. Mondal, N. R. Jana, S. M. Islam, *RSC Adv.* **2014**, *4*, 10001.
- [17] W.-J. Sun, F.-G. Xi, W.-L. Pan, E.-Q. Gao, *J. Mol. Catal. A: Chem.* **2017**, *430*, 36.

- [18] K. N. Sharma, A. K. Sharma, H. Joshi, A. K. Singh, *ChemistrySelect* **2016**, *1*, 3573.
- [19] M. Trivedi, G. Singh, A. Kumar, N. P. Rath, *Inorg. Chim. Acta* **2015**, *438*, 255.
- [20] O. Prakash, H. Joshi, U. Kumar, A. K. Sharma, A. K. Singh, *Dalton Trans.* **2015**, *44*, 1962.
- [21] J.-J. Chen, Z.-L. Gan, Q. Huang, X.-Y. Yi, *Inorg. Chim. Acta* **2017**, *466*, 93.
- [22] A. Gorrane, E. Álvarez, H. García, A. Corma, *Chem. Eur. J.* **2016**, *22*, 340.
- [23] a) C.-H. Cheng, D.-F. Chen, H.-B. Song, L.-F. Tang, *J. Organomet. Chem.* **2013**, *726*, 1; b) M.-T. Chen, B. Landers, O. Navarro, *Org. Biomol. Chem.* **2012**, *10*, 2206; c) Q. Li, Y.-F. Xie, B.-C. Sun, J. Yang, H.-B. Song, L.-F. Tang, *J. Organomet. Chem.* **2013**, *745–746*, 106; d) Q. Li, X. Li, J. Yang, H.-B. Song, L.-F. Tang, *Polyhedron* **2013**, *59*, 29; e) Y. He, M.-F. Lv, C. Cai, *Dalton Trans.* **2012**, *41*, 12428; f) P. Li, L. Wang, Y. Zhang, M. Wang, *Tetrahedron Lett.* **2008**, *49*, 6650.
- [24] a) A. Beillard, E. Golliard, V. Gillet, X. Bantreil, T.-X. Métro, J. Martinez, F. Lamaty, *Chem. Eur. J.* **2015**, *21*, 17614; b) A. Beillard, X. Bantreil, T.-X. Métro, J. Martinez, F. Lamaty, *Dalton Trans.* **2016**, *45*, 17859; c) A. Beillard, X. Bantreil, T.-X. Métro, J. Martinez, F. Lamaty, *New J. Chem.* **2017**, *41*, 1057.
- [25] a) B. Jiang, L. Han, CN102924205A, **2013**; b) D. Wang, B. Zhang, C. He, P. Wu, C. Duan, *Chem. Commun.* **2010**, *46*, 4728; c) A. Biffis, G. G. Lobbia, G. Papini, M. Pellei, C. Santini, E. Scattolin, C. Tubaro, *J. Organomet. Chem.* **2008**, *693*, 3760.
- [26] G. Shore, W.-J. Yoo, C.-J. Li, M. G. Organ, *Chem. Eur. J.* **2010**, *16*, 126.
- [27] T. Razzaq, C. O. Kappe, *Chem. Asian J.* **2010**, *5*, 1274.
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