NAFION AS A CATALYST IN ORGANIC SYNTHESIS

The Nafion catalyst, a perfluoroalkanesulfonic acid resin was developed by DuPont chemists in early 1960 during work with General Electric on a fuel cell. The IUPAC nomenclature of Nafion is tetrafluoroethylene-perfluoro-3,6-dioxa-4-methyl-7-octensulfonic acid and the chemical formula is shown in Figure 1.

![Figure 1](image)

Where is the value of $m$ could be as low as 1 and the value of $n$ ranges between 6 to 13. It has hydrophobic (-CF₂-CF₂-) and hydrophilic (-SO₃H) regions in its structure and its super acidity due to the electron withdrawing effect of the perfluoroalkyl backbone to which the sulfonic acid group is attached. The estimated Hammett ($H_0$) value for Nafion-H is comparable to that of 96-100% sulfuric acid ($H_0 = -12.0$).

Nafion was first synthesized by the copolymerization of tetrafluoroethylene (TFE) i.e. monomer in Teflon and the derivatives of a perfluoro (alkyl vinyl ether) with sulfonic acid fluoride. The resulting product is an -SO₂F- containing thermoplastic that is extracted into films. Hot aqueous NaOH converted these sulfonyl fluoride (-SO₂F-) groups into sulfonate groups (-SO₃⁻Na⁺). This form of Nafion is referred to as a neutral or salt form, is finally converted to the acid form containing the sulfonic acid (-SO₃H) groups.
Nafion, the acidic form of the polymeric fluorinated sulfonic acid has been widely investigated as an acidic catalyst for organic reactions.\textsuperscript{4} Nafion containing substantial amount of water has been shown to be composed principally a source of $\text{R}_3\text{SO}_3^-\cdot\text{H}_2\text{O}^+$ ion pairs and is potentially a source of $\text{H}^+\text{aq}$. However, in its catalytic chemistry, the material behaves as a much stronger acid than $\text{H}^+\text{aq}$. The composition of the materials explains its catalytic behavior.

Nafion is a heterogeneous recyclable Bronsted solid acid catalyst, acts as water tolerant ion exchange resin. The swelling properties of the dried Nafion in different solvents (i.e. methanol, water and triglyceride) were examined. Swelling in water was investigated because it may be present in lower-quality biodiesel feedstocks. The kinetics of transesterification of vegetable oils, a highly refined olive oil (acid value $= 0.04$) is also used, as a solvent for comparison. The catalyst dimensions (obtained with a vernier caliper) and weights were measured for several Nafion cylindrical-shaped pellets before and after soaking in the pure solvent at 60 °C (typical transesterification reaction temperature) until equilibrium were reached. Irreversible swelling after cooling has been proved to be a good assumption for this type of system.\textsuperscript{5} The volume increase was measured and also estimated using the relationship suggested\textsuperscript{6} to consider that the Nafion and the solvent volume are additive. The resin was treated in methanol resulted in the high degree of swelling as a result of physicochemical changes. Water showed a moderate capability for swelling the resin, which is advantageous from the standpoint of greater acid site accessibility. However, water may also lower the acid strength of the active sites\textsuperscript{7} or cause deactivation \textit{via} hydrolysis, as has been suggested for related sulfonic acid catalytic materials.\textsuperscript{8} It has been reported that the mixture of short-chain alcohols and water cause a greater degree of swelling than either the short chain alcohol or alone.
THF/water mixture provides the great degree of swelling of the Nafion resin (as communicated by DuPont). Both short chain (triacetin) and long chain (olive oil) triglycerides showed essentially no swelling capability for the perfluorinated resin, which is analogous to the swelling characteristics obtained with free fatty acids such as oleic acid. A change in color from transparent to dark amber was observed when Naﬁon was soaked in either short-chain or long-chain triglycerides, indicating the presence of possible side reactions (formation of carbonaceous deposits).

Naﬁon is unaffected by strong bases, strong oxidizing and reducing acids, chlorine, oxygen, hydrogen, and hydrogen peroxide at temperature up to 125 °C. It is thermally stable to about 170 °C in the acid form and stable to higher temperature 200-235 °C on replacement of protons by metal counter-ions.

Naﬁon is a recyclable Bronsted acid catalyst and hence is able to catalyze a variety of organic reactions such as transalkylation, ether synthesis, esterification, the condensation of ketones, Pinacol-Pinacolone and Fries rearrangements.

The perfluorinated resin sulfonic acid (Naﬁon) is a recyclable heterogeneous Bronsted acid catalyst which facilitates the various organic synthesis. Due to this reason, it has received more attention in the area of organic synthesis.

Friedel-Crafts alkylation of benzene (1) with substituted alkenes (2) was catalyzed by Naﬁon-H at 125-210 °C to yield the substituted benzene (3) (Scheme 1).
Subsequently, Olah et al. has reported the use of Nafion-H in the Friedel-Crafts acylation of aroyl chlorides (4) with toluene (5) to give substituted methylbenzophenones (6) (Scheme 2).\(^\text{13}\)

\[
\begin{align*}
  & \text{R} = \text{H, 4-CH}_3, \text{2-F, 3-F, 4-F, 3-Cl} \\
  & \text{(4) \quad (5) \quad (6)} \\
\end{align*}
\]

Scheme 2

The synthesis of mesitylene (8) and bromotoluene (9) was carried out by the nucleophilic reaction of bromomesitylene (7) with toluene (5) in the presence of Nafion-H catalyst under heating condition (Scheme 3).\(^\text{14}\)

\[
\begin{align*}
  & \text{(7) \quad (5) \quad (8) \quad (9)} \\
\end{align*}
\]

Scheme 3

Christian et al. has described the formation of pyrylium salts (12) from tertiary and secondary alcohols (10) with carboxylic acid anhydrides (11) in the presence of perfluorinated resinsulphonic acid Nafion-H (Scheme 4).\(^\text{15}\)

\[
\begin{align*}
  & \text{R = t-Butyl alcohol, 2-Methylbutan-2-ol, 2-Methylpentan-2-ol,} \\
  & \quad \text{3-Methylpentan-3-ol} \\
  & \text{R}^1 = \text{Me, Et} \\
  & \text{(10) \quad (11) \quad (12)} \\
\end{align*}
\]

Scheme 4
The 1,1-diacetates (15) were generally prepared by the equivalent amount of aldehydes (13) and freshly distilled acetic anhydride (14) using catalytic amount of Nafion-H at ambient temperature (Scheme 5).\textsuperscript{16}

![Scheme 5](image)

Fries rearrangement of phenol esters (16) to hydroxyphenyl ketones (17) was carried out in the presence of Nafion-H (Scheme 6).\textsuperscript{17}

![Scheme 6](image)

The reductive cleavage of acetals (18) to the corresponding ethers (20) and triethylsilane alkylethers (21) were carried out under Nafion-H catalysis with triethylsilane (19) in refluxing dichloromethane solution (Scheme 7).\textsuperscript{18}

![Scheme 7](image)
The Ritter reaction of alcohols (10) with nitriles (22) was described by Olah et al. to yield the corresponding amides (23) using recyclable Nafion-H catalyst (Scheme 8). \(^{19}\)

\[
\begin{align*}
R^1\text{-OH} + R\text{-C≡N} \xrightarrow{\text{Nafion-H, } \Delta} R^1\text{-N} & \equiv C - R
\end{align*}
\]

(10) \hspace{1cm} (22) \hspace{1cm} (23)

R = PhCH\_2, 2,4-Dimethyl-benzyl, 1-Adamantane, 2-Adamantane, 2-Norbornane, \textit{exo}-2-Phenyl-2-norbornane

R\(^1\) = CH\_3, Ph

Scheme 8

Nafion-H was reported an effective acid resin catalyst for the intramolecular aromatic substitution of \(N\)-aryldiazoacetamides (24) to form the corresponding 2(3\(H\))-indolinones (25) in refluxing chloroform (Scheme 9). \(^{20}\)

\[
\begin{align*}
\text{R} & \text{N} \equiv \text{O} \xrightarrow{\text{Nafion-H}} \text{R} & \equiv \text{N} \equiv \text{O}
\end{align*}
\]

(24) \hspace{1cm} (25)

R = H, 2,3-(CH\_3)\_2, \text{\textit{m}}-CH\_3, 3,4-CH\_2(O)\_2, \text{\textalpha}-\text{Naphthyl}

R\(^1\) = H, Et, Ben; Z = H, CH\_3CO

Scheme 9

The condensation of acetophenones (26) to 1,3,5-triarylbenzenes (27) was catalyzed by Nafion-H under relatively mild reaction conditions at 145-150 °C (Scheme 10). \(^{21}\)
Nafion-H was found to be an excellent acid catalyst for the direct conversion of acetals (18) to thioacetals (28) with 1,2-ethanedithiol in methylene chloride solution (Scheme 11).22

Kobayashi *et al.* has described Sc-Nafion catalyzed allylation reaction of carbonyl compounds (31) with tetraallyltin (32) to afford the desired homoallylic alcohols (33) in high yields at room temperature (Scheme 13).\(^{24}\)

\[
\begin{align*}
\text{R} & = \text{t-Bu, H} \\
\text{R}^1 & = \text{H, CH}_3, \text{COOMe} \\
\text{(31)} & = \text{D-arabinose, D-ribose, D-glucose}
\end{align*}
\]

Nafion-H was found to be an highly efficient solid acid catalyst for the biomolecular conversion of alcohols (10) to ethers (34) in excellent yields (Scheme 14).\(^{25}\)

\[
\begin{align*}
\text{R} & = \text{CH}_3(\text{CH}_2)_4, \text{CH}_3(\text{CH}_2)_5, \text{CH}_3(\text{CH}_2)_6, \text{CH}_3(\text{CH}_2)_7, \\
& \quad \text{CH}_3(\text{CH}_2)_8, \text{CH}_3(\text{CH}_2)_9, 3-\text{MeC}_4\text{H}_9, 2-\text{EtC}_6\text{H}_{12}, \\
& \quad 3,7-\text{Me}_2\text{C}_8\text{H}_{15}, 3,5,5-\text{Me}_3\text{C}_6\text{H}_{10}, \text{c-C}_8\text{H}_{11}, 1-\text{MeC}_4\text{H}_8, \\
& \quad 1-\text{EtC}_4\text{H}_8, 1-\text{MeC}_7\text{H}_{14}
\end{align*}
\]
Mukaiyama aldol condensation was carried out between aromatic aldehydes (35) and the Danishefsky diene (36) which undergo Diels-Alder cyclization to form the 2,3-dihydro-γ-pyridones (38) through the formation of imine intermediate (37) in the presence of Nafion-H (Scheme 15).\(^2^6\)

![Scheme 15](image)

Vankar et al. has reported that the catalytic amount of Nafion-H along with NaI (1 equiv.), in methanol cleaved a variety of tert-butyldimethyl silyl ether (TBDMS) (39) readily into corresponding alcohols (10) in high yields (Scheme 16).\(^2^7\)

![Scheme 16](image)

The deprotection of trimethylsilyl ethers (40) to their corresponding alcohols (10) was carried out in the presence of Nafion-H and wet SiO\(_2\) in n-hexane at room temperature (Scheme 17).\(^2^8\)
The one-pot three-component synthesis of 2,3-disubstituted 4-(3H)-quinazolinones (44) from o-aminobenzoic acid (41), alkyl/aryl-trietoxymethanes (42) and aromatic amines (43) was catalyzed by Nafion-H under solvent-free microwave irradiation conditions (Scheme 18). 

The multicomponent reaction of cyclic β-diketones (45), urea (46) and aldehydes (13) was reported for the synthesis of octahydroquinazolinone derivatives (47 & 48) over Nafion-H with good yield and selectivity (Scheme 19).
Narsaiah et al. has developed a one-pot multicomponent condensation of aryl aldehydes (13), enolisable ketones (49) and acetyl chloride (50) using Nafion-H catalyst for the synthesis of β-acetamido ketones in acetonitrile (51) at room temperature (Scheme 20).31

\[
\begin{align*}
R &= \text{H, CH}_3 \\
R^1 &= \text{C}_6\text{H}_5, 4-\text{FC}_6\text{H}_4, 3-\text{ClC}_6\text{H}_4, 4-\text{ClC}_6\text{H}_4, 2-\text{BrC}_6\text{H}_4, 3-\text{BrC}_6\text{H}_4, 4-\text{BrC}_6\text{H}_4, 4-\text{O}_2\text{NC}_6\text{H}_4, \\
&\quad 4-\text{CH}_3\text{OC}_6\text{H}_4, 4-\text{FC}_6\text{H}_4, 3-\text{FC}_6\text{H}_4, 2,4-\text{Cl}_2\text{C}_6\text{H}_3, 3-\text{Pyridine}, 4-\text{Pyridine}
\end{align*}
\]

Scheme 19

The hydroamination of vinylpyridines (52) with aliphatic and aromatic amines (53) was developed for the synthesis of disubstituted-(2-pyridin-2-yl-ethyl)-amines (54) using cation exchange resin Nafion-NR50 under milder reaction conditions (Scheme 21).32
A novel one-pot solvent-free synthesis of 1,3,4-oxadiazoles (57) was reported by the condensation of acid hydrazides (55) and triethyl orthoalkanates (56) using solid supported Nafion®NR50 under microwave irradiation (Scheme 22).33

The Ritter reaction of nitriles (58) and alcohols (59) was reported for solvent-free synthesis of amides (60) catalyzed by Nafion®NR50 under microwave irradiation (Scheme 23).34
Chapter I

The one-pot synthesis of nitrones (62) via direct condensation/oxidation of aldehydes (13) and primary amines (61) using Nafion immobilized MoOCl₄ as catalyst and solid urea-hydrogen peroxide (UHP) as oxidant was described under very mild reaction conditions (Scheme 24).³⁵

\[
\begin{align*}
R^1 & : \text{Ph, 4-MeOC}_6\text{H}_4, 4-\text{O}_2\text{NC}_6\text{H}_4, 2-\text{Furyl, CH}_3(\text{CH}_2)_2\text{CH}_2 \\
R^2 & : \text{PhCH}_2, n-\text{Bu, t-Bu}
\end{align*}
\]

Scheme 24

Kidwai et al. has reported the synthesis of 2-aminothiazoles (65) from α-bromoketones (63) with thiourea derivatives (64) using Nafion-H as a solid acid catalyst coupled with aqueous PEG-400 system (Scheme 25).³⁶

\[
\begin{align*}
\text{CH}_2\text{Br} + \text{C}_6\text{H}_4\text{NHR}^1 & \xrightarrow{\text{Nafion-H, 50 °C}} \text{S} \quad \text{PEG:water (60:40)} \\
\text{(63)} & \text{(64)} \quad \text{(65)}
\end{align*}
\]

R = H, p-Me, p-Br
R¹ = H, Ph, 2-Naphthyl, p-BrC₆H₄, p-MeOC₆H₄, p-MeC₆H₄, p-HO₆C₆H₄, p-Ø₂NC₆H₄

Scheme 25
PROPARGYLAMINES

Propargylamine or propargylic amines (66) are highly useful building blocks in organic synthesis and the corresponding structural motif has been found in various natural products and compounds of pharmaceutical relevance.37

The classical methodologies for the preparation of propargylic amines have usually exploited the relatively high acidity of terminal acetylenic C-H bond to form alkynes-metal reagents by the reaction with strong base.

Propargylamines are versatile synthetic intermediates for organic synthesis, especially for the synthesis of heterocyclic compounds such as oxazolidinones, imidazoles and pyrroles etc.

4-Methylene-2-imidazolidinones (69) were obtained by the base catalyzed cyclization of propargylic ureas (68), which were synthesized by the reaction of 3-alkylamino-1-butyne (67) with isocyanate (Scheme 26).38

\[ R^1 = c\text{-}C_6H_{11}, (CH_3)_2C\text{-}CH_2\text{-}(CH_3)_2C; R^2 = 4\text{-}ClC_6H_4, 2,5\text{-}Cl_2C_6H_3 \]

Scheme 26

Reaction of β-oxodithioesters (70) with propargylamine (71) afforded the corresponding 2-(acylalkylidene)-5-(methylene)thiazolidines (72) (Scheme 27).39
Reaction of 1-(N-methyl-N-phenylaminomethyl) benzotriazole (73) with alkynylalkylaluminates (74) gave corresponding propargylamines (75) (Scheme 28).

Copper(I)-catalyzed direct alkyne-imine addition reaction of \( N \)-benzylideneanilines (77) with phenylacetylene (76) was carried out in the presence of \( \text{H}_2\text{O} \) resulted in the formation of propargylamines (78) (Scheme 29).
Enantioselective, Copper(I)-catalyzed three-component reaction of alkynes (76), aldehydes (13) and secondary amines (53) was reported to afford the corresponding propargylamines (79) in toluene at room temperature by using CuBr (5 mol%) and (R)-quinap (R)-2 (5.5 mol%) (Scheme 30).  

\[
\text{H} \equiv \equiv R + \text{O} + \begin{array}{c} \text{R}^1 \text{H} \\ \text{N} \end{array} \begin{array}{c} \text{R}^2 \\ \text{R}^3 \end{array} \xrightarrow{\text{CuBr (5 mol%)}} \xrightarrow{\text{Toluene, rt}} \xrightarrow{(R)\text{-quinap (R)-2 (5.5 mol%)}} \text{R}^2 \equiv \equiv R
\]

\( R = \text{C}_6\text{H}_5, \text{n-Bu, 4-BrC}_6\text{H}_4, \text{SiMe}_3, \text{c-Hex}; \) \( R^1 = \text{Ph, i-Bu, i-Pro, c-Hex, 1-Ethylpropyl,} \) 4-MeOC\_6H\_4, 4-F\_3CC\_6H\_4, 2-H\_3CC\_6H\_4, 3-Furanyl, 3-Benzothiophenyl; \( R^2 = R^3 = \text{Bn, Allyl} \)

Scheme 30

Substituted propargylamides (82) were obtained by the metal catalyzed coupling of imines (80) with alkynes (76) and acid chlorides (81) (Scheme 31).

\[
\text{H} \equiv \equiv R + \begin{array}{c} \text{R}^1 \text{H} \\ \text{R}^2 \text{Cl} \end{array} \xrightarrow{\text{CuI, i-Pr}_2\text{NEt}} \xrightarrow{\text{CH}_3\text{CN, rt}} \text{R}^3 \equiv \equiv R
\]

\( R = \text{C}_6\text{H}_5, (\text{CH}_3)_3\text{Si, CH}_2\text{Cl, n-C}_4\text{H}_9} \)
\( R^1 = 4-\text{H}_3\text{CC}_6\text{H}_4, 4-\text{H}_3\text{CSC}_6\text{H}_4, 4-\text{BrC}_6\text{H}_4 \)
\( R^2 = \text{Bn, H}_2\text{COOCCH}_3, \text{C}_2\text{H}_5; R^3 = \text{C}_6\text{H}_5, \text{CH}_3, \text{i-Pr} \)

Scheme 31

Reaction of activated quinolines (83) with terminal acetylenes (76) in the presence of copper iodide and \( i-\text{Pr}_2\text{NEt} \) afforded the corresponding 2-alkynyl-1,2-dihydroquinolines (84) (Scheme 32).
Reaction of alkynes (76) to N-tert-butanesulfinimines (85) in the presence of a base lithium hexamethyldisilazide (LiHMDS) provided the corresponding N-tert-butylsulfinylpropargylamines (86) (Scheme 33).45

α-[4-(1-Substituted)-1,2,3-triazol-4-yl]benzylacetamides (88) were obtained via microwave-assisted Cu(I)-catalyzed reaction of chiral propargylamines (87) with phenyl azide or sodium azide (Scheme 34).46
Au-nanoparticles were catalyzed multicomponent $A^3$-coupling reaction of aldehydes (13), amines (53) and alkynes (76) to give the propargylamines (89) in excellent yields at 70-80 °C under nitrogen atmosphere (Scheme 35).\(^{47}\)

$$
\begin{align*}
\text{R} &= \text{C}_6\text{H}_5, 4-\text{MeC}_6\text{H}_4, 4-\text{MeOC}_6\text{H}_4, 3-\text{ClC}_6\text{H}_4, 4-\text{BrC}_6\text{H}_4, 2-\text{Furfuryl}, 2-\text{Thiophenyl}, 3-\text{Pyridenyl} \\
\text{R}^2\text{R}^3\text{NH} &= \text{Piperidine, Morpholine, Pyrrolidine}
\end{align*}
$$

Scheme 35

Addition of lithium trifluoromethylacetylide (90), *in situ* prepared from lithium diisopropylamide and 2-bromo-3,3,3-trifluoropropene to various $N$-tert-butanesulfinyl imines (91) provided the corresponding trifluoromethylated propargyl sulfinamides (92) (Scheme 36).\(^{48}\)

$$
\begin{align*}
\text{R}^1 &= \text{CH}_3; \text{R}^2 = \text{C}_2\text{H}_5, \text{C}_6\text{H}_5, \text{i-Pr, i-Bu}
\end{align*}
$$

Scheme 36

Propargylamines (94) were obtained by the reaction of phenylacetylene (93) and aldehydes (13) with heterocyclic amines (53) using zinc titanate nanopowder in aqueous medium at 100 °C (Scheme 37).\(^{49}\)
R = Ph, 4-ClC₆H₄, 4-BrC₆H₄, 2-HOC₆H₄, 3,4-(MeO)₂C₆H₃, 4-Me₂NC₆H₄, 4-ClC₆H₄, CH₃CH₂CH₂
R¹R²NH = Piperidine, Pyrrolidine, Morpholine, Piperazine, N-Methylpiperazine

Scheme 37

NiCl₂-catalyzed A³-coupling reaction of alkynes (76), aldehydes (13) and amines (53) gave the corresponding propargyllamines (89) in quantitative yields (Scheme 38).⁵⁰

R = Ph, CH₃(CH₂)₅, 4-MeC₆H₄, (CH₃)₃Si
R¹ = H, C₆H₅, 4-O₂NC₆H₄, 3-O₂NC₆H₄, 4-FC₆H₄, 4-MeC₆H₄, 4-MeOC₆H₄,
4-ClC₆H₄, 4-BrC₆H₄, Cyclohexyl, 2-ClC₆H₄, 3-ClC₆H₄, 2,4-Cl₂C₆H₃, Me₂CH,
2-Thiophene
R²R³NH = Piperidine, Pyrrolidine, Morpholine, Piperazine, N-Methylpiperazine,
N-Methylaniline, Aniline, Dibenzyl amine, N-Methylpiperazine, Ammonia,
Benzyamine, Methyl amine, n-Butylamine, Ethyl-1-piperazinecarboxylate

Scheme 38

Fe₃O₄ nanoparticle-supported copper(I) pybox-catalyzed enantioselective direct-addition reactions of terminal alkynes (76) to imines (95) gave the corresponding propargyllamines derivatives (96) (Scheme 39).⁵¹
The synthesis of various propargylamines (97) was achieved by the simple Barbier–Grignard-type reaction of phenylacetylene (93) with a variety of aldimines (80) catalyzed by a bimetallic In–Cu system under aqueous condition (Scheme 40).\(^{52}\)

Gold nanoparticles impregnated on alumina catalyzed A³-coupling reaction of aldehydes (13), amines (53) and alkynes (76) to give corresponding propargylamines (89). The aldimine (98) formation was catalyzed by Montmorillonite K10 beforehand (Scheme 41).\(^{53}\)

\[R = R^1 = H, 4-\text{ClC}_6\text{H}_4, 4-\text{MeC}_6\text{H}_4, 4-\text{MeOC}_6\text{H}_4, 4-\text{O}_2\text{NC}_6\text{H}_4, 4-\text{MeC}_6\text{H}_4\text{SO}_2\]

\[R = C_6\text{H}_5, C_5\text{H}_5\text{N}, C_4\text{H}_3\text{O}, C_6\text{H}_5\text{CH}_2\text{CH}_2, \text{CH}_3(\text{CH}_2)_3\]

\[R^1 R^1 \text{NH} = \text{Piperidine, Morpholine, Pyrrolidine, Diethylamine, 2-(Methylamino)ethanol}\]

\[R^2 = C_6\text{H}_5\]
Chapter I

Pargyline derivatives (99) and (100) were prepared from 8-(methylaminomethyl)quinoline and exhibited anti-monoamine oxidase activity.\(^{54}\)

\[
\text{(99)} \quad \text{H}_2\text{C} - \text{NCH}_2\text{C} = \text{CH} \\
\text{Me}
\]

\[
\text{(100)} \quad \text{Me} - \text{N} - \text{CH}_2\text{C} = \text{CH}
\]

The propargylamine derivative (101) potentiated tryptamine convulsions of rats similar to Pargyline had slight stimulating effect.\(^{55}\)

\[
\text{(101)} \quad \text{H}_2\text{C} - \text{NMeCH}_2\text{C} = \text{CH}
\]

A series of 10-propargyl-5,8-dideazafolic acid derivatives (102) were synthesized and tested for inhibition of purified L1210 thymidylate synthase and for inhibition of L1210 cell growth \textit{in vitro}.\(^{56}\)

\[
\text{(102)} \quad \text{R} = \text{NH}_2; \text{R}^1 = \text{H, Cl, MeO} \\
\text{R}^2 = \text{H, Cl, Ac, F, CN, CONH}_2, \text{SO}_2\text{NMe}_2, \text{NO}_2, \text{COCF}_3, \text{OCF}_3 \\
\text{R}^3 = \text{H, MeO}
\]

A series of acetylenic imidazoles (103) related to oxotremorine were prepared and evaluated as cholinergic agents with \textit{in vitro} binding assays and \textit{in vivo} pharmacological tests in mice.\(^{57}\)
Chapter I

2-Alkynyl and 2-cycloalkynyl derivatives of adenosine-5'-N-ethyluronamide (NECA) (104) were prepared as selective A<sub>2</sub> adenosine receptor agonists with potent inhibitory activity on platelet aggregation.<sup>58</sup>

Cyclo-hexapeptide analogue (105) was synthesized starting from propargylamine and found to possess anti-parallel β-sheet structure.<sup>59</sup>
2-(2,6-Difluorophenyl)-4-phenylalkynyl oxazolines (106) were prepared as a potent insect growth regulators.\textsuperscript{60}

![Chemical Structure of 106](image)

\[ R = \text{Me}_3\text{C}, \text{Me}_3\text{CO}, \text{H}, \text{CF}_3, 4-\text{CF}_3\text{SO}_3\text{C}_6\text{H}_4, 4-\text{BrC}_6\text{H}_4, 4-\text{FC}_6\text{H}_4, \text{Ph} \]

Compound (107) related to 2-azatidinone was synthesized as single enantiomer and found to be potent cholesterol absorption inhibitors.\textsuperscript{61}

![Chemical Structure of 107](image)
Chapter I

\[(N\text{-propargyl)-(3R)-aminoindan-5-yl\text{-ethyl methyl carbamate (108) was synthesized as anti-apoptotic-neuroprotective agent and as a novel cholinesterase monoamine oxidase inhibitor.}^{62}\]

\[
\begin{align*}
\text{(108)}
\end{align*}
\]

1,8-Naphthyridine-3-carboxamide derivatives (109) were synthesized as anticancer and anti-inflammatory agent and tested for \textit{in vitro} cytotoxicity against eight cancer cell lines and a normal cell line with IC\textsubscript{50} = 1.37 μM for HBL-100 (breast) cell line.\textsuperscript{63}

\[
\begin{align*}
\text{(109)}
\end{align*}
\]

1-alkyl-N-propargyl-1,2,3,4-tetrahydroisoquinoline derivatives (110) were synthesized from 2-phenylethylamine and showed cytotoxic effect on PC12 cells.\textsuperscript{64}

\[
\begin{align*}
\text{(110)}
\end{align*}
\]

R = Ph, Methyl, Ethyl, \textit{n}-Propyl, \textit{n}-Butyl, \textit{n}-Pentyl, \textit{n}-Hexyl cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl, 3-Hydroxypropyl, 3-Acetoxypropyl

\text{Rasagiline (N-propargyl-1-(R)-aminoindan (111) was synthesized as potent irreversible monoamine oxidase (MAO)-B inhibitor, \textit{anti}-Parkinsonian drug and}
effected as monotherapy or adjunct to L-Dopa for patients with early and late Parkinson’s disease (PD).65

\[ 
\text{HN} \]
\[ (111) \]

The length of synthesis is dependent upon the average molecular complexity produced per operation, which depend in turn on the number of chemical bonds being created. Therefore, devising reaction that achieves multi-bond formation in single operation is becoming a major challenge in search of step economy synthesis. Multicomponent Reactions (MCRs) found to be a straight forward route to generate complexity with diversity in a single operation. MCRs processes\(^6\), in which three or more reactants are combined in a single chemical process to produce product that incorporate substantial portions of all the components, naturally comply with many of stringent methods required for ideal organic synthesis.

MCRs, though fashionable these days, have in fact a long history. Indeed, many important reactions such as the Strecker amino acid synthesis (1850)\(^67\), the Hantsch dihydropyridine synthesis (1882)\(^68\), the Biginelli dihydropyrimidine (1891)\(^69\) and the Mannich reaction\(^70\) \textit{etc.} are all multicomponent in nature. Inspite of the significant contribution of MCRs to the state of the art of the modern organic chemistry and their potential use in complex organic syntheses, little attention was paid to the development MCRs. However, with the introduction of molecular biology and high-throughput biological screening, the demand on the number and the quality of compounds for drug delivery has increased enormously. By virtue of their inherent convergence and high productivity, together with their exploratory and complexity-
generating power, MCRs became a rapidly evolving field of research and have attracted the attention of both academic and industrial scientists.

Carbon-Carbon bond-forming reactions are arguably the most important processes in chemistry, as they represent the key step in the building of more complex molecules from simple precursors. In the past few years, organic chemists have developed a plethora of reactions for carbon-carbon bond formation between saturated sp³ C-atoms. However, until the discovery and development of metal-mediated cross-coupling reactions, starting in 1970s, there was no simple, general direct methodology known for carbon-carbon bond formation between unsaturated species such as aryl, vinyl and alkynyl moieties. In other words, carbon-carbon bond formation between sp and sp² C-atom centers are often difficult and tedious. In the intervening 25 years, a wide variety of cross-coupling methodologies have been developed and cross-coupling reactions have emerged among the most powerful and useful synthetic tools in chemistry.⁷¹
OBJECT OF THE PRESENT WORK

An increasing awareness of the environmental cost of traditional acid-catalyzed chemical processes has created an opportunity for new solid acid-based approaches to many important industrial reactions.72,73 The replacement of conventional, toxic and polluting Bronsted and Lewis acid catalysts with eco-friendly reusable solid acid heterogeneous catalysts like acidic zeolites, clays, sulfated zirconia and ion exchange resins is an area of current interest.74-77 The use of solid acid catalyst instead of liquid includes many advantages such as reduced equipment corrosion, ease of product separation, recycling of the catalyst and environmentally acceptability.

In recent years, resins containing perfluorosulphonic acid group such as Nafion®NR5078 (copolymer of tetrafluoroethylene and perfluoro-2-(fluorosulfonylethoxy) propyl vinyl ether), which is strongly acidic in nature and chemically as well as thermally stable has been found to be an excellent catalyst for a variety of major organic reactions like alkylation, acylation, esterification, etherification, dehydration and nitration.79,80

Multicomponent coupling reactions (MCRs) provide a powerful synthetic strategy to access complicated structure from rather simple starting material via a one-pot methodology, and in particular, exhibit high atom economy and selectivity.81 As continuation, a very good example of such a process that has been studied widely in recent years is three-component coupling of aldehydes, amines and alkynes (A3-coupling) via C-H activation.82,83 The propargylamines that result from A3-coupling reactions are versatile building blocks for organic synthesis. They are generally used as precursors for the synthesis of N-containing heterocyclic compounds such as pyrrolidines, oxazoles and pyrroles84 and also act as key intermediates85 for the
construction of biologically active compounds like isosteres, β-lactams, oxotremorine substrates, conformationally restricted peptides and therapeutic drug molecules.\textsuperscript{86} Traditionally, propargylamines are synthesized by nucleophilic attack of lithium acetylates or Grignard reagents to imines.\textsuperscript{87} In recent years, enormous progress has been made in expanding the scope of the direct addition of alkynes to carbon-nitrogen double bonds either from prepared imines or from aldehydes and amines in one-pot procedure by several transition-metal catalysts via C-H activation of terminal alkynes. These include Ag(I) salts\textsuperscript{88}, Au(I)/Au(II) salts\textsuperscript{89}, Au(III)-salen complexes\textsuperscript{90}, Cu(I) salts\textsuperscript{91}, Hg\textsubscript{2}Cl\textsubscript{2}\textsuperscript{92} and Cu/Ru\textsuperscript{93} bimetallic system under homogeneous conditions. Recently, Au(III)\textsuperscript{94}, Ag(I)\textsuperscript{95}, in ionic liquids and Cu-supported hydroxyapatite\textsuperscript{96} were used to catalyze A\textsuperscript{3}-coupling reactions. Also, more sophisticated alternative energy sources like microwave\textsuperscript{91} and ultrasonic\textsuperscript{97} radiation has been used in the presence of Cu(I) salt.

Unfortunately, these reagents used in stoichiometric amounts are often lost at the end of the reaction (non-recyclable) and required drastic reaction conditions. Most of these reactions were carried out either in toxic solvents\textsuperscript{88} or in the presence of expensive solvents.\textsuperscript{98} Thus, there has been an ongoing interest to develop solid acid catalysts for C-H bond activation of terminal alkynes\textsuperscript{99} under mild reaction conditions.

As a part of our ongoing program on the development of new synthetic methods and the use of recyclable heterogeneous catalyst in organic synthesis\textsuperscript{100,101} herein, we wish to report for the first time a simple and highly efficient methodology for the synthesis of propargylamines in excellent yields using Nafion\textsuperscript{®}NR50 as recyclable and heterogeneous solid acid catalysts.
RESULTS AND DISCUSSION

As a model reaction, we initially examined an efficient and environmentally benign protocol for A³-coupling of benzaldehyde (112a) (1.0 mmol), piperidine (113a) (1.2 mmol) and phenylacetylene (114) (1.5 mmol) in the presence of Nafion®NR50 in acetonitrile at 70-80 °C under nitrogen atmosphere (Scheme 42). As a result, the expected reaction proceeded clearly to produce the desired propargylamine in 96% yield (115a).

The effect of catalyst loading was studied by carrying out the experiments with different amounts of Nafion®NR50. Increasing the loading of catalyst up to 0.35 gm gave desired propargylamines in 96% yield. However, the increase in the concentration of catalyst not only promotes the reaction but also results in an increase of the yield with decrease in the time (Table 1).

In addition, it was found that at higher temperature Nafion®NR50 showed good catalytic activity at 70-80 °C, 96% yield was obtained, however at room temperature lower yields were obtained even after longer reaction times. Comparable results were obtained when the reaction was carried out at 70-80 °C with 0.25 gm of Nafion®NR50. Thus, to reduce the amount of catalyst, all optimization was carried out at 70-80 °C with 0.25 gm of Nafion®NR50.

The nature of reaction media has an important role in A³-coupling reaction in the presence of Nafion®NR50 (0.25 gm). Among the various solvents studied such as acetonitrile, methanol, THF, DCM and dioxane, acetonitrile was found to be the most efficient solvent of choice (Table 2, Entry 1) and no products were obtained when the reaction was carried out in dichloromethane or dioxane.
A possible mechanism was proposed involving the activation of C-H bond of the terminal alkyne by Nafion®NR50 catalyst (Scheme 43). The sulfur acetylide intermediate thus generated will react with the iminium ion prepared in situ from aldehyde and secondary amine to produce the corresponding propargylamines, water and Nafion®NR50. The regenerated Nafion®NR50 participates further in the reaction and completes the catalytic cycle.

For the practical application of the catalyst Nafion®NR50, the life-time of the catalyst and its level of reusability are important factors. The catalyst showed excellent recyclability and could be reused for three to four runs with only slight drop in activity. After completion of fresh reaction the catalyst was recovered by forceps, washed with dichloromethane, dried and new reaction was then performed under similar reaction conditions (Table 3).

After completing the search of optimized conditions, we chose a variety of structurally different aldehydes, and amines possessing a wide range of functional group to understand the scope and generality of Nafion®NR50 promoted A³-coupling reaction. A variety of aromatic aldehydes were coupled with secondary amines and phenylacetylene and it was found that aryl aldehydes possessing an electron withdrawing groups (Table 4, Entries 4-6) afforded better yields with good reactivity and lesser reaction times than those with electron donating groups (Table 4, Entries 2 and 3) bound to the benzene ring required longer reaction times. Heterocyclic aldehyde (Table 4, Entry 7) also displayed high reactivity with good yield.
Scheme 42: Coupling of aldehydes, secondary amines and phenylacetylene catalyzed by Nafion®NR50.

Scheme 43: Tentative mechanism for A³-Coupling.
EXPERIMENTAL

In a 50 mL round bottom flask, aromatic aldehydes/heterocyclic aldehydes (1 mmol), secondary amines (1.2 mmol) and phenylacetylene (1.5 mmol) in CH$_3$CN (5 mL) was taken. To this Nafion® NR50 (0.25 gm) was added and the reaction mixture was stirred at 70-80 °C for the appropriate time mentioned in Table 4 under nitrogen atmosphere. The progress of reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled. The organic layer was extracted with diethyl ether and the remaining Nafion® NR50 was reused for further reactions. The organic layer was dried over anhydrous Na$_2$SO$_4$ and the solvent was removed in vacuo. The crude product was subjected to purification by silica gel column chromatography using 20% ethyl acetate and 80% hexane as an eluent to yield the propargylamines (115a-n, Table 4). The structures of all the products were unambiguously established on the basis of their spectral analysis (IR, $^1$H NMR, $^{13}$C NMR and mass spectral data).
Table 1: Optimization of Concentration of Nafion® NR50 for A³-coupling.a

```
<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Time (h)</th>
<th>Yield (%) b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>0.05</td>
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<td>3</td>
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<td>10</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>0.20</td>
<td>5</td>
<td>92</td>
</tr>
<tr>
<td>5</td>
<td>0.25</td>
<td>5</td>
<td>96</td>
</tr>
<tr>
<td>6</td>
<td>0.35</td>
<td>4</td>
<td>96</td>
</tr>
</tbody>
</table>
```

*aReaction Conditions: benzaldehyde (1.0 mmol), piperidine (1.2 mmol), phenylacetylene (1.5 mmol), Nafion® NR50 (0.05-0.35 gm); solvent CH₃CN (5 mL); temperature 70-80 °C, N₂ atm. bIsolated yields.

Table 2: Effect of solvent on A³-coupling.a

```
<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Yield (%) b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Acetonitrile</td>
<td>5</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>Methanol</td>
<td>5</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>Tetrahydrofuran</td>
<td>5</td>
<td>87</td>
</tr>
<tr>
<td>4</td>
<td>Dichloromethane</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Dioxane</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>
```

*aReaction Conditions: benzaldehyde (1.0 mmol), piperidine (1.2 mmol), phenylacetylene (1.5 mmol), Nafion® NR50 (0.25 gm); solvent (5 mL); temperature 70-80 °C, N₂ atm. bIsolated yields.

Table 3: Recycling of Nafion® NR50.a

```
<table>
<thead>
<tr>
<th>No. of cycles a</th>
<th>Fresh</th>
<th>Run 1</th>
<th>Run 2</th>
<th>Run 3</th>
<th>Run 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yield (%) b</td>
<td>96</td>
<td>96</td>
<td>95</td>
<td>93</td>
<td>92</td>
</tr>
<tr>
<td>Time (h)</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>
```

*aReaction Conditions: benzaldehyde (1.0 mmol), piperidine (1.2 mmol), phenylacetylene (1.5 mmol), Nafion® NR50 (0.25 gm); solvent CH₃CN (5 mL); temperature 70-80 °C, N₂ atm. bIsolated yields.
**Table 4: Nafion® NR50 catalyzed A³-coupling.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>R</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yield (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Piperidine</td>
<td>C₆H₅</td>
<td>115a</td>
<td>5.0</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>Piperidine</td>
<td>4-MeC₆H₄</td>
<td>115b</td>
<td>5.5</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>Piperidine</td>
<td>4-MeOC₆H₄</td>
<td>115c</td>
<td>6.0</td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td>Piperidine</td>
<td>4-BrC₆H₄</td>
<td>115d</td>
<td>4.5</td>
<td>94</td>
</tr>
<tr>
<td>5</td>
<td>Piperidine</td>
<td>4-ClC₆H₄</td>
<td>115e</td>
<td>4.0</td>
<td>93</td>
</tr>
<tr>
<td>6</td>
<td>Piperidine</td>
<td>4-O₂NC₆H₄</td>
<td>115f</td>
<td>4.5</td>
<td>95</td>
</tr>
<tr>
<td>7</td>
<td>Piperidine</td>
<td>2-Furfuryl</td>
<td>115g</td>
<td>4.0</td>
<td>90</td>
</tr>
<tr>
<td>8</td>
<td>Piperidine</td>
<td>Cyclohexyl</td>
<td>115h</td>
<td>3.5</td>
<td>88</td>
</tr>
<tr>
<td>9</td>
<td>Morpholine</td>
<td>C₆H₅</td>
<td>115i</td>
<td>5.0</td>
<td>85</td>
</tr>
<tr>
<td>10</td>
<td>Morpholine</td>
<td>4-MeC₆H₄</td>
<td>115j</td>
<td>6.5</td>
<td>91</td>
</tr>
<tr>
<td>11</td>
<td>Morpholine</td>
<td>4-MeOC₆H₄</td>
<td>115k</td>
<td>7.0</td>
<td>87</td>
</tr>
<tr>
<td>12</td>
<td>Morpholine</td>
<td>4-ClC₆H₄</td>
<td>115l</td>
<td>4.5</td>
<td>90</td>
</tr>
<tr>
<td>13</td>
<td>Pyrrolidine</td>
<td>C₆H₅</td>
<td>115m</td>
<td>6.5</td>
<td>87</td>
</tr>
<tr>
<td>14</td>
<td>Pyrrolidine</td>
<td>4-MeOC₆H₄</td>
<td>115n</td>
<td>7.5</td>
<td>84</td>
</tr>
</tbody>
</table>

$^a$Reaction Conditions: aldehydes (1.0 mmol), secondary amines (1.2 mmol), phenylacetylene (1.5 mmol), Nafion® NR50 (0.25 gm); solvent CH₃CN (5 mL); temperature 70-80 °C, N₂ atm. $^b$Isolated yields.
Spectroscopic data of synthesized propargylamines (115a-n)

1-(1,3-Diphenyl-prop-2-ynyl)-piperidine (115a): Yellowish oil; IR (film/cm\(^{-1}\)): \(\nu_{\text{max}} = 3051, 2936, 2253, 1617, 1520, 1451, 1320, 1160\); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta = 7.16-7.35 \text{ (m, 10H, 2Ph)}\), 4.56 (s, 1H, CH), 2.56-2.62 (m, 4H, 2CH\(_2\)), 1.85-1.91 (m, 4H, 2CH\(_2\)), 1.35-1.50 (m, 2H, CH\(_2\)); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta = 138.7, 132.1, 128.5, 128.2, 128.1, 127.6, 123.4, 88.1, 86.3, 62.5, 50.9, 26.3, 24.5\); \(m/z\) 275.68 (M+1, C\(_{20}\)H\(_{21}\)N requires 275.17).

1-[1-(4-Methylphenyl)-3-phenyl-prop-2-ynyl]-piperidine (115b): Slightly yellowish oil; IR (film/cm\(^{-1}\)): \(\nu_{\text{max}} = 2939, 2815, 1580, 1510, 1319, 1154\); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta = 7.56-7.61 \text{ (m, 9H, 2Ph)}\), 4.78 (s, 1H, CH), 2.52-2.61 (m, 4H, 2CH\(_2\)), 2.40 (s, 3H, CH\(_3\)), 1.64-1.73 (m, 4H, 2CH\(_2\)), 1.45-1.58 (m, 2H, CH\(_2\)); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta = 137.3, 135.8, 132.1, 129.0, 128.7, 128.5, 127.1, 123.6, 87.9, 86.6, 62.8, 62.4, 50.9, 26.4, 24.7, 21.4\); \(m/z\) 290.19 (M+1, C\(_{21}\)H\(_{23}\)N requires 289.18).

1-[1-(4-Methoxyphenyl)-3-phenyl-prop-2-ynyl]-piperidine (115c): Slightly yellowish oil; IR (film/cm\(^{-1}\)): \(\nu_{\text{max}} = 3015, 2943, 2812, 2203, 1523, 1318, 1168, 1041\); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta = 7.69-7.81 \text{ (m, 9H, 2Ph)}\), 4.80 (s, 1H, CH), 3.74 (s, 3H, OCH\(_3\)), 2.55-2.65 (m, 4H, 2CH\(_2\)), 1.74-1.80 (m, 4H, CH\(_2\)), 1.45-1.59 (m, 2H, CH\(_2\)); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta = 158.3, 132.2, 130.4, 129.3, 128.6, 128.2, 123.0, 114.0, 85.6, 82.6, 58.8, 55.3, 26.1, 24.2\); \(m/z\) 305.90 (M+1, C\(_{21}\)H\(_{23}\)NO requires 305.18).

1-[1-(4-Bromophenyl)-3-phenyl-prop-2-ynyl]-piperidine (115d): Yellowish oil; IR (film/cm\(^{-1}\)): \(\nu_{\text{max}} = 3040, 2955, 2815, 2780, 2270, 1544, 1495, 1314, 1169, 1052\); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta = 7.89-7.92 \text{ (m, 9H, 2Ph)}\), 4.81 (s, 1H, CH), 2.52-2.66 (m, 4H, 2CH\(_2\)), 1.66-1.79 (m, 4H, 2CH\(_2\)), 1.46-1.50 (m, 2H, CH\(_2\)); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta = 138.1, 132.1, 130.1, 128.4, 128.3, 123.1, 121.5, 88.6, 88.5, 61.8, 52.9, 26.3, 24.5\); \(m/z\) 354.17 (M+1, C\(_{20}\)H\(_{20}\)NBr requires 353.08).
1-[1-(4-Chlorophenyl)-3-phenyl-prop-2-ynyl]-piperidine (115e): Yellowish oil; IR (film/cm\(^{-1}\)): \(\nu_{\text{max}} = 3042, 2947, 2811, 2783, 2240, 1549, 1492, 1316, 1167, 1055\); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta = 7.84-7.91\) (m, 9H, 2Ph), 4.85 (s, 1H, CH), 2.50-2.65 (m, 4H, 2CH\(_2\)), 1.62-1.71 (m, 4H, 2CH\(_2\)), 1.43-1.51 (m, 2H, CH\(_2\)); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta = 137.4, 134.2, 131.3, 130.4, 128.4, 128.3, 115.2, 86.9, 80.9, 59.2, 53.3, 25.0, 24.1\); \(m/z\) 310.17 (M+1, C\(_{20}\)H\(_{20}\)ClN requires 309.13).

1-[1-(4-Nitrophenyl)-3-phenyl-prop-2-ynyl]-piperidine (115f): Yellowish oil; IR (film/cm\(^{-1}\)): \(\nu_{\text{max}} = 2945, 2849, 2190, 1685, 1597, 1334, 1155, 1089\); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta = 7.75-7.89\) (m, 9H, 2Ph), 4.83 (s, 1H, CH), 2.48-2.59 (m, 4H, 2CH\(_2\)), 1.55-1.65 (m, 4H, 2CH\(_2\)), 1.41-1.53 (m, 2H, CH\(_2\)); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta = 138.5, 138.0, 129.7, 128.4, 128.1, 123.6, 122.6, 86.8, 80.0, 59.1, 53.2, 25.3, 24.1\); \(m/z\) 320.87 (M+1, C\(_{20}\)H\(_{20}\)N\(_2\)O\(_2\) requires 320.15).

1-[1-(2-Furfuryl)-3-phenyl-prop-2-ynyl]-piperidine (115g): Sticky compound; IR (film/cm\(^{-1}\)): \(\nu_{\text{max}} = 2920, 2850, 2367, 2250, 1560, 1314, 1156\); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta = 7.47-7.52\) (m, 5H, Ph), 6.12-6.34 (m, 3H, furfuryl) 4.86 (s, 1H, CH), 2.86-3.10 (m, 4H, 2CH\(_2\)), 1.59-1.66 (m, 4H, 2CH\(_2\)), 1.38-1.50 (m, 2H, CH\(_2\)); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta = 152.5, 142.1, 128.2, 128.3, 122.7, 110.6, 86.8, 80.9, 60.5, 24.7, 24.5\); \(m/z\) 265.93 (M+1, C\(_{18}\)H\(_{19}\)NO requires 265.15).

1-[1-(1-Cyclohexyl)-3-phenyl-prop-2-ynyl]-piperidine (115h): Yellowish Oil; IR (film/cm\(^{-1}\)): \(\nu_{\text{max}} = 3054, 2842, 2334, 3334, 1585, 1318, 1156, 890\); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta = 7.52-7.54\) (m, 2H, CH\(_2\)), 7.23-7.26 (m, 3H, CH\(_3\)), 3.12 (d, \(J = 8.2\)Hz, 1H), 2.44-2.65 (m, 4H, CH\(_2\)), 2.14-2.34 (m, 4H), 2.15-2.19 (m, 2H), 1.70-1.83 (m, 4H), 1.37-1.48 (m, 4H), 1.12-1.35 (m, 3H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta = 131.9, 128.3, 128.0, 122.7, 89.4, 86.6, 64.2, 38.8, 33.1, 30.5, 27.9, 26.0, 25.3, 24.9, 24.5\); \(m/z\) 282.41 (M+1, C\(_{20}\)H\(_{27}\)N requires 281.21).
1-(1,3-Diphenyl-prop-2-ynyl)-morpholine (115i): Slightly yellowish oil; IR
(film/cm\(^{-1}\)): \(\nu_{\text{max}} = 3050, 2965, 2301, 1584, 1480, 1320, 1151, 756;\) \(^1\)H NMR (CDCl\(_3,\)
400 MHz): \(\delta = 7.42-7.70\) (m, 10H, 2Ph), 4.83 (s, 1H, CH), 2.94-3.09 (m, 4H, 2CH\(_2\)),
2.57-2.67 (m, 4H, 2CH\(_2\)); \(^{13}\)C NMR (CDCl\(_3,\) 100 MHz): \(\delta = 139.6, 131.2, 128.7,
128.3, 128.1, 127.2, 122.6, 86.7, 80.1, 66.1, 59.3, 52.3; m/z 278.22 (M+1, \(\text{C}_{19}\text{H}_{19}\text{NO}\)
requires 277.15).

1-[1-(4-Methylphenyl)-3-phenyl-prop-2-ynyl]-morpholine (115j): Colourless solid,
m. p. 80.5-81.5 °C; IR (film/cm\(^{-1}\)): \(\nu_{\text{max}} = 3360, 3048, 2972, 2308, 1592;\) \(^1\)H NMR
(CDCl\(_3,\) 400 MHz): \(\delta = 7.32-7.45\) (m, 9H, 2Ph), 4.77 (s, 1H, CH), 3.17-3.22 (m, 4H,
2CH\(_2\)), 2.54-2.66 (m, 4H, 2CH\(_2\)), 2.33 (s, 3H, CH\(_3\)); \(^{13}\)C NMR (CDCl\(_3,\) 100 MHz): \(\delta =
136.2, 134.7, 128.6, 128.3, 128.2, 122.6, 86.8, 80.9, 66.0, 59.2, 52.2, 21.7. m/z 292.01 (M+1, \(\text{C}_{20}\text{H}_{21}\text{NO}\)
requires 291.16).

1-[1-(4-Methoxyphenyl)-3-phenyl-prop-2-ynyl]-morpholine (115k): Yellowish oil;
IR (film/cm\(^{-1}\)): \(\nu_{\text{max}} = 3045, 2962, 2312, 1594, 1349, 1190, 1017, 713;\) \(^1\)H NMR
(CDCl\(_3,\) 400 MHz): \(\delta = 7.33-7.56\) (m, 9H, 2Ph), 4.73 (s, 1H), 3.73-3.89 (m, 3H), 2.16-
2.26 (m, 4H), 1.25-1.56 (m, 4H); \(^{13}\)C NMR (CDCl\(_3,\) 100 MHz): \(\delta = 159.1, 132.2,
128.8, 128.4, 128.2, 122.6, 112.8, 86.3, 80.6, 66.1, 55.8, 52.3; m/z 307.98 (M+1, \(\text{C}_{20}\text{H}_{21}\text{NO}_2\)
requires 307.16).

1-[1-(4-Chlorophenyl)-3-phenyl-prop-2-ynyl]-morpholine (115l): Yellowish oil;
IR (film/cm\(^{-1}\)): \(\nu_{\text{max}} = 3040, 2965, 1619, 1520, 1411, 1338, 1175, 1069;\) \(^1\)H NMR
(CDCl\(_3,\) 400 MHz): \(\delta = 7.32-7.50\) (m, 9H, 2Ph), 4.62 (s, 1H, CH), 3.47-3.54 (m, 4H,
2CH\(_2\)), 2.59-2.62 (m, 4H, 2CH\(_2\)); \(^{13}\)C NMR (CDCl\(_3,\) 100 MHz): \(\delta = 136.2, 134.7,
131.1, 129.1, 128.6, 122.7, 88.8, 84.3, 67.1, 59.5, 49.6; m/z 312.38 (M+1, \(\text{C}_{19}\text{H}_{18}\text{ClNO}\) requires 311.11).
1-(1,3-Diphenyl-prop-2-ynyl)-pyrrolidine (115m): Yellowish oil; IR (film/cm⁻¹): \( \nu_{\text{max}} = 3040, 2965, 2807, 2694, 2278, 1619, 1520, 1411, 1338, 1175, 756; \)
\( ^1 \text{H} \) NMR (CDCl₃, 400 MHz): \( \delta = 7.58-7.63 \) (m, 10H, 2Ph), 4.20 (s, 1H, CH), 1.83-2.44 (m, 8H, 4CH₂); \( ^{13} \text{C} \) NMR (CDCl₃, 100 MHz): \( \delta = 139.1, 131.0, 128.6, 128.2, 126.8, 123.5, 86.1, 86.0, 59.4, 58.6, 50.5, 23.6; \) m/z 262.03 (M+1, C₁₉H₁₉N requires 261.15).

1-[1-(4-Methoxyphenyl)-3-phenyl-prop-2-ynyl]-pyrrolidine (115n): Yellowish oil; IR (film/cm⁻¹): \( \nu_{\text{max}} = 3076, 2961, 2811, 2646, 1522, 1490, 1348, 1145; \)
\( ^1 \text{H} \) NMR (CDCl₃, 400 MHz): \( \delta = 7.59-7.62 \) (m, 9H, 2Ph), 4.89 (s, 1H, CH), 3.83 (s, 3H), 1.80-2.62 (m, 8H, 4CH₂); \( ^{13} \text{C} \) NMR (CDCl₃, 100 MHz): \( \delta = 159.2, 132.2, 129.7, 128.4, 128.3, 122.6, 114.2, 86.0, 80.9, 56.9, 55.2, 23.0; \) m/z 292.35 (M+1, C₂₀H₂₁NO requires 291.16).
REFERENCES


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