Tetrahedron Letters 51 (2010) 1493–1496

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Gold(I)-catalyzed one-pot reaction between 2-alkynylanilines and alkynols leading to the formation of C-3-substituted indoles: a case of formal carboamination of alkynes

Nitin T. Patil *, Vipender Singh, Ashok Konala, Anil Kumar Mutyala

Organic Chemistry Division-II, Indian Institute of Chemical Technology, Hyderabad 500 607, India

ARTICLE INFO

Article history:
Received 19 December 2009
Revised 5 January 2010
Accepted 10 January 2010
Available online 15 January 2010

Keywords:
Alkynes
Gold catalyst
Hydroamination
Hydroalkoxylation
Hydroarylation

ABSTRACT

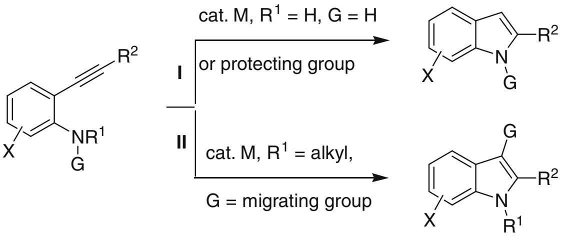
A process involving gold(I)-catalyzed formal carboamination of alkynes for the synthesis of C-3-substituted indoles has been developed. The procedure utilizes easily accessible starting materials such as 2-alkynylanilines and alkynols. A series of C-3-functionalized indoles are accessible by using this one-pot strategy. Mechanistically, the reaction involves three catalytic cycles and each of them is essentially catalyzed by a single metal catalyst, that is, $Ph_3PAuOTf$.

1. Introduction

Substituted indoles have attracted great attention due to their widespread occurrence in nature as well as their remarkable biological activities.[1] Their synthesis has been the objective of research for over a century, and a variety of well-established classical methods are now available in the literature.[2] Among a variety of methods, transition metal-catalyzed reactions are the most attractive, since those reactions can directly construct multiply-substituted indole from readily accessible starting materials under mild conditions.[3] One of the straightforward ways to access indoles is the metal-mediated intramolecular hydroamination of 2-alkynylanilines (Scheme 1, path I).[4] Another powerful method for their synthesis involves the metal-mediated intramolecular carboamination of *N*-protected 2-alkynylanilines (Scheme 1, path II).[5]

Recently, we[6] and others[7] reported a new approach for the synthesis of C-3-functionalized indoles, by metal-catalyzed reactions between alkynols and indoles. Metal-catalyzed reactions of 2-alkynylanilines **1** with electrophiles such as α,β-enones[4g] and ethyl propiolate[8] have been known to give C-3-functionalized indoles (Scheme 2, path I). Against this background, we questioned whether it might be possible to use 2-alkynylanilines, instead of indoles, for the metal-catalyzed cascade process as shown in Scheme 2 (path II). More specifically, we hypothesized that a single metal catalyst having acidic property[9] should promote three reactions such as hydroalkoxylation, hydroamination, and hydroarylation with the formation of C–O, C–N, and C–C bonds in one-pot without isolating any intermediates.[10] A successful reaction as envisioned above would provide access to C-3-substituted indoles starting from 2-ethynylanilines and alkynols. Herein, we report successful realization of the reaction by utilizing 5 mol % $Ph_3PAuOTf$, generated in situ by mixing $Au(PPh_3)Cl$ and AgOTf (5 mol % each), as a catalyst. The method shows very broad substrate scope towards alkynols and 2-alkynylanilines. Since overall formation of C–C and C–N bonds across alkynes take place, we termed this process as formal carboamination of alkynes.[11]

Initially, 4-pentyn-1-ol **1a** was treated with 2-aminophenyl alkyne **2a** in the presence of 5 mol % AgOTf in DCE at 60 °C for 12 h (Table 1, entry 1). Pleasingly, this led to the formation of C-3-

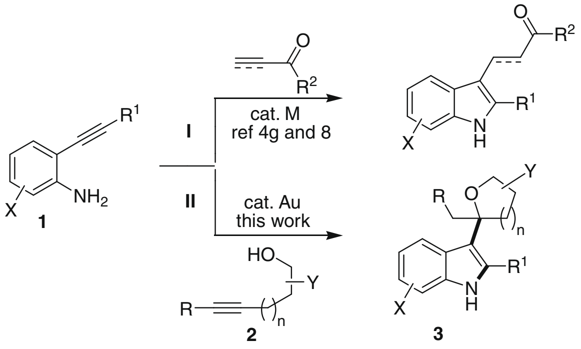


Scheme 1.

---

* Corresponding author. Tel.: +91 40 27191471; fax: +91 40 27193382.
E-mail addresses: nitin@iict.res.in, patilnitint@yahoo.com (N.T. Patil).

0040-4039/$ - see front matter © 2010 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2010.01.036

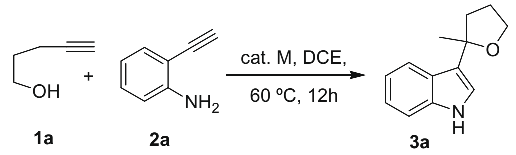


Scheme 2.

substituted indole **3a** in 52% yield. Under the same conditions, $Cu(OTf)_2$ catalyst gave **3a** in 30% yield (entry 2). The use of platinum salts such as $PtCl_2$ and $PtCl_4$ afforded **3a** in 70 and 65% yield, respectively (entries 3 and 4). When $Au(PPh_3)Cl$ and AuCl alone were employed as catalyst, the desired product was obtained in 45 and 75% yield, respectively (entries 5 and 6). The catalyst PPh_3AuOTf generated from mixing equimolar amount of $Au(PPh_3)Cl$ and AgOTf gave a slightly higher yield (entry 7). A combination of $Au(PPh_3)Cl$ with other silver salts such as $AgBF_4$ (entry 8) and $AgSbF_6$ (entry 9) was examined; however, both of them gave inferior results. The result of the study indicates that Ph_3PAuCl in combination with AgOTf is the catalyst of choice for this transformation (entry 7).

Under the optimal conditions,[12] we studied the scope of the reaction. As shown in Table 2, alkynylanilines were varied keeping 4-pentyn-1-ol **1a** as a model substrate. It is evident that a wide range of substituted 2-alkynylanilines **2b–k** reacted well to furnish **3b–k** in moderate to high yields (60–81%) regardless of the electronic nature of the aromatic ring. Particularly noteworthy is the fact that electron-withdrawing substituents on the aromatic rings were not detrimental to the reactivity as $-NO_2$, –CN–COOMe, and $-CF_3$ groups were all well tolerated (entries 1, 4, 5, 8, and 9). The reaction was also successful for halo-substituted amino-alkynes (entries 2, 6, and 7). It should be noted that this method is applicable to only terminal amino-alkynes and therefore internal alkynes cannot be employed as substrates.

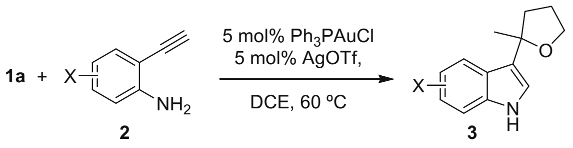
Table 1
Optimization studies[a]

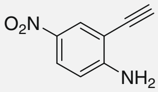
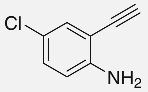
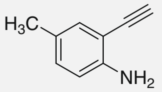
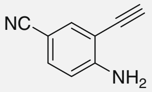
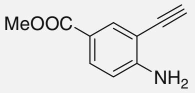
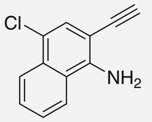
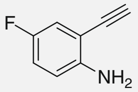
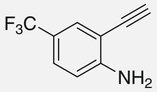
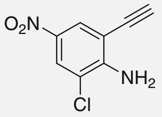
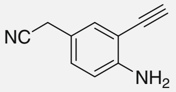


Entry	Catalyst[a]	Yield[b] (%)
1	AgOTf	52
2	$Cu(OTf)_2$	30
3	$PtCl_2$	70
4	$PtCl_4$	65
5	Ph_3PAuCl	45
6	AuCl	75
7	**Ph_3PAuCl + AgOTf**	81
8	Ph_3PAuCl + $AgBF_4$	**58**
9	Ph_3PAuCl + $AgSbF_6$	60

[a] Reaction conditions: 0.59 mmol **2a**, 1.1 equiv **1a**, 5 mol % catalyst, DCE (0.3 M), 60 °C, 12 h.
[b] Isolated yields based on **2a**.

Table 2
Scope with 2-alkynylanilines[a]



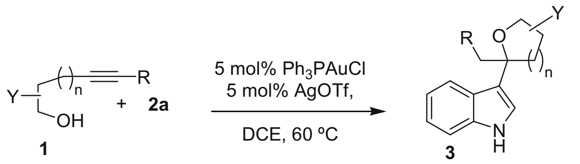
Entry	2		3	Time (h)	Yield[b] (%)
1		**2b**	**3b**	18	60
2		**2c**	**3c**	12	72
3		**2d**	**3d**	12	75
4		**2e**	**3e**	18	70
5		**2f**	**3f**	15	68
6		**2g**	**3g**	12	71
7		**2h**	**3h**	12	81
8		**2i**	**3i**	12	70
9		**2j**	**3j**	18	69
10		**2k**	**3k**	12	73

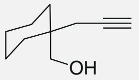
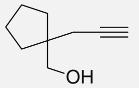
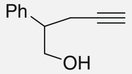
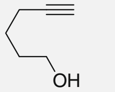
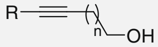
[a] Reaction conditions: 0.59 mmol **2**, 1.1 equiv **1a**, Ph_3PAuCl and AgOTf (5 mol % each with respect to **2**), DCE (0.3 M), 60 °C.
[b] Isolated yields based on **2**.

Next, the scope of the reaction with various alkynols was studied by using **2a** as a model substrate (Table 3). The alkynols bearing sterically demanding substituents in the tether such as **1b**, **1c**, and **1d** reacted well giving corresponding products **3l**, **3m**, and **3n** in high yields (entries 1–3). As can be judged from the entry 4, 5-hexyn-1-ol **1e** can also be used as a substrate. Even internal alkynes such as **1f–i** were tolerated giving the corresponding products **3p–s** in good yields (entries 5–8). It should be noted that in the latter case only one regioisomer **3s** was formed indicating that the **1i** cyclized in 5-*exo-dig* fashion (entry 8).

A plausible mechanism for the gold-catalyzed formal carboamination of alkynes is described in Figure 1. A first step would be the complexation of Au(I) catalysts to the alkyne function in **1a** which lead to intermediate **4** (Fig. 1, cycle **A**). The cyclization step may then occur directly by the attack of proximal hydroxyl group lead-

Table 3
Scope with alkynols[a]



Entry	Alkynol **1**	**3**	Time (h)	Yield[b] (%)
1	 **1b**	**3l**	18	73
2	 **1c**	**3m**	18	67
3	 **1d**	**3n**	12	65
4	 **1e**	**3o**	15	79
5	 $n = 1$, R = Me **1f**	**3p**	12	67
6	$n = 1$, R = Et **1g**	**3q**	12	65
7	$n = 1$, R = *n*Hex **1h**	**3r**	12	71
8	$n = 2$, R = *p*-Me-C_6H_4 **1i**	**3s**	18	63[c]

[a] Reaction conditions: 0.59 mmol **2a**, 1.1 equiv. **1**, Ph_3PAuCl and AgOTf (5 mol % each with respect to **2a**), DCE (0.3 M), 60 °C.

[b] Isolated yields based on **2a**.

[c] Only one regioisomer was isolated.

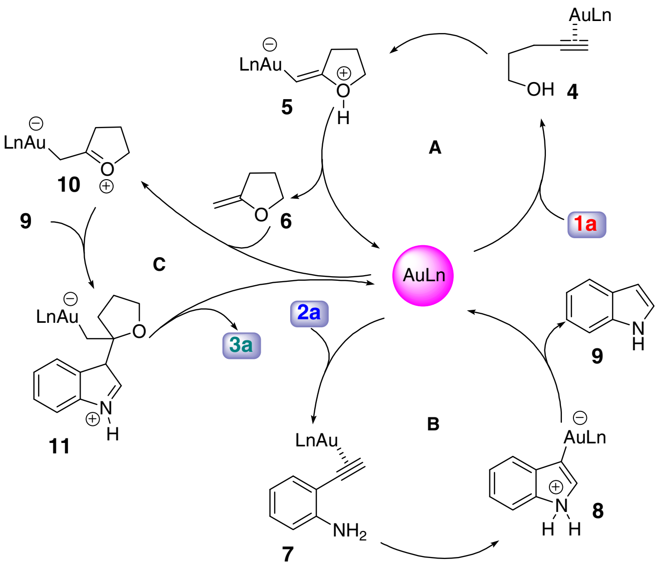


Figure 1. A proposed mechanism.

ing to vinylgold intermediate **5**.[13] The next step would be the proto-demetalation to generate exocyclic enol ether **6** with the release of the catalyst. Simultaneously, as shown in cycle **B**, indole **9** would be generated from **2a** via an intramolecular hydroamination catalyzed by PPh_3AuOTf through intermediates **7** and **8**. Once **6** and **9** are formed, they enter into another catalytic cycle **C** where PPh_3AuOTf is supposed to act as a Lewis acid. Thus, the Lewis acidic Au(I) complex catalyzes the formation of oxonium ion **10** from 2-methylenetetrahydrofuran **6**. Intermolecular nucleophilic addition of the indole **9** to **10** (cf. **11**) followed by re-aromatization and proto-demetalation lead to the final product **3a** with the liberation of the catalyst.

During the course of the reaction, traces of TfOH could be generated from $Ph_3PAuOTf$ in the presence of **1a**/**2a** or trace amount of water present in reaction medium. A Brönsted acid thus formed might be responsible for catalytic cycles A and B or at least C. To ascertain the above possibility, the reaction was conducted between **1a** and **2a** in the presence of 1 mol % TfOH in DCE at 60 °C. The product **3a** was not obtained; instead, **2a** and **1a** were recovered. This clearly indicates that the metal catalyst is responsible for cycle A[14] and B.[4] To examine the involvement of Brönsted acid catalysis in cycle C, a controlled experiment was performed using a proton scavenger. When **1a** was treated with **2a** in the presence of Ph_3PAuCl/AgOTf (5 mol % each) and 2 mol % 2-tert-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2 diazaphosphorine (BEMP) in DCE at 60 °C for 18 h, **3a** was obtained, albeit in a low yield. This suggests that the residual TfOH is not responsible for the cycle C, as this would be quenched by BEMP.[15] Therefore, it became clear that the metal catalyst is essential for all the three proposed catalytic cycles.

2. Conclusions

A number of reports on the synthesis of indoles from 2-alkynylanilines are reported in the literature.[4] However, most of them involve the reaction of the internal alkynes and protected amines. There are limited examples that involve terminal alkynes and free amines.[4e,i,k–m] The present method not only utilizes terminal alkynes and free amines but also appends additional substituents at C-3 position of indoles.

Similarly, the reaction which involves several catalytic cycles[10] in the same vessel are very interesting due to their ability to construct desired molecules from readily accessible starting materials. The present Au(I)-catalyzed one-pot method for the synthesis of C-3 substituted indoles from 2-alkynylanilines and alkynols involves three catalytic cycles (cycle A: hydroalkoxylation, cycle B: hydroamination, cycle C: hydroarylation) with the formation of three bonds with 100% atom economy.[16] Concerning the accessibility of C-3-substituted indoles, the present method should prove superior to the previously reported methods[6,7] since the prior formation of indoles is not necessary.

Acknowledgments

We gratefully acknowledge the financial support by the Council of Scientific and Industrial Research, India. NTP is grateful to Dr. J. S. Yadav, Director, IICT and Dr. V. V. N. Reddy, Head, Org-II Division for their support and encouragement.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.01.036.

References and notes

1. (a) Li, S.-M. *Nat. Prod. Rep.* **2010**, *27*, 57–78; (b) Weng, J.-R.; Tsai, C.-H.; Kulp, S. K.; Chen, C.-S. *Cancer Lett.* **2008**, *262*, 153–163; (c) Rieck, G. C.; Fiander, A. N. *Mol. Nutr. Food Res.* **2008**, *52*, 105–113; (d) Brancale, A.; Silvestri, R. *Med. Res. Rev.* **2007**, *27*, 209–238; (e) Somei, M.; Yamada, F. *Nat. Prod. Rep.* **2005**, *22*, 73–103; (f) McKay, M. J.; Carroll, A. R.; Quinn, R. J.; Hooper, J. N. A. *J. Nat. Prod.* **2002**, *65*, 595–597; (g) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, fourth ed.; Blackwell Science: Oxford, 2000; (h) Sundberg, R. J. *Indoles*; Academic Press: London, 1996.

2. Reviews: (a) Ackermann, L. *Synlett* **2007**, 507–526; (b) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875–2911; (c) Bandini, M.; Melloni, A.; Tommasi, S.; Umani-Ronchi, A. *Synlett* **2005**, 1199–1222; (d) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045–1075.
3. Review: (a) Krügar, K.; Tillack, A.; Beller, M. *Adv. Synth. Catal.* **2008**, *350*, 2153–2167; (b) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873–2920; (c)*Palladium in Heterocyclic Chemistry*; Li, J. J., Gribble, W., Eds.; Pergamon: Oxford, 2000. Chapter 3; For recent references on synthesis of indoles by metal catalysis, see: (d) Hsieh, T. H. H.; Dong, V. M. *Tetrahedron* **2009**, *65*, 3062–3068; (e) Stuart, D. R.; Bertrand-Laperle, M.; Burgess, K. M. N.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 16474–16475; (f) Banerjee, S.; Barnea, E.; Odom, A. L. *Organometallics* **2008**, *27*, 1005–1014; (g) Alex, K.; Tillack, A.; Schwarz, N.; Beller, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 2304–2307; (h) Kurisaki, T.; Naniwa, T.; Yamamoto, H.; Imagawa, H.; Nishizawa, M. *Tetrahedron Lett.* **2007**, *48*, 1871–1874; (i) Liu, F.; Ma, D. *J. Org. Chem.* **2007**, *72*, 4844–4850; (j) Ohno, H.; Ohta, Y.; Oishi, S.; Fujii, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 2295–2298; (k) Cariou, K.; Ronan, B.; Mignani, S.; Fensterbank, L.; Malacria, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1881–1884; (l) Kamijo, S.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 3230–3233; (m) Kamijo, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 11940–11945.
4. For metal catalyzed hydroamination of 2-alkynylanilines, see: (a) Okuma, K.; Seto, J.; Sakaguchi, K.; Ozaki, S.; Nagahora, N.; Shioji, K. *Tetrahedron Lett.* **2009**, *50*, 2943–2945; (b) Sakai, N.; Annaka, K.; Fujita, A.; Sato, A.; Konakahara, T. *J. Org. Chem.* **2008**, *73*, 4160–4165; (c) Zhang, Y.; Donahue, J. P.; Li, C.-J. *Org. Lett.* **2007**, *9*, 627–630; (d) Ambrogio, I.; Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F. *Synlett* **2007**, 1775–1779; (e) Trost, B. M.; McClory, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 2074–2077; (f) Li, X.; Chianese, A. R.; Vogel, T.; Crabtree, R. H. *Org. Lett.* **2005**, *7*, 5437–5440; (g) Alfonsi, M.; Arcadi, A.; Aschi, M.; Bianchi, G.; Marinelli, F. *J. Org. Chem.* **2005**, *70*, 2265–2273; (h) Hiroya, K.; Itoh, S.; Sakamoto, T. *Tetrahedron* **2005**, *61*, 10958–10964; (i) Hiroya, K.; Itoh, S.; Sakamoto, T. *J. Org. Chem.* **2004**, *69*, 1126–1136; (j) Sakai, N.; Annaka, K.; Konakahara, T. *Org. Lett.* **2004**, *6*, 1527–1530; (k) Arcadi, A.; Bianchi, G.; Merinelli, F. *Synthesis* **2004**, 610–618; (l) Hiroya, K.; Itoh, S.; Ozawa, M.; Kanamori, Y.; Sakamoto, T. *Tetrahedron Lett.* **2002**, *43*, 1277–1280; (m) Kondo, T.; Okada, T.; Suzuki, T.; Mitsudo, T. *J. Organomet. Chem.* **2001**, *622*, 149–154; (n) Cacchi, S.; Carnicelli, V.; Marinelli, F. *J. Organomet. Chem.* **1994**, *475*, 289–296; (o) McDonald, F. E.; Chatterjee, A. K. *Tetrahedron Lett.* **1997**, *38*, 7687–7690; (p) Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron Lett.* **1989**, *30*, 2581–2584; (q) Rudisill, D. E.; Stille, J. K. *J. Org. Chem.* **1989**, *54*, 5856–5866; (r) Iritani, K.; Matsubara, S.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 1799–1802.
5. (a) Nakamura, I.; Sato, Y.; Konta, S.; Terada, M. *Tetrahedron Lett.* **2009**, *50*, 2075–2077; (b) Fürstner, A.; Davies, P. W. *J. Am. Chem. Soc.* **2005**, *127*, 15024–15025; (c) Shimada, T.; Nakamura, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 10546–10547; (d) Cacchi, S.; Fabrizi, G.; Pace, P. *J. Org. Chem.* **1998**, *63*, 1001–1011.
6. Patil, N. T.; Raut, V. S.; Kavthe, R. D.; Reddy, V. V. N.; Raju, P. V. K. *Tetrahedron Lett.* **2009**, *50*, 6576–6579.
7. (a) Barluenga, J.; Fernández, A.; Rodríguez, F.; Fañanás, F. J. *J. Organomet. Chem.* **2009**, *694*, 546–550; (b) Bhuvaneswari, S.; Jeganmohan, M.; Cheng, C.-H. *Chem. Eur. J.* **2007**, *13*, 8285–8293; (c) Ferrer, C.; Amijs, C. H. M.; Echavarren, A. M. *Chem. Eur. J.* **2007**, *13*, 1358–1373.
8. Li, X.; Wang, J.-Y.; Yu, W.; Wu, L.-M. *Tetrahedron* **2009**, *65*, 1140–1146.
9. Selected recent reviews: (a) Fürstner, A. *Chem. Soc. Rev.* **2009**, *38*, 3208–3221; (b) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395–3442; (c) Kirsch, S. F. *Synthesis* **2008**, 3183–3204; (d) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351–3378; (e) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239–3265; (f) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266–3325; (g) Bongers, N.; Krause, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 2178–2181; (h) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410–3449; (i) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180–3211; (j) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395–403; (k) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333–346; (l) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7896–7936; (m) Ma, S.; Yu, S.; Gu, Z. *Angew. Chem., Int. Ed.* **2006**, *45*, 200–203; (n) Nevado, C.; Echavarren, A. M. *Synthesis* **2005**, 167–182.
10. Wasilke, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001–1020.
11. Report on formal processes from our laboratory, see: (a) Patil, N. T.; Kavthe, R. D.; Raut, V. S.; Reddy, V. V. N. *J. Org. Chem.* **2009**, *74*, 6315–6318; (b) Ref. 6.
12. *Typical experimental procedure:* To a screw-cap vial containing stir bar, were added the aromatic amines **2** (0.59 mmol), alkynols **1** (1.1 equiv), and catalyst Au(PPh_3)Cl/Ag(OTf) (5 mol % each with respect to **2**) in DCE (0.3 M). The reaction vial was fitted with a cap, evacuated, and filled with nitrogen. The reaction vial was heated with stirring at 60 °C for the specified time. The reaction mixture was cooled to ambient temperature, diluted with ethyl acetate, and filtered through a plug of silica gel. The filtrate was concentrated and the residue thus obtained was purified by silica gel column chromatography using hexane and ethyl acetate as an eluent. The details are given in the Supplementary data.
13. Hashmi, A. S. K.; Schuster, A. M.; Rominger, F. *Angew. Chem., Int. Ed.* **2009**, *48*, 8247–8249.
14. For metal catalyzed hydroalkoxylation of alkynes, see: (a) Harkat, H.; Blanc, A.; Weibel, J.-M.; Pale, P. *J. Org. Chem.* **2008**, *73*, 1620–1623; (b) Harkat, H.; Weibel, J.-M.; Pale, P. *Tetrahedron Lett.* **2007**, *48*, 1439–1442; (c) Barluenga, J.; Diéguez, A.; Rodríguez, F.; Fañanás, F. J.; Sordo, T.; Campomanes, P. *Chem. Eur. J.* **2005**, *11*, 5735–5741; (d) Peng, A.-Y.; Ding, Y.-X. *Org. Lett.* **2005**, *7*, 3299–3301; (e) Liu, Y.; Song, F.; Song, Z.; Liu, M.; Yan, B. *Org. Lett.* **2005**, *7*, 5409–5412; (f) Peng, A.-Y.; Ding, Y.-X. *J. Am. Chem. Soc.* **2003**, *125*, 15006–15007; (g) Pale, P.; Chuche, J. *Eur. J. Org. Chem.* **2000**, 1019–1025.
15. BEMP has previously been used as nonpoisoning proton scavenger, see: (a) Barluenga, J.; Fernández, A.; Diéguez, A.; Rodríguez, F.; Fañanás, F. J. *Chem. Eur. J.* **2009**, *15*, 11660–11667; (b) Yang, T.; Campbell, L.; Dixon, D. J. *J. Am. Chem. Soc.* **2007**, *129*, 12070–12071.
16. Reviews on atom economy: (a) Sheldon, R. A. *Pure Appl. Chem.* **2000**, *72*, 1233–1246; (b) Trost, B. M. *Science* **1991**, *254*, 1471–1477; (c) Trost, B. M. *Angew. Chem., Int. Ed.* **1995**, *34*, 259–281.