COMMUNICATION

ChemComm
www.rsc.org/chemcomm

Highly efficient Grignard-type imine additions *via* C–H activation in water and under solvent-free conditions

Chao-Jun Li* and Chunmei Wei

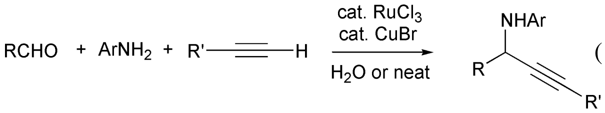
Department of Chemistry, Tulane University, New Orleans, Louisiana, USA. E-mail: cjli@tulane.edu; Fax: +1-504-8655596; Tel: +1-504-8655573

Received (in Corvallis, OR, USA) 26th September 2001, Accepted 3rd December 2001
First published as an Advance Article on the web 15th January 2002

A highly effective Cu–Ru catalyzed addition of terminal alkynes to imines *via* C–H activation has been achieved in water or under solvent-free conditions.

Recently, great efforts have been made on developing chemical technologies that can intrinsically reduce or eliminate the use or generation of hazardous substances during the design, manufacture, and use of chemical products and processes—Green Chemistry.[1] Metal-mediated C–C bond formations are among the most important reactions in organic synthesis.[2] However, the standard practice for carrying out such reactions involves the reaction of organic halides mediated by a stoichiometric amount of metal in an anhydrous organic solvent and under an inert atmosphere. Such a practice reveals fundamental drawbacks as it requires a large volume of organic solvent, excess drying agent, protection–deprotection of hydroxy groups, a stoichiometric amount of metal, and a stoichiometric amount of organic halide. On the other hand, an alternative reaction *via* catalytic C–H activation[3] in water[4] by using a water-soluble catalyst, would provide a green-approach[5] for such reactions.

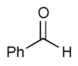
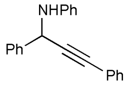
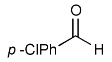
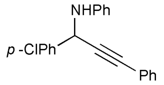
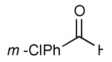
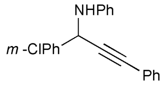
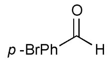
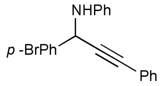
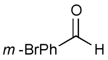
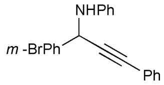
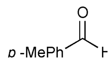
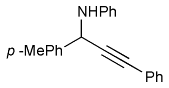
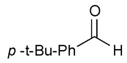
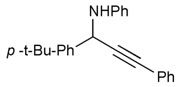
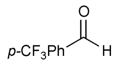
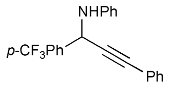
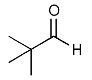
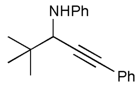
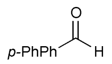
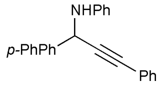
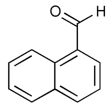
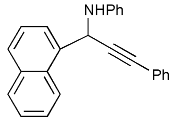
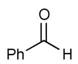
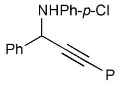
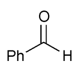
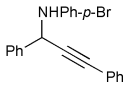
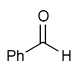
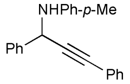
Recently, we described a Grignard-type reaction of alkyne to aldehyde to generate propargyl alcohols *via* catalytic C–H activation in water.[6] An equally important reaction is the corresponding addition of alkynes to imines, to generate propargyl amines.[7] For generating propargyl amine derivatives, Miura *et al.* reported the addition of acetylene to nitrones through the initial formation of a dipolar cycloaddition.[8] 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*-hydroxyamine adducts.[9] Herein, we wish to report (to the best of our knowledge) the first direct addition of acetylene to various imines to generate propargyl amines *via* C–H activation in water or under solvent-free conditions (eqn. (1)).



$$\mathrm{RCHO} + \mathrm{ArNH_2} + \mathrm{R'{-}C{\equiv}C{-}H} \xrightarrow[\mathrm{H_2O\ or\ neat}]{\mathrm{cat.\ RuCl_3,\ cat.\ CuBr}} \mathrm{R{-}CH(NHAr){-}C{\equiv}C{-}R'} \quad (1)$$

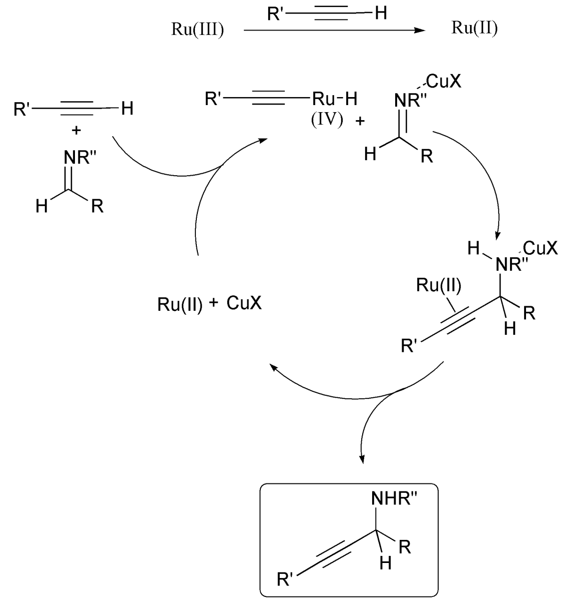
Initially, we reacted imines, which were readily accessible by the *in situ* condensation of aldehydes with anilines, with phenylacetylene by using a Ru/In catalytic system in water. Although this catalytic system was very effective for carbonyl additions, it did not provide any imine addition product.[6] Subsequently, we found that the desired addition product was formed in moderate yields by using Cu catalysts in water. Among the catalysts being tested, copper salts such as CuCl, $CuCl_2$, CuBr, CuI, and CuO all showed catalytic activities, with $CuSO_4$ CuCN, and $Cu(OAc)_2$ being less effective. The best yield of the addition product was obtained with CuBr as the catalyst.[10] By using $RuCl_3$ (3 mol%) as a co-catalyst, the yield of the desired product was dramatically increased (from 30% to 90%). However, no imine addition product was observed with $RuCl_3$ alone as the catalyst. As shown in Table 1, this catalytic system could be applied to a broad range of substituted aromatic imines and aliphatic imines (without α-hydrogen to avoid competing aldol condensation under these conditions) to afford the corresponding propargyl amines in high yields. In a few cases (entries 10–14) the imines were found to be prone to

Table 1 Catalytic addition of phenylacetylene to imines in water (or neat)

Entry	Aldehyde	Aniline/ conditions[a]	Product	Yield (%)
1		$PhNH_2$/A		91
2		$PhNH_2$/A		90
3		$PhNH_2$/A		89
4		$PhNH_2$/A		95
5		$PhNH_2$/A		93
6		$PhNH_2$/A		87
7		$PhNH_2$/A		86
8		$PhNH_2$/A		87
9		$PhNH_2$/A		64
10		$PhNH_2$/B		85
11		$PhNH_2$/B		96
12		p-$ClPhNH_2$/B		82
13		p-$BrPhNH_2$/B		88
14		p-$MePhNH_2$/B		77

[a] Conditions: A, in water; B, solvent free. Yields were referred to isolated ones after column chromatography on silica gel.

DOI: 10.1039/b108851n



Scheme 1 Tentative mechanism for imine addition *via* C–H activation.

hydrolysis in water and the yields of the products were significantly reduced. However, in these cases, we found that the imine additions were highly effective under solvent-free conditions. It was found that good yields of the addition products could be achieved in a mixture of 1.0 eq. of the imine and 1.2 eq. of phenylacetylene along with the Cu/Ru catalysts under neat conditions. Aliphatic alkynes, such as hexyne and trimethylsilylacetylene, were also effective for the reaction. Their couplings with the imine generated from benzaldehyde and aniline provided the desired product in 86% (hexyne, neat) and 83% (trimethylsilylacetylene, neat) respectively. A tentative mechanism was proposed which involves the simultaneous activation of the C–H bond of alkyne by a Ru(II) species[11] (possibly generated *in situ* from reduction of Ru(III) by the alkyne) and the imine by the copper complex. The ruthenium intermediate generated then underwent Grignard-type addition to the activated imine to give the desired nucleophilic addition product and regenerated the ruthenium and copper catalysts for further reactions (Scheme 1).

In conclusion, a highly effective Cu–Ru catalyzed addition of acetylenes to imines *via* C–H activation has been achieved in water or under solvent-free conditions. The process was simple and generated a diverse range of acetylenic amines in excellent yields. The scope, mechanism, stereoselectivity, and synthetic applications of this novel reaction as well as other C–C bond formations *via* C–H activations in water or under solvent-free conditions are under investigation.

A typical experimental procedure follows: a mixture of the aldehyde (2 mmol) and aniline (2.4 mmol) was heated at 60 °C for about two hours. Then, ruthenium trichloride (3 mol%), copper(I) bromide (30 mol%), phenylacetylene (2.4 mmol) and water (flashed with nitrogen) (2 mL) were added into the mixture under nitrogen.[12] The mixture was stirred at room temperature for 10 min and then at 40 °C overnight. The reaction mixture was poured into water, and extracted with diethyl ether (or methylene chloride). The organic layer was washed with water and dried over anhydrous Mg_2SO_4. The solvent was removed *in vacuo*. The product was isolated by flash column chromatography on silica gel eluting with EtOAc–hexane (1:40).

We are grateful to the NSF-EPA joint program for a Sustainable Environment and the NSF CAREER Award program for the support of this research.

Notes and references

1 For general references on green chemistry, see: P. T. Anastas and J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, Oxford, 1998; *Green Chemistry: Designing Chemistry for the Environment*, American Chemical Society Symposium Series, No. 626, ed. P. T. Anastas and T. C. Williamson, Washington D.C. 1996.

2 For representitative monographs and reviews, see: B. J. Wakefield, *Organomagnesium Methods in Organic Chemistry*, Academic Press, 1995; C. Blomberg, *The Barbier Reaction and Related One-Step Processes*, Springer-Verlag, 1993; Y. H. Lai, *Synthesis*, 1981, 585; G. Courtois and L. Miginiac, *J. Organomet. Chem.*, 1974, **69**, 1; H. Normant, *Adv. Org. Chem.*, 1960, **2**, 1; S. T. Ioffe and A. N. Nesmeyanov, *The Organic Compounds of Magnesium, Beryllium, Calcium, Strontium and Barium*, North-Holland, Amsterdam, 1976.

3 For an excellent recent review, see: G. Dyker, *Angew. Chem.*, 1999, **38**, 1698; T. Naota, H. Takaya and S. I. Murahashi, *Chem. Rev.*, 1998, **98**, 2599; K. A. Horn, *Chem. Rev.*, 1995, **95**, 1317.

4 C. J. Li and T. H. Chan, *Organic Reactions in Aqueous Media*, John Wiley & Sons, New York, 1997; A. Lubineau, J. Auge and Y. Queneau, *Synthesis*, 1994, 741; *Organic Synthesis in Water*, ed. P. A. Grieco, Blackie Academic & Professional, Glasgow, 1998.

5 B. M. Trost, *Science*, 1991, **254**, 1471; R. A. Sheldon, *Chemtech*, 1994, **24**, 38; P. A. Wender and B. L. Miller, in *Organic Synthesis: Theory and Applications*, ed. T. Hudlicky, JAI Press, Vol. 2, 1993.

6 C. J Li and C. M. Wei, *Green Chem.*, 2002, **4**, in press.

7 R. Bloch, *Chem. Rev.*, 1998, **98**, 1407; B. A. Katherine, D. W. Mark and B. C. David, *J. Am. Chem. Soc.*, 2000, **122**, 11084.

8 M. Miura, M. Enna, K. Okuro and M. Nomura, *J. Org. Chem.*, 1995, **60**, 4999.

9 D. E. Frantz, R. Fâssler and E. M. Carreira, *J. Am. Chem. Soc.*, 1999, **121**, 11245.

10 The use of 30 mol% of CuBr as co-catalyst was necessary for the reaction to go to completion. The conversion was decreased when a smaller amount of CuBr was used.

11 B. M. Trost, F. D. Toste and A. B. Pinkerton, *Chem. Rev.*, 2001, **101**, 2067.

12 The reaction also proceeded under an air atmosphere; however a significant amount of oligomerization of alkynes was observed.