ACS Catalysis

Research Article

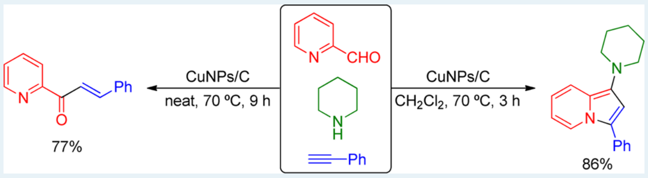
pubs.acs.org/acscatalysis

Synthetic and Mechanistic Studies on the Solvent-Dependent Copper-Catalyzed Formation of Indolizines and Chalcones

María José Albaladejo,[†] Francisco Alonso,[*] and María José González-Soria

Departamento de Química Orgánica, Facultad de Ciencias and Instituto de Síntesis Orgánica (ISO), Universidad de Alicante, Apdo. 99, E 03080 Alicante, Spain

Supporting Information



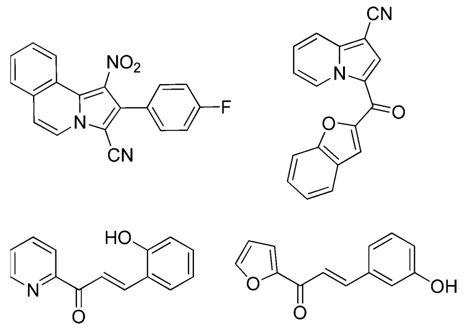
ABSTRACT: Copper nanoparticles supported on activated carbon have been found to catalyze the multicomponent synthesis of indolizines from pyridine-2-carbaldehyde derivatives, secondary amines, and terminal alkynes in dichloromethane; in the absence of solvent, however, heterocyclic chalcones are formed. We provide compelling evidence that both processes take place through aldehyde−amine−alkyne coupling intermediates. In contrast to other well-known mechanisms for chalcone formation from aldehydes and alkynes, a new reaction pathway involving propargyl amines as intermediates that do not undergo rearrangement is presented. The formation of indolizines or chalcones is driven by inductive and solvent effects, with a wide array of both being reported. In both reactions, the nanoparticulate catalyst has been shown to be superior to some commercially available copper catalysts, and it could be recycled in the case of the chalcone synthesis.

KEYWORDS: *chalcones, copper nanoparticles, indolizines, multicomponent reactions, nitrogen heterocycles, propargylamines, reaction mechanisms*

INTRODUCTION

Indolizines[1] and chalcones[2] share a large variety of pharmacological activities, including anticancer, antibacterial, antifungal, anti-inflammatory, antitubercular, antioxidant, or analgesic activity, among others (Chart 1). In particular, some heterocyclic chalcones have been recently shown to possess prominent antibacterial activity.[3] The indolizine system is also an important scaffold in natural product synthesis,[4] whereas in recent years, chalcones have been studied in materials science because of their interesting photophysical properties.[5]

Chart 1. Structure of Some Bioactive Indolizines and Heterocyclic Chalcones



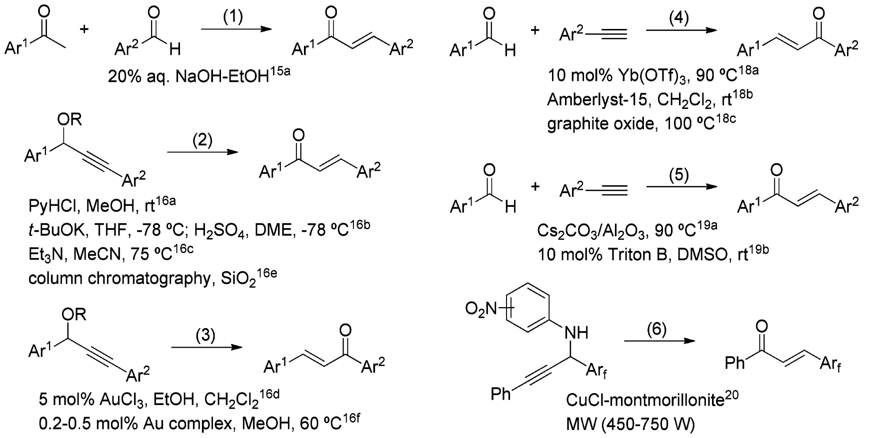
Indolizines have been synthesized following classical methods[6] or by iodine-mediated[7] and transition-metal-catalyzed[8] cycloisomerization of pyridines bearing alkynyl, propargyl, allenyl, or cyclopropenyl substituents at the 2 position. Some methods based on two-component annulations catalyzed by copper have also been reported.[9] However, the multicomponent reaction of 2-pyridinecarbaldehyde derivatives, secondary amines, and terminal alkynes has emerged as a powerful tool whereby the synthesis of indolizines can be attained in a single operation and atom-efficient manner. Catalytic processes with gold,[10] silver,[11] iron,[12] copper,[13] and zinc[14] have been described for this purpose.

Chalcone synthesis is normally accomplished following the classical Claisen−Schmidt condensation between aromatic ketones and aldehydes (Scheme 1, eq 1);[15a] other methods, such as the Suzuki coupling, Friedel−Crafts acylation, or Julia-Kocienski olefination, have been also practiced.[15b] Propargyl alcohol derivatives[16] have been used as chalcone precursors by isomerization to the corresponding enones (Scheme 1, eq 2)[16a−c,e] or through the Meyer−Schuster rearrangement[17] (Scheme 1, eq 3).[16d,f] More interesting is the direct reaction of aromatic aldehydes and alkynes to furnish chalcones. Ytterbium(III) triflate,[18a] Amberlyst-15,[18b] or graphite oxide[18c] have been found to promote the latter transformation with rearrangement (Scheme 1, eq 4), whereas the solid base Cs_2CO_3/Al_2O_3[19a] or the quaternary ammonium hydroxide base Triton B[19b] produced the nonrearranged products (Scheme 1, eq 5). More recently, propargyl amines derived from fluorinated aldehydes, *m*- and *p*-nitroaniline, and phenylacetylene gave the rearranged chalcone when irradiated with

Received: February 26, 2015
Revised: April 24, 2015
Published: April 27, 2015

DOI: 10.1021/acscatal.5b00417
ACS Catal. 2015, 5, 3446−3456

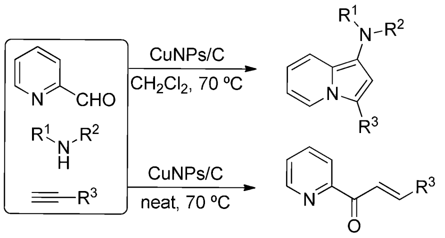
Scheme 1. Different Methods for Chalcone Synthesis



microwaves in the presence of montmorillonite doped with copper(I) chloride (Scheme 1, eq 6).[20] It was considered that the nitroaniline moiety acted as a good leaving group, generating allenic cation species that led to the chalcone after reaction with water, in a manner similar to that which was invoked for propargyl alcohol derivatives (Scheme 1, eq 3).[16d,f,17]

In organic chemistry, selective transformations of the same starting materials into two or more different products can be done by the choice of the catalyst.[21] More challenging is to reach the same objective conversely, by deploying a single catalyst but different solvent systems. Owing to our interest in metal colloids[22] and the application of supported copper nanoparticles (CuNPs) in organic chemistry,[23] we have recently communicated the multicomponent synthesis of indolizines from pyridine-2-carbaldehyde derivatives, secondary amines, and terminal alkynes catalyzed by copper nanoparticles on activated carbon in dichloromethane (Scheme 2).[24]

Scheme 2. Synthesis of Indolizines and Chalcones Catalyzed by CuNPs/C



Interestingly, the same starting materials (with piperidine as the secondary amine) and catalyst used for this purpose gave rise to heterocyclic chalcones in the absence of solvent, with this representing the first copper-catalyzed synthesis of chalcones (without rearrangement) from aromatic aldehydes and alkynes. We wish to present herein a complete study, which includes the scope of this methodology more focused on the synthesis of chalcones and, most importantly, our endeavor to understand mechanistically the formation of both the indolizines and chalcones.

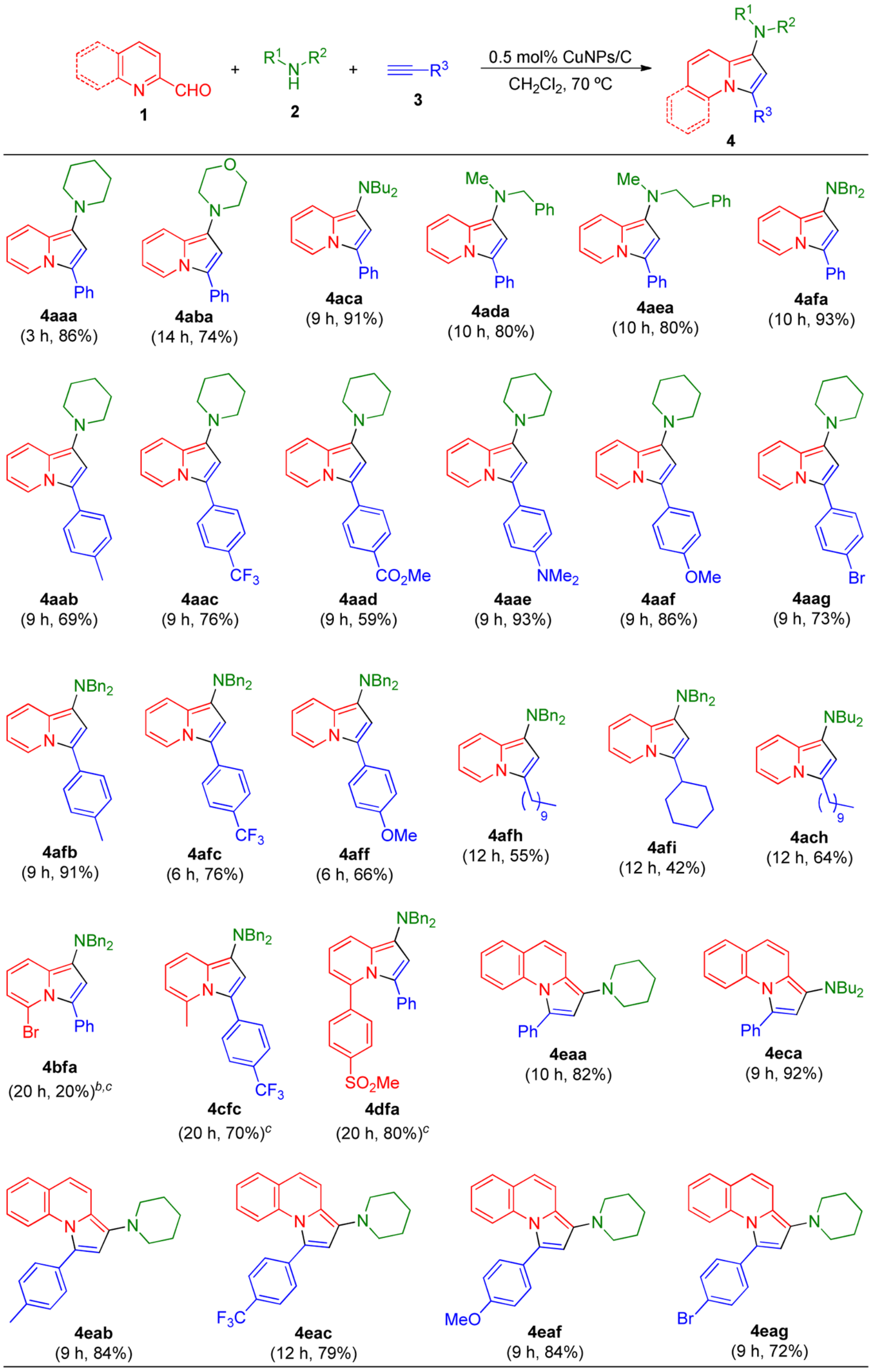
■ RESULTS AND DISCUSSION

All the supported copper catalysts used in this study were prepared by adding a variety of supports to a recently prepared suspension of the CuNPs,[25] readily generated, in turn, by reduction of anhydrous copper(II) chloride with lithium metal and a catalytic amount of 4,4′-di-*tert*-butylbiphenyl (DTBB, 10 mol %) in THF at room temperature;[26] the supported catalysts were not subjected to any treatment prior to use.

Synthesis of Indolizines. The metal support, solvent and conditions were previously optimized using pyridine-2-carbaldehyde (**1a**), piperidine (**2a**) and phenylacetylene (**3a**) as model compounds; oxidized copper nanoparticles (Cu_2O and CuO) on activated carbon (CuNPs/C) was found to be the catalyst of choice in dichloromethane at 70 °C.[24] With the optimized conditions in hand, a wide range of indolizines were synthesized in modest-to-high isolated yields by using low catalyst loading (0.5 mol %) (Table 1). Pyridine-2-carbaldehyde (**1a**) was successfully combined with six different secondary amines (**2a**–**f**) and seven aryl acetylenes containing electron-neutral, -withdrawing, or -releasing substituents (**3a**–**g**). Aliphatic alkynes (**3h**, **3i**) were found to be more reluctant to react, leading to the expected indolizines (**4afh**, **4afi**, **4ach**) in relatively lower yields (42–64%) because of partial decomposition during chromatographic purification. Likewise, reactions with pyridine-2-carbaldehydes substituted at the 6 position (**1b**–**d**) required prolonged heating, probably for steric reasons. Poor yield was noted for the 5-bromoindolizine **4bfa** as a result of the major formation of the A^3 coupling product; however, we could make use of this result to prove the reaction mechanism (vide infra). This methodology was also effectual when applied to quinoline-2-carbaldehyde (**1e**), giving the corresponding pyrrolo[1,2-*a*]quinolines **4eaa**–**eag** in good-to-high isolated yields (72–92%). Unfortunately, this catalyst, which showed good recycling properties in other multicomponent reactions,[25] could not be efficiently recycled in the present case (40% yield in a second cycle). The substantial metal leaching observed, together with the possible catalyst poisoning, could account for this behavior. This fact is not so important if we take into account that the copper loading used in these experiments is low.

In principle, any laboratory-made catalyst should be more efficient than commercially available catalysts used for the same purpose. Otherwise, it is difficult to economically justify the time, materials and human resources employed during its preparation. Taking into account this premise, we undertook a comparative study on the reactivity of CuNPs/C with that of some commercial copper catalysts. The standard conditions were applied to the model reaction of pyridine-2-carbaldehyde (**1a**), piperidine (**2a**), and phenylacetylene (**3a**). As shown in

Table 1. Multicomponent Synthesis of Indolizines Catalyzed by CuNPs/C[a]

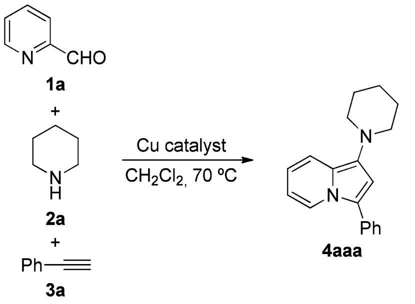


[a] Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), **3** (0.5 mmol), CuNPs/C [20 mg, ~0.5 mol %, determined from the Cu content (1.4 wt %) and the Cu_2O/CuO area from XPS (~1:1)], CH_2Cl_2 (1 mL), 70 °C; reaction time and isolated yield in parentheses. [b] The propargylamine **5bfa** was the major product (72%). [c] NMR yield based on the starting aldehyde.

Table 2, the best performance was attained with CuNPs/C (entry 11) in terms of catalyst loading, reaction time, and conversion. The kinetic profile for the synthesis of **4aaa** shows almost a linear increase in the conversion within the first 3 h (up to 92%), being nearly quantitative after 4 h (98%) (Figure 1). For this particular reaction, TON and TOF of up to 200 and 65 h^{-1}, respectively, have been recorded.

On the basis of our previous mechanistic studies on the aldehyde−amine−alkyne coupling (A^3 coupling),[23b] as well as on other methodologies,[10−13] we can propose a reaction mechanism for this multicomponent synthesis of indolizines, including (a) CuNPs-mediated enhancement of the alkyne acidity by coordination to the carbon−carbon triple bond,[27] enabling the formation of the corresponding copper(I) acetylide; (b) addition of the latter to the in situ-generated iminium ion derived from the aldehyde and the secondary amine; (c) copper-promoted cycloisomerization of the resulting propargylamine (A^3 product) through a 5-*endo-dig* and

Table 2. Comparison of CuNPs/C with Commercial Copper Catalysts[a]



entry	catalyst	mol %	*t* (h)	conv (%)[b]
1	CuCl	1	20	27
2	$CuCl_2$	1	20	55
3	CuBr	1	20	28
4	CuI	1	20	50
5	CuO	1	20	55
6	Cu_2O	1	20	57
7	$Cu(OAc)_2$	1	20	23
8	CuOAc	1	20	24
9	$CuBr{\cdot}SMe_2$	1	20	40
10	CuOTf	1	20	42
11	CuNPs	0.5	4	98

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), **3a** (0.5 mmol), catalyst, CH_2Cl_2 (1 mL), 70 °C. [b] Conversion into **4aaa** was determined by GC.

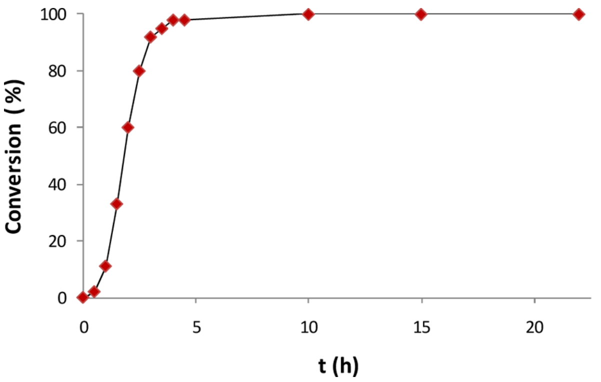


Figure 1. Plot showing the evolution of the synthesis of **4aaa** catalyzed by CuNPs/C.

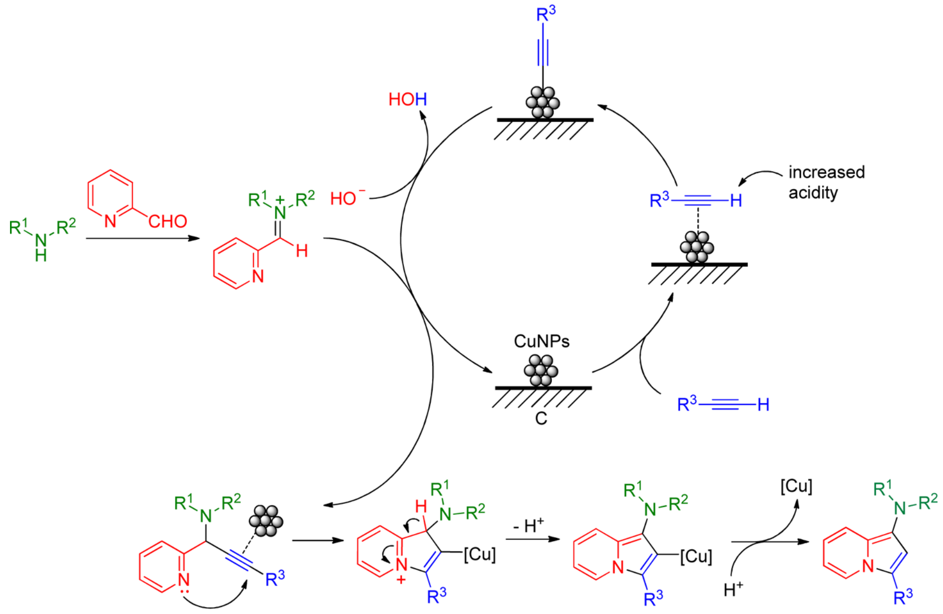
aromatization processes; and (d) protonolysis of the intermediate copper indolizide (Scheme 3). The participation of propargyl amines as indolizine precursors has been often postulated,[10−14] but to the best of our knowledge, never demonstrated. These pyridinyl propargyl amines must be rather elusive intermediates that, once generated in the reaction medium, rapidly cyclize to the corresponding indolizines. It is noteworthy that tiny peaks attributable to propargylamines were detected by GC/MS (same *m*/*z* as that of indolizines) in some of the reaction crudes derived from pyridine-2-carbaldehyde (**1a**). Notwithstanding the limitations to isolate a pyridinyl propargylamine and transform it into the corresponding indolizine, we turned our attention to the 6-substituted pyridine-2-carbaldehyde derivatives. The steric hindrance arisen between the 6-substituent of the pyridine and the alkyne substituent prior to ring closure could be a chance to isolate the pursued propargylamine. We capitalized on the low indolizine conversion recorded for some 6-bromopyridin-2-carbaldehyde derivatives and managed to isolate propargylamine **5bfa**. Subsequent treatment of **5bfa** with CuNPs/C in dichloromethane furnished the expected indolizine **4bfa** after prolonged heating (Scheme 4). These results distinctly unveil that 2-pyridinyl propargyl amines are the precursor intermediates of indolizines.

Synthesis of Chalcones. We discovered that the reaction of pyridine-2-carbaldehyde (**1a**), piperidine (**2a**), and phenylacetylene (**3a**) catalyzed by CuNPs/C, when performed in the absence of solvent, mainly led to the corresponding chalcone (**6aa**). We considered it convenient to optimize the copper catalyst to get the best possible conversion into the desired chalcones. The aforementioned substrates were used in a model reaction, carried out with CuNPs on diverse supports at 70 °C in the absence of solvent (Table 3). In a control experiment, we confirmed the necessity of copper for the reaction to take place (Table 3, entry 1). Among the different catalysts tested, NPsCu/C and NPsCu/graphite gave the highest conversions, with the former reaching a higher one with lower metal content (Table 3, entries 2 and 3). Other supports based on metal oxides or microporous or organic materials were not effective in this transformation (Table 3, entries 5−12). The introduction of a second metal in the catalyst supported on carbon had a deleterious effect in the conversion (Table 3, entries 13−16).

With CuNPs/C as the catalyst of choice, we undertook the optimization of the base, amount of catalyst, and reaction temperature (Table 4). The results obtained were found to be crucial to understanding the reaction pathway (vide infra). For instance, tertiary amines, such as Et_3N, pyridine, DABCO, $(i\text{-}Pr)_2NEt$, *N*,*N*-dimethylaniline, *N*-methylpiperidine, or TMEDA, were found to be ineffective, with no trace of chalcone **6aa** being detected. The reaction was also unfruitful with the inorganic bases $NaHCO_3$ or K_2HPO_4 (<1% and 0% conversion, respectively). Bases such as Et_2NH, *t*-BuOK, or Cs_2CO_3 led to poor conversions of ∼10% (Table 4, entries 1−3), whereas a better one was recorded with pyrrolidine (Table 4, entry 4). Piperidine was found to be the best base, even though a stoichiometric amount was required to achieve high conversion (Table 4, entries 5−8). Other amounts of catalyst or reaction temperatures gave conversions <60% (Table 4, entries 9−15). The kinetic profile for the synthesis of **6aa** shows a conversion of up to 82% within the first 3 h, to reach a maximum fixed at 85% after prolonged heating (Figure 2).

The optimized reaction conditions (Table 4, entry 8) were extended to the reaction of a variety of aldehydes and alkynes (Table 5). Pyridine-2-carbaldehyde (**1a**) and its derivatives substituted at the 6 position (**1b**,**c**,**f**) were reacted with several phenylacetylenes, producing the corresponding chalcones in modest-to-good yields (40−77%). In general, the 6-substituted carbaldehydes were found to be less reactive than the unsubstituted counterparts. This method was also applicable to other heteroaromatic aldehydes, such as quinoline-2-carbaldehyde (**1e**), 1-methyl-1*H*-imidazole-2-carbaldehyde (**1g**), and thiazole-2-carbaldehyde (**1h**), with a scanty conversion being obtained in the latter case. We sought to extend this procedure to nonheteroaromatic aldehydes by combining different *p*-substituted benzaldehydes (**1i**−**k**) with phenylacetylene (**1a**) and *p*-(trifluoromethyl)phenylacetylene (**1c**). The electron-withdrawing effect exerted by the CF_3 group in the alkyne improved the yield with respect to the unsubstituted phenylacetylene. It is worth noting that the presence of electron-withdrawing groups, either (or both) in

Scheme 3. Reaction Mechanism Proposed for the Three-Component Synthesis of Indolizines Catalyzed by CuNPs/C



Scheme 4. Transformation of Propargylamine 5bfa into Indolizine 4bfa

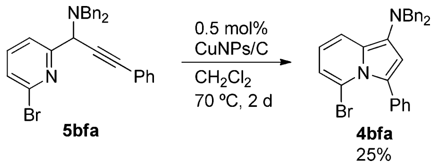
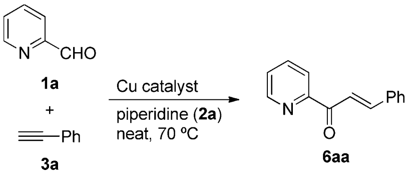


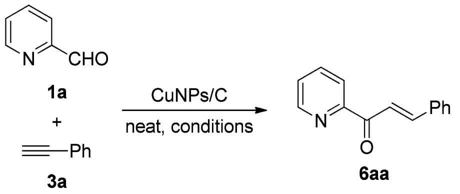
Table 3. Optimization of the Copper Catalyst in the Chalcone Synthesis[a]



entry	catalyst	% wt Cu[b]	conv (%)[c]
1	none	0	0
2	NPsCu/C	1.4	85
3	NPsCu/graphite	2.3	70
4	NPsCu/MWCNT[d]	2.4	26
5	NPsCu/TiO_2	3.0	39
6	NPsCu/MgO	1.5	45
7	NPsCu/ZnO	1.8	39
8	NPsCu/zeolite Y	3.7	57
9	NPsCu/MK-10[e]	1.8	47
10	NPsCu/cellulose	2.9	49
11	NPsCu/chitosan	2.5	53
12	NPsCu/Al silicate	1.2	<4
13	NPsCu-Co/C	0.6 (0.9)	22
14	NPsCu-Ni/C	0.9 (0.9)	27
15	NPsCu-Fe/C	0.4 (1.2)	0
16	NPsCu-Zn/C	1.4 (0.8)	50

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), **3a** (0.5 mmol), catalyst (20 mg), neat, 70 °C, 20 h. [b] Cu % wt in the catalyst; second metal % wt in parentheses. [c] Conversion into **6aa** was determined by GC. [d] Multiwalled carbon nanotube. [e] Montmorillonite K-10.

Table 4. Optimization of the Reaction Conditions in the Chalcone Synthesis[a]



entry	base (equiv)	*T* (°C)	conv (%)[b]
1	Et_2NH (1.0)	70	10
2	*t*-BuOK (1.0)	70	10
3	Cs_2CO_3 (1.0)	70	10
4	pyrrolidine (1.0)	70	40
5	piperidine (0.3)	70	5
6	piperidine (0.4)	70	8
7	piperidine (0.5)	70	32
8	piperidine (1.0)	70	85
9	piperidine (1.0)[c]	70	0
10	piperidine (1.0)[d]	70	2
11	piperidine (1.0)[e]	70	60
12	piperidine (1.0)	rt	0
13	piperidine (1.0)	60	10
14	piperidine (1.0)	80	34
15	piperidine (1.0)	100	56

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), **3a** (0.5 mmol), CuNPs/C (20 mg), neat, 20 h. [b] Conversion into **6aa** was determined by GC. [c] 5 mg CuNPs/C. [d] 10 mg CuNPs/C. [e] 30 mg CuNPs/C.

the aldehyde or (and) the alkyne, was fundamental for the chalcones being formed. In fact, pyridine-2-carbaldehyde (**1a**) did not react with phenylacetylenes containing electron-donating groups, such as 4-methoxyphenylacetylene (**3f**) or 4-*N*,*N*-(dimethylamino)phenylacetylene (**3e**), to form the expected chalcones, but the corresponding indolizines in variable amounts (2% **4aaf**, 16 h; 77% **4aae**, 17 h); quinoline-2-carbaldehyde (**1e**) and 4-methoxyphenylacetylene (**3f**) gave indolizine **4eaf** (18%, 17 h) and the corresponding chalcone in only 7% conversion. Likewise, the reaction of

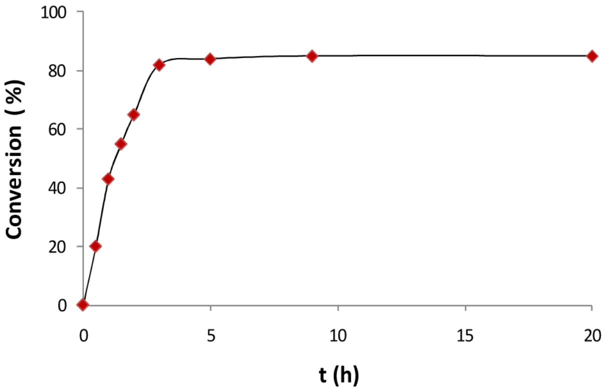


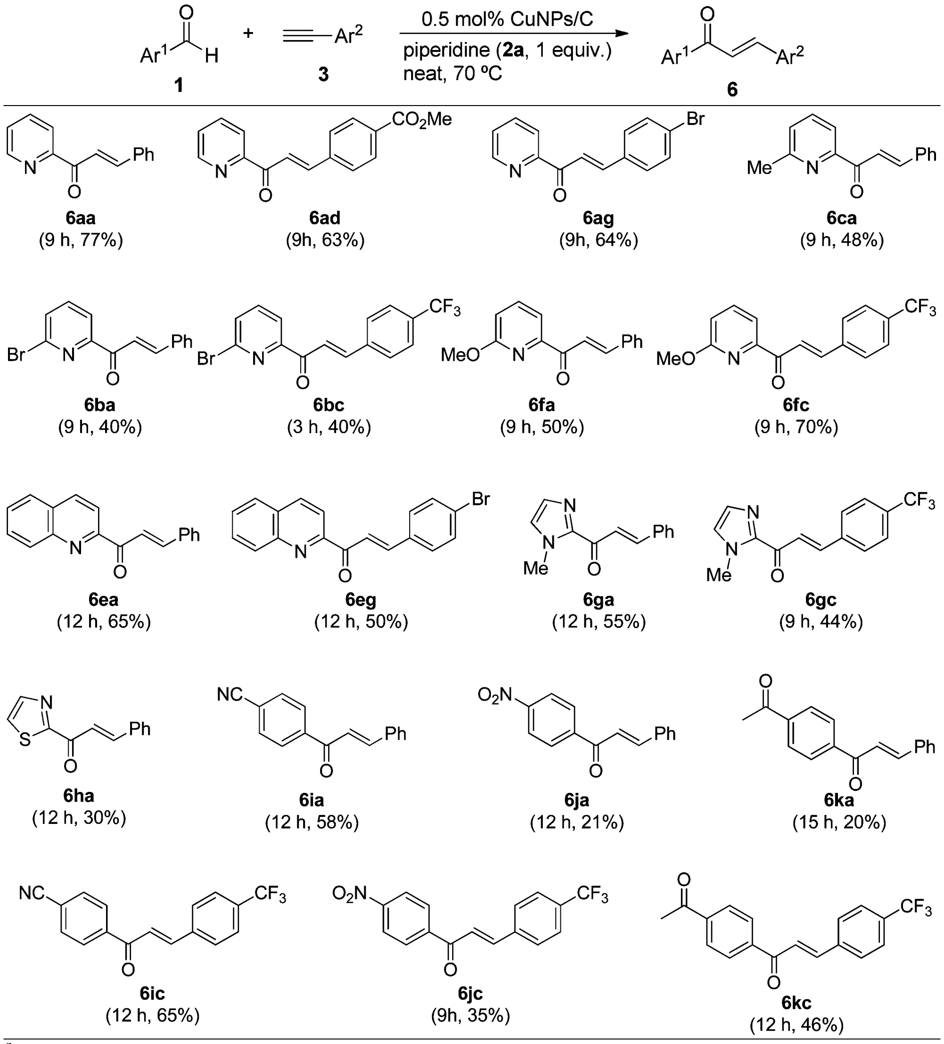
Figure 2. Plot showing the evolution of the synthesis of **6aa** catalyzed by CuNPs/C.

benzaldehyde with phenylacetylenes bearing any kind of substituents led to 10−38% chalcone conversion [4-bromophenylacetylene (10%), methyl 4-ethynylbenzoate (22%), 4-methylphenylacetylene (34%), 4-methoxyphenylacetylene (38%) and 4-ethynyl-*N*,*N*-dimethylaniline (12%)]; side products derived from the A^3 coupling or alkyne homocoupling were detected. Aliphatic alkynes as well as aliphatic aldehydes did not react toward the formation of the enones in any case. Other nonheteroaromatic aldehydes, such as 4-methylbenzaldehyde, 4-methoxybenzaldehyde, 4-*N*,*N*-dimethylaminobenzaldehyde, 4-bromobenzaldehyde, or piperonal, reacted with phenylacetylene to give the A^3 and alkyne homocoupling products.

Despite the fact that this methodology is not high-yielding, it is worthy of note that, under the same conditions, the alkyne homocoupling[23a] and A^3 coupling[23b] (or indolizine formation) can take place and compete with the chalcone formation. Nevertheless, efficient chalcone synthesis was achieved in some cases by using a minute catalyst loading (0.03 mol %, TON 2367, TOF 197 h^{-1}) (Scheme 5).

Moreover, contrary to the behavior observed for CuNPs/C in the synthesis of indolizines, when recovered by filtration or centrifugation, the catalyst could be reused over four cycles in the synthesis of chalcone **6ia** using low loading (0.13 mol %) with a decrease in the catalytic activity (Figure 3). Attempts to reutilize the catalyst in the synthesis of heterocyclic chalcone **6aa** were unfruitful, which was ascribed to the known tendency

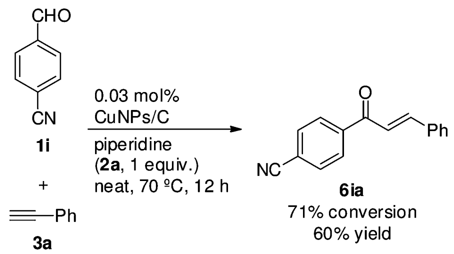
Table 5. Synthesis of Chalcones from Aldehydes and Alkynes Catalyzed by CuNPs/C[a]



6aa (9 h, 77%)
6ad (9h, 63%)
6ag (9h, 64%)
6ca (9 h, 48%)
6ba (9 h, 40%)
6bc (3 h, 40%)
6fa (9 h, 50%)
6fc (9 h, 70%)
6ea (12 h, 65%)
6eg (12 h, 50%)
6ga (12 h, 55%)
6gc (9 h, 44%)
6ha (12 h, 30%)
6ia (12 h, 58%)
6ja (12 h, 21%)
6ka (15 h, 20%)
6ic (12 h, 65%)
6jc (9h, 35%)
6kc (12 h, 46%)

[a] Reaction conditions: **1** (0.5 mmol), **2a** (0.5 mmol), **3** (0.5 mmol), CuNPs/C (20 mg, 0.5 mol %), 70 °C; reaction time and isolated yield in parentheses.

Scheme 5. Synthesis of Chalcone 6ia Using Very Low Catalyst Loading



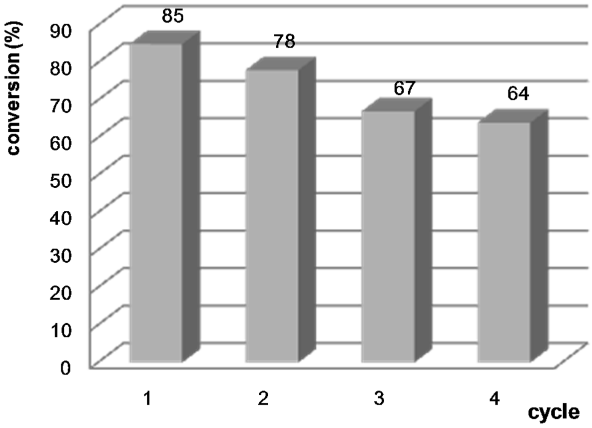
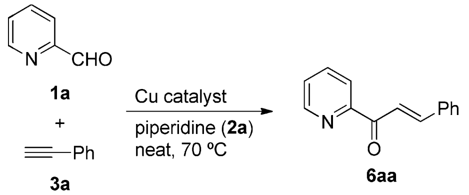


Figure 3. Reutilization of the catalyst in the synthesis of the chalcone **6ia** using 0.13 mol % CuNPs/C.

of this type of compounds to form stable complexes with copper,[28] in this case with a poisoning effect.

As previously studied for the synthesis of indolizines, we compared the performance of CuNPs/C with that of some commercial copper catalysts in the synthesis of chalcones (Table 6). Chalcone **6aa** was used as the model target, which was obtained in <50% conversion in all cases, with the exception of CuI (Table 6, entry 4); moderate conversion was obtained with the latter, though a larger amount of this nonrecyclable catalyst and a longer reaction time were required than with CuNPs/C (Table 6, entry 12). Moreover, an increase in the amount of CuI had a detrimental effect on the conversion (Table 6, entry 5).

Table 6. Comparison of CuNPs/C with Commercial Copper Catalysts[a]



entry	catalyst	mol %	*t* (h)	conv (%)[b]
1	CuCl	1	20	47
2	$CuCl_2$	1	20	33
3	CuBr	1	20	44
4	CuI	1	20	70
5	CuI	10	20	18
6	CuO	1	20	2
7	Cu_2O	1	20	25
8	$Cu(OAc)_2$	1	20	10
9	CuOAc	1	20	4
10	$CuBr\cdot SMe_2$	1	20	18
11	CuOTf	1	20	28
12	CuNPs	0.5	9	85

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), **3a** (0.5 mmol), Cu catalyst, neat, 70 °C. [b]Conversion into **6aa** was determined by GC.

From a structural point of view, we must underline that all chalcones were obtained as single *E* diastereoisomers, showing typical values of trans-coupled vinylic protons ($^3J_{H-H}$ = 15.7–16.4 Hz). The regiochemistry of the products was originally proposed by comparison of the NMR chemical shifts with those in the literature (Figure 4)[29] and unequivocally established by X-ray crystallographic analysis of chalcone **6fc** (Figure 5).[30] This information proves that no rearrangement is involved in the chalcone formation.

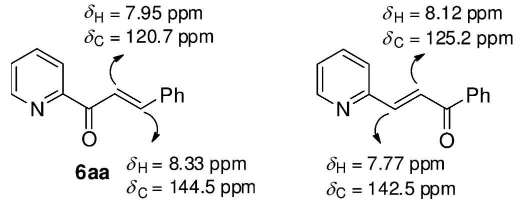


Figure 4. Comparison of the chemical shifts of **6aa** and its regioisomer.[29]

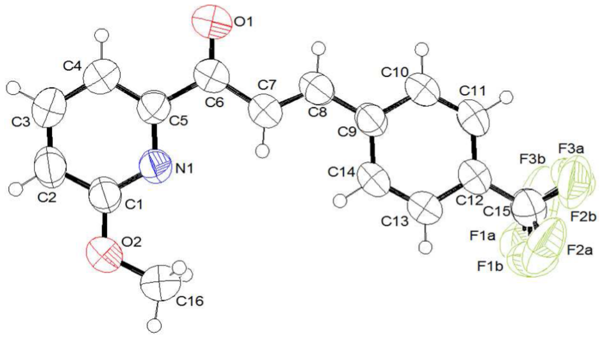
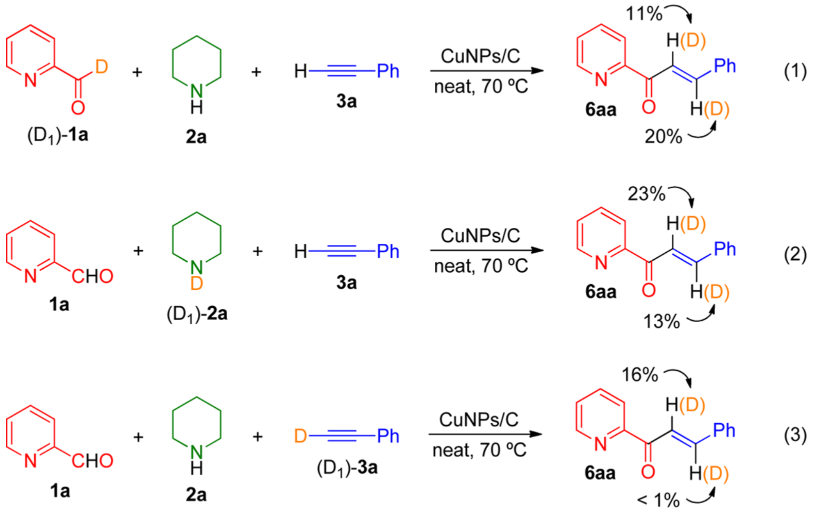


Figure 5. Plot showing the X-ray structure and atom numbering for compound **6fc**; 50% disorder was observed for the CF_3 group.[30]

To gain insight into the reaction mechanism of the chalcone formation, three isotopic-labeling experiments were conducted (Scheme 6) using deuterated pyridine-2-carbaldehyde [(D_1)-**1a**, eq 1], piperidine [(D_1)-**2a**, eq 2], and phenylacetylene [(D_1)-**3a**, eq 3]. The deuterium incorporation was estimated by integrating the triplet signals of the H−D coupling relative to those of the H−H coupling (Figure 1, Supporting Information). The corresponding chalcone **6aa** was formed with different degrees of deuterium incorporation at the *α* and *β* positions with respect to the carbonyl group. The low deuteration degree achieved in all cases suggests a favored D−H exchange for the three reagents in play. This behavior was somewhat expected for phenylacetylene (D_1)-**3a** and piperidine (D_1)-**2a** beause of the acidity of the acetylenic D and N-D, respectively. The scarce deuterium incorporation also observed in the case of pyridine-2-carbaldehyde (D_1)-**1a** points to a new mechanism different from those previously published.[16−19] The k_H/k_D = 0.47 determined for eq 1 in Scheme 6 reveals the absence of a primary kinetic isotopic effect and rules out the cleavage of the formyl group C−H as

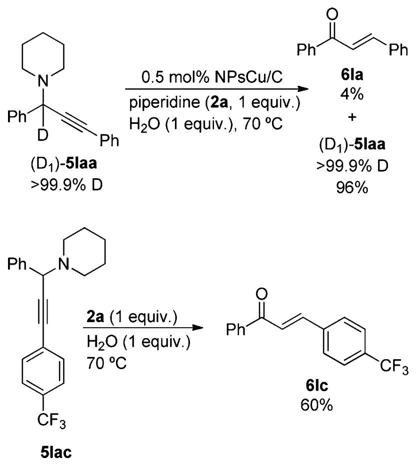
Scheme 6. Deuterium-Labeling Experiments in the Synthesis of Chalcone 6aa Catalyzed by 0.5 mol % CuNPs



being the determining step of the reaction (Figure 2, Supporting Information). This number is closer to that of an inverse secondary kinetic isotopic effect, implying a sp^2-to-sp^3 rehybridization of the carbonyl group of **1a** during the reaction.[31]

The fact that the chalcone **6aa** was not formed in the presence of tertiary amines and that the best conversions were achieved with the secondary amines piperidine and pyrrolidine (Table 4, entries 4 and 8, respectively), led us to conceive the reaction taking place through the A^3 coupling product. It is well-known that this coupling is especially favored when using piperidine as the secondary amine and involves a sp^2−sp^3 rehybridization as commented above. In this sense, piperidine-derived propargyl amine (D$_1$)-**5laa** was subjected to the reaction with piperidine (**2a**) in the presence of CuNPs/C and water under prolonged heating (Scheme 7). It was gratifying to observe the formation of the corresponding chalcone (**6la**), albeit the conversion was low, in agreement with the absence of electron-withdrawing groups in the aldehyde and alkyne components, as noted above. In contrast, the propargyl amine **5lac**,[32] bearing the electron-withdrawing trifluoromethyl group, led to the expected chalcone **6lc** in either the presence or the absence of the copper catalyst. Therefore, copper seems to be essential to obtain the A^3 coupling product but not to transform it into the chalcone. The fact that no D−H exchange was detected in (D$_1$)-**5laa** supports a type of irreversible process driven to the formation of the chalcone.

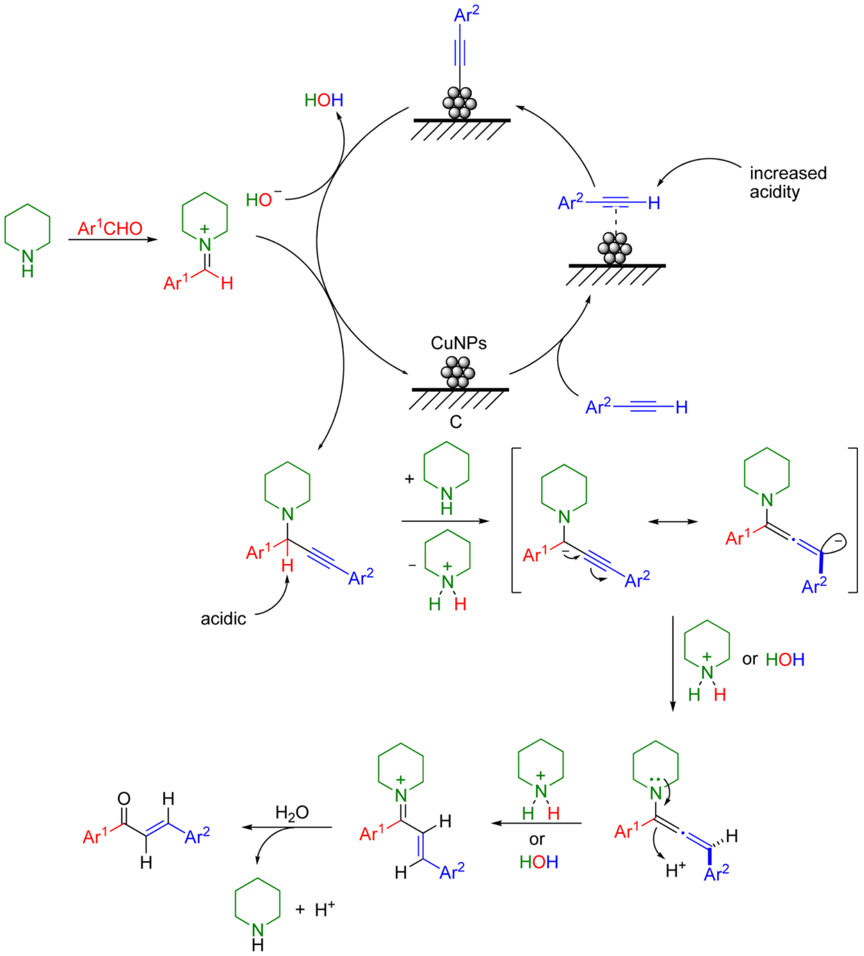
Scheme 7. Experimental Evidence on Propargyl Amines Acting As Chalcone Precursors



On the basis of all the aforementioned experiments, we can propose a mechanism for the copper-catalyzed synthesis of chalcones from aldehydes and alkynes, including (a) the formation of the piperidine-derived propargylamine catalyzed by CuNPs/C, in the terms shown in Scheme 3 and previously published by our group;[23b] (b) piperidine-promoted isomerization of the propargylamine to the corresponding allenylamine; and (c) hydrolysis of the allenylamine to the *E* chalcone (Scheme 8). There are several features in this mechanism that, in our opinion, play a decisive role in the outcome of the reaction. First, the acidity of the propargylic hydrogen; we believe that this hydrogen atom is particularly acid because it is at the same time propargylic, benzylic, and at the α-position with respect to the nitrogen. This acidity might also be enhanced in certain cases by coordination of the CuNPs to the carbon−carbon triple bond. Up to this point, the scenario is the same as previously described for the A^3 coupling or the multicomponent synthesis of indolizines. However, it is the absence of solvent, in conjunction with the presence of electron-withdrawing groups in the starting materials, that really makes a difference in the pathway toward the synthesis of chalcones. We believe that piperidine plays a double role, acting as both a component in the A^3 coupling and as a base; the unsolvated piperidine would manifest a more effective basic power, deprotonating the propargyl hydrogen atom and driving the course of the reaction on the chalcone formation. The negative inductive effect caused by the presence of electron-withdrawing groups would work in the same direction: increasing the acidity of the propargylic hydrogen atom and stabilizing the negative charge generated after deprotonation in the propargyl-to-allenyl amine isomerization. This explanation is concordant with the observation that the synthesis of chalcones from aromatic aldehydes or alkynes with electron-donating substituents is troublesome.

Although it may well be plausible that the hydrolysis step leading to the chalcone takes place in situ, it is important not to overlook the possibility that this step occurred during the workup. With this aim, we studied by NMR the progress of the

Scheme 8. Reaction Mechanism Proposed for the Synthesis of Chalcones from Aldehydes and Alkynes Catalyzed by CuNPs/C



reaction of 2-pyridinecarbaldehyde (**1a**), piperidine (**2a**), and phenylacetylene (**3a**) under solvent-free conditions at 70 °C; DMSO-d_6 was used as an external reference. It is noteworthy that the formation of the chalcone **6aa** was observed at an early stage (∼1 h), as proven by the coupling constant of the two vinylic protons (J = 16.1 Hz) in ^{1}H NMR and the chemical shift of C═O (180.2 ppm) in ^{13}C NMR (Figure 4, Supporting Information). This lends weight to the argument that hydrolysis of the chalcone precursor occurs to some extent in the reaction medium, involving the in situ-formed water, although probably not fast enough to allow piperidine to work catalytically.

Nature of the Catalysis. The following experiments were implemented in order to ascertain the nature of the catalysis: the standard indolizine (**4aaa**) and chalcone (**6aa**) syntheses were run up to 42% and 38% conversion (referred to the starting aldehyde), respectively. The catalyst was removed by filtration, and the filtrates were subjected to additional heating for a total reaction time of 5 h (40% and 37% conversion, respectively) and 10 h. After the latter time, 54% conversion was recorded in the indolizine synthesis, albeit to the detriment of the indolizine (15% **4aaa** + 39% byproducts), and 34% conversion in the chalcone synthesis. Apparently, decomposition of the indolizine occurs in the absence of the supported catalyst after prolonged heating.

On the other hand, ICP-OES analyses of the filtrates showed substantial Cu leaching in the indolizine synthesis (39.7%) and some leaching in the chalcone synthesis (1.4%). These data are in agreement with the fact that catalyst reutilization was more effective in the later than in the former and also suggest that the leached species into solution are catalytically inactive, thus pointing to a catalysis of heterogeneous nature.

■ CONCLUSIONS

The multicomponent synthesis of a series of indolizines and pyrrolo[1,2-*a*]quinolines has been effectively accomplished from pyridine-2-carbaldehyde derivatives, secondary amines, and alkynes using CuNPs/C as catalyst in dichloromethane. The methodology has been applicable to a variety of amines and alkynes, with the latter including aryl alkynes (bearing electron-neutral, -releasing, and -withdrawing groups) as well as aliphatic alkynes (42−93%). Interestingly, the same procedure, when applied in the absence of solvent using piperidine as the secondary amine, has led to heterocyclic chalcones as major products in modest-to-good yields (40−77%). Nonheterocyclic chalcones have also been obtained, although the presence of electron-withdrawing groups is crucial for their formation. In both processes, the catalyst was shown to be superior to some commercially available copper catalysts, and it could be reused in the chalcone synthesis over four cycles with a decrease in activity (85−64% conversion). Reaction mechanisms have been proposed for the indolizine and chalcone formation, based on the strong experimental evidence of participation of propargyl amines as intermediates in both cases. To the best of our knowledge, there is only one example in the literature in which propargyl amines have been used as chalcone precursors, albeit the rearranged products are obtained [Scheme 1, eq 6].[20] It can be inferred, therefore, that the synthesis of chalcones from aryl aldehydes and alkynes disclosed herein and the corresponding mechanism are unprecedented. On the basis of leaching studies, both the indolizine and chalcone syntheses are suggested to proceed under heterogeneous catalysis.

■ EXPERIMENTAL SECTION

General Procedure for the Synthesis of Indolizines 4 Catalyzed by CuNPs/C. The aldehyde (**1**, 0.5 mmol), amine (**2**, 0.5 mmol) and alkyne (**3**, 0.5 mmol) were added to a reactor tube containing CuNPs/C (20 mg, ∼0.5 mol %) and dichloromethane (1.0 mL). The reaction mixture was warmed to 70 °C without the exclusion of air and monitored by TLC or GLC until total or steady conversion of the starting materials. The solvent was removed in vacuo; EtOAc (2 mL) was added to the resulting mixture, followed by filtration through Celite and washing with additional EtOAc (4 mL). The reaction crude obtained after evaporation of the solvent was purified by column chromatography (silica gel, hexane/EtOAc) or preparative TLC (hexane/EtOAc) to give the corresponding indolizine **4**.

General Procedure for the Synthesis of Chalcones 6 Catalyzed by CuNPs/C. The aldehyde (**1**, 0.5 mmol), piperidine (**2a**, 0.5 mmol), and alkyne (**3**, 0.5 mmol) were added to a reactor tube containing CuNPs/C (20 mg, ∼0.5 mol %) in the absence of solvent. The reaction mixture was warmed to 70 °C without the exclusion of air and monitored by TLC or GLC until total or steady conversion of the starting materials. EtOAc (2 mL) was added to the resulting mixture, followed by filtration through Celite and washing with additional EtOAc (4 mL). The reaction crude obtained after evaporation of the solvent was purified by column chromatography (silica gel, hexane/EtOAc) to give the corresponding chalcone **6**.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.5b00417.

Procedures, characterization data, NMR spectra, kinetic isotope effect graphic (PDF)

X-ray crystallographic data (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*Phone. +34-965909614. Fax: +34-965903549. E-mail: falonso@ua.es.

Present Address

†(M.J.A.) Sharda Cropchem España S. L., Carril Condomina (Atalaya Business Center), 30006 Murcia, Spain.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was generously supported by the Spanish Ministerio de Economía y Competitividad (MINECO; CTQ2011-24151). M.J.A. and M.J.G.-S. acknowledge the Instituto de Síntesis Orgánica (ISO) of the Universidad de Alicante for both grants.

■ REFERENCES

(1) For reviews, see: (a) Vemula, V. R.; Vurukonda, S.; Bairi, C. K. *Int. J. Pharm. Sci. Rev. Res.* **2011**, *11*, 159−163. (b) Sing, G. S.; Mmatli, E. E. *Eur. J. Med. Chem.* **2011**, *46*, 5237−5257.

(2) For reviews, see: (a) Nowakoswka, Z. *Eur. J. Med. Chem.* **2007**, *42*, 125−137. (b) Batovska, D. I.; Todorova, I. T. *Curr. Clin. Pharmacol.* **2010**, *5*, 1−29. (c) Katsori, A.-M.; Hadjipavlou-Litina, D. *Expert Opin. Ther. Pat.* **2011**, *21*, 1575−1596. (d) Bukhari, S. N. A.; Jasamai, M.; Jantan, I. *Mini-Rev. Med. Chem.* **2012**, *12*, 1394−1403. (e) Prashar, H.; Chawla, A.; Sharma, A. K.; Kharb, R. *Int. J. Pharm. Sci. Res.* **2012**, *3*, 1913−1927. (f) Handzlik, J.; Matys, A.; Kieć-Knonowicz, K. *Antibiotics* **2013**, *2*, 28−45. (g) Singh, P.; Anand, A.; Kumar, V. *Eur. J. Med. Chem.* **2014**, *85*, 758−777.

(3) (a) Zheng, C.-J.; Jiang, S.-M.; Chen, Z.-H.; Ye, B.-J.; Piao, H.-R. *Arch. Pharm.* **2011**, *344*, 689−695. (b) Tran, T.-D.; Nguyen, T.-T.-N.; Do, T.-H.; Huynh, T.-N.-P.; Tran, C.-D.; Thai, K.-M. *Molecules* **2012**, *17*, 6684−6696. (c) Raj, C. G. D.; Sarojini, B. K.; Hegde, S.; Sreenivasa, S.; Ravikumar, Y. S.; Bhanuprakash, V.; Revanaiah, Y.; Ragavendra, R. *Med. Chem. Res.* **2013**, *22*, 2079−2087. (d) Sharma, P.; Karma, S.; Ali, F.; Anthal, S.; Gupta, V. K.; Khan, I. A.; Singh, S.; Sangwan, P. L.; Suri, K. A.; Gupta, B. D.; Gupta, D. K.; Dutt, P.; Vishwakarma, R. A.; Satti, N. K. *Med. Chem. Res.* **2013**, *22*, 3969−3983.

(4) Bronner, S. M.; Im, G.-Y. J.; Garg, N. K. In *Heterocycles in Natural Product Synthesis*; Majumdar, K. C., Chattopadhyay, S. K., Eds.; Wiley-VCH: Weinheim, 2011; pp 221−265.

(5) (a) Mashraqui, S. H.; Khan, T.; Sundaram, S.; Ghadigaonkar, S. *Tetrahedron Lett.* **2008**, *49*, 3739−3743. (b) El-Daly, S. A.; Gaber, M.; Al-Shihry, S. S.; El Sayed, Y. S. *J. Photochem. Photobiol., A* **2008**, *195*, 89−98. (c) El-Sayed, Y. S. *Opt. Laser Technol.* **2013**, *45*, 89−95.

(6) Shipman, M. In *Science of Synthesis*; Thomas, E. J., Ed.; Georg Thieme Verlag: Stuttgart, 2001; Vol. *10*, pp 745−787.

(7) (a) Kim, I.; Choi, J.; Won, H. K.; Lee, G. H. *Tetrahedron Lett.* **2007**, *48*, 6863−6867. (b) Kim, I.; Kim, S. G.; Kim, J. Y.; Lee, G. H. *Tetrahedron Lett.* **2007**, *48*, 8976−8981.

(8) For reviews, see: (a) Majumdar, K. C.; Debnath, P.; De, N.; Roy, B. *Curr. Org. Chem.* **2011**, *15*, 1760−1801. (b) Dudnik, A. S.; Gevorgyan, V. In *Catalyzed Carbon−Heteroatom Bond Formation*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, 2011; pp 317−410. (c) For a leading reference, see: Kel'in, A. V.; Sromek, A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074−2075. (d) See, also: Yan, B.; Zhou, Y.; Zhang, H.; Chen, J.; Liu, Y. *J. Org. Chem.* **2007**, *72*, 7783−7786. (e) Li, Z.; Chernyak, D.; Gevorgyan, V. *Org. Lett.* **2012**, *14*, 6056−6059 and the references cited therein . (f) Zhang, C.; Zhang, H.; Zhang, L.; Wen, T. B.; He, X.; Xia, H. *Organometallics* **2013**, *32*, 3738−3743.

(9) (a) Barluenga, J.; Lonzi, G.; Riesgo, L.; López, L. A.; Tomás, M. *J. Am. Chem. Soc.* **2010**, *132*, 13200−13202. (b) Yang, Y.; Xie, C.; Xie, Y.; Zhang, Y. *Org. Lett.* **2012**, *14*, 957−959. (c) Hu, H.; Feng, J.; Zhu, Y.; Gu, N.; Kan, Y. *RSC Adv.* **2012**, *2*, 8637−8644.

(10) Yan, B.; Liu, Y. *Org. Lett.* **2007**, *9*, 4323−4326.

(11) Bai, Y.; Zeng, J.; Ma, J.; Gorityala, B. K.; Liu, X.-W. *J. Comb. Chem.* **2010**, *12*, 696−699.

(12) Patil, S. S.; Patil, S. V.; Bobade, V. D. *Synlett* **2011**, *2011*, 2379−2383.

(13) (a) Dighe, S. U.; Hutait, S.; Batra, S. *ACS Comb. Sci.* **2012**, *14*, 665−672. (b) Mishra, S.; Naskar, B.; Ghosh, R. *Tetrahedron Lett.* **2012**, *53*, 5483−5487. (c) Pan, C.; Zou, J.; Zeng, R. *Chin. J. Chem.* **2013**, *31*, 799−804.

(14) Mishra, S.; Bagdi, A. K.; Ghosh, M.; Sinha, S.; Hajra, A. *RSC Adv.* **2014**, *4*, 6672−6676.

(15) (a) For the synthesis of pyridinyl chalcones by Claisen-Schmidt condensation, see: Marvel, C. S.; Coleman, L. E.; Scott, G. P. *J. Org. Chem.* **1955**, *20*, 1785−1792. (b) For a review, see: Bukhari, S. N. A.; Jasamai, M.; Jantan, I.; Ahmad, W. *Mini-Rev. Org. Chem.* **2013**, *10*, 73−83.

(16) (a) Erenler, R.; Biellmann, J.-F. *Tetrahedron Lett.* **2005**, *46*, 5683−5685. (b) Yoshizawa, K.; Shioiri, T. *Tetrahedron Lett.* **2006**, *47*, 4943−4945. (c) Braun, R. U.; Ansorge, M.; J. Müller, T. J. *Chem.−Eur.*

J. **2006**, *12*, 9081−9094. (d) Engel, D. A.; Dudley, G. B. *Org. Lett.* **2006**, *8*, 4027−4029. (e) Seregin, I. V.; Schammel, A. W.; Gevorgyan, V. *Tetrahedron* **2008**, *64*, 6876−6883. (f) Wang, D.; Zhang, Y.; Harris, A.; Gautam, L. N. S.; Chen, Y.; Shi, X. *Adv. Synth. Catal.* **2011**, *353*, 2584−2588.

(17) For reviews, see: (a) Swaminathan, S.; Narayanan, K. V. *Chem. Rev.* **1971**, *71*, 429−438. (b) Engel, D. A.; Dudley, G. B. *Org. Biomol. Chem.* **2009**, *7*, 4149−4158. (c) Cadierno, V.; Crochet, P.; García-Garrido, S. E.; Gimeno, J. *Dalton Trans.* **2010**, *39*, 4015−4031. (d) Bauer, E. B. *Synthesis* **2012**, *44*, 1131−1151. (e) Zhu, Y.; Sun, L.; Lu, P.; Wang, Y. *ACS Catal.* **2014**, *4*, 1911−1925.

(18) (a) Curini, M.; Epifano, F.; Maltese, F.; Rosati, O. *Synlett* **2003**, 552−554. (b) Yadav, J. S.; Subba Reddy, B. V.; Vishumurthy, P. *Tetrahedron Lett.* **2008**, *49*, 4498−4500. (c) Jia, H.-P.; Dreyer, D. R.; Bielawski, C. W. *Adv. Synth. Catal.* **2011**, *353*, 528−532.

(19) (a) Baba, T.; Kizuka, H.; Handa, H.; Ono, Y. *Appl. Catal., A* **2000**, *194−195*, 203−211. (b) Ishikawa, T.; Mizuta, T.; Hagiwara, K.; Aikawa, T.; Kudo, T.; Saito, S. *J. Org. Chem.* **2003**, *68*, 3702−3705.

(20) Chen, X.-L.; Zhang, J.-M.; Shang, W.-L.; Lu, B.-Q.; Jin, J.-A. *J. Fluorine Chem.* **2012**, *133*, 139−145.

(21) For a review, see: Mahatthananchai, J.; Dumas, A. M.; Bode, J. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 10954−10990.

(22) For reviews, see: (a) Alonso, F.; Radivoy, G.; Yus, M. *Russ. Chem. Bull.* **2003**, *52*, 2563−2576. (b) Alonso, F.; Yus, M. *Chem. Soc. Rev.* **2004**, *33*, 284−293. (c) Alonso, F.; Yus, M. *Pure Appl. Chem.* **2008**, *80*, 1005−1012. (d) Alonso, F.; Riente, P.; Yus, M. *Acc. Chem. Res.* **2011**, *44*, 371−391. (e) Alonso, F. In *Metal Nanoparticles for Catalysis: Advances and Applications*; Tao, F., Ed.; The Royal Society of Chemistry: Cambridge, 2014; pp 83−98.

(23) For selected examples, see: (a) Alonso, F.; Melkonian, T.; Moglie, Y.; Yus, M. *Eur. J. Org. Chem.* **2011**, *2011*, 2524−2530. (alkyne homocoupling). (b) Albaladejo, M. J.; Alonso, F.; Moglie, Y.; Yus, M. *Eur. J. Org. Chem.* **2012**, *2012*, 3093−3104. (A^3 coupling). (c) Alonso, F.; Moglie, Y.; Radivoy, G.; Yus, M. *J. Org. Chem.* **2013**, *78*, 5031−5037 (click chemistry) .

(24) Albaladejo, M. J.; Alonso, F.; Yus, M. *Chem.−Eur. J.* **2013**, *19*, 5242−5245.

(25) (a) Alonso, F.; Moglie, Y.; Radivoy, G.; Yus, M. *Adv. Synth. Catal.* **2010**, *352*, 3208−3214. (b) Alonso, F.; Moglie, Y.; Radivoy, G.; Yus, M. *Org. Biomol. Chem.* **2011**, *9*, 6385−6395.

(26) (a) Alonso, F.; Calvino, J. J.; Osante, I.; Yus, M. *Chem. Lett.* **2005**, *34*, 1262−1263. (b) Alonso, F.; Calvino, J. J.; Osante, I.; Yus, M. *J. Exp. Nanosci.* **2006**, *1*, 419−433.

(27) (a) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2632−2657. (b) Alonso, F.; Moglie, Y.; Radivoy, G.; Yus, M. *J. Org. Chem.* **2011**, *76*, 8394−8405.

(28) Gaber, M.; El-Daly, S. A.; El-Sayed, Y. S. Y. *J. Mol. Struct.* **2008**, *922*, 51−57.

(29) Jovanović, B. Ž.; Mišić-Vuković, M.; Marinković, A. D.; Csanádi, J. *J. Mol. Struct.* **1999**, 482−483.

(30) CCDC-1019390 (**6fc**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

(31) Amaral, L.; Bull, H. G.; Cordes, E. H. *J. Am. Chem. Soc.* **1972**, *94*, 7579−7580.

(32) It was rather difficult to obtain substantial amounts of a propargylamine, derived from piperidine and bearing electron-withdrawing groups, because of its tendency to give the chalcone in the reaction medium.