Shiraz University

ShirazUniversity
Faculty of Sciences

M.Sc. Thesis in Organic Chemistry

Metal Complexes of
N,N-bis(2-hydroxyphenyl) pyridine-2,6-dicarboxamide
as Heterogeneous, Reuseable and Highly Efficient Catalysts
in Organic Synthesis

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September 2012

Dedicated to:

My Parents

&

My Teachers

ACKNOLEDGEMENT

Thanks to the almighty God for giving me opportunity and ability to complete my research.

I would like to express my greatest gratitude to Prof. Hashem Sharghi, my seniorsupervisor, for his incisive guidance, supervision and encouragement. I am extremely grateful to Dr. Reza Khalifeh, my advisor,for keeping me on the right track with his knowledge, experience, and very helpful ideas. I thank my committee members, Dr. Ali Khalafi-nezhad and Dr. Jarrahpour for their careful review of the manuscript and helpful suggestions.

I thank the entire Dr. Sharghi research group for their support and help in the lab, sharingtheir ideas and skills, and also for making the lab a very enjoyable workplace.

Finally, I want to thank my parents. After all, I would not be where I amtoday without their love, support, encouragement and patience.

ABSTRACT

Metal Complexes of N,N-bis(2-hydroxyphenyl) pyridine-2,6-dicarboxamide as Heterogeneous, Reuseable and Highly Efficient Catalystsin Organic Synthesis

By:

Zahra Rashidi

In this thesis two new applications of N, N-bis (2-hydroxyphenyl) pyridine 2,6-dicarboxamide [BHPPDAH] complexes are investigated:

A: Application of reusable [Zn(BHPPDAH)] as an efficient heterogeneous catalyst for a facile, one-pot, three-component synthesis of propargylamine derivatives.

B: Application of reusable [Cu(BHPPDAH)] as an efficient heterogeneous catalyst for a facile synthesis of chromeno[3,4-*b*]quinoline derivatives under mild condition in "polyethylen glycole" as a green solvent.

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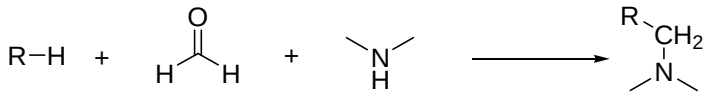
CHAPTER ONE

INTRODUCTION

1.1 Mannich Reaction

Mannich aminomethylation consists of the condensation of a substrate(R-H)possessing at least one active hydrogen (alkyl ketones, phenols, terminal alkyne, NH-heterocycles, etc.) with formaldehyde(or, occasionally, other aldehydes) and a primary or secondary amine(or, occasionally, ammonia) (Scheme 1).



Scheme 1

Studies on the chemistry of Mannich bases are of interest in various areas of application such as:

-A large number of aminoalkyl derivatives have been prepared in order to correlate their structure and reactivity with their pharmacological activity. Particularly, noteworthy are some general studies such as those concerning cytostatic Mannich bases derived from, e. g., bis-[2-chloroethyl]-amine, melamine, or ethylenediamines, and those regarding Mannich base derivatives possessing antimicrobial or cardiotonic activity.

- Mannich bases represent easily obtainable intermediate for the synthesis of other compounds, such as heterocycles, amino-alcohols, etc.

- Finally, Mannich bases have been investigated as potential biological agents, as dyes for synthetic fibres, as reactive dyes, and also as surface active compounds.

1.1.1.Propargylamines

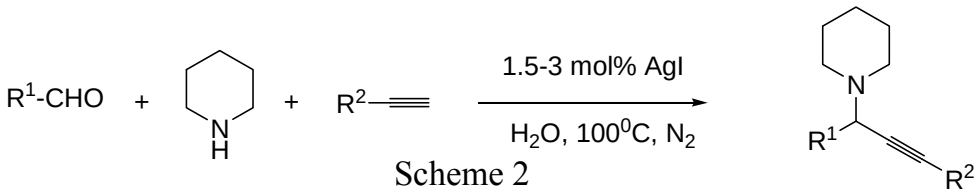
Propargylamines can be easily formed via a Mannich reaction by mixing terminal alkyne, aldehyde, and amine (three component condensation), or addition of alkynes to imines. Propargylamines are frequent skeletons[1] and synthetically versatile key intermediates[2] for the preparation of many nitrogen-containing biologically active compounds such as β-lactams, oxotremorine analogues, conformationally restricted peptides, isosteres, natural products, and therapeutic drug molecules.[3]

Traditionally these compounds have been synthesized by nucleophilic attack of lithium acetylides or Grignard reagents to imines or their derivatives. However these reagents must be used in stoichiometric amounts, are highly moisture sensitive, and sensitive functionalities such as esters are not tolerated. Therefore, the most convenient synthetic method for preparing propargylamines has been the Mannich one-pot three component coupling reaction of an aldehyde, a secondary amine and a terminal alkyne. The reactions are usually performed in polar solvents (mostly dioxane) and in the presence of a catalytic amount of a copper salt (CuCl, $Cu(OAc)_2$)[4]which increases the nucleophilicity of the acetylenic substrate towards the Mannich reaction.

A variety of transition metals such as Ag^I salts[5], Au^I/Au^{III} salts[6], Au^{III} salen complexes[7], Cu^1 salts[8], Ir complexes[9], $InCl_3$[10], Hg_2Cl_2[11] and Cu/Ru^{II} bimetallic system[12] have been employed as catalysts under homogeneous conditions. In addition, alternative energy sources like microwave[13] and ultrasonic[14] radiations have been used in the presence of Cu^I salts.

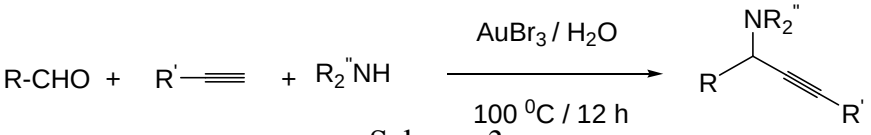
Several examples of propargylamines synthesis under homogeneous system have been reported such as:

Silver iodide was used as a homogeneous catalyst by C. Wei *et al*. for generate propargylamine in water (Scheme2).[15]



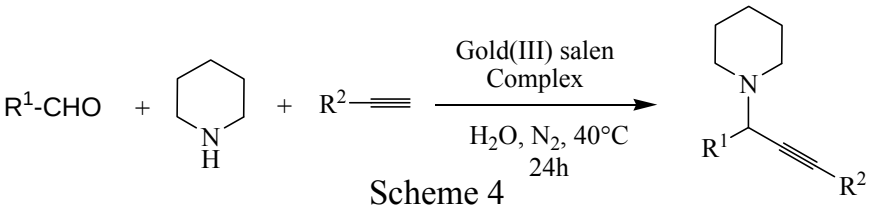
Scheme 2

C. Wei *et al*. also reported a golgd catalyzed Mannich reaction in water (Scheme3).[16]



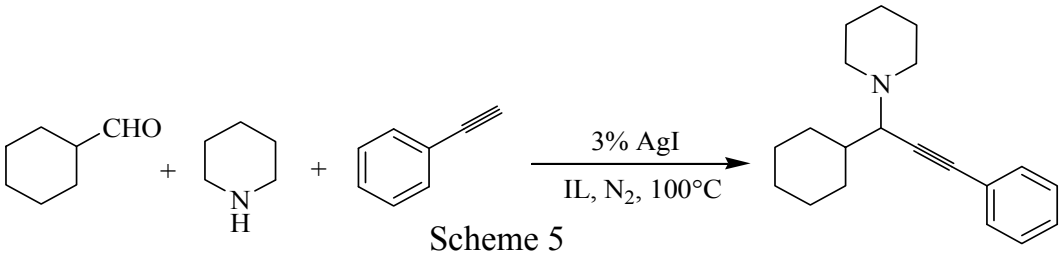
Scheme 3

M. K. Wong *et al.* synthesized a series of propargylamines derivatives by Mannich reaction of aldehydes, amines, and alkynes catalyzed by gold(III)salen complexes in water at 40 °C(Scheme4).[17]



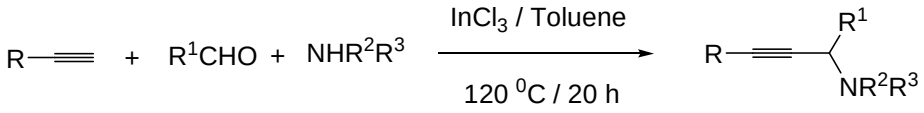
Scheme 4

Z. Li and co-workers reported a highly efficient three-component coupling reaction through C–H activation using salts of silver in ionic liquids (Scheme 5).[18]



Scheme 5

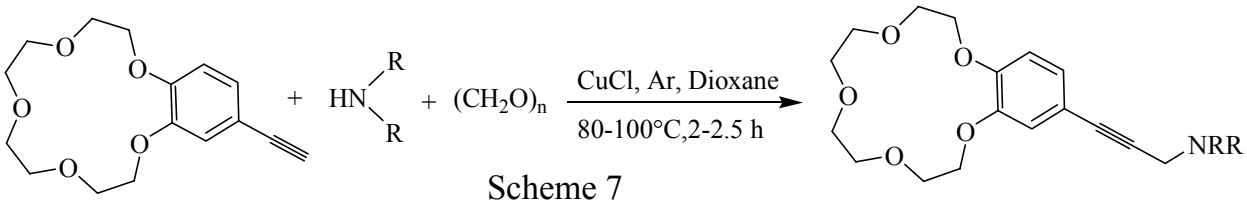
Lei Wang *et al.* reported an indium catalyzed three-component coupling reaction in toluene (Scheme 6).[19]



Scheme 6

C. J. Li *et al.* used Cu /Ru^{II} as a bimetallic catalyst to generate propargylamine in water.[20]

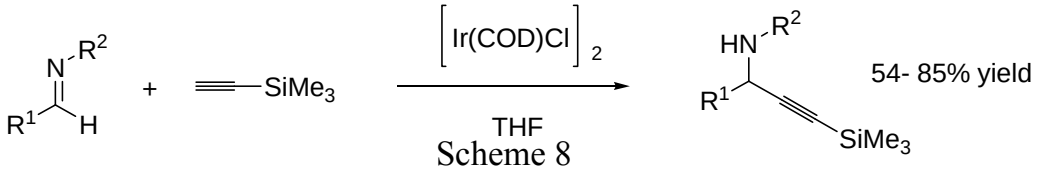
The copper-catalysed aminomethylation of ethynylcrown ethers was performed in dioxane under argon atomespher (Scheme 7).[21]



Scheme 7

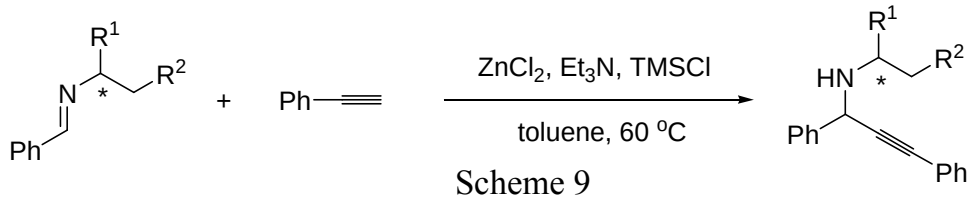
Another way for synthesis of propargylamines in the presence of homogenous catalyst, is addition of alkynes to imines:

Carreira developed a process to prepare propargylamine involving the direct addition of trimethylsilylacetylene to *N*-alkyl or *N*-aryl aldimines in the presence of the $[Ir(COD)Cl]_2$ catalyst.The additions can be carried out under neat conditions to provide a highly atom-economical process. However, only silylacetylenes were reactive for this addition reaction (Scheme 8).[22]



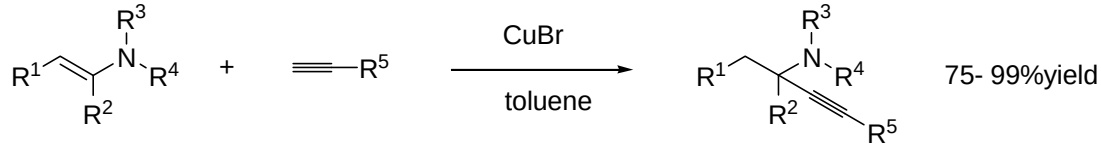
Scheme 8

Jiang*et al.* reported the addition of terminal alkynes to imines by using $ZnCl_2$ and Et_3N as catalysts and TMSCl as the Lewis acid for the activation of imines(Scheme 9).[23]



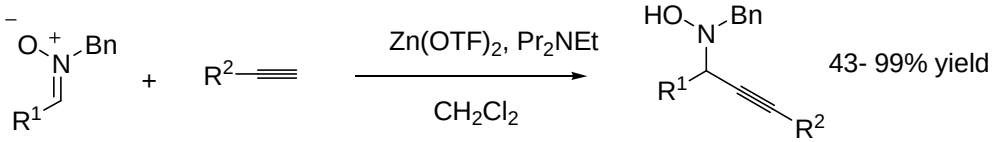
Scheme 9

Knochel *et al.* reported an enantioselective synthesis of propargylamines by copper-catalyzed addition of alkynes to enamines (Scheme 10).[24]



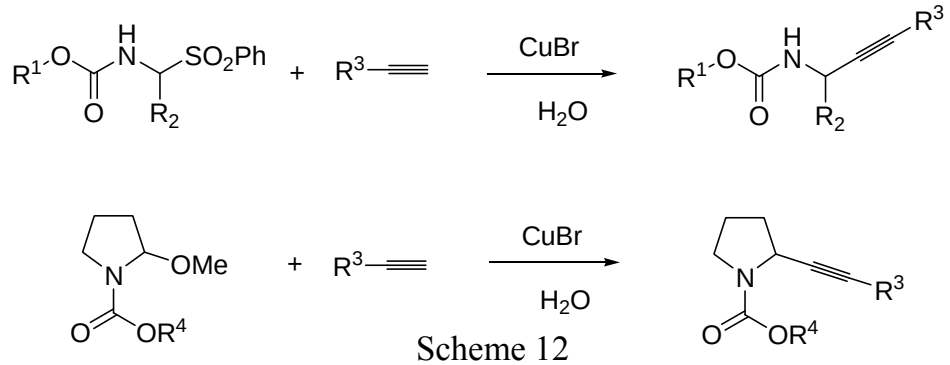
Scheme 10

Carreira *et al.* used a Zn(II)- catalyzed process in CH_2Cl_2 for the addition of terminal alkynes to nitrones to form propargyl *N*-hydroxyl amine adducts(Scheme 11).[25]



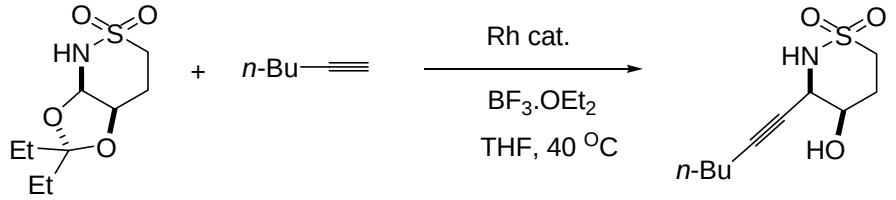
Scheme 11

Zhang, J. H. and coworker reported a copper-mediated coupling of alkyneswith *N*-acylimines and *N*-acyliminium ions in water to generate propargylamide derivatives (Scheme 12).[26]



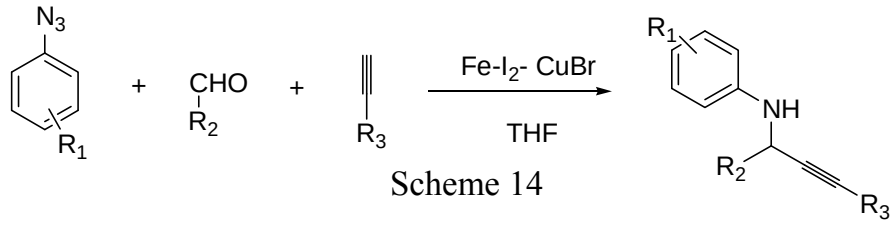
Scheme 12

DuBois and co-workers reported a stereocontrolled synthesis of functionalized propargylic amine derivatives from *N,O*-acetals and alkynylzinc reagent (generated from trans-metalation of the lithium acetylide with $ZnCl_2$) by Rh-catalyzed C-H insertion(Scheme 13).[27]



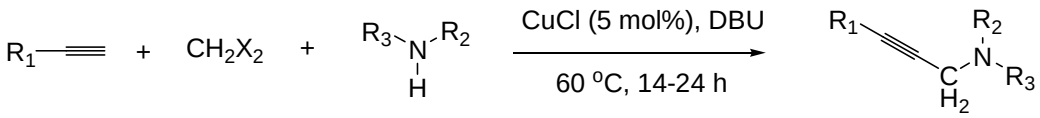
Scheme 13

You Huang *et al.* developed a method for the synthesis of propargylamines through a three-component coupling of aryl azides, aldehydes, and alkynes in the presence of iron–iodine–copper(I) bromide as catalyst (Scheme 14).[28]



Scheme 14

The Mannich reaction of alkynes, dihalomethanes and amines in the presence of CuCl gives propargylamine derivatives (Scheme 15).[29]



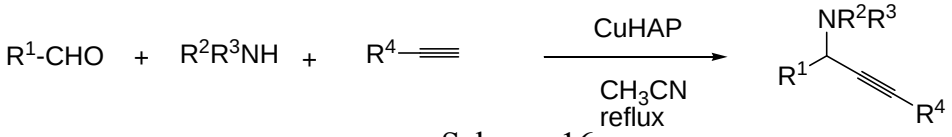
Scheme 15

However, operating under homogenous media two main drawbacks must be considered: the difficulty to recover and reuse the catalyst and the possible absorption of some of the metal catalyst on the final product (fine chemical). Currently the upper tolerance limit for the contamination of drugs or other compounds set aside for human consumption by transition

metals is 5 ppm and future regulations are expected to lower this threshold to the ppb range.

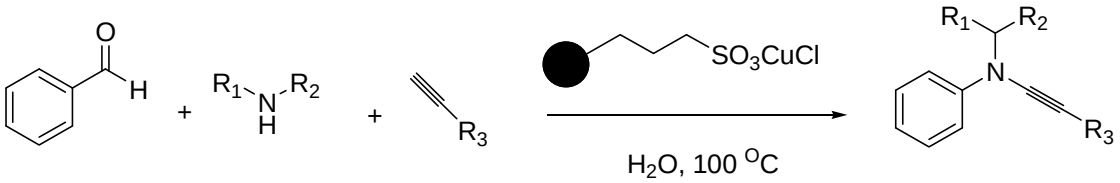
In order to achieve the recyclability of transition metal catalysts, some heterogeneous catalysts have been used to obtain propargylamines such as:

1) Different metal exchanged hydroxyapatites (metal–HAP) are able to catalyze the condensation of benzaldehyde, piperidine and phenylacetylene in acetonitrile under reflux temperature.Cu–HAP have the best result and was reused several times showing consistent activity even after the fourth cycle(Scheme 16).[30]



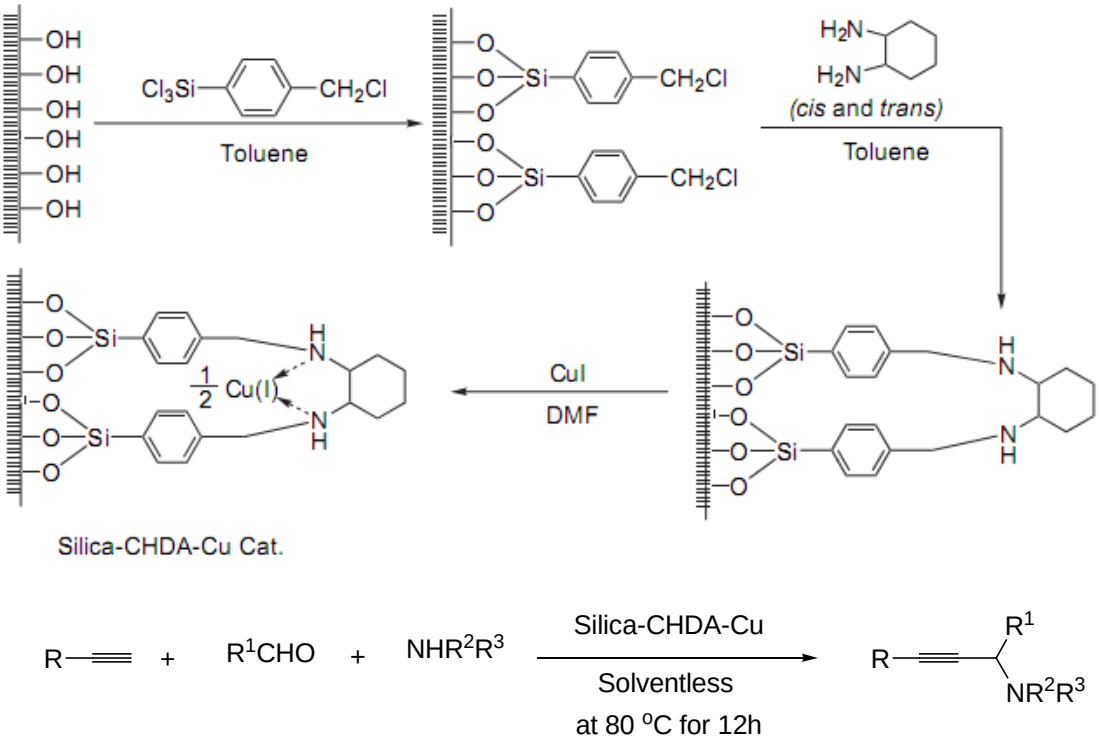
Scheme 16

2) Silica gel anchored copper chloride has been described by Sreedhar *et al*. as an efficient catalyst for the synthesis of propargylamines via C–H activation (Scheme 17).[31]



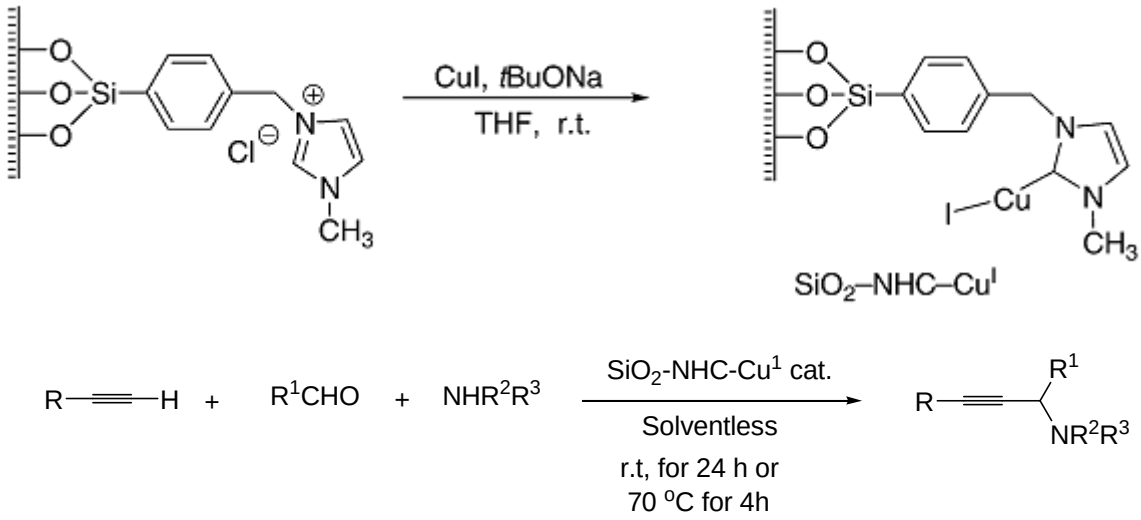
Scheme 17

3) Immobilized Cu(I) on organic–inorganic hybrid materials was prepared by Li *et al*. Reactions performed in the absence of solvent and the catalyst remained active through at least 15 consecutive runs. The silica gel immobilized copper catalyst was prepared according to the four-step procedure summarized in Scheme 18. Others immobilized metals such a Ag(I) and Au(I) exhibited lower activity than Cu catalysts while silica supported Pd(II) failed in this reaction. [32]



Scheme 18

4) Recently Wang *et al*. have reported a novel silica-immobilizedN-heterocyclic carbene metal complex (Si–NHC–CuI) as anefficient and reusable catalyst for the synthesis of propargylamines (Scheme 19).[33]

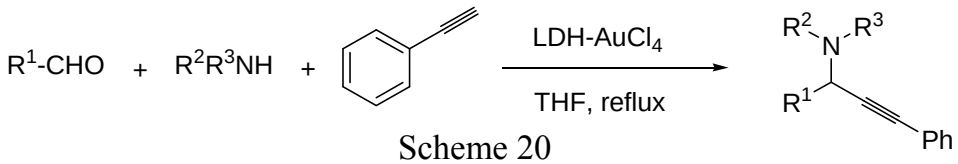


Scheme 19

5) Cu/C nanoparticles have also been used by Sharghi *et al*. as active and recyclable catalysts in the synthesis of propargylamines following the Mannich protocol. The reaction proceed in water at room temperature. Different amines and terminal alkynes was used and a range of propargylamine was obtained.[34]

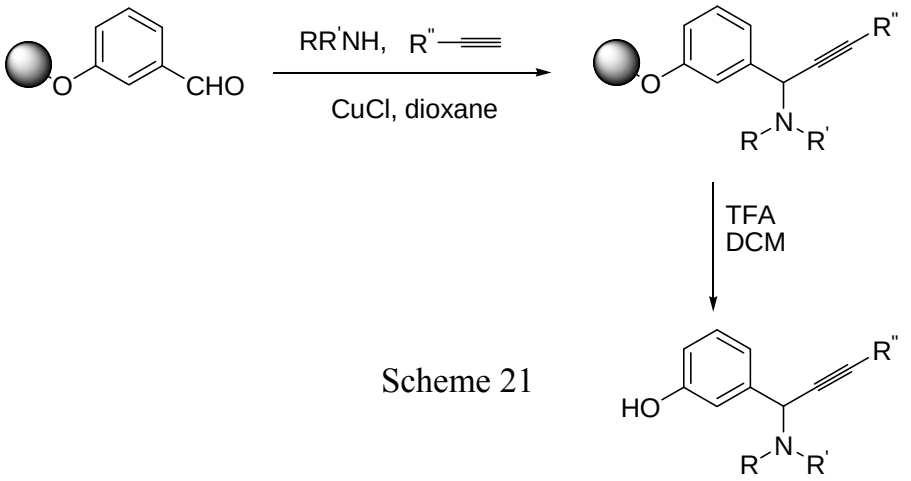
6) A silver salt of 12-tungstophosphoric acid (AgTPA) has been reported by Reddy and coworkers as a heterogeneous catalyst to prepare different propargylamines via a three component coupling reaction in good yields. [35]

7) Kantam *et al*. reported the use of a gold support onto a layered double hydroxide (LDH–$AuCl_4$) for the Mannich reaction. A range of propargylamines was obtained in excellent yields (89–93%) at reflux of THF. However a significant deactivation of LDH–$AuCl_4$ after the second and third reuse was detected (Scheme 20).[36]



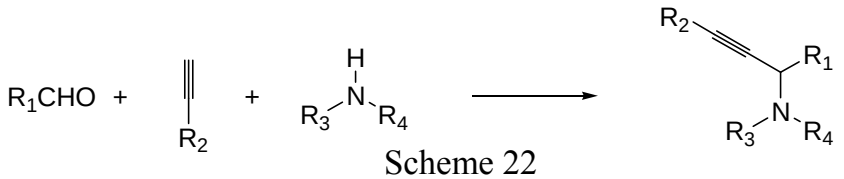
Scheme 20

8) McNally and co-workers report the Solid Phase Organic Synthesis (SPOS) Mannich reaction where either the aldehyde or the amine could be attached to the solid support. For example 3-hydroxybenzaldehyde was attached to the Wang resin to furnish polymer-bound aldehyde and the Mannich reaction of a secondary amine and terminal alkyne with the supported aldehyde occurred by applying CuCl in dioxane at 70-75 °C. The substituted propargylamines could be cleaved from the resin with triftuoroacetic acid (TFA) in dichloromethane (DCM) (Scheme 21).[37]



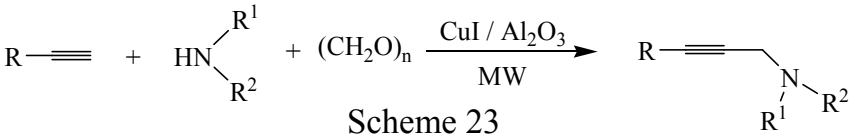
Scheme 21

9) Raimondo Maggi *et al.* showed that Ag-NaY zeolite can be utilized as an efficient heterogeneous catalyst for the ecoefficient preparation of propargylamines following a threecomponent strategy (Scheme 22).[38]



Scheme 22

10) A microwave-enhanced, solventless Mannich condensation of terminal alkynes and secondary amines with *para*-formaldehyde on cuprous iodide doped alumina has been developed (Scheme 23).[39]



Scheme 23

11) Different metal-supported zeolites such as Cu-modifiedzeolites (H–USY, HY, H–Beta, Mordenite and ZSM-5), havebeen successfully used for the synthesis of propargylamines. Cu^{I}–USY catalyst has the best result and could be recycled up to four timesthough long reaction times (15 h) were required.Different metal exchanged zeolites (Cu–NaY, Ag–NaYand Au–

NaY) were prepared by conventional ion exchangemethod and used as a catalyst in the synthesis of substituted propargylamines.[40]

12) I. Luz *et al.*found that Cu–MOFs were active andselective solid catalysts for the A^3 coupling ofaldehydes, amines and alkynes.One type ofcoordination polymers are the so-called metal–organic frameworks(MOFs) in where metal nodes are connected by organic linkersthrough strong coordination bonds in a tridimensional net,forming crystalline, hybrid microporous materials. Examples of such materials are $[Cu(2\text{-pymo})_2]$ and $[Cu(im)_2]$(2-pymo = 2-hydroxypyrimidinolate; im = imidazolate).The Cu–MOF catalyst deactivatesbecause of a loss of crystallinity, but the original activity was restored by treating with DMF at reflux andregenerating the initial MOF structure.[41]

13) Corma *et al.*reported thatAu nanoparticlessupported on nanocrystalline ZrO_2 and $CeO_2$are an active andrecyclable catalyst for coupling benzaldehyde, piperidine andphenylacetylene.Different studies and theoretical calculations have evidenced thatcationic gold species can be stabilized on ZrO_2 and CeO_2 but noton other supports.[42]

14) 1,4-dihydroxyanthraquinone-copper(II) complexe was prepared by Sharghi *et al.* for the synthesis of different propargylamines under solvent free conditions.[43a]Furthermore, graphite,[43b] CaO[43c] and $CaCl_2$[43d] were used in Mannich reaction as heterogeneous catalysts for synthesis of various lariat ethers.

Table 1 summarizes the results obtained in the multicomponent reaction (MCR) of benzaldehyde,piperidine, and phenylacetylene using different solid catalysts.

Table 1.

Catalyst	Yield (%)	Solvent	T ºC	t (h)	Ref.
Cu–HAP	85	CH_3CN	reflux	6	30
Silica gel CuCl	86	H_2O	reflux	10	31
SiCHDA–Cu[1]	92	_	80	12	32
SiNHC–Cu[1]	79-91	_	rt	24	33
Cu/C	90	H_2O	rt	3	34
AgTPA	92	CH_3CN	80	6	35
LDH–$AuCl_4$	92	THF	reflux	5	36
SPOS	65	Dioxane	75	12	37
Ag–NaY	81	_	100	15	38
USY–Cu[1]	95	_	80	15	40
Ni–HY	85	_	80	10	40
Cu-MOFs	30-90	Dioxane	50	4-48	41
Au/CeO_2	>99	H_2O	100	6	42

1.2. Chromenoquinolines

Heterocyclic compounds constitute the largest and diverse family of organiccompounds. A substantial number of them occur widely in naturc and exhibitprofound biological activity. As a consequence, many of the drug molecules used in therapy today are heterocycles.[44] Among the heterocyclic compounds, oxygen hetcrocycles are spccial because of their wide occurrence as a part structure of carbohydrates. The low molecular weight oxygen heterocycles find application as solvents and synthetic intermcdiates. Some of the fundamental small ring oxygen heterocycles are epoxide (3-member), oxetane (4-member), tetrahydrofuran (THF; 5-member) and tetrahydropyran (6-member).

Compounds in which a benzene and pyran ring are fused together with various levels of saturation and oxidation are very common in nature.[45]The