



Synthesis of quinoxaline derivatives from terminal alkynes and *o*-phenylenediamines by using copper alumina catalyst

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Abstract. An efficient method for the synthesis of quinoxaline derivatives through oxidative coupling of *o*-phenylenediamines (OPD) with terminal alkynes by using copper-alumina (Cu-Al) catalyst was described. A series of Cu-Al catalysts with different mole ratios of Cu²⁺/Al³⁺, 2:1 (Cu-Al-1), 2.5:1 (Cu-Al-2) and 3:1 (Cu-Al-3) were prepared by co-precipitation method followed by calcination and their activity was checked for the synthesis of quinoxaline derivatives. Cu-Al-2 showed excellent activity at 60 °C in presence of K₂CO₃. The catalyst is inexpensive, recyclable and environmentally benign. The fresh and recycled catalysts were characterized by different analytical techniques. Different reaction parameters were optimized; catalyst screening, solvent, base and temperature. The protocol was extended towards different substrates.

Keywords. Copper alumina catalyst; heterogeneous catalyst; quinoxaline; oxidative coupling; *O*-phenylenediamines.

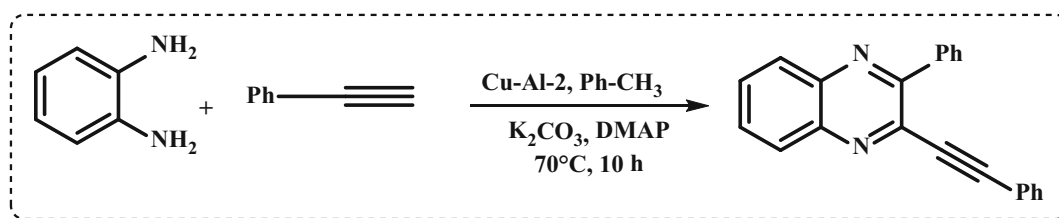
1. Introduction

Over the last few decades, heterocyclic compounds have occupied a prominent place in organic chemistry. Quinoxaline derivatives are one of the important biologically active heterocyclic compounds within which benzene and pyrazine rings are clubbed together.^{1,2} It has evoked considerable attention as they exhibit pharmacological activity; antibacterial, antifungal, antiviral, antimicrobial, antimalarial, anti-inflammatory, antidepressant and anticancer activity.^{3–6} Quinoxaline derivatives are also used in agriculture⁷ (fungicides, herbicides, and insecticides), dye industries and as corrosion inhibitors.^{8,9} Further, quinoxaline derivatives are building blocks of antibiotics such as levomycin, actinomycin and echinomycin. They control the growth of Gram-positive bacteria and exhibit antitumor activity.¹⁰ Thus, these intermediates have shown significant importance as target molecules in organic chemistry and became an attractive topic for research in academia as well as industrial point of view.

A variety of synthetic methodologies are available for construction of skeleton of such heterocyclic molecules. Among these, most widely used methods for the synthesis of quinoxaline derivatives involve the condensation of 1,2-dicarbonylic compounds and α -diketones with *o*-phenylenediamine (OPD) as a common starting material in the presence of transition metal catalysts.^{11–15} They can also be synthesized by oxidative coupling of OPD with 1,2-diols,^{16,17} ethanolamine,¹⁸ and epoxides.¹⁹ These synthetic methods have some drawbacks, use of strong acids, oxidants, costlier reagents, elevated temperature, and long reaction time. Thus, there is a need to develop an economical methodology with a reusable and robust catalyst for the synthesis of quinoxaline derivatives. In recent years, efforts are made to improve the synthesis of different quinoxaline derivatives with slight modification in the core structure of quinoxalines. These derivatives can be used as active molecules in pharmaceuticals. 2-phenyl-3-(phenylethynyl)-quinoxaline is one of such compounds. In literature, these compounds have been

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Scheme 1. Terminal alkynes with OPD for the synthesis of quinoxalines.

synthesized by different routes. Wang *et al.*,²⁰ have reported $\text{Fe}_3\text{O}_4@\text{Cu}_2\text{O}$ supported on the graphene oxide heterogeneous catalyst with Cs_2CO_3 as a base, Chen *et al.*,²¹ and Zhang *et al.*,²² reported $\text{Cu}(\text{OAc})_2$ and CuCl as homogeneous catalysts for the synthesis of quinoxaline derivatives, respectively. Homogeneous catalysts require tedious workup procedures and effluent treatment problems. Thus, there is still scope for the development of catalysts for the synthesis of quinoxaline derivatives.

Our efforts were to develop a simple and robust Cu based catalyst. Thus, synthesis of quinoxaline derivatives over copper-alumina catalyst was explored.^{23–27} Cu-Al possesses excellent catalytic activity for several reactions such as amination of alcohol,²⁸ Michel addition²⁹ and coupling reactions.³⁰

In this protocol, our aim was to develop a cost-efficient, sustainable and economical process for the synthesis of quinoxaline derivatives. We synthesized different Cu-Al catalysts with varying ratios of $\text{Cu}^{2+}/\text{Al}^{3+}$, 2:1 (Cu-Al-1), 2.5:1 (Cu-Al-2) and 3:1 (Cu-Al-3) by co-precipitation method followed by calcination and their activity was studied for the quinoxaline derivatives synthesis by coupling of OPD with phenylacetylene as a model reaction (Scheme 1). In this reaction, Cu-Al-2 showed excellent activity towards the desired product with wide substrate scope in the synthesis of the quinoxaline derivatives.

2. Experimental

2.1 Chemicals

All chemicals were purchased from reputed firms; Alfa Aesar, Merck, High-Media and used as such without further purification. Phenylacetylene (and substituted phenylacetylene), o-phenylenediamine (OPD) (and substituted OPD), 4-Dimethylaminopyridine (DMAP), potassium carbonate (K_2CO_3), toluene, $\text{Cu}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$, $\text{Al}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ and NaOH .

2.2 Catalyst preparation and characterisation

The series of Cu-Al/hydroxalicates (HT) with different mole ratios of $\text{Cu}^{2+}/\text{Al}^{3+}$, 2:1 (HT-1), 2.5:1 (HT-2) and 3:1 (HT-

3) were prepared by co-precipitation method as described in previous synthesis methods^{31,32} and calcined before using them to obtain copper-alumina catalysts in the synthesis of quinoxaline derivatives. Detail synthesis process is mentioned in ESI†. Further, the catalysts were well-characterized by XRD (1730 series Phillips Diffractometer with Cu-K α radiation), surface area and porosity by N_2 adsorption desorption isotherm (Micromeritics ASAP 2020 instrument at 77.25 K), morphology and chemical composition by SEM and EDXA (JEOL-JSM 6380 LA instrument) and XPS (Thermo Scientific K – α XPS spectrometer and Al K α ($E = 1486.6$ eV) radiation).

2.3 General synthesis procedure for quinoxaline derivative

In a generalised process, 15 mL Schlenk tube was charged with OPD (1 mmol), terminal alkyne (2.2 mmol), K_2CO_3 (2.2 mmol w.r.t. limiting reactant), 4-dimethylaminopyridine (DMAP) (2.2 mmol), 10 wt.% of catalyst and chlorobenzene (5 mL). The resulting solution was agitated at 70°C for 10 h and progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled and extracted with ethyl acetate ($3 \times 30\text{ mL}$), washed with $2 \times 20\text{ mL}$ water and brine. The ethyl acetate layer was separated and dried over anhydrous sodium sulphate. Ethyl acetate was evaporated under reduced pressure to get crude oily mass. It was further purified by silica gel (60–120 mesh) column chromatography using a mixture of ethyl acetate and hexane (1:10) as an eluent. The ^1H and ^{13}C -NMR were recorded.

3. Results and Discussion

3.1 XRD

Figure 1(a–c) shows the XRD diffraction patterns of the calcined Cu-Al catalyst with different Cu/Al molar ratios; 2:1, 2.5:1 and 3:1, respectively. The diffraction spectra of Cu-Al-1, Cu-Al-2 and Cu-Al-3 show sharp peaks, which indicate the crystalline nature of the material. Dominant phase of CuO was found and no diffraction pattern of Al_2O_3 phase was observed.³³ Cu-Al catalyst shows diffraction pattern due to CuO at 2θ 35.6° , 38.8° , 48.8° , 53.6° , 58.5° , 61.5° , 66.3° , 68.1° and 75.4° [JCPDS card no: 33-0448].^{34,35} The catalyst

from the 4th cycle was also analyzed by XRD and it shows no significant change in the XRD pattern even after reuse (Figure 1d).

3.2 XPS

Chemical integrity and oxidation state of the catalyst was studied by XPS analysis. Survey spectra of Cu-Al-2 showed their respective elements Al and Cu (Figure 2a–b). High-resolution spectra of Cu-Al-2 shows Cu $2p_{3/2}$ and Cu $2p_{1/2}$ level binding energy appeared at 934.3 and 954.0 eV, respectively. These values correspond to the presence of Cu^{2+} chemical state as an indication for the formation of CuO on the surface of the oxidized sample. The satellite peak of Cu $2p_{3/2}$ and Cu $2p_{1/2}$ at 942.5 and 962.6 eV, respectively confirmed the formation of Cu^{2+} on the surface of the catalyst (Figure 2a).³⁶ Alumina exhibited sharp peaks namely, Al ($2p_{3/2}$) at binding energy 74.12 eV associated with the Al_2O_3 (Figure 2b).³⁷

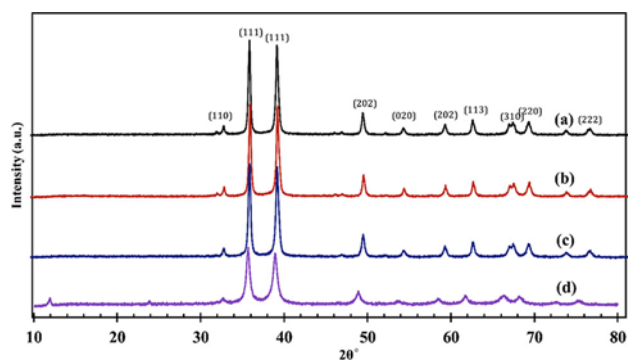


Figure 1. XRD of (a) Cu-Al-1 (b) Cu-Al-2 (c) Cu-Al-3 (d) 4th cycle Cu-Al-2.

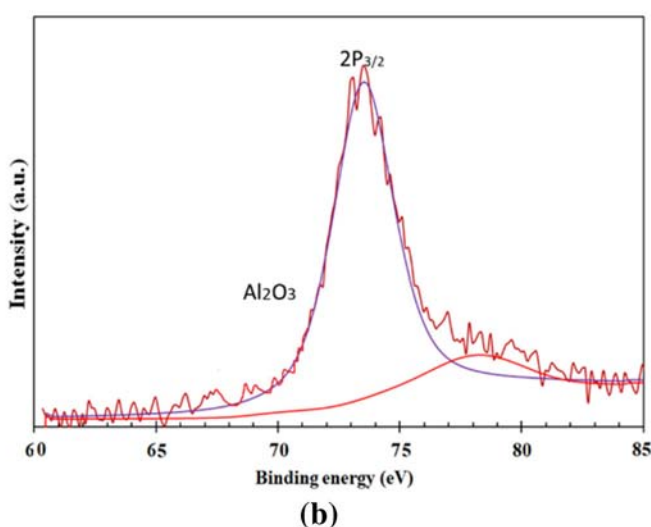
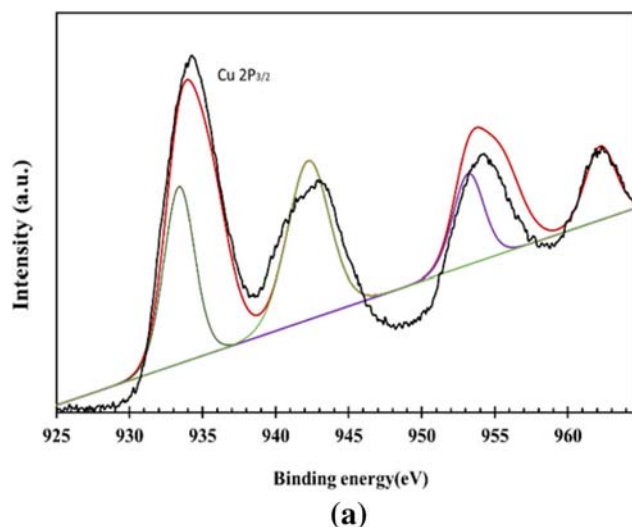


Figure 2. XPS of Cu-Al-2 (a) Cu 2p spectra (b) Al 2p spectra.

3.3 N_2 adsorption-desorption isotherm

N_2 adsorption-desorption isotherm of series of Cu-Al catalysts shows type IV isotherm with H3 type hysteresis loop. The surface area, pore volume and average pore size of Cu-Al-1, Cu-Al-2 and Cu-Al-3 are listed in Table 1 and Figure S1. The desorption isotherm with lagging loop at high pressure indicates that N_2 adsorption was mainly due to the pores with a small diameter.

3.4 Surface morphology (SEM)

Topography of series of Cu-Al-1, Cu-Al-2 and Cu-Al-3 show agglomerated particles. No significant change in morphology was observed for the different ratios of $\text{Cu}^{2+}/\text{Al}^{3+}$ (2, 2.5 and 3) (Figure 3a–c). The reused catalyst was also analyzed by SEM and it does not show any change in morphology (Figure S2). EDX analysis of the catalysts is consistent with the elemental composition of Cu, Al and O, with respective percentage as shown in Table 2.

3.5 FTIR

The broad peaks at $3400\text{--}3500\text{ cm}^{-1}$ of Cu-Al-1, Cu-Al-2 and Cu-Al-3 can be assigned to the stretching mode of

Table 1. N_2 adsorption-desorption isotherm for Cu-Al catalyst.

Catalyst	Surface area	Pore size (Å°)	Pore volume (cm^3/g)
Cu-Al-1	55.6	199.5	0.24
Cu-Al-2	73.1	230.2	0.38
Cu-Al-3	63.8	178.2	0.23

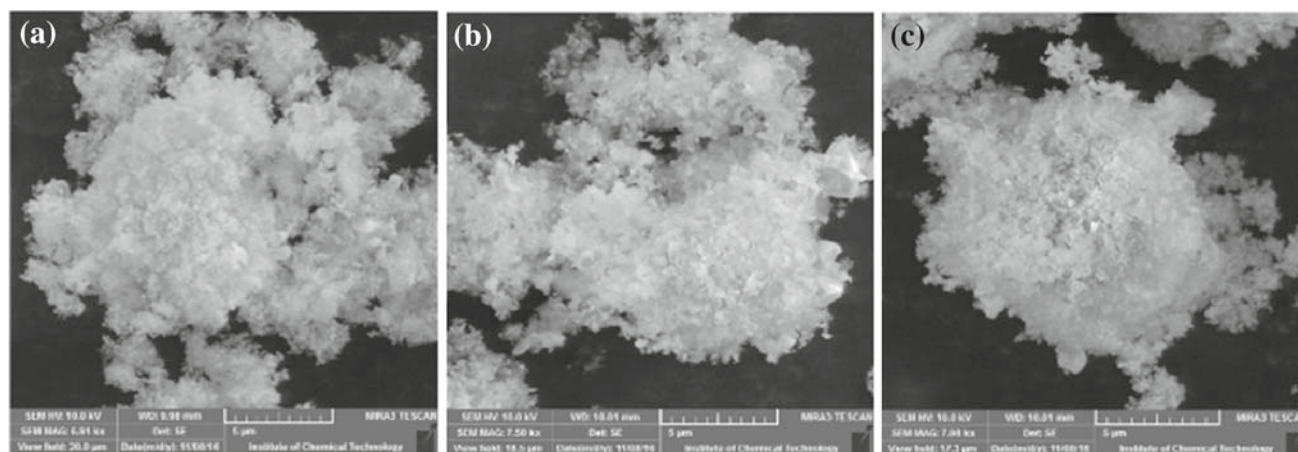


Figure 3. SEM of (a) Cu-Al-1 (b) Cu-Al-2 (c) Cu-Al-3.

Table 2. EDX of Cu-Al catalyst.

Catalyst	Copper (%)	Aluminium (%)
Cu-Al-1 (2:1)	10.66	5.21
Cu-Al-2 (2.5:1)	15.27	5.97
Cu-Al-3 (3:1)	26.48	9.37

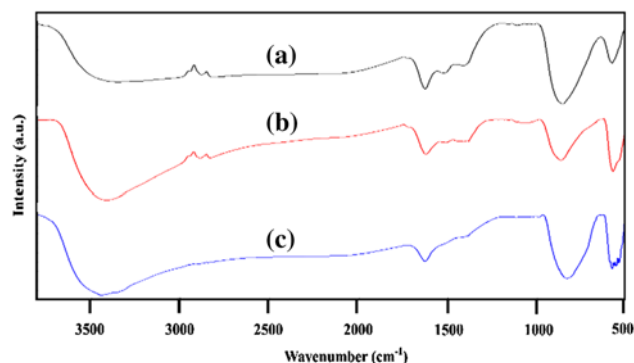


Figure 4. FTIR of (a) Cu-Al-1 (b) Cu-Al-3 (c) Cu-Al-2.

hydrogen-bonded hydroxyl groups from the interlayer water molecules. There are two IR active absorption bands observed at 890–850 and 573–580 cm^{-1} corresponding to amorphous alumina.^{38,39} The ν Al–O stretching vibration at 890–850 cm^{-1} and the δ Al–O bending vibration at around 573–580 cm^{-1} may be assigned to the octahedrally coordinated oxygens around aluminium⁴⁰ (Figure 4).

3.6 Optimization of reaction parameters

To optimize the reaction parameters, oxidative coupling of OPD with phenylacetylene was studied as a model reaction (Scheme 1). Various reaction parameters such

as the effect of catalyst, reaction temperature, solvents and bases were systematically studied.

Cu-Al with 10 wt.% catalyst loading, different compositions were screened (Cu-Al-1, Cu-Al-2 and Cu-Al-3) using toluene as solvent at 60 °C. After 12 h of reaction time, we got 12, 21 and 24% yield of the desired product with Cu-Al-1, Cu-Al-2 and Cu-Al-3, respectively (Table 3, #1–3). Insignificant change in the yield was observed for Cu-Al-2 and Cu-Al-3. Thus, further studies were carried out using a Cu-Al-2 catalyst. The temperature has a strong influence on the rate of reaction. Thus, we studied this coupling reaction in the range of 60–80 °C. We found that at 80 °C, self-condensation of phenylacetylene overcomes the rate of formation of the desired product, hence we got lower yield (Table 3, #4–5). Thus, 70 °C was optimized as temperature for reaction. The selection of solvent can have a significant effect on the performance of a reaction. Different solvents for the reaction such as toluene, chlorobenzene and ethylene dichloride (EDC) were screened. Among, toluene and chlorobenzene gave better yields as compared to EDC (Table 3, #5–7). This shows that non-polar solvent favoured the coupling reaction. For further studies, toluene was selected over chlorobenzene as it comparatively gave better yields and is environmentally safe.

3.7 Screening of bases

Further, the reaction was carried out in the presence of different bases such as Cs_2CO_3 , K_3PO_4 , Et_3N and K_2CO_3 (Table 3, #8–11). Among these, K_2CO_3 and Cs_2CO_3 afforded the same yield towards the desired product i.e., 61 and 63%, respectively. K_2CO_3 is inexpensive and easy to handle as compared to Cs_2CO_3 . Thus, K_2CO_3 was chosen as the base. Further, we tried DMAP (4-dimethylaminopyridine) as a base with and without K_2CO_3 . It was observed that the yield in toluene

Table 3. Optimization of reaction parameters for cyclization of OPD and phenylacetylene^a.

#	Catalyst	Solvent	Temperature (°C)	Base	Yield ^b (conv.) (%)
1	Cu-Al-1	Toluene	60	–	12
2	Cu-Al-2	Toluene	60	–	21
3	Cu-Al-3	Toluene	60	–	24
4	Cu-Al-2	Toluene	70	–	33
5	Cu-Al-2	Toluene	80	–	30
6	Cu-Al-2	Chlorobenzene	70	–	27
7	Cu-Al-2	EDC	70	–	NR
8	Cu-Al-2	Toluene	70	K ₂ CO ₃	61
9	Cu-Al-2	Toluene	70	K ₃ PO ₄	46
10	Cu-Al-2	Toluene	70	CsCO ₃	63
11	Cu-Al-2	Toluene	70	Et ₃ N	51
12 ^c	Cu-Al-2	Toluene	70	K ₂ CO ₃ + DMAP	95 (100)
13	Cu-Al-2	Toluene	70	DMAP	73
14 ^c	Cu-Al-2	Chlorobenzene	70	K ₂ CO ₃ + DMAP	81 (85)
15	Cu-Al-2	Chlorobenzene	70	K ₂ CO ₃	53
16	Cu-Al-2	Chlorobenzene	70	DMAP	62

^a Reaction conditions: 1 mmol of OPD, 2.2 mmol of phenylacetylene, 10 wt.% catalyst, 2.2 mmol base, reaction temperature 70° C, reaction time 10 h.

^b isolated yield.

^c K₂CO₃ (2.2 mmol) + DMAP (2.2 mmol).

as a solvent was 73% with DMAP as a base and DMAP in combination with K₂CO₃ afforded 95% yield of the desired product (Table 3, # 12–13), but using chlorobenzene as solvent in the presence of both bases i.e. K₂CO₃ and DMAP, the yield dropped to 81% (Table 3 # 14), thus we selected toluene as a solvent for further studies. We have also tried the reactions with K₂CO₃ and DMAP in chloroform, with the desired product yields 53 and 62%, respectively (Table 3 # 15–16).

We concluded that toluene was the best suitable solvent for this reaction and the final optimized reaction conditions were; OPD (1 mmol), phenylacetylene (2.2 mmol), Cu-Al-2 (10 wt.%) catalyst with base K₂CO₃ (2.2 mmol) and DMAP (2.2 mmol) at 70°C for 10 h.

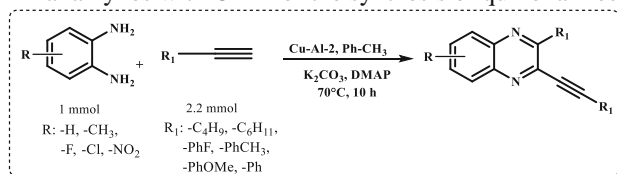
3.8 Substrate study

With the optimized reaction conditions mentioned above, a variety of substrates were studied to check limitation of this reaction using several derivatives of substituted *o*-phenylenediamines and terminal alkynes (Table 4 # 1–15). The terminal aryl alkynes bearing an electron-deficient group such as -F with *o*-phenylenediamine afforded an excellent yield (Table 4 # 1). Electron-rich groups such as -OMe and -Me gave good yields i.e., 56 and 85%, respectively (Table 4 # 2–3). Further, the high yield obtained in *para*-methyl substituted alkyne as compared to *para*-methoxy indicates that strong electron donating group decreases the yield of the desired product. The substrate scope was further extended to aliphatic alkynes such as hexyne and cyclohexyne with

OPD. Considerably good yields of the desired products (Table 4 # 5–6) were obtained. Further, the substrate scope was extended for OPD derivatives (Table 4 # 7–10). OPD bearing an electron-rich group such as -Me, afforded a good yield of the desired product but the strong electron-deficient group such as -NO₂ does not tolerate the reaction, hence no product formation was observed. But it was observed that -F substituted OPD afforded lower yield (Table 4 # 11, 12). Therefore, in case of substituted terminal aryl alkynes, reverse reactivity trend w.r.t. OPD was observed. Hence, we concluded that terminal alkynes with electron-deficient groups afforded excellent yields as compared to the electron-rich species.

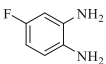
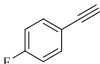
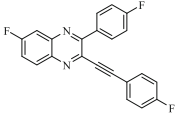
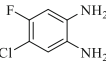

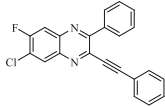
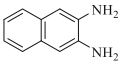

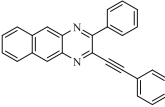
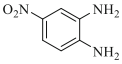

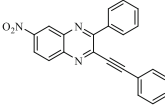
3.9 Reusability of catalyst

Reusability of catalyst is an essential part of cost-efficient and environmentally sustainable processes. As shown in Figure 5, the Cu-Al-2 catalyst was used four times without significant loss in catalytic activity. After each run, the catalyst was recovered by simple filtration and washed with methanol three times. It was dried in an oven at 80°C and used for the next cycle. The heterogeneity of the catalyst was examined by the leaching test. The reaction was stopped after 5 h (solid catalyst removed by filtration) and then the reaction continued with filtrate for next 5 h, No further progress in the reaction was observed. Furthermore, we did the ICP-AES of reaction mass, it was found that leaching of copper is below detection level.

Table 4. Substrate scope of terminal alkynes with OPD for the synthesis of quinoxalines with optimized conditions^a.

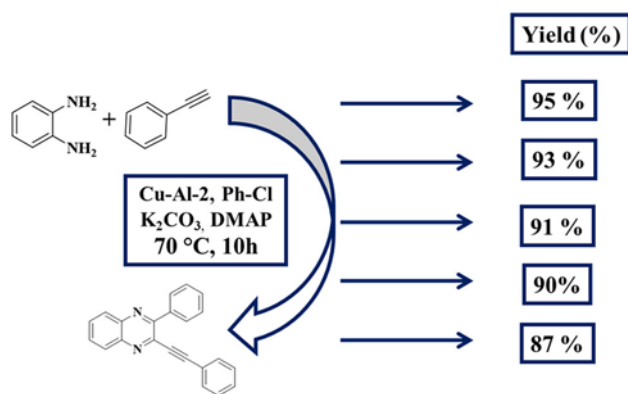
#	OPD	Terminal alkyne	Product	Isolated yield (%) ^b
1				95
2				99
3				78
4				81
5				79
6				74
7				97
8				72
9				92
10				76
11				57

Table 4. (contd.)

#	OPD	Terminal alkyne	Product	Isolated yield (%) ^b
12				62
13				68
14				55
15				NR

^a Reaction conditions: 1 mmol of OPD, 2.2 mmol of phenylacetylene, 10 wt.% catalyst, reaction temperature 70 °C, 2.2 mmol K₂CO₃, 2.2 mmol DMAP and reaction time 10 h.

^b Isolated yield

**Figure 5.** Reusability study of Cu–Al-2 catalyst.

4. Conclusions

In conclusion, an efficient and simple procedure was developed for the synthesis of quinoxaline derivatives over the heterogeneous Cu–Al catalyst. Different catalysts with Cu/Al (2:1, 2.5:1 and 3:1) ratios were synthesized and characterized by various analytical techniques, XRD, SEM, EDX, XPS and N₂ adsorption desorption isotherm. Among all the catalysts, Cu–Al 2.5:1 was found to be most active towards the synthesis of the quinoxaline derivatives. Wide substrate scope is tested for the quinoxaline synthesis with good to excel-

lent yields. The catalyst is robust and recycled up to four cycles without significant loss in activity.

Supplementary Information (SI)

The supporting material provides the product characterization through NMR and SEM spectra of fresh and reused Cu–Al catalyst. Supplementary Information (SI) is available at www.ias.ac/chemsci

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