Tetrahedron Letters 50 (2009) 239–242

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A highly regioselective Cu-exchanged tungstophosphoric acid catalyst for hydroarylation and hydroamination of alkynes

Nayeem Pasha, N. Seshu Babu, K. T. Venkateswara Rao, P. S. Sai Prasad, N. Lingaiah *

Catalysis Laboratory, Inorganic and Physical Chemistry Division, Indian Institute of Chemical Technology, Hyderabad 500 607, India

ARTICLE INFO

Article history:
Received 17 September 2008
Revised 23 October 2008
Accepted 28 October 2008
Available online 31 October 2008

Keywords:
Hydroarylation
Hydroamination
Friedal–Craft's alkenylation
Cu-exchanged tungstophosphoric acid

ABSTRACT

An efficient and reusable Cu-exchanged tungstophosphoric acid catalyst is demonstrated for the solvent free hydroarylation and hydroamination reactions of alkynes with numerous arene and amine derivatives, respectively. The catalyst exhibited exceptionally high activity and regioselectivity in both the reactions.

1. Introduction

The formation of new C–C and C–N bonds is of great importance in both academia and synthetic organic chemistry. The alkenylation of arenes or hydroarylation of alkynes leading to the formation of C–C bonds is an important transformation in the synthesis of pharmaceuticals, agrochemicals, and fine chemicals. Friedel–Craft's alkylation of various arenes, especially electron-rich arenes with alkyl halides, alcohols, or alkenes, involves the formation of new C–C bonds via the alkylation/alkenylation of arenes.[1] On the other hand, C–N bond-forming processes are highly interesting due to the presence of nitrogen-containing molecules as building blocks in industrial applications.

Hydroarylation has received much attention due to its simple approach when compared to existing methods such as Heck reactions,[2] cross-coupling reactions,[3] and olefin cross-metathesis reactions.[4] Alkenylation of arenes with alkynes proceeds via alkenyl carbocation intermediates, which is followed by an electrophilic attack to the arene that can be promoted by Lewis acids. However, due to the instability of vinyl cationic intermediates, the oligomerization of alkynes takes place during the alkenylation[5] of arenes. Some Lewis acid metal chlorides such as $ZrCl_4$ and $AlCl_3$ are known to produce the desired alkenylated products with lower yields.[6] Later, Tsuchimoto et al. reported several metal triflates, $Sc(OTf)_3$, $In(OTf)_3$, and $Zr(OTf)_4$ as catalysts for the alkenylation of arenes with both internal and terminal alkynes through the formation of alkenyl cationic intermediates.[6] Several other transition metal catalysts such as rhodium,[7] ruthenium,[8–10] palladium, platinum,[11–13] gold[14–16] or rare earth-metals,[17] $FeCl_3$,[18] and transitional metal triflates[19–23] in the presence of ionic liquid media also promote the alkenylation of arenes.

On the other hand, the synthesis of nitrogen-containing building blocks has gained significant importance in the pharmaceutical industry. One of the potential approaches for the synthesis of nitrogen-containing molecules is hydroamination, which is an atom-economic process for the formation of amines, enamines, and imines. The hydroamination process converts inexpensive and readily available starting materials into the desired products in a single step reaction without the formation of any other side products. Based on this concern, an efficient hydroamination reaction is always considered economically and environmentally benign. However, the hydroaminations of alkynes can only be achieved in the presence of certain catalysts, as the amines generally do not react spontaneously with alkynes due to the electron-rich nature of both the species. The alkynes are converted into reactive species (enamines and imines), which are reactive intermediates and can be used for various sorts of subsequent transformations. The hydroamination of alkynes has been accomplished with different cationic metals (e.g., Ag^{1+}, Cu^{2+}, Zn^{2+}, and Pd^{2+}) supported on acidic materials such as montmorillonite clay K-10, phosphotungstic acid, and zeolite HBEA.[24–28]

Despite the advantages of the above catalysts in both reactions, a few drawbacks are associated with them such as moisture sensitivity, high cost of metal, difficult catalyst preparation, and low recyclability. Therefore, the use of new, mild, and efficient catalysts remains to be explored for both hydroarylation and hydroamination protocols. As part of our ongoing programs on the use of

---

* Corresponding author. Tel: +91 40 27193163; fax: +91 40 27160923.
E-mail address: nakkalingaiah@iict.res.in (N. Lingaiah).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.10.131

heteropoly acid catalysts for various organic transformations such as hydroamination, hydroarylation and the synthesis of propargyl amines and selective oxidation of alcohols,[24,29–32] we sought to evaluate the feasibility of a Cu-exchanged TPA catalyst for hydroarylation and hydroamination reactions under identical reaction conditions. Herein, we disclose our preliminary findings toward this end.

2. Experimental

2.1. Preparation of Cu-exchanged tungstophosphoric acid catalyst

The copper-exchanged TPA was prepared as a precipitate by adding the required amount of barium hydroxide (to neutralize the three protons) to an aqueous solution of TPA. Later, the Ba ions were replaced by precipitating it as $BaSO_4$ by adding a calculated amount of $CuSO_4{\cdot}6H_2O$ solution. The resultant Cu salt of TPA was recovered from the solution by recrystallization and then oven dried at 120 °C for 12 h. The catalyst was finally calcined at 300 °C for 2 h. The retention of the Keggin structure after the exchange of Cu ions was confirmed by XRD, Laser Raman, and FT-IR analysis.

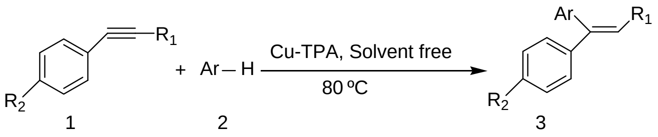
2.2. Catalytic activity measurements: hydroarylation and hydroamination of alkynes

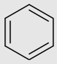
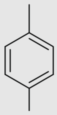
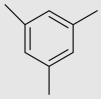
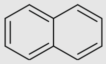
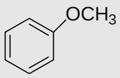
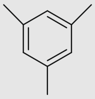
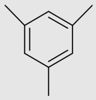
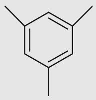
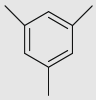
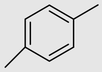
In a general experimental procedure of hydroarylation reaction, 1 mmol of alkyne and 1.1 mmol of arene were taken in a 10 mL round-bottomed flask, and the reaction mixture was allowed to stir at 80 °C under a nitrogen atmosphere. After ensuring the reaction was complete, the crude mixture was filtered to separate the catalyst, and the product mixture was purified by column chromatography. The structure of the purified product was analyzed by ^1H NMR spectroscopy. A similar procedure was adopted for the hydroamination of alkynes with amines, instead of arenes. The structures of the compounds were determined by ^1H NMR spectroscopy, and the data were compared with reports in the existing literature.

3. Results and discussion

The present catalyst is studied for both the C–C (hydroarylation) and C–N (hydroamination) bond-forming reactions under mild and solvent free conditions (Scheme 1). The results obtained from both reactions are shown in Tables 1 and 2, respectively.

Table 1
Hydroarylation of phenyl alkyne derivatives with arenes[a]

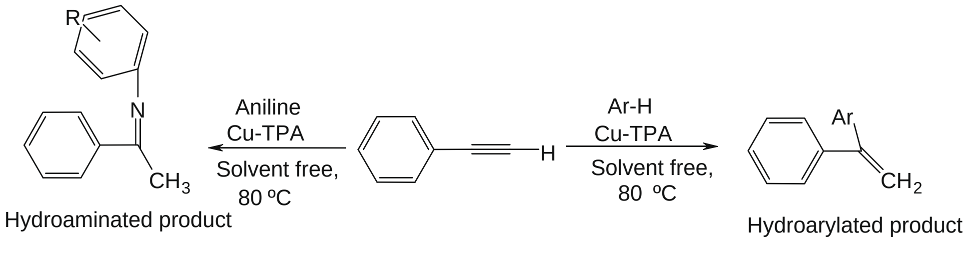


Entry	R_1	R_2	Ar–H	Time (h)	Yield of **3**[b] (%)
1	H	H		6	86
2	H	H		4	89
3	H	H		4	93.91[c]
4	H	H		5	81
5	H	H		4	88
6	H	OMe		3	95
7	H	Me		3	91
8	H	Cl		6	83
9	Ph	H		12	69
10	Ph	H		12	67

[a] *Reaction conditions:* Alkyne derivative (1 mmol); arene derivative (1.1 mmol); catalyst wt: 0.05 g; temperature: 80 °C.
[b] Isolated yields.
[c] Yield determined after 4th reaction cycle.

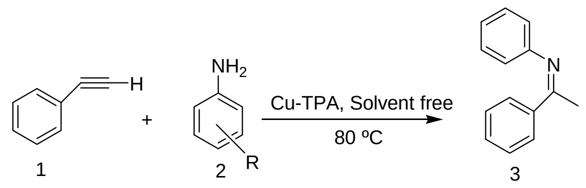
3.1. Hydroarylation of alkynes

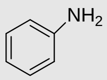
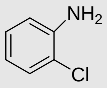
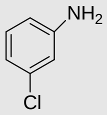
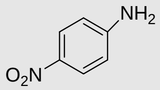
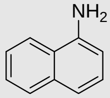
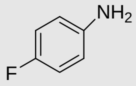
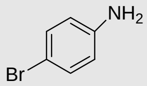
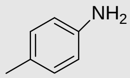
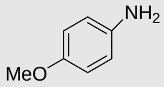
The hydroarylation of various substrates is carried out over Cu–TPA catalysts, and the results are shown in Table 1. The results suggest that the yields of hydroarylated products are varied according to the electronic nature of the arene and alkyne. For example, in the addition of phenyl acetylene to benzene (Table 1, entry 1), the reaction proceeds slowly as compared to *para*-xylene, mesitylene, naphthalene, and anisole (Table 1, entries 2–5). The addition of phenyl acetylene to chlorobenzene (electron-poor arene) results in no net reaction even at longer reaction times (24 h) (not shown in Table 1). This implies that more electron-rich arenes than ben-



Scheme 1. Hydroarylation and hydroamination of alkyne.

Table 2
Hydroamination of phenyl acetylene with various amine derivatives using Cu–TPA catalyst[a]



Entry	Amine	Time (h)	Yield of **3**[b] (%)
1		3	92
2		2.5	95
3		2	93
4		2	97.93[c]
5		2.5	89
6		2	91
7		2	92
8		4	86
9		4	83

[a] *Reaction conditions:* Alkyne derivative (1 mmol); amine derivative (1.1 mmol); catalyst wt: 0.05 g; temperature: 80 °C.

[b] Isolated yields.

[c] Yield determined after 4th reaction cycle.

zene react easily with phenyl acetylene as compared to electron-poor arenes, which is due to the characteristics of electrophilic metallation of the aromatic C–H bond. It clearly demonstrates that the electronic factors of arenes play a prominent role during the hydroarylation of alkynes. In general, selectivity of the hydroarylated product is a challenging task, as the reaction forms both *E* and *Z* isomers. Indeed, in all the reactions, it is interesting to observe that regioselectivity of the resulting hydroarylated product is high (>98:2). With the success of the present catalyst, the substrate scope of electronically varied alkynes is also studied under the same reaction conditions. The terminal alkynes bearing electron-rich groups such as *para*-methoxy and *para*-methyl phenyl acetylene react easier with mesitylene, affording high yields (Table 1, entries 6 and 7), while electron-poor alkynes, that is, *para*-chloro phenyl acetylene reacted relatively slower (Table 1, entry 8). It is noteworthy that the addition of electron-rich arenes such as mesitylene and *para*-xylene to diphenylacetylene also takes place in acceptable yields at their stipulated reaction time (Table 1, entries 9 and 10). The hydroarylation activity of internal alkynes is relatively lower when compared to that of terminal alkynes.

3.2. Hydroamination of alkynes

Based on the results during a hydroarylation reaction using a Cu–TPA catalyst, we sought to evaluate the feasibility of the same catalyst for the hydroamination of alkynes under the same reaction conditions. To our delight, the hydroamination of alkynes with various amines takes place with good to excellent product yields. The results are shown in Table 2. The results reveal that amines bearing electron-withdrawing groups underwent hydroamination with phenyl acetylene quickly as compared to electron-donating amines. For example, in the reaction of phenyl acetylene and aniline, the corresponding ketimine is obtained with 92% yield within 3 h. With the addition of phenyl acetylene to electron-poor aniline derivatives including naphthyl amine, hydroamination takes place to give corresponding ketimines in excellent yields within 2 h of reaction time irrespective of the position of the substituent (Table 2, entries 1–6). The addition of electron-rich amines such as *para*-methyl and *para*-methoxy anilines to phenyl acetylene proceeds at a slower reaction rate, and moderate product yields are obtained compared to electron-poor anilines (Table 2, entries 8 and 9). These results also lead to the conclusion that the electronic nature of the amines plays a vital role in the hydroamination of alkynes as in the case of hydroarylation.

Mechanistic illustrations of hydroarylation and the hydroamination reaction of alkynes are shown in Scheme 2. The hypothesis of the reaction mechanism demonstrates that the presence of cationic Cu species promotes the hydroarylation reaction due to the interaction of Cu with a triple bond of alkynes. Consequently, this undergoes an electrophilic aromatic substitution with arenes to form a vinyl-Cu intermediate (Ib) with the release of H^+ that protonates the complex and forms the product by regenerating the catalyst. Unlike the preceding case, the hydroamination of alkynes proceeds through the coordination of cationic Cu species with amine rather than with alkyne, which subsequently attacks the phenylacetylene resulting enamine intermediate (IIb), which is further transformed into the desired ketimine (IIc).

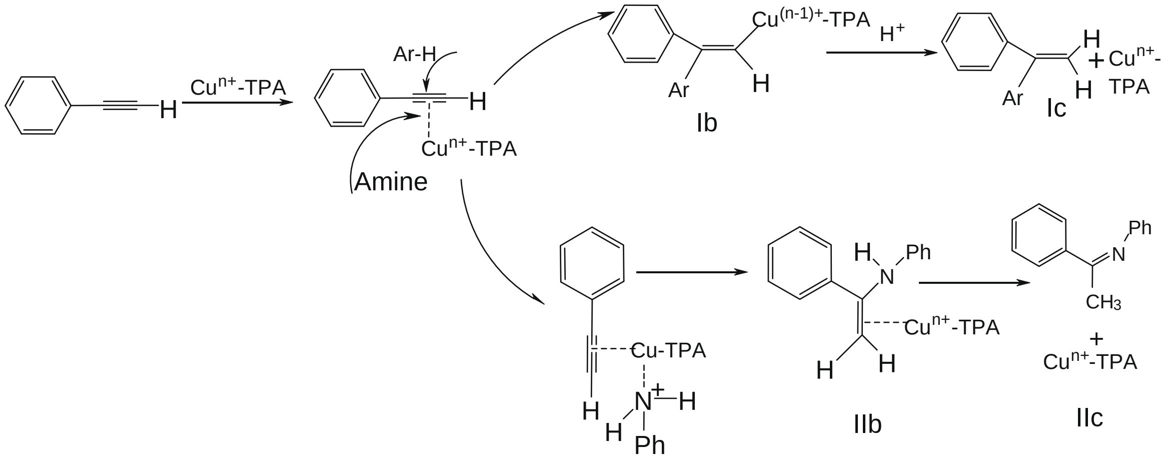
In order to reiterate the significance of the Cu species for hydroarylation and hydroamination reactions, separate experiments were conducted with a Cu-free TPA catalyst under the reaction conditions used in the case of Cu–TPA. The results reveal that the Cu-free TPA catalyst cannot facilitate both the reactions. Thus, it is clear from the above results that the presence of cationic Cu species promotes both hydroarylation and hydroamination reactions.

4. Recycled experiments

The reusability of the catalyst was studied for both hydroarylation and hydroamination reactions. The crude reaction mixture was filtered to separate the catalyst, and washed with dichloromethane to wash off organic residues. Further, the catalyst was oven dried at 120 °C for 2 h and used for the recycled experiments. The results obtained from the recycled runs (Table 1, entry 3 and Table 2, entry 4) showed the consistent activity of the Cu–TPA catalyst.

5. Conclusions

In summary, Cu–TPA is demonstrated as an efficient and reusable catalyst for the new C–C and C–N bond formation reactions under mild and neat reaction conditions. The presence of cationic Cu species is deemed to be responsible for the exceptional activity of both hydroamination and hydroarylation reactions. The present



Scheme 2. Plausible reaction mechanism for the Cu–TPA catalyzed hydroarylation and hydroamination of alkynes.

protocol offers advantages due to catalyst reusability and neat reaction conditions.

Acknowledgement

The authors N.P. and K.T.V.R. thank the Council of Scientific and Industrial Research (CSIR) for the award of senior and junior research fellowships, respectively.

References and notes

1. Olah, G. A.; Krishnamurti, R.; Prakash, G. K. S. Friedel–Crafts Alkylations in Comprehensive Organic Synthesis. In Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, UK, 1991.
2. Belteskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009–3066.
3. Espinet, P.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *32*, 4704–4734.
4. Grubbs, R. H. *Hand Book of Metathesis*; Wiley-VCH: Weinheim, 2003.
5. Reilly, J. A.; Nieuwland, J. A. *J. Am. Chem. Soc.* **1928**, *50*, 2564–2566.
6. Tsuchimoto, T.; Maeda, T.; Shirakawa, E.; Kawakami, Y. *Chem. Commun.* **2000**, 1573–1574.
7. Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731–1770.
8. Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529–531.
9. Merlic, C. A.; Pauly, M. E. *J. Am. Chem. Soc.* **1996**, *118*, 11319–11320.
10. Murakami, M.; Hori, S. *J. Am. Chem. Soc.* **2003**, *125*, 4720–4721.
11. Jia, C.; Piao, D.; Oyamada, J.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Science* **2000**, *287*, 1992–1995.
12. Jia, C.; Lu, W.; Oyamada, J.; Kitamura, T.; Matsuda, K.; Irie, M.; Fujiwara, Y. *J. Am. Chem. Soc.* **2000**, *122*, 7252–7263.
13. Lu, W.; Jia, C.; Kitamura, T.; Fujiwara, Y. *Org. Lett.* **2000**, *2*, 2927–2930.
14. Reetz, M. T.; Sommer, K. *Eur. J. Org. Chem.* **2003**, 3485–3496.
15. Shi, Z.; He, C. *J. Org. Chem.* **2004**, *69*, 3669–3671.
16. Ne-vado, C.; Echavarren, A. M. *Chem. Eur. J.* **2005**, *11*, 3155–3164.
17. Song, C.; Jung, D.; Choung, S.; Roh, E.; Lee, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 6183–6185.
18. Nakao, Y.; Kanyiva, K.; Oda, S.; Hiyama, T. *J. Am. Chem. Soc.* **2006**, *128*, 8146–8147.
19. Bolm, C.; Legros, J.; Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217–6254.
20. Jovel, I.; Mertins, K.; Kischel, J.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3913–3917.
21. Kischel, J.; Jovel, I.; Mertins, K.; Zapf, A.; Beller, M. *Org. Lett.* **2006**, *8*, 19–22.
22. Nakamura, M.; Hirai, A.; Nakamura, E. *J. Am. Chem. Soc.* **2000**, *122*, 978–979.
23. Komeyama, K.; Morimoto, T.; Takaki, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 2938–2941.
24. Lingaiah, N.; Seshu Babu, N.; Mohan Reddy, K.; Sai Prasad, P. S.; Suryanarayana, I. *Chem. Commun.* **2007**, *3*, 278–279.
25. Penzien, J.; Haeßner, C.; Jentys, A.; Köhler, K.; Müller, T. E.; Sievers, C.; Lercher, J. A. *J. Catal.* **2004**, *221*, 302–312.
26. Penzien, J.; Müller, T. E.; Lercher, J. A. *Chem. Commun.* **2000**, 1753–1754.
27. Ganapati, V.; Shanbhag, G. V.; Kumbar, S. M.; Joseph, T.; Halligudi, S. B. *Tetrahedron Lett.* **2006**, *47*, 141–143.
28. Richmond, M. K.; Scout, S. L.; Alper, H. J. *J. Am. Chem. Soc.* **2001**, *123*, 10521–10525.
29. Mohan Reddy, K.; Seshu Babu, N.; Suryanarayana, I.; Sai Prasad, P. S.; Lingaiah, N. *Tetrahedron Lett.* **2006**, *47*, 7563–7566.
30. Nagaraj, P.; Pasha, N.; Sai Prasad, P. S.; Lingaiah, N. *Green Chem.* **2007**, *9*, 1126–1129.
31. Seshu Babu, N.; Mohan Reddy, K.; Sai Prasad, P. S.; Lingaiah, N. *Tetrahedron Lett.* **2007**, *48*, 7642–7645.
32. Mohan Reddy, K.; Seshu Babu, N.; Sai Prasad, P. S.; Lingaiah, N. *Catal. Commun.* **2008**, *9*, 2525–2531.