Magnetically Separable Nano Fe_3O_4 Catalyzed Direct Azidation of Allylic and Benzylic Alcohols Followed by Copper-Catalyzed Click Reaction

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Abstract: A competent one-pot method comprising magnetically separable nano Fe_3O_4 catalyzed direct azidation of allylic and benzylic alcohols followed by the copper-catalyzed click reaction of the corresponding azides with alkynes is reported. This method gave a direct access to several 1,2,3-triazoles starting from various allylic and benzylic alcohols via their respective azides.

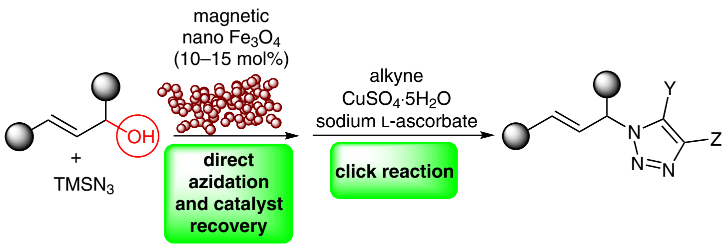
Key words: alcohols, azides, click reaction, cycloaddition, triazoles, magnetite

In recent years numerous protocols have been developed for the direct catalytic substitution of the hydroxyl group in allylic and benzylic alcohols by various nucleophiles.[1–6] The direct catalytic substitution of allylic and benzylic alcohols is considered as an atom-economical reaction.[1–4] The construction of a C–C bond via the direct catalytic substitution of allylic and benzylic alcohols using the carbon-based nucleophiles is also well explored.[1–4] Similarly, the Lewis acid/transition-metal-salt-catalyzed direct substitution of allylic and benzylic alcohols using nitrogen-based nucleophiles leading to the formation of a C–N bond is an attractive route for the synthesis of allylic and benzylic amines/azides and other related compounds.[5–13] In general, allylated nitrogen compounds including allylic and benzylic amines/azides are considered as important building blocks for the synthesis of heterocycles, natural products, and biologically active molecules.[13]

There are notable reports on the direct azidation of allylic and benzylic alcohols under homogeneous catalysis.[6–12] Recently, Rueping's group reported the direct catalytic azidation of allylic and benzylic alcohols using silver salts under homogeneous catalysis.[12d] With the aim of developing heterogeneous catalytic methods with clean recovery of the catalyst after the reaction and efficient recyclability of the catalyst, organic transformations catalyzed by magnetic nanoparticles have attracted the attention of synthetic chemists.[14]

Recently, Sreedhar's group[8] reported the synthesis of 1,2,3-triazoles from homoallyl alcohols via the palladium-catalyzed azidation followed by click reaction. Click-reaction protocols to synthesize 1,2,3-triazoles are well established, and 1,2,3-triazoles are considered as very important biologically active synthetic moieties in medicinal chemistry.[15] To the best of our knowledge, the direct catalytic azidation of allylic and benzylic alcohols has not been explored using magnetically separable heterogeneous catalysts. In this paper, we report sequential processes comprising the magnetic nano Fe_3O_4 catalyzed direct azidation of allylic and benzylic alcohols, followed by the copper-catalyzed click reaction of the corresponding azides with alkynes affording several new 1,2,3-triazoles (Scheme 1).

Initially, we carried out optimization reactions to find out the best reaction conditions to effect the direct azidation of allylic alcohol **1a** (0.5 mmol) with $TMSN_3$ (1.25 mmol, Table 1). Treatment of allylic alcohol **1a** with $TMSN_3$ in the absence of any catalyst in DCE at room temperature or 70 °C did not provide the desired product (*E*)-(3-azidoprop-1-ene-1,3-diyl)dibenzene (**2**, Table 1, entry 1). The reaction of allylic alcohol **1a** with $TMSN_3$ in the presence of nano Fe_3O_4 (15 mol%, particle size ≤50 nm) in 1,4-dioxane, MeCN, and MeOH was equally ineffective (Table 1, entries 2–4). The direct azidation of **1a** with $TMSN_3$ in the presence of nano Fe_3O_4 (15 mol%) in acetone, THF,



Scheme 1 Theme of this work

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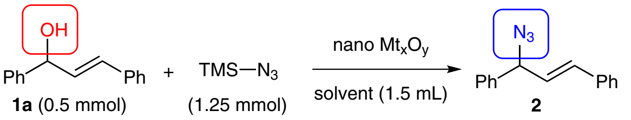
and toluene gave **2** in 20–55% yields (Table 1, entries 5–7). The product **2** was obtained in 85% and 92% yields when the reaction was performed in CH_2Cl_2 at room temperature or at reflux, respectively (Table 1, entries 8 and 9). The reaction of **1a** (1 equiv) with $TMSN_3$ (2.5 equiv) in the presence of nano Fe_3O_4 (15 mol%) in DCE at room temperature furnished the product **2** in 89% (Table 1, entry 10). Under the similar conditions, the reaction of alcohol **1a** (1 equiv) with 1.1 equivalents or 1.5 equivalents of $TMSN_3$ gave the product **2** in 80% and 83% yields, respectively (Table 1, entries 11 and 12).

Table 1 Nano Fe_3O_4 Catalyzed Direct Azidation of **1a**



Entry	Catalyst (mol%)	Solvent	Conditions	Yield (%) of **2**
1	–	DCE	70 °C, 40 h	0
2	nano Fe_3O_4 (15)	1,4-dioxane	r.t., 30 h	0
3	nano Fe_3O_4 (15)	MeCN	r.t., 30 h	0
4	nano Fe_3O_4 (15)	MeOH	r.t., 30 h	0
5	nano Fe_3O_4 (15)	acetone	r.t., 30 h	23
6	nano Fe_3O_4 (15)	THF	r.t., 30 h	20
7	nano Fe_3O_4 (15)	toluene	r.t., 30 h	55
8	nano Fe_3O_4 (15)	CH_2Cl_2	r.t., 10 h	85
9	nano Fe_3O_4 (15)	CH_2Cl_2	reflux, 8 h	92
10	nano Fe_3O_4 (15)	DCE	r.t., 15 h	89
11	nano Fe_3O_4 (15)	DCE	r.t., 15 h	80[a]
12	nano Fe_3O_4 (15)	DCE	r.t., 15 h	83[b]
13	nano Fe_3O_4 (15)	DCE	70 °C, 6 h	98
14	nano Fe_3O_4 (15)	DCE	70 °C, 6 h	85[a]
15	nano Fe_3O_4 (15)	DCE	70 °C, 6 h	89[b]
16	nano Fe_3O_4 (10)	DCE	70 °C, 16 h	92
17	nano Fe_2O_3 (15)	DCE	70 °C, 30 h	<5
18	powder Fe_3O_4 (15)	DCE	70 °C, 48 h	35

[a] In this case, 0.55 mmol of $TMSN_3$ were used.
[b] In this case, 0.75 mmol of $TMSN_3$ were used.

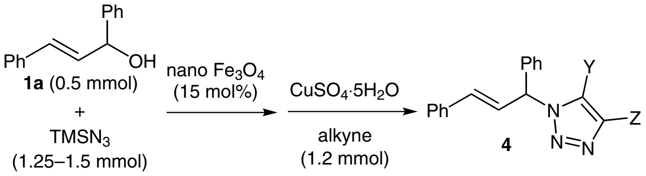
The reaction of **1a** (1 equiv) with $TMSN_3$ (2.5 equiv) in the presence of nano Fe_3O_4 (15 mol%) in DCE at 70 °C furnished the product **2** in 98% yield (Table 1, entry 13). Under similar conditions, the reaction of alcohol **1a** (1 equiv) with 1.1 equivalents or 1.5 equivalents of $TMSN_3$ gave **2** in 85% and 89% yields, respectively (Table 1, entries 14 and 15). The reaction of alcohol **1a** with $TMSN_3$ in the presence of 10 mol% of nano Fe_3O_4 in DCE at 70 °C for 16 hours afforded the product **2** in 92% yield (Table 1, entry 16). Use of other catalysts, such as nano Fe_2O_3 or powdered Fe_3O_4 gave **2** in less than 5% and 35% yields, respectively (Table 1, entries 17 and 18). We also tested the recyclability of the magnetic nano Fe_3O_4 for the reaction of direct azidation of allylic alcohol **1a**, which gave the product **2** in 95% yield in the seventh run (Table 2).[16,17] Then, we analyzed the condition of the recovered nano Fe_3O_4 catalyst after different runs. FT-IR spectroscopic analysis of the fresh and recovered magnetic nano Fe_3O_4 revealed no distinctive changes. HRTEM analysis of the used magnetic nano Fe_3O_4 showed no obvious change in the morphology of the nanoparticles (see the Supporting Information for FT-IR and HRTEM analysis data).

Table 2 Catalyst Recycling[a]

Run	Time (h)	Yield (%) of **2**
1	6	98
2	6	97
3	8	97
4	10	97
5	12	97
6	15	96
7	20	95

[a] The reaction was performed using **1a** (0.5 mmol), $TMSN_3$ (1.25 mmol) and nano Fe_3O_4 (15 mol%) in DCE (1.5 mL) at 70 °C.

Table 3 Magnetic Nano Fe_3O_4 Catalyzed Azidation of **1a** Followed by Click Reaction[a]



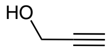
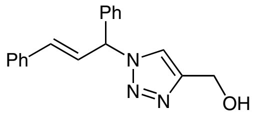
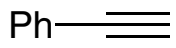
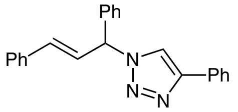
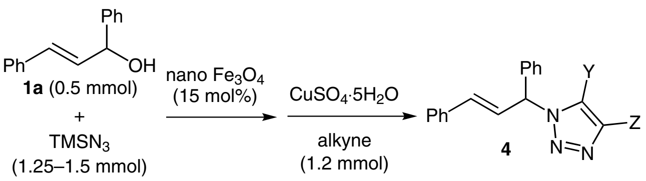
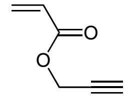
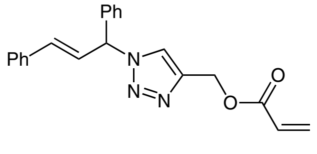
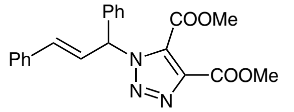
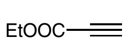
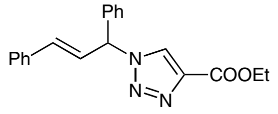
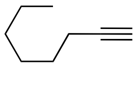
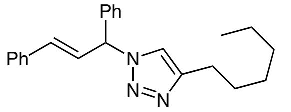
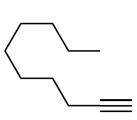
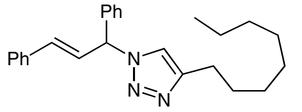
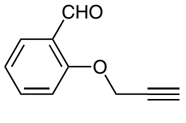
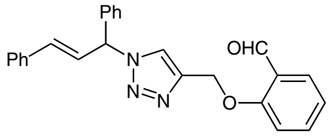
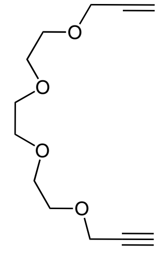
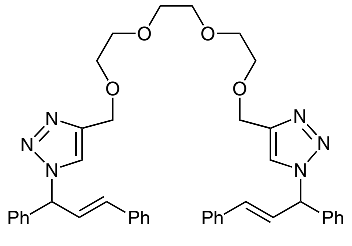
Entry	Alkyne	1,2,3-Triazole **4**, yield (%)
1	 **3a**	 **4a** 82
2	 **3b**	 **4b** 90

Table 3 Magnetic Nano Fe_3O_4 Catalyzed Azidation of **1a** Followed by Click Reaction[a] (continued)



Entry	Alkyne	1,2,3-Triazole **4**, yield (%)
3	 **3c**	 **4c** 93
4	DMAD **3d**	 **4d** 86
5	 **3e**	 **4e** 86
6	 **3f**	 **4f** 85
7	 **3g**	 **4g** 92
8	 **3h**	 **4h** 85
9	 **3i**	 **4i** 75

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[a] Reaction conditions: The azidation of **1a** was carried out using nano Fe_3O_4 (15 mol%) in DCE (1.5 mL) at 70 °C for 6 h, the solvent was evaporated, and then the click reaction was carried out using alkyne (1.2 mmol) in THF (3 mL) and H_2O (3 mL) in the presence of $CuSO_4 \cdot 5H_2O$ (30 mol%) and sodium L-ascorbate (30 mol%) at r.t. for 12 h.

Having optimized conditions for the direct azidation of **1a** (Table 1, entry 11), we envisaged performing the copper-catalyzed click reaction using the product **2**. Thus, we first performed nano Fe_3O_4 catalyzed azidation of allylic alcohol **1a**, followed by the copper-catalyzed click reaction of the product (*E*)-(3-azidoprop-1-ene-1,3-diyl)dibenzene (**2**) with various alkynes **3a**–**i**, leading to the construction of several new 1,2,3-triazole derivatives **4a**–**i** in 75–93% yields, respectively (Table 3).[16]

Subsequently, we used various allylic alcohols **1b**–**g** in the nano Fe_3O_4 catalyzed direct azidation reaction, followed by copper-catalyzed click reaction to give the corresponding 1,2,3-triazoles **4j**–**p** in 45–82% yields (Table 4).[16] Products **4j** and **4k** were obtained as a mixture of regioisomers since the allylic alcohols **1b** and **1c** underwent an allylic rearrangement under the reaction conditions, thereby leading to their corresponding regioisomers. Similarly, the products **4o** and **4p** were also obtained as a mixture of regioisomers (Table 4).

Subsequently, we tested the scope of the nano Fe_3O_4 catalyzed direct azidation reaction of several benzylic alcohols **5a**–**e** followed by the click reaction of the corresponding azides with alkynes (Table 5)[16] and successfully obtained the corresponding 1,2,3-triazole derivatives **6a**–**e** in 35–71% yields. A gram-scale process involving the direct azidation of **1a** followed by the click reaction gave 1,2,3-triazole **4b** in 88% yield under the optimized reaction conditions (Scheme 2).

To show the utility of the 1,2,3-triazoles obtained in this work, we methylated 1,2,3-triazole **4k** and observed the formation of an ionic liquid **8** via elimination of the allylic moiety present in **4k** (Scheme 2). Since we found the allylic moiety is eliminated in the reaction of **4k** with MeI, in a subsequent process we first hydrogenated the olefin moiety present in **4b** which gave the 1,2,3-triazole derivative **9**. Further treatment of **9** with MeI gave an ionic liquid product **10**. Finally, the hydrogenation of (*E*)-(3-azidoprop-1-ene-1,3-diyl)dibenzene (**2**) led to the formation of 1,3-diphenylpropan-1-amine (**11**) in 50% yield.

In summary, we have shown a competent catalytic protocol comprising the magnetically recoverable nano Fe_3O_4 catalyzed direct azidation of allylic and benzylic alcohols followed by a click reaction. Construction of several new 1,2,3-triazole derivatives directly from allylic and benzylic alcohols via their respective azides was accomplished.

Acknowledgment

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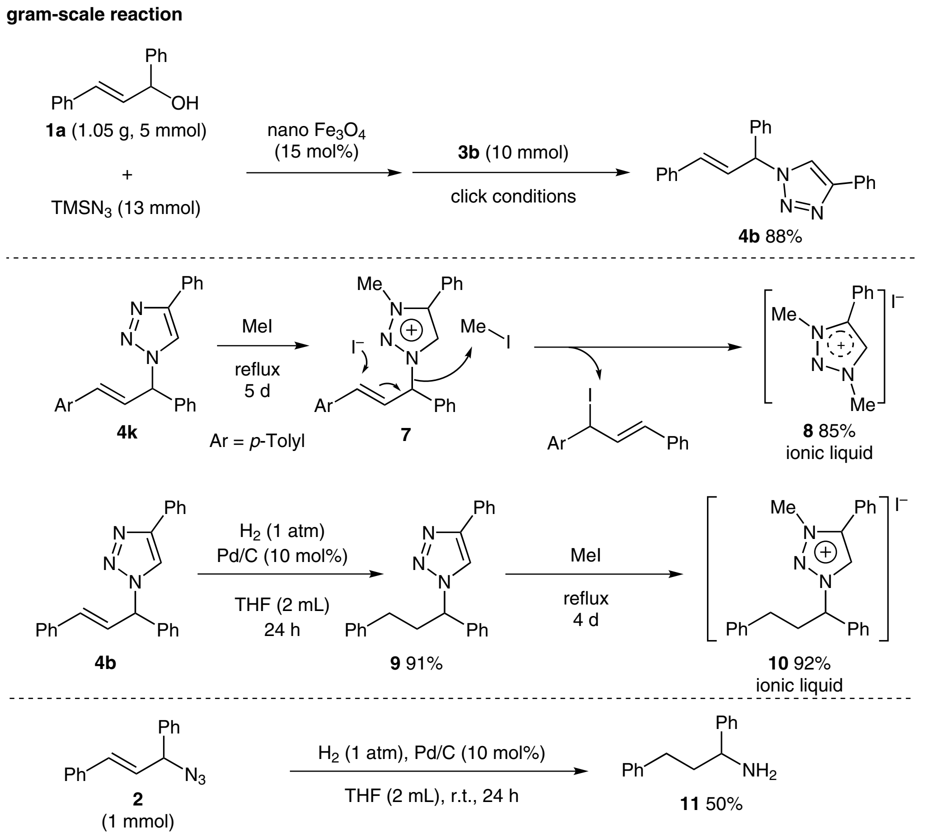
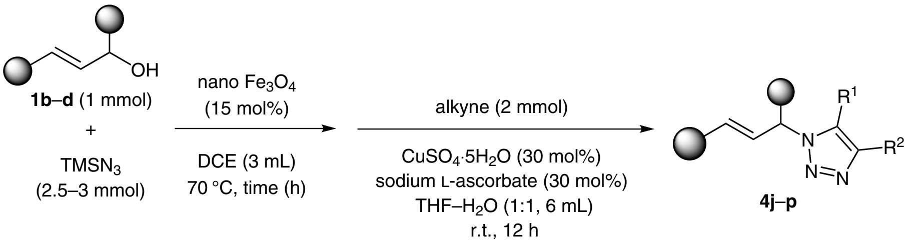
Supporting Information for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083.



Scheme 2 Gram-scale reaction and synthetic transformations

Table 4 Azidation of **1b**–**d** Followed by Click Reaction[a]



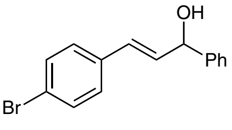
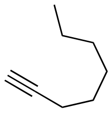
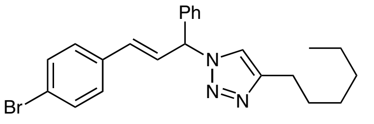
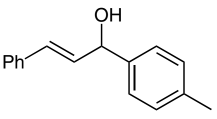
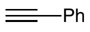
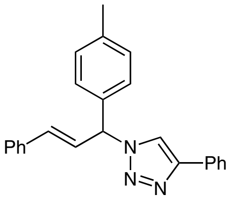
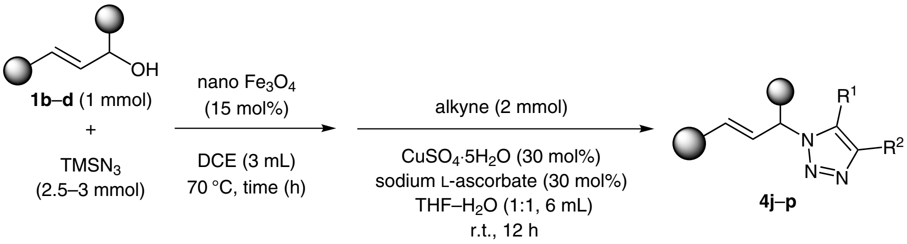
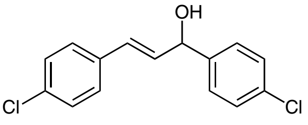
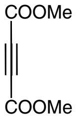
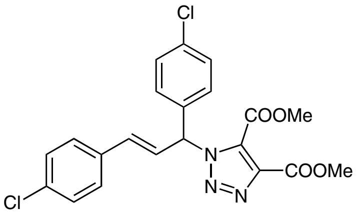
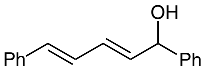
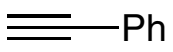
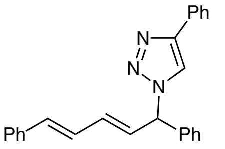
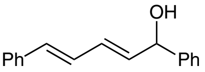
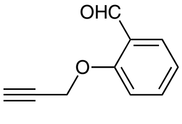
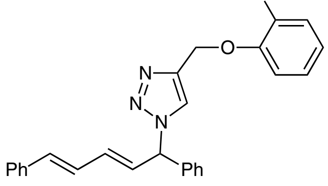
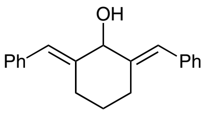
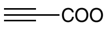
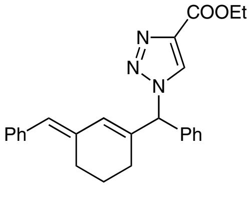
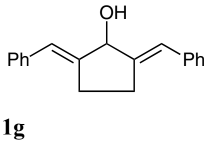
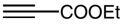
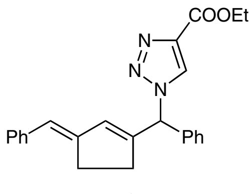
Entry	Substrate **1**	Time (h)	Alkyne	Product **4**, yield (%)
1	 **1b**	12	 **3f**	 **4j** 82 (50:50)[b]
2	 **1c**	15	 **3b**	 **4k** 72 (50:50)[b]

Table 4 Azidation of **1b–d** Followed by Click Reaction[a] (continued)

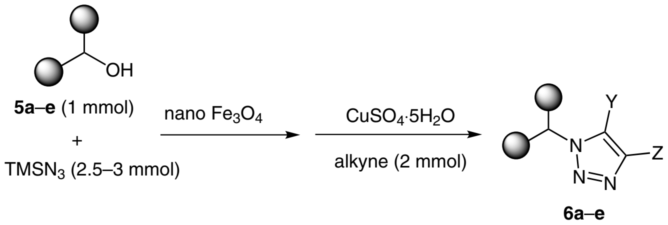


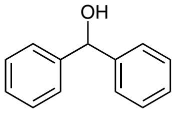
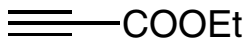
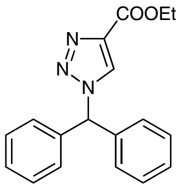
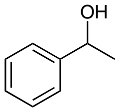
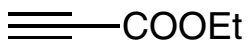
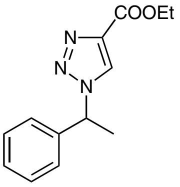
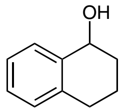
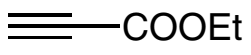
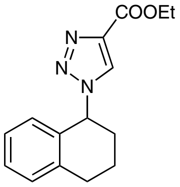
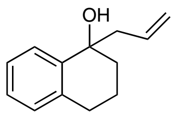
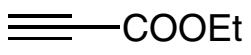
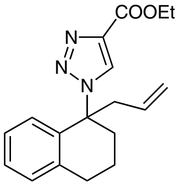
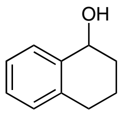
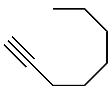
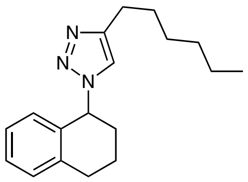
Entry	Substrate **1**	Time (h)	Alkyne	Product **4**, yield (%)
3	 **1d**	14	 **3d**	 **4l** 52
4	 **1e**	18	 **3b**	 **4m** 62
5	 **1e**	18	 **3h**	 **4n** 57
6	 **1f**	30	 **3e**	 **4o** 62 (76:24)[b]
7	 **1g**	24	 **3e**	 **4p** 45 (88:12)[b]

[a] After the azidation reaction the magnetic nano Fe_3O_4 was separated then the click reaction was performed.

[b] Products were obtained as a mixture of regioisomers due to an allylic rearrangement under the experimental conditions.

Table 5 Nano Fe_3O_4 Catalyzed Azidation of **5a–e** Followed by Click Reaction[a]



Entry	Alcohol	Alkyne	Yield (%) of **6**
1	 **5a**	 **3e**	 **6a** 71
2	 **5b**	 **3e**	 **6b** 35
3	 **5c**	 **3e**	 **6c** 70
4	 **5d**	 **3e**	 **6d** 52
5	 **5e**	 **3f**	 **6e** 70

[a] Reaction conditions: The azidation of **1a** was carried out using nano Fe_3O_4 (15 mol%) in DCE (3 mL) at 70 °C for 14–20 h, the solvent was evaporated, and then the click reaction was carried out using alkyne (2 mmol) in THF (3 mL) and H_2O (3 mL) in the presence of $CuSO_4 \cdot 5H_2O$ (30 mol%) and sodium L-ascorbate (30 mol%) at r.t. for 12 h.

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(16) **General Procedure for the Magnetic Nano Fe_3O_4 Catalyzed Direct Azidation of Allylic Alcohol 1a**
A mixture of alcohol **1a** (0.5 mmol), trimethylsilyl azide (1.25 mmol), and magnetic nano Fe_3O_4 (particle size <50 nm, 15 mol%; the particles can be handled using a Teflon spatula) in DCE (3 mL) was stirred at 70 °C for 6 h. At this stage a magnet was externally applied to the reaction flask to attract the magnetic Fe_3O_4 nanoparticles, and the resulting clear solution was transferred to another flask using a pipette. The catalyst was washed using EtOAc (2 mL), and the residual Fe_3O_4 nanoparticles were heated in an oven at 100–110 °C overnight, and the catalyst was reused in subsequent cycles. The combined organic layers were evaporated under vacuum and purified by column chromatography to give the product **2**.
General Procedure for the One-Pot Magnetic Nano Fe_3O_4 Catalyzed Direct Azidation of Allylic Alcohols and Click Reaction
The direct azidation of **1a** (0.5 mmol) was carried out as above, the catalyst was removed using an external magnet, and the solvent was evaporated. Then to the residue THF (3 mL), H_2O (3 mL), alkyne (1 mmol), $CuSO_4{\cdot}5H_2O$ (30 mol%), and sodium L-ascorbate (30 mol%) were added, and the mixture was stirred at r.t. for 12 h. The reaction mixture was then extracted using EtOAc, the combined organic layers were evaporated, and the resulting reaction mixture was purified by column chromatography, eluting with EtOAc–hexanes (50:50), to afford the product **4a** as a colorless liquid. Yield: 82% (238 mg). FT-IR (neat): ν = 3375, 2954, 1731, 1450, 1223, 1091 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.57 (s, 1 H), 7.41–7.28 (m, 10 H), 6.70 (dd, J_1 = 15.6 Hz, J_2 = 7.2 Hz, 1 H), 6.52–6.47 (m, 2 H), 4.79 (s, 2 H), 3.36 (br s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.8, 137.7, 135.5, 134.7, 129.2, 128.8, 128.7, 128.6, 127.5, 126.9, 125.5, 121.2, 66.5, 56.4. ESI-HRMS: *m/z* calcd for $C_{18}H_{18}N_3O$ $[M + H]^+$: 292.1450; found: 292.1100.

(17) The nano Fe_3O_4 used in this work was purchased from Sigma-Aldrich, and the size of the particles was checked through HRTEM analysis/images (see the Supporting Information) before using the nano Fe_3O_4. For communications dealing with the preparation and characterization of nano Fe_3O_4, see: (a) Sun, J.; Zhou, S.; Hou, P.; Yang, Y.; Weng, J.; Li, X.; Li, M. *J. Biomed. Mater. Res., Part A* **2007**, *80*, 333. (b) Yuanbi, Z.; Zumin, Q.; Jiaying, H. *Chin. J. Chem. Eng.* **2008**, *16*, 451. (c) Wu, S.; Sun, A.; Zhai, F.; Wang, J.; Xu, W.; Zhang, Q.; Volinsky, A. A. *Mater. Lett.* **2011**, *65*, 1882. (d) Yang, T.; Shen, C.; Li, Z.; Zhang, H.; Xiao, C.; Chen, S.; Xu, Z.; Shi, D.; Li, J.; Gao, H. *J. Phys. Chem. B* **2005**, *109*, 23233.