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Magnetically separable Fe_3O_4 nanoparticles: an efficient catalyst for the synthesis of propargylamines

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ABSTRACT

Magnetically separable Fe_3O_4 nanoparticles endow with an efficient and economic route for the synthesis of propargylamines by the three-component coupling of aldehyde, amine, and alkyne through C–H activation. The reaction is especially effective for reactions involving aliphatic aldehydes and no additional co-catalyst or activator is required. High catalytic activity and ease of recovery using an external magnetic field are additional eco-friendly attributes of this catalytic system. The catalyst was recycled for five times without a significant loss of catalytic activity.

Magnetic nanoparticles are a class of nanostructured materials of current interest, due largely to their advanced technological and medical applications, envisioned or realized.[1] Among the various magnetic nanoparticles under investigation, Fe_3O_4 nanoparticles are arguably the most extensively studied.[1a,e,2] Furthermore, recent reports show that Fe_3O_4 nanoparticles are efficient supports for catalysts and can facilitate their separation effectively from the reaction media by magnetization with a permanent magnetic field.[3]

Propargylamines are versatile synthetic intermediates in organic synthesis and are also important structural elements in natural products and therapeutic drug molecules.[4] These compounds have traditionally been synthesized by nucleophilic attack of lithium acetylides or Grignard reagents on imines or their derivatives.[5] However, these reagents must be used in stoichiometric amounts, are highly moisture sensitive, and require strictly controlled reaction conditions. An alternative atom-economical approach to their synthesis is to perform this type of reaction by a catalytic coupling of alkyne, aldehyde, and amine (A3 coupling) by C–H activation, where water is only the theoretical by-product.[6,7]

In recent years, the scope of direct addition of alkynes to carbon nitrogen double bonds either from prepared imines or from aldehydes and amines in one-pot procedure by several noble transition-metal catalysts via C–H activation of terminal alkynes both under homogeneous (Ag^I salts,[6] Au^I/Au^{III} salts,[7] Au^{III}-salen complexes,[8] Cu^I salts,[9] Ir complexes,[10] $InCl_3$,[11] $FeCl_3$[12] and Cu/Ru^{II} bimetallic system,[13] and so on) and heterogeneous[14] (Au^I, Ag^I, and Cu^I in ionic liquids and supported Au^{III}, Ag^I, Cu^I, and so on) conditions have been successfully used to catalyze three-component coupling reactions. However, heterogenized catalyst generally requires tedious preparation and/or separation procedures, there is a need to find new materials with speciality properties such as magnetic in order to overcome these limitations. Recently, Kidwai et al.[15] have reported gold and copper nanoparticles as reusable catalysts for the synthesis of propargylamines. The main difficulty, however, is that such small particles are almost impossible to separate by conventional means, which can lead to the blocking of filters and valves by the catalyst. The efficient separation of suspended magnetic catalyst bodies from the liquid product by using an external magnetic field offers a solution to this problem and would be of immense interest.

In the present work, as part of our ongoing interest in the synthesis of propargylamines,[9d,14i] we report our investigations on the application of Fe_3O_4 nanoparticles[16] for the practical and atom-economic synthesis of propargylamines through three-component coupling of aldehyde, alkyne, and amine via C–H activation (Scheme 1).

Initially, in an effort to develop an improved catalytic system, different solvents were screened for the reaction of benzaldehyde, piperidine, and phenylacetylene in the presence of 20 mol % of Fe_3O_4 at their reflux temperatures and the results are summarized in Table 1. The outcome of the reaction was dependent on the nature of the solvent and temperature. It was observed that much better yield was obtained when the reaction was carried out in toluene at 110 °C compared to other solvents (Table 1, entry 1). Among the other solvents screened, acetonitrile and THF gave

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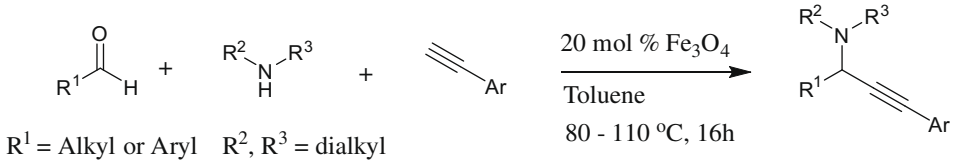


Scheme 1.

Table 1
Screening of various solvents for the three-component coupling reaction between benzaldehyde, piperidene and phenylacetylene[a]

Entry	Solvent	Temp (°C)	Yield[b] (%)
1	Toluene	110	75
2	Acetonitrile	65	30
3	THF	65	25
4	Methanol	65	60
5	Water	100	Trace
6	Neat	100	Trace

[a] Reaction conditions: benzaldehyde (1 mmol), piperidine (1.2 mmol), phenylacetylene (1.5 mmol) Fe_3O_4 (20 mol %), solvent 3 mL.
[b] Yields are based on ^1H NMR integration.

Table 2
Three-component coupling reaction of various aldehydes with piperidine and phenyl acetylene[a]

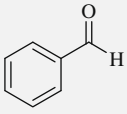
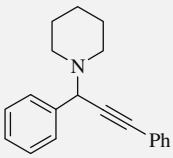
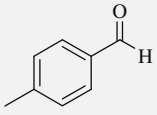
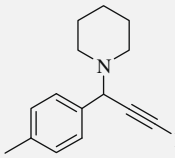
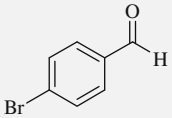
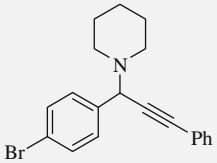
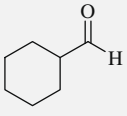
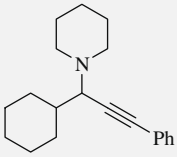
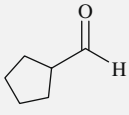
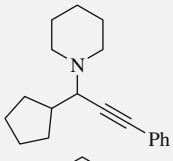
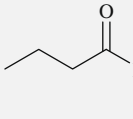
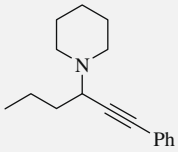
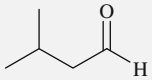
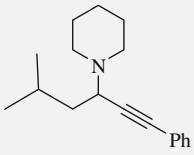
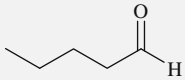
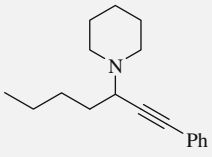
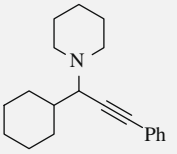
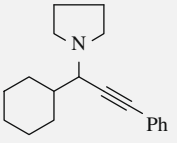
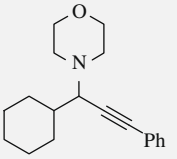
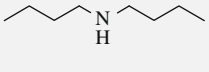
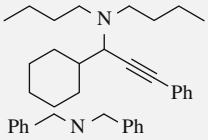
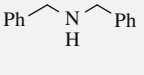
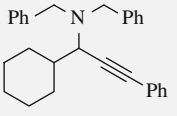
Entry	Aldehyde	Product	Yield (%)	Ref.
1[b]			75	14f
2[b]			56	14f
3[b]			40	7
4			85	14f
5			80	6
6			90	14i

Table 2 (*continued*)

Entry	Aldehyde	Product	Yield (%)	Ref.
7			92	14i
8			90	17

[a] Reaction conditions: aldehyde (1 mmol), piperidine (1.2 mmol), phenylacetylene (1.5 mmol), Fe_3O_4 (20 mol %) in toluene (3 mL) at 80 °C for 16 h.
[b] Reaction carried out at 110 °C.[21]

Table 3
Three-component coupling reaction of various amines with cyclohexanecarboxaldehyde and phenylacetylene[a]

Entry	Amine	Product	Yield (%)	Ref.
1			85	6
2			90	6
3			80	9a
4			15	14c
5			11	11

[a] Reaction conditions: cyclohexanecarboxaldehyde (1 mmol), amine (1.2 mmol), phenylacetylene (1.5 mmol), Fe_3O_4 (20 mol %) in toluene (3 mL) at 80 °C for 16 h.[21]

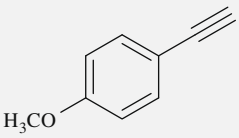
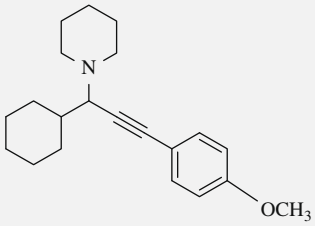
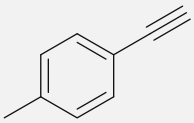
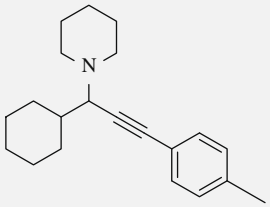
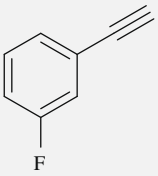
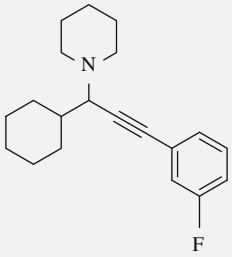
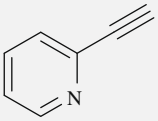
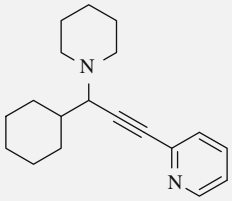
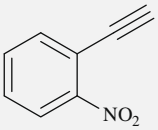
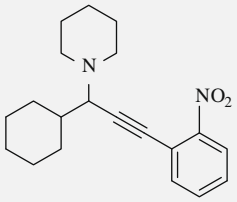
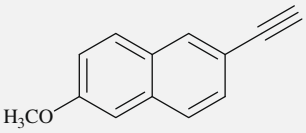
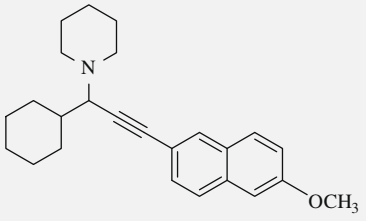
the product in low yield (Table 1, entries 2 and 3), whereas the reaction in methanol gave the desired product in a moderate yield (Table 1, entry 4). However, only a trace amount of the product was

formed in water and neat conditions (Table 1, entries 5 and 6). Further, the optimum ratio of aldehyde, amine, and alkyne was found to be 1:1.2:1.5.

Subsequently, a variety of propargylamines were prepared from various aldehydes, alkynes, and amines using the optimized reaction conditions and the results are summarized in Tables 2–4. Initially, the scope of the aldehyde substrate was evaluated and the results are given in Table 2. The aldehydes used in this study included aromatic and aliphatic examples and the reaction was found to be highly effected by the nature of the aldehyde. Aryl aldehyde decreased the reactivity of the reaction, required longer reaction time for reaction completion to give the desired product in good yields (Table 2, entries 1–3). The reactions involving aliphatic aldehydes gave both higher conversions and greater yields (Table 2, entries 4–8). While unwanted trimerization of aldehyde was a major limitation of the reactions catalyzed by gold and copper, almost no trimer was found with aliphatic aldehydes when using Fe_3O_4 as the catalyst.

To expand the scope of the amine substrates, we used cyclohexanecarboxaldehyde and phenyl acetylene as model substrates and examined various secondary amines in the synthesis of propargylamines and the results are given in Table 3. The order of reactivity

Table 4
Three-component coupling of various terminal alkynes with cyclohexanecarboxaldehyde and piperidine[a]

Entry	Alkyne	Product	Yield (%)
1			90
2			92[b]
3			85
4			70
5			60
6			85

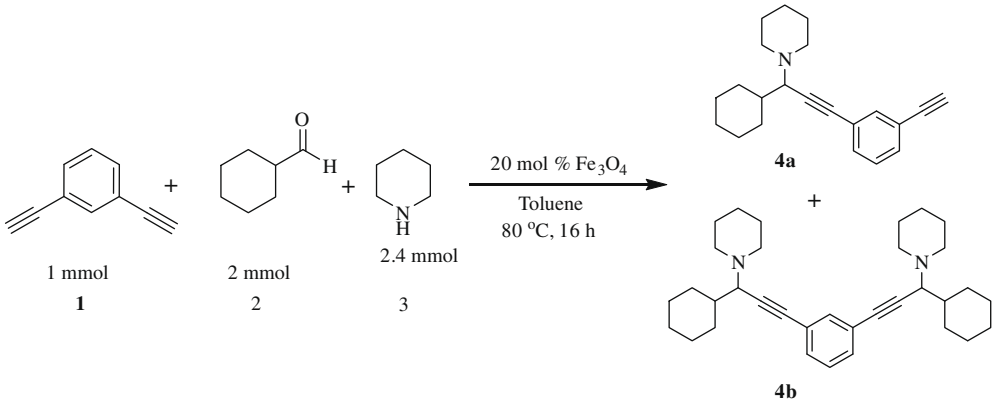
[a] Reaction conditions: cyclohexanecarboxaldehyde (1 mmol), piperidine (1.2 mmol), terminal alkyne (1.5 mmol), Fe_3O_4 (20 mol %) in toluene (3 mL) at 80 °C for 16 h.[21]
[b] Ref. 6.

for these amines in terms of yield and reaction time was found to pyrrolidine > piperidine > morpholine > dialkylamine. Cyclic amines gave the desired products in good yield when compared to acyclic amines, such as dibutylamine and dibenzylamine. As can be seen in the table, acyclic amines are less reactive in reactions with phenylacetylene and cyclohexanecarboxaldehyde, and only trace amounts of the desired products were isolated.

Furthermore, as shown in Table 4, several terminal alkynes were examined for the synthesis of propargylamines using cyclohexanecarboxaldehyde and piperidine as the model substrates and good to excellent yields of the desired products were obtained in each case. The reactions were completed within 16 h affording 60–95% yields. Both aryl and heteroaryl alkynes underwent the reaction to furnish the desired products in good yields except 2-nitrophenylacetylene (Table 4, entries 1–6). With aliphatic alkynes such as octyne and butyne only a trace amount of the product was obtained. It was observed that when the reaction was carried out with 1,3-diethynylbenzene using 2 equiv of cyclohexanecarboxaldehyde and 2.4 equiv of piperidine, mono and disubstituted products (**4a** and **4b**) were obtained in the ratio of 1:3 using toluene as the solvent in 80% yield (Scheme 2).

To check the recyclability of the catalyst, as can be seen from Table 5, the reaction was performed with both aliphatic and aromatic aldehydes and the catalyst was separated from the reaction mixture by applying external magnetic field and reused without a significant loss of catalytic activity.

On the basis of these results, together with the literature reports,[6–9] we propose a plausible mechanism as shown in Scheme 3. Fe_3O_4 is of cubic inverse spinel crystal structure, in which the oxygen anions (O^{2-}) form a closely packed face-centered cubic (fcc) sublattice with iron cations located in interstitial sites and there are two different kinds of cation sites: tetrahedrally coordinated sites occupied by Fe^{3+} and octahedrally coordinated sites occupied by Fe^{3+} and Fe^{2+} ions in equal numbers.[18] The Fe^{2+} cation can be considered to be Fe^{3+} plus an 'extra' electron, with rapid valence oscillation between the Fe(III) and Fe(II) octahedral sites. Initially, in the presence of amine, deprotonation of terminal alkyne occurs resulting in the activation of C–H bond and

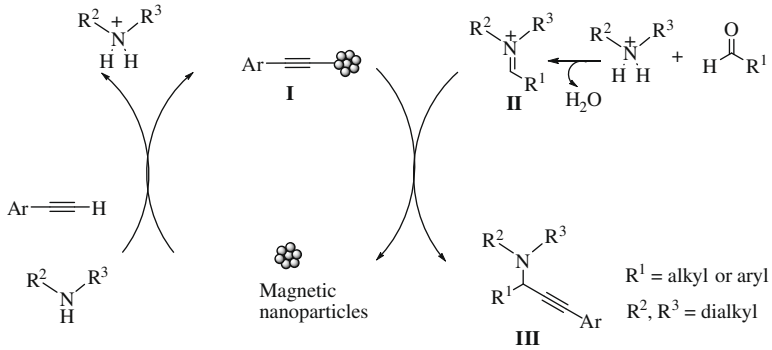


Scheme 2.

Table 5
Recovery and reuse of Fe_3O_4 nanoparticles for the synthesis of propargylamines[a]

Entry	Aldehyde	Yield[b] (%)					Average yield (%)
		First	Second	Third	Fourth	Fifth	
1[c]	Cyclohexanecarboxaldehyde	85	80	82	80	80	81
2[d]	Benzaldehyde	75	72	70	70	65	70

[a] Reaction conditions: aldehyde (1 mmol), piperidine (1.2 mmol), phenylacetylene (1.5 mmol), toluene (3 mL), Fe_3O_4 (20 mol %), 16 h.
[b] Yields are based on ^{1}H NMR integration.
[c] Reaction carried out at 80 °C.
[d] Reaction carried out at 110 °C.



Scheme 3.

generation of the terminal iron-acetylide intermediate **I**, which could be presumably due to the reduction of Fe^{3+} to a low valent Fe^{2+} oxidation state.[19] Iron cations also acts as Lewis acid and play a significant role in increasing the electrophilic character of the starting aldehyde and stabilizing the immonium salt by the coordination of the oxygen or nitrogen lone electron pair.[20] The formed iron-acetylide intermediate **I**, further undergoes nucleophilic addition to the immonium ion **II**, to yield the corresponding propargylamine **III** and regeneration of the catalyst.

In conclusion, we have developed a simple and efficient method for the synthesis of propargylamines via C–H activation using magnetically separable Fe_3O_4 as the catalyst under mild reaction conditions. The reaction is especially effective for reactions with aliphatic aldehydes and no additional co-catalyst or activator is required. The simple procedure for catalyst preparation, easy recovery and reusability of the catalyst are expected to contribute to its utilization for the development of benign chemical processes and products.

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References and notes

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21. *Typical procedure for the synthesis of propargylamines*: A mixture of aldehyde (1 mmol), amine (1.2 mmol), alkyne (1.5 mmol), catalyst (20 mol %), and toluene (3 mL) was taken in a round-bottomed flask and stirred at 110 °C (aromatic aldehydes) or 80 °C (aliphatic aldehydes) temperature. After completion of the reaction (monitored by TLC) the catalyst was easily separated from the reaction mixture with an external magnet. After removing the solvent, the crude material was chromatographed on silica gel to afford the pure product. The spectroscopic data of all known compounds were identical to those reported in the literature.[6–9] Spectroscopic data for all new compounds synthesized are reported herein.
1-(1-Cyclohexyl-3-(4-methoxyphenyl)prop-2-ynyl)piperidine (Table 4, entry 1): Half-white Solid. Mp: 73–76 °C. IR (neat): 3038, 2930, 2848, 2748, 2213, 2058, 1899, 1605, 1508, 1246, 1108, 1033, 996, 830 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.87–1.78 (m, 15H), 2.00–2.12 (m, 2H), 2.33–2.42 (m, 2H), 2.56–2.65 (m, 2H), 3.04 (d, 1H, J = 10.0 Hz), 3.79 (s, 3H), 6.76 (d, 2H, J = 8.8 Hz), 7.31 (d, 2H, J = 8.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.6, 26.0, 26.1, 26.7, 30.4, 31.2, 39.5, 55.2, 64.3, 85.8, 85.9, 113.7, 115.8, 132.9, 159.0. ESI MS (m/z): 312 (M+H).
1-(1-Cyclohexyl-3-(3-fluorophenyl)prop-2-ynyl)piperidine (Table 4, entry 3): IR (neat): 2958, 2851, 2800, 1608, 1483, 1444, 1150, 996, 868, 780 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.86–1.78 (m, 15H), 1.99–2.09 (m, 2H), 2.31–2.41(m, 2H), 2.55–2.64 (m, 2H), 3.06 (d, 1H, J = 9.5 Hz), 6.96 (t, 1H, J = 7.8 Hz), 7.08–7.24 (m, 2H), 7.25 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.6, 26.0, 26.1, 26.7, 30.3, 31.2, 64.2, 85.0, 88.8, 114.7, 115.0, 118.2, 118.5, 127.5, 129.5 (d, J = 8.7 Hz). ESI MS (m/z): 300 (M+H).
2-(3-Cyclohexyl-3-piperidin-1-yl)prop-1-ynyl)pyridine (Table 4, entry 4): IR (neat): 3055, 2929, 2850, 2794, 2219, 1635, 1582, 1458, 1262, 1103, 993, 785 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.89–1.80 (m, 15H), 1.99–216 (m, 2H), 2.37–2.47 (m, 2H), 2.61–2.70 (m, 2H), 3.12 (d, 1H, J = 9.8 Hz), 7.14–7.19 (m, 1H), 7.38(d, 1H, J = 7.5 Hz), 7.60(ddd, 1H, J = 2.2 Hz, 7.5 Hz, 9.8 Hz), 8.54 (d, 1H, J = 6.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.7, 26.2, 26.4, 26.9, 30.5, 31.5, 39.5, 64.3, 86.1, 88.3, 96.2, 122.2, 127.2, 135.7, 143.9, 149.8. ESI MS (m/z): 283 (M+H).
1-(1-Cyclohexyl-3-(2-nitrophenyl)prop-2-ynyl)piperidine (Table 4, entry 5): IR (neat): 2926, 2851, 2803, 2215, 1699, 1609, 1447, 1344, 1103, 853, 746 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.89–1.80 (m, 15H), 2.00–2.16 (m, 2H), 2.27–2.36 (m, 2H), 2.60–2.70 (m, 2H), 3.15 (d, 1H, J = 10.3 Hz), 7.36–7.43 (m, 1H), 7.47–7.55 (m, 1H), 7.58–7.63 (m, 1H), 7.97–8.02 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.7, 26.3, 26.9, 29.8, 30.5, 31.4, 39.5, 64.6, 85.1, 85.3, 120.4, 124.4, 127.8, 132.2, 135.1, 146.0. ESI MS (m/z): 327 (M+H).
1-(1-Cyclohexyl-3-(6-methoxynapthalen-2-yl)prop-2-ynyl)piperidine (Table 4, entry 6): White Solid. Mp: 100–103 °C. IR (neat):3057, 2931, 2849, 2795, 1908, 1626, 1482, 1448, 1241, 1156, 1030, 993, 846, 743 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.88–1.78 (m, 15H), 2.05–2.18 (m, 2H), 2.36–2.47 (m, 2H), 2.60–2.69 (m, 2H), 3.10 (d, 1H, J = 10.2 Hz, 1H), 3.91 (s, 3H), 7.02–7.11 (m, 2H), 7.41 (d, 1H, J = 8.3 Hz), 7.59 (d, 1H, J = 8.5, 7.63 (d, 1H, J = 8.8 Hz), 7.81(s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.6, 26.1, 26.2, 26.7, 29.6, 30.4, 31.3, 39.6, 50.7, 64.4, 86.5, 87.3, 105.7, 118.6, 119.1, 126.6, 129.1, 129.4, 130.7, 130.7, 130.9, 157.9. ESI MS (m/z): 362 (M+H).
1-(1-Cyclohexyl-3-(3-ethnylphenyl)prop-2-ynyl)piperidine **4a** (Scheme 2): IR (neat): 3302, 2928, 2851, 2800, 2749, 1593, 1473, 1447, 1229, 1104, 996, 894, 793 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.84–1.78 (m, 15H), 1.99–2.11 (m, 2H), 2.32–2.41 (m, 2H), 2.55–2.64 (m, 2H), 2.99 (s, 1H), 3.05 (d, 1H, J = 10.0 Hz), 7.19–7.23 (m, 1H), 7.33–7.39 (m, 2H), 7.52 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.6, 26.0, 26.2, 26.7, 30.3, 31.2, 39.4, 20.6, 64.3, 77.5, 82.9, 85.1, 88.6, 122.1, 124.0, 128.2, 131.1, 131.9, 135.2. ESI MS (m/z): 306 (M +H).
1,3-Bis(3-cyclohexyl-3-(piperidin-1-yl)prop-1-ynyl)benzene **4b** (Scheme 2): IR (neat): 2928, 2852, 2801, 1666, 1447, 1263, 1228, 1103, 997, 755 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.86–1.20 (m, 30H), 2.01–2.10 (m, 4H), 2.36–2.48 (m, 4H), 2.58–2.69 (m, 4H), 3.11 (d, 2H, J = 9.8 Hz), 7.16–7.22 (m, 1H), 7.31 (d, 2H, J = 9.8 Hz), 7.44 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.4, 25.9, 26.1, 26.6, 30.4, 31.2, 39.5, 64.2, 86.7, 87.7, 128.1, 131.1, 134.5, 134.5. ESI MS (m/z): 485 (M+H).