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An efficient and facile one-pot synthesis of propargylamines by three-component coupling of aldehydes, amines, and alkynes via C–H activation catalyzed by $NiCl_2$

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ABSTRACT

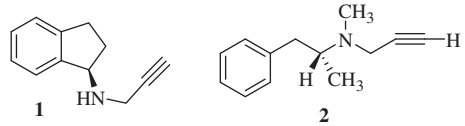
$NiCl_2$ was found to be a highly efficient and effective catalyst for the one-pot three-component (A^3) coupling of aldehydes, amines, and alkynes to produce propargylamines in nearly quantitative yields. Structurally divergent aldehydes, amines, and alkynes were converted into the corresponding propargylamines. No co-catalyst or activator is needed and water is the only byproduct of this novel protocol.

One-pot multicomponent reactions (MCRs) are an attractive synthetic strategy[1] to generate multiple molecular scaffolds and to increase structural as well as skeletal diversity from simple and easily available molecules. In a MCR, several organic moieties are coupled in one-pot exhibiting economy of atom and steps, and often selectivity. Three-component coupling of an aldehyde, alkyne, and amine (A^3-coupling) is one of the best examples of acetylene-Mannich MCR and has received much attention in recent times.[2] The resultant propargylamines[3] are important building blocks for a variety of organic transformations and also are valuable precursors for therapeutic drug molecules[4a–c] such as β-lactams, oxotremorine analogs, conformationally restricted peptides, isosteres, allylamines, oxazoles, and other natural products.

A series of propargylamines were shown to suppress the apoptotic cascade preventing collapse of mitochondrial membrane potential, activation of caspase, and fragmentation of nucleosomal DNA.[4d] Among propargylamines; (*R*)-*N*-propargyl-1-aminoindane (Rasagiline **1**, Fig. 1) was the most potent at preventing cell death. Several propargylamine derivatives have been synthesized, and shown to be highly potent and selective irreversible monoamine oxidase type-B (MAO-B) inhibitors.[5] Some of these new inhibitors have even been tested in the treatment of neuropsychiatric disorders (Alzheimer's disease[6]). The MAO-B inhibitor deprenyl (Selegiline **2**, Fig. 1) has been used as an effective adjuvant to L-DOPA in the treatment of Parkinson's disease.[7]

Classical methods for the preparation of propargylamines have usually exploited the relatively high acidity of the terminal acetylenic C–H bond to form alkynyl-metal reagents by reaction with strong bases such as butyl lithium,[8a] organomagnesium compounds,[8b] or LDA[9] in a separate step. Unfortunately, these reagents are used in stoichiometric ratios, are highly moisture-sensitive, and require strictly controlled reaction conditions.

In recent years, enormous progress has been made on C–H bond activation reaction of terminal alkynes. The alkyne C–H bond can be activated by employing various homogeneous metal catalysts such as Cu(I) salts,[10] Au(I)/Au(III) salts,[11] Au(III) salen complexes,[12] silver(I) salts,[13] zinc salts,[14] iron(III) salts,[15] $InCl_3$,[16a] $InBr_3$,[16b] Ir-complexes,[17] Hg_2Cl_2,[18] and Cu/Ru(II) bimetallic system.[19] Different heterogeneous catalysts such as LDH-$AuCl_4$,[20] AgI,[21a–d] silver



1 Rasagiline (Azilect) **2** Deprenyl (Selegiline)

Figure 1. Propargylamine inhibitors of type-B monoamine oxidase.

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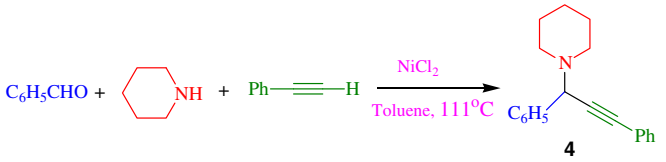
nanoparticles,[21e] Ag nanoparticles supported by Ni,[21f] Cu(I) complexes,[22a–d] CuCl,[22e] silica-immobilized CuI,[22f] Ni–Y–zeolite,[23] Zn dust,[24] copper ferrite nanoparticles,[25a] nanocrystalline copper (II) oxide,[25b] copper-nanoparticles,[25c] impregnated copper on magnetite,[25d] copper-zeolites,[25e] and Fe_3O_4 nanoparticles[26] have also been utilized for alkyne C–H activation. They are directly added to carbon–nitrogen double bonds (imines) either preformed or in one-pot (from aldehyde and amine) for the synthesis of propargylamines. In addition, microwave[10,27a] and ultrasonic radiations[27b] have also been used in the presence of Cu(I) salt.

Although, most of the above described processes work well for the synthesis of propargylamines, the improved synthesis of propargylamines via the activation of a terminal alkyne C–H bond using transition metal-catalyzed multicomponent strategies remains of continued interest to organic chemists in terms of operational simplicity and cost effectiveness. As a continued interest to develop efficient protocols for the synthesis of biologically active molecular scaffolds via one-pot multicomponent reactions[28] herein, we report a highly efficient three-component coupling of aldehydes, amines, and alkynes (A^3-coupling) catalyzed by $NiCl_2$. Nearly quantitative yields were obtained in most of the cases. Furthermore, the reaction did not require any co-catalyst or activator. In comparison to other metal catalysts, $NiCl_2$ is relatively cheaper. Thus, it can replace traditionally costly metal catalysts like Au, Ag, Cu, and Ru salts making this process more practical and economically favorable.

A test reaction using benzaldehyde, piperidine, and phenylacetylene in refluxing toluene in the absence of $NiCl_2$ was performed in order to establish the effectiveness of the catalyst. It was observed that no conversion to product was obtained even after 12 h of refluxing. To optimize the reaction conditions, the above model reaction was carried out under different reaction conditions. The results are summarized in Table 1. The effects of $Ni(OAc)_2{\cdot}4H_2O$, $Ni(NO_3)_2{\cdot}6H_2O$, and $NiCl_2$ have been examined and it was found that $NiCl_2$ afforded excellent yield (Table 1, entry 5). The lower catalytic activities of $Ni(OAc)_2{\cdot}4H_2O$ and $Ni(NO_3)_2{\cdot}6H_2O$ may be due to their filled coordination sites that hardly interact with C–H bond of the alkyne (Table 1, entries 13 and 14). The $NiCl_2$ being tetracoordinated can increase its coordination number and consequently binds with the C–H bond of the terminal alkyne effectively showing better catalytic performance (Scheme 1).

To check the solvent effect on the outcome of the reaction, the above model reaction was carried out with 5 mol % of $NiCl_2$ in solvents such as THF, EtOH, and CH_3CN at 65 °C (Table 1, entries 1, 2 and 3). Further, the above reaction was performed in high boiling solvents such as water, toluene, dioxane, DMF, and DMSO at 100 °C (Table 1, entries 4–12). It was observed that toluene was the most effective solvent in which the reaction proceeded smoothly giving the maximum yield in minimum time (Table 1, entry 5). It is noteworthy that when water was used as the solvent, only a trace amount of product was observed even after a prolonged reaction time (Table 1, entry 4). Employing a lower percentage of $NiCl_2$ reduced the yield (Table 1, entry 8). Higher percentage loading of the catalyst neither increased the yield nor lowered the reaction time (Table 1, entry 9). We next performed the reaction in toluene at different temperatures using 5 mol % of $NiCl_2$. It was found that at lower temperatures the reaction proceeds slowly giving lower yields (Table 1, entries 6 and 7). Thus, all the reactions were performed in toluene under an argon atmosphere with 5 mol % of $NiCl_2$ at 111 °C.



Scheme 1. $NiCl_2$-catalyzed A^3-coupling leading to propargylamine.

Using the optimized reaction conditions, the scope of the reaction was tested finding excellent results for the different combinations of aldehydes, amines, and alkynes. To generalize the applicability of the $NiCl_2$-promoted A^3-coupling reaction,[29] we used a variety of structurally divergent aldehydes, amines, and alkynes (Table 2). The results in Table 2 indicate that the aromatic aldehydes with both electron-donating and electron-withdrawing substituents displayed high reactivity and generated the desired products in good to excellent yields. However, unfortunately, 4-nitrobenzaldehyde did not yield the desired product, which is in accordance with earlier studies[21b,22c] (Table 2, entry 27). In addition to aromatic aldehydes, aliphatic aldehydes such as formaldehyde, isobutyraldehyde, and cyclohexanecarboxaldehyde afforded the corresponding propargylic amines in good yields (Table 2, entries 11–14). Similarly, heteroaromatic thiophene-2-carboxaldehyde also participated well in this protocol (Table 2, entry 9). To extend the scope of the reaction, various cyclic secondary amines such as piperidine, morpholine, pyrrolidine, *N*-phenyl piperazine, *N*-methyl piperazine, and ethyl-1-piperazinecarboxylate, and acyclic secondary amines such as dibenzylamine and *N*-methyl aniline were used and tolerated well. Further, some primary amines such as aniline, benzyl amine, methyl amine, *n*-butyl amine, and ammonia were used but unfortunately, in the case of methyl amine and *n*-butyl amine only trace of the desired product was obtained even after a prolonged period of time (Table 2, entries 37 and 38). Furthermore, several terminal alkynes such as phenylacetylene, 4-methyl phenylacetylene, and TMSacetylene were examined for the synthesis of various propargylamines. On the other hand, when 1-octyne was used in place of phenylacetylene, the corresponding propargylamine was obtained in low yield after a longer reaction time (Table 2, entry 26).

A tentative mechanism (Scheme 2) is proposed for the probable sequence of events involving the activation of the C–H bond of alkyne **3** by $NiCl_2$. The nickel–acetylide intermediate **A** generated by the reaction of acetylene and $NiCl_2$ reacted with the iminium ion **B** (generated in situ from aldehyde **1** and amine **2**) to give the corresponding propargylamine **4**.

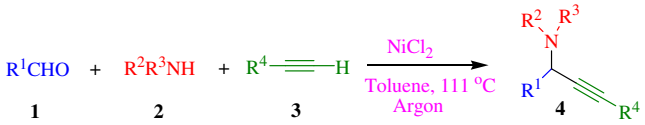
In conclusion, an efficient $NiCl_2$-catalyzed three-component one-pot coupling of aldehydes, amines, and alkynes has been achieved.[29] The process is simple and generated a diverse range of propargylamines in good to excellent yields. The reaction has high atom effi-

Table 1
Optimization of the reaction conditions[a]

Entry	Solvent	Catalyst (mol %)	Temp (°C)/time (h)	Yield[b] (%)
1	THF	$NiCl_2$ (5)	65/12	72
2	EtOH	$NiCl_2$ (5)	65/12	10
3	CH_3CN	$NiCl_2$ (5)	65/12	52
4	Water	$NiCl_2$ (5)	100/14	Trace
5	Toluene	$NiCl_2$ (5)	111/8	95
6	Toluene	$NiCl_2$ (5)	100/8	80
7	Toluene	$NiCl_2$ (5)	80/8	60
8	Toluene	$NiCl_2$ (2)	111/12	80
9	Toluene	$NiCl_2$ (10)	111/8	95
10	Dioxane	$NiCl_2$ (5)	100/12	22
11	DMF	$NiCl_2$ (5)	100/12	17
12	DMSO	$NiCl_2$ (5)	100/12	20
13	Toluene	$Ni(OAc)_2{\cdot}4H_2O$ (10)	111/12	60
14	Toluene	$Ni(NO_3)_2{\cdot}6H_2O$ (10)	111/12	40

[a] Phenylacetylene:piperidine:benzaldehyde (1.5:1.2:1).
[b] Yields of isolated pure products.

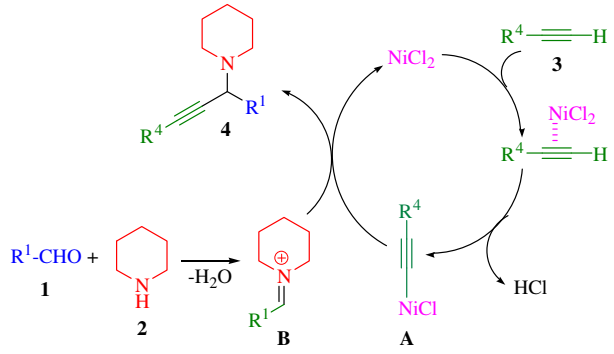
Table 2
A^3-coupling of aldehydes, amines, and alkynes catalyzed by $NiCl_2$[a]



Entry	R^1	Amine	R^4	Product	Time (h)	Yield[b] (%)
1	C_6H_5	Piperidine	C_6H_5	**4a**	8	95
2	*p*-Me·C_6H_4	Piperidine	C_6H_5	**4b**	8.5	90
3	*o*-Cl·C_6H_4	Piperidine	C_6H_5	**4c**	8	80
4	*p*-MeO·C_6H_4	Piperidine	C_6H_5	**4d**	9	85
5	*p*-Br·C_6H_4	Piperidine	C_6H_5	**4e**	8	89
6	*p*-F·C_6H_4	Piperidine	C_6H_5	**4f**	8	90
7	*p*-Cl·C_6H_4	Piperidine	C_6H_5	**4g**	9	87
8	*m*-NO_2·C_6H_4	Piperidine	C_6H_5	**4h**	8.5	90
9	2-Thiophene	Piperidine	C_6H_5	**4i**	7.5	91
10	*m*-Cl·C_6H_4	Piperidine	C_6H_5	**4j**	8	85
11	H	Piperidine	C_6H_5	**4k**	8	81
12	Me_2CH	Piperidine	C_6H_5	**4l**	9	73
13	H	Morpholine	C_6H_5	**4m**	8	83
14	Cyclohexyl	Morpholine	C_6H_5	**4n**	9	78
15	C_6H_5	Morpholine	C_6H_5	**4o**	8	88
16	*p*-Me·C_6H_4	Morpholine	C_6H_5	**4p**	8.5	81
17	*p*-Br·C_6H_4	Morpholine	C_6H_5	**4q**	8	88
18	2,4-Cl_2·C_6H_3	Morpholine	C_6H_5	**4r**	9	81
19	*p*-MeO·C_6H_4	Morpholine	C_6H_5	**4s**	8	84
20	*p*-F·C_6H_4	Morpholine	C_6H_5	**4t**	8	89
21	C_6H_5	Pyrrolidine	C_6H_5	**4u**	8	91
22	*p*-Me·C_6H_4	Pyrrolidine	C_6H_5	**4v**	9	87
23	*p*-Cl·C_6H_4	Pyrrolidine	C_6H_5	**4w**	8.5	90
24	C_6H_5	*N*-Phenyl piperazine	C_6H_5	**4x**	8	86
25	*p*-Me·C_6H_4	*N*-Phenyl piperazine	C_6H_5	**4y**	8	81
26	C_6H_5	Piperidine	$CH_3(CH_2)_5$	**4z**	12	52
27	*p*-NO_2·C_6H_4	Morpholine	C_6H_5	**4a′**	24	n.r.[c]
28	C_6H_5	Piperidine	*p*-Me·C_6H_4	**4b′**	7.5	85
29	C_6H_5	Piperidine	$(CH_3)_3Si$	**4c′**	8	86
30	C_6H_5	*N*-Methyl aniline	C_6H_5	**4d′**	9	78
31	C_6H_5	Aniline	C_6H_5	**4e′**	9	66
32	C_6H_5	Dibenzyl amine	C_6H_5	**4f′**	10	74
33	C_6H_5	*N*-Methyl piperazine	C_6H_5	**4g′**	9	85
34	C_6H_5	Ethyl-1-piperazinecarboxylate	C_6H_5	**4h′**	12	82
35	C_6H_5	Ammonia	C_6H_5	**4i′**	16	25
36	C_6H_5	Benzylamine	C_6H_5	**4j′**	16	56
37	C_6H_5	Methyl amine	C_6H_5	**4k′**	48	Trace
38	C_6H_5	*n*-Butyl amine	C_6H_5	**4l′**	48	Trace

[a] Aldehyde:phenylacetylene:amine (1:1.5:1.2).
[b] Isolated yields.
[c] n.r. = no reaction.

ciency, since water is the only byproduct. All these facts together with easy work-up and clean reaction profile, the wide scope of the substrates, and cost effectiveness of the catalyst permitted us to anticipate a good future for this protocol not only in academia but also in industry. The scope, mechanism, stereoselectivity, and synthetic applications of this reaction are under investigation.



Scheme 2. Tentative mechanism for the nickel-catalyzed synthesis of propargylamines.

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29/ce:label>*Typical procedure for A^3-coupling reaction*: A 50-mL round-bottomed flask was charged with aldehyde (1.0 mmol), secondary amine (1.2 mmol), and phenylacetylene (1.5 mmol) in toluene (5 mL). The reaction mixture was refluxed at 111 °C under an argon atmosphere in the presence of 5 mol % of $NiCl_2$. After completion of the reaction (monitored by TLC) the solvent was evaporated under vacuum. Water (40 mL) was added to the reaction mixture and the product was extracted with ethyl acetate (3 × 15 mL). The organic layer was dried over anhydrous $MgSO_4$ and the solvent was evaporated under vacuum. The crude product obtained was purified by column chromatography using ethyl acetate-*n*-hexane (1:25) to afford the pure desired product. Spectroscopic data of some of the compounds are given below:

N-[1-(4-Methylphenyl)-3-phenyl-prop-2-ynyl]piperidine (**4b**)

FT-IR (KBr): 2937, 2744, 1605, 1502, 1320, 1152, 760, 691 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.51–7.31 (m, 5H), 7.30 (d, J = 2.7 Hz, 2H), 7.17 (d, J = 7.8 Hz, 2H), 4.74 (s, 1H), 2.54–2.46 (m, 4H), 2.35 (s, 3H), 1.60–1.56 (m, 4H), 1.45–1.43 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.9, 135.5, 131.7, 128.6, 128.4, 128.1, 127.9, 123.3, 87.5, 86.3, 62.0, 55.6, 26.1, 24.2, 21.0; ESI-MS: 290.25 (M^++1); Anal. Calcd for $C_{21}H_{23}N$: C, 87.15; H, 8.01; N, 4.84. Found: C, 87.19; H, 8.05; N, 4.76.

4-(1,3-Diphenyl-prop-2-ynyl)-morpholine (**4o**)

FT-IR (KBr): 2930, 2745, 1598, 1500, 1318, 1152, 754, 693 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.63 (d, J = 6.9 Hz, 2H), 7.50 (d, J = 6.9 Hz, 2H), 7.36–7.31 (m, 6H), 4.78 (s, 1H), 3.71–3.64 (m, 4H), 2.62–2.56 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.6, 131.6, 128.4, 128.1, 128.1, 128.0, 127.6, 122.8, 88.3, 84.9, 66.9, 61.8, 49.7; ESI-MS: 278.30 (M^++1); Anal. Calcd for $C_{19}H_{19}NO$: C, 82.28; H, 6.90; N, 5.05. Found: C, 82.38; H, 6.86; N, 5.10.

1-(1,3-Diphenyl-prop-2-ynyl)-4-phenylpiperazine (**4x**)

FT-IR (KBr): 2933, 2745, 1601, 1510, 1316, 1155, 755, 695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.68 (d, J = 7.2 Hz, 2H), 7.51 (d, J = 3.3 Hz, 2H), 7.41–7.22 (m, 8H), 6.94–6.82 (m, 3H), 4.98 (s, 1H), 3.22–3.20 (m, 4H), 2.81–2.79 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.2, 137.9, 131.7, 128.9, 128.4, 128.2, 128.1, 127.6, 122.9, 119.5, 115.9, 88.4, 85.0, 61.6, 49.3, 49.2; ESI-MS: 353.10 (M^++1); Anal. Calcd for $C_{25}H_{24}N_2$: C, 85.19; H, 6.86; N, 7.95. Found: C, 85.16; H, 6.92; N, 7.92.