ChemPubSoc Europe

DOI: 10.1002/chem.201304111

CHEMISTRY
A European Journal
Communication

Organic Synthesis

Tandem Pd/Au-Catalyzed Route to α-Sulfenylated Carbonyl Compounds from Terminal Propargylic Alcohols and Thiols

Srijit Biswas, Rahul A. Watile, and Joseph S. M. Samec*[a]

Abstract: An efficient and highly atom-economical tandem Pd/Au-catalyzed route to α-sulfenylated carbonyl compounds from terminal propargylic alcohols and thiols has been developed. This one-step procedure has a wide substrate scope with respect to substituents at the α-position of the alcohol. Both aromatic and aliphatic thiols generated the α-sulfenylated carbonyl products in good to excellent yields. A mechanism is proposed in which the reaction proceeds through a Pd-catalyzed regioselective hydrothiolation at the terminal triple bond of the propargyl alcohol followed by an Au-catalyzed 1,2-hydride migration.

α-Sulfenylated carbonyl compounds belong to an important class of compounds. The structural motif is often found in agrochemicals and pharmaceuticals (Figure 1).[1] From a synthetic perspective, these types of compounds have frequently been used as valuable starting materials or reactive intermediates in a variety of organic transformations.[2]

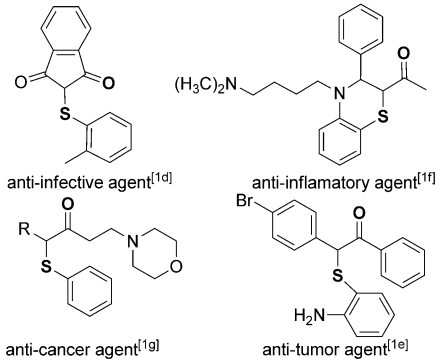
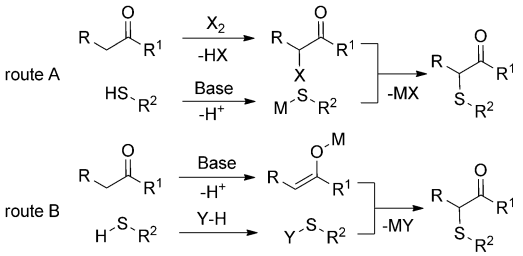


Figure 1. Biologically active molecules containing an α-sulfenylated carbonyl structural motif.

[a] *Dr. S. Biswas, R. A. Watile, Prof. Dr. J. S. M. Samec*
Department of Chemistry, BMC
Uppsala University, Box 576
75123, Uppsala (Sweden)
Fax: (+46) 18 471 38 18
E-mail: joseph.samec@kemi.uu.se

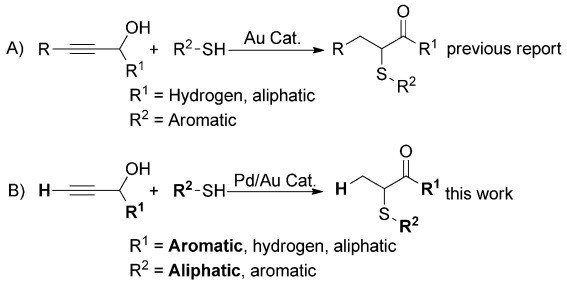
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201304111.

The traditional synthesis of α-sulfenylated carbonyl compounds involves substitution of the corresponding α-halogenated intermediate by sulphide anions (Scheme 1, route A).[2] Alternatively, the reaction between a parent carbonyl compound or preformed enolate with sulfenylating agents, such as disulfides, *N*-(phenylsulfanyl)succinimides, or sulfenyl chlorides also produces the α-sulfenylated carbonyl compounds (Scheme 1, route B).[3] These traditional synthetic methods are associated with limitations including: 1) use of toxic and difficult to handle intermediates, 2) multiple reaction steps, 3) low-atom efficiency with a stoichiometric use of reagents and formation of chemical waste. Asymmetric versions of stoichiometric electrophilic α-sulfenylations have been reported by using a chiral auxiliary,[4] an organocatalyst,[5] or chiral complexes of titanium(IV) or nickel(II).[6] The lack of a mild, efficient, and atom-economical route to synthesize α-sulfenylated carbonyl compounds motivated further studies.



Scheme 1. Traditional synthesis of α-sulfenylated carbonyl compounds.

Recently, a gold(I)-catalyzed route to α-sulfenylated carbonyl compounds from propargylic alcohols and aryl thiols has been reported by our group (Scheme 2A).[7] The reaction was found to be highly atom efficient in which different primary and secondary propargylic alcohols with internal carbon–carbon triple



Scheme 2. Tandem Pd/Au catalysis.

bonds reacted with aromatic thiols to generate the corresponding α-sulfenylated aldehydes and ketones. The transformation proceeded by two sequential reaction steps; the first step consisted of a gold-catalyzed regioselective hydrothiolation reaction[8] forming a sulfenylated allylic alcohol as the reactive intermediate that underwent an isomerization through a gold-catalyzed 1,2-hydride migration to generate the α-sulfenylated carbonyl product. When propargylic alcohols containing a terminal carbon–carbon triple bond were employed under similar reaction conditions, the regioselectivity and chemoselectivity of the initial gold-catalyzed[9] hydrothiolation reaction was completely lost resulting in multiple thiol attack to the carbon–carbon triple bond. The methodology was also limited to propargylic alcohols with hydrogen or aliphatic substituents at the R^1-position. Furthermore, only aromatic thiols were found to be reactive under the reported reaction conditions.

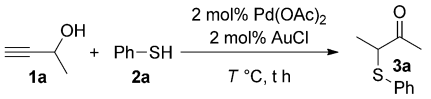
We herein report a complementary method to synthesize α-sulfenylated carbonyl compounds by using terminal propargylic alcohols and thiols in which the limitations of the previous report,[7] such as 1) the problems of regioselectivity in the hydrothiolation step for terminal propargylic alcohols, 2) wrong reactivity for propargylic alcohols with aromatic groups at the R^1-position, and 3) lack of reactivity for aliphatic thiols, were successfully resolved employing a tandem Pd/Au[10] catalytic[11] system (Scheme 2B). These results significantly enhance the scope of the methodology in terms of diversity and thereby complement the previous report.[7]

To optimize the reaction parameters, propargyl alcohol **1a** and thiophenol **2a** were chosen (Table 1). Different solvents were screened over different reaction temperatures. An 82% yield for the formation of product **3a** was observed after running the reaction for 8 h at 80 °C in nitromethane solvent (Table 1, entry 1). The yield could be increased to 99% by using 1.2 equivalents of **2a** with respect to **1a** (entry 2). Lowering the reaction temperature to 60 °C reduced the yield of **3a** to 69% (entry 3). By using toluene and 1,2-dichloroethane as solvents produced the product **3a** in 96 and 80% yields (entries 4 and 5, respectively), whereas acetonitrile gave 72% formation of **3a** (entry 6). Ethanol was also screened as the solvent for which a 51% yield of **3a** was observed (entry 7). Non-regioselective and multiple thio-attack at the C–C triple bond was observed by using only AuCl catalyst leading to a mixture of sulfenylated alcohols (entry 9), whereas exclusive formation of the intermediate sulfenylated allylic alcohol was observed using only $Pd(OAc)_2$ as the catalyst through a regioselective hydrothiolation reaction (entry 10; see Scheme 4 for details). A 28% product formation was observed upon replacing AuCl by CuI (entry 11).

The optimized reaction conditions were applied to a variety of terminal propargylic alcohols and aryl thiols (Table 2). Primary propargylic alcohol reacted with thiophenol to produce the corresponding α-sulfenylated aldehyde **3b** in a quantitative yield. Secondary propargylic alcohols with different aliphatic groups, such as ethyl, *iso*-butyl, and *n*-butyl, at the R^1-position generated the corresponding α-sulfenylated ketones (**3c**–**e**), respectively, in excellent yields. Aromatic thiols with different electron-donating or -withdrawing substituents, such as *p*-chloro, *p*-bromo, *m*,*p*-dichloro, *p*-fluoro, *p*-methoxy, and *p*-isopropyl, at the aromatic ring also reacted smoothly to generate the desired products (**3f**–**k**) in 94–98% yields.

A drawback with the previously reported gold(I)-catalyzed route was the restriction to aryl thiols.[7] The combination of

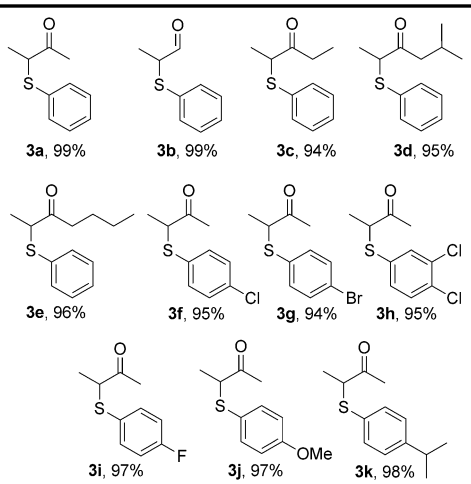
Table 1. Optimization of reaction parameters.[a]



Entry	Solvent	T [°C]	t [h]	Yield [%][b]
1[c]	$MeNO_2$	80	8	82
2	**$MeNO_2$**	**80**	**8**	**99**
3	$MeNO_2$	60	8	69
4	PhMe	80	8	96
5	1,2-DCE[d]	80	8	80
6	AcCN	80	8	72
7	EtOH	80	8	51
8	$MeNO_2$	80	6	90
9[e]	$MeNO_2$	80	8	trace[f]
10[g]	$MeNO_2$	80	8	0[h]
11[h]	$MeNO_2$	80	8	28

[a] Reaction conditions: **1a** (1 mmol), **2a** (1.2 mmol), $Pd(OAc)_2$ (2 mol%), and AuCl (2 mol%) were treated in 2 mL solvent. [b] Isolated yield. [c] 1 mmol of **2a** was used. [d] 1,2-Dichloroethane. [e] Only AuCl was used as the catalyst. [f] Nonregioselective multiple attack of thiol to the triple bond was observed. [g] Only $Pd(OAc)_2$ was used as the catalyst. [h] Exclusive formation of intermediate sulfenylated allylic alcohol was observed by regioselective hydrothiolation reaction (see Scheme 4). [i] 5 mol% CuI was used in place of AuCl.

Table 2. α-Sulfenylated carbonyl compounds from terminal propargylic alcohols and aryl thiols.[a,b]

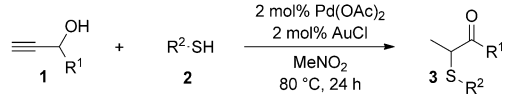


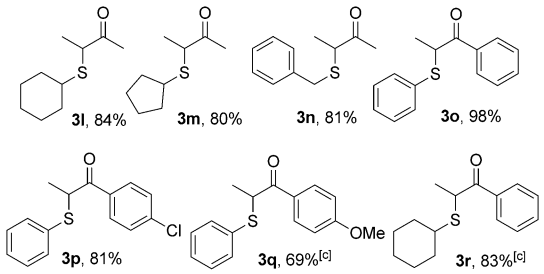
[a] Reaction conditions: **1** (1 mmol), **2** (1.2 mmol), $Pd(OAc)_2$ (2 mol%), and AuCl (2 mol%) were treated in nitromethane (2 mL). [b] Isolated yield.

Pd/Au was found to overcome this limitation. Different aliphatic thiols were found to be reactive under the present reaction conditions to generate the α-sulfenylated ketones in good to excellent yields (Table 3). Cyclohexyl thiol reacted with alcohol **1a** to produce product **3l** in an 84% yield, whereas 80 and 81% yields were obtained utilizing cyclopenyl thiol and benzyl thiol, respectively. This outcome was in sharp contrast to the previously reported gold-catalyzed method[7] in which no reactivity was observed for aliphatic thiols.

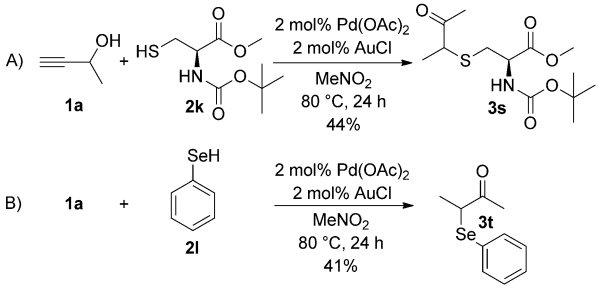
Another class of challenging substrates was propargylic alcohols containing an aromatic group in the benzylic position (R^1) of the alcohol. Previously, these substrates gave poor reactivity in the α-sulfenylation reaction due to a competing direct substitution reaction of the activated hydroxyl group. Gratifyingly, the combination of Pd/Au catalysis overcame the problem of chemoselectivity in favor of the α-sulfenylation reaction. Propargyl alcohol with a phenyl group at the R^1-position produced the desired α-sulfenylated product **3o** in a 98% yield under the present reaction conditions. Propargyl alcohol with an electron-withdrawing chloro substituent at the *para*-position of the phenyl ring generated the desired product **3p** in 81% yield. Also, propargyl alcohol with an electron-donating methoxy group at the *para*-position of the phenyl ring, that is expected to promote the direct substitution reaction, generated **3q** in a 69% yield. Diversity of the substrate scope of the present method was demonstrated when cyclohexyl (aliphatic) thiol reacted with 1-phenylprop-2-yn-1-ol containing a phenyl substituent at the R^1-position to generate the desired product **3r** in 83% yield.[7]

Table 3. Extension of the substrate scope to aliphatic thiols and benzylic alcohols with terminal triple bonds.[a,b]



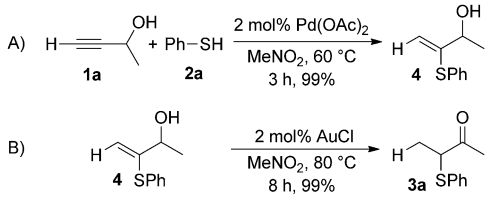


To further explore the present synthetic protocol, a protected cysteine derivative was employed as the sulphenylating reagent (Scheme 3A). The reaction between the propargylic alcohol **1a** and *N*-(*tert*-butoxycarbonyl) L-cysteine methyl ester **2k** generated the substituted cysteine derivative **3s** in a 44% yield after 24 h.[12a] Additionally, applicability of the synthetic protocol was shown when the thiol was successfully replaced by selenol (Scheme 3B). Benzeneselenol **2l** reacted with the terminal propargylic alcohol **1a** under a similar protocol to generate the α-selenium substituted ketone **3t** in a 41% yield.[12b]



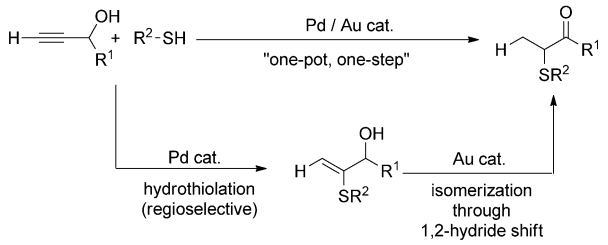
Scheme 3. Application to a cysteine derivative and selenol.

To understand the mechanism,[13] control experiments were performed by using alcohol **1a** and thiophenol **2a** (Scheme 4). Alcohol **1a** was treated with thiophenol **2a** in the presence of $Pd(OAc)_2$ which produced the sulfenylated allylic alcohol **4** (Scheme 4A). Compound **4** was treated with AuCl catalyst in a separate experiment that generated the product **3a** in a quantitative yield (Scheme 4B).



Scheme 4. Control experiments to support the mechanistic proposal.

The necessity to apply tandem Pd/Au catalysis in the case of terminal propargylic alcohols is explained by the initial Pd-mediated regioselective hydrothiolation step. As mentioned earlier, using only Au salt as the catalyst gave a nonregioselective reaction with multiple attacks of the thiol to the terminal triple bond of the propargylic alcohol. However, using a mixture of Pd and Au catalysts, Pd initially promoted the regioselective attack of the thiol at the β-position of the terminal propargylic alcohol to produce exclusively the desired sulfenylated allylic alcohol intermediate.[14] Noteworthy in this respect was that the high degree of regioselectivity and chemoselectivity by the Pd catalyst was also observed in the presence of Au salt. Thereby, sequential addition of the catalysts was not required. On using only Pd catalyst, the reaction stopped after the formation of the sulfenylated allylic alcohol intermediate. No further isomerization of this intermediate leading to the final product was observed. This intermediate was converted to the desired product by the Au-catalyzed[15] isomerization of the intermediate through a 1,2-hydride migration (Scheme 5).



Scheme 5. Present report of tandem Pd/Au-catalyzed synthesis of α-sulfenylated carbonyl compounds from terminal propargylic alcohols and thiols.

In conclusion, a highly atom efficient transformation of terminal propargylic alcohols and thiols through a tandem Pd/Au catalysis to synthesize a variety of α-sulfenylated carbonyl compounds has been developed. Diversity in substrate scope was observed in which both aromatic and aliphatic thiols and alcohols containing an aryl-, alkyl-group, or hydrogen at the R^1-position generated the desired products in good to excellent yields. The developed protocol was found to be applicable in the functionalization of a protected cystein derivative. By replacing thiol with selenol, the corresponding α-selenium substituted ketone was generated. A reaction mechanism is proposed that proceeds through a Pd-catalyzed regioselective hydrothiolation reaction followed by an Au-catalyzed 1,2-hydride migration.

Experimental Section

Representative experimental procedure for the synthesis of 3-(phenylthio)butan-2-one (3 a)

$Pd(OAc)_2$ (5 mg, 2 mol%) and AuCl (5 mg, 2 mol%) were weighed and transferred to a 5 mL microwave vial containing a small magnet in a glove box under a nitrogen atmosphere. The vial was capped tightly and was taken out from the glove-box. 2.0 mL of dry nitromethane solvent followed by alcohol **1 a** (78 μL, 1 mmol) were added and stirred at room temperature for 5 min. Benzenethiol **2 a** (123 μL, 1.2 mmol) was added and the reaction mixture was heated at 80 °C (oil bath) for 8 h. After completion of the reaction (by TLC analysis), nitromethane was evaporated under reduced pressure and the residue was purified by silica-gel (100–200 mess) column chromatography using 3% (v/v) ethyl acetate/pentane solution to afford the desired product **3 a** as a pale-yellow oil (178 mg, 0.99 mmol, 99%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.43$ (d, $J = 7.2$ Hz, 3H; H-4), 2.29 (s, 3H; H-1), 3.80 (q, $J = 7.2$ Hz, 1H; H-3), 7.27–7.31 (m, 3H; H-arom), 7.32–7.40 ppm (m, 2H; H-arom); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 16.0$, 26.3, 52.0, 128.0, 129.0, 132.6, 132.6, 132.7, 205.5 ppm.

Acknowledgements

This research was funded by the Swedish Research Council, Stiftelsen Olle Engkvist Byggmästare, Wenner Gren Foundation, and Swedish Institute.

Keywords: atom efficiency · gold · palladium · sulfenylated carbonyl · tandem catalysis

[1] a) R. J. Cremlyn, *An Introduction to Organo-Sulfur Chemistry*, Wiley & Sons, New York, **1996**; b) T. Kondo, T. A. Mitsudo, *Chem. Rev.* **2000**, *100*, 3205; c) *Organosulfur Chemistry in Asymmetric Synthesis* (Eds.: T. Toru, C. Bolm) Wiley & Sons, New York, **2008**; d) D. Giles, M. S. Prakash, K. V. Ramseshu, *E- Journal of Chem.* **2007**, *4*, 428; e) I. Hartman, A. R. Gillies, S. Arora, C. Andaya, N. Royapet, W. J. Welsh, D. W. Wood, R. J. Zauhar, *Pharm. Res.* **2009**, *26*, 2247; f) J. Krapcho, C. F. Turk, *J. Med. Chem.* **1973**, *16*, 776; g) T. Siatra-Papastaikoudi, A. Tsotinis, I. Chinou, C. Roussakis, *Farmaco* **1994**, *49*, 221.

[2] a) B. M. Trost, *Chem. Rev.* **1978**, *78*, 363; b) B. M. Trost, *Acc. Chem. Res.* **1978**, *11*, 453; c) R. M. Coates, *Angew. Chem.* **1973**, *85*, 630; *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 586; d) R. B. Woodward, I. J. Pachter, M. L. Scheinbaum, *J. Org. Chem.* **1971**, *36*, 1137; e) B. M. Trost, T. N. Salzmann, K. Hiroi, *J. Am. Chem. Soc.* **1976**, *98*, 4887.

[3] a) M. E. Kuehne, *J. Org. Chem.* **1963**, *28*, 2124; b) S. Murai, Y. Kuroki, K. Hasegawa, S. Tsutsumi, *J. Chem. Soc., Chem. Commun.* **1972**, 946; c) E. Okragla, S. Demkowicz, J. Rachon, D. Witt, *Synthesis* **2009**, 1720.

[4] D. A. Evans, K. R. Campos, J. S. Tedrow, F. E. Michael, M. R. Gagné, *J. Am. Chem. Soc.* **2000**, *122*, 7905.

[5] a) G.-L. Zhao, R. Rios, J. Vesely, L. Eriksson, A. Córdova, *Angew. Chem.* **2008**, *120*, 8596; *Angew. Chem. Int. Ed.* **2008**, *47*, 8468; *Angew. Chem.* **2008**, *120*, 8596; b) L. Fang, A. J. Lin, H. W. Hu, C. J. Zhu, *Chem. Eur. J.* **2009**, *15*, 7039 and references citer therein.

[6] a) M. Jereb, A. Togni, *Org. Lett.* **2005**, *7*, 4041; b) S. K. Srisailam, A. Togni, *Tetrahedron: Asymmetry* **2006**, *17*, 2603; c) M. Jereb, A. Togni, *Chem. Eur. J.* **2007**, *13*, 9384; d) T. Ishimaru, S. Ogawa, E. Tokunaga, S. Nakamura, N. Shibata, *J. Fluorine Chem.* **2009**, *130*, 1049.

[7] a) S. Biswas, J. S. M. Samec, *Chem. Commun.* **2012**, *48*, 6586; b) S. Biswas, C. Dahlstrand, R. A. Watile, M. Kalek, F. Himo, J. S. M. Samec, *Chem. Eur. J.* **2013**, *19*, 17939; c) R. A. Watile, S. Biswas, J. S. M. Samec, *Green Chem.* **2013**, *15*, 3176.

[8] For Gold-catalyzed hydrothiolation reactions, see a) Menggenbateer, M. Narsireddy, G. Ferrara, N. Nishina, T. Jin, Y. Yamamoto, *Tetrahedron Lett.* **2010**, *51*, 4627; b) A. Corma, C. González-Arellano, M. Iglesias, F. Sánchez, *Appl. Catal. A* **2010**, *375*, 49; c) for a mechanistic outlook on transition-metal-mediated hydrothiolation of unsaturated carbon–carbon bonds, see, R. Castarlenas, A. D. Giuseppe, J. J. Pérez-Torrente, L. A. Oro, *Angew. Chem.* **2013**, *125*, 223; *Angew. Chem. Int. Ed.* **2013**, *52*, 211; d) for gold-catalyzed cycloisomerization of α-thioallenes to 2,5-dihydrothiophenes, see, N. Morita, N. Krause, *Angew. Chem.* **2006**, *118*, 1930; *Angew. Chem. Int. Ed.* **2006**, *45*, 1897.

[9] For a recent study on gold–carbon bonding in gold–alkynyl complexes, see H.-T. Liu, X. G. Xiong, P. D. Dau, Y. L. Wang, D. L. Huang, J. Li, L. S. Wang, *Nature Commun.*, **2013**, *4*, DOI: 10.1038/ncomms3223.

[10] a) A. S. K. Hashmi, M. Ghanbari, M. Rudolph, F. Rominger, *Chem. Eur. J.* **2012**, *18*, 8113; b) A. S. K. Hashmi, C. Lothschütz, R. Döpp, M. Ackermann, J. de Buck, M. Rudolph, C. Scholz, F. Rominger, *Adv. Synth. Catal.* **2012**, *354*, 133; c) J. J. Hirner, K. E. Roth, Y. Shi, S. A. Blum, *Organometallics* **2012**, *31*, 6843; d) M. N. Pennell, M. G. Unthank, P. Turner, T. D. Sheppard, *J. Org. Chem.* **2011**, *76*, 1479; e) T. Lauterbach, M. Livendahl, A. Rosellón, P. Espinet, A. M. Echavarren, *Org. Lett.* **2010**, *12*, 3006; f) A. S. K. Hashmi, C. Lothschütz, R. Döpp, M. Rudolph, T. D. Ramamurthi, F. Rominger, *Angew. Chem.* **2009**, *121*, 8392; *Angew. Chem. Int. Ed.* **2009**, *48*, 8243; g) Y. Shi, K. E. Roth, S. D. Ramgren, S. A. Blum, *J. Am. Chem. Soc.* **2009**, *131*, 18022; h) Y. Shi, S. M. Peterson, W. W. Haberaecker III, S. A. Blum, *J. Am. Chem. Soc.* **2008**, *130*, 2168.

[11] For some representative reports on dual-metal catalysis, see a) D. C. Koester, M. Kobayashi, D. B. Werz, Y. Nakao, *J. Am. Chem. Soc.* **2012**, *134*, 6544; b) J. J. Hirner, Y. Shi, S. A. Blum, *Acc. Chem. Res.* **2011**, *44*, 603; c) Y. Hirata, A. Yada, E. Morita, Y. Nakao, T. Hiyama, M. Ohashi, S. Ogoshi, *J. Am. Chem. Soc.* **2010**, *132*, 10070; d) M. R. Grochowski, T. Li, W. W. Brennessel, W. D. Jones, *J. Am. Chem. Soc.* **2010**, *132*, 12412; e) D. J. Arriola, E. M. Carnahan, P. D. Hustad, R. L. Kuhlman, T. T. Wenzel, *Science* **2006**, *312*, 714; f) N. Jeong, S. D. Seo, J. Y. Shin, *J. Am. Chem. Soc.* **2000**, *122*, 10220; g) K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett.* **1975**, *16*, 4467.

[12] a) 1.5 equivalents of **2 k** was used with respect to **1 a**; b) reaction conditions: **1 a** (1 mmol), **2 l** (1.5 mmol), $Pd(OAc)_2$ (2 mol%) were heated at 80 °C for 12 h followed by another 12 h after adding AuCl (2 mol%) to the reaction mixture.

[13] A. S. K. Hashmi, *Angew. Chem.* **2010**, *122*, 5360; *Angew. Chem. Int. Ed.* **2010**, *49*, 5232.

[14] a) V. P. Ananikov, N. V. Orlov, S. S. Zalesskiy, I. P. Beletskaya, V. N. Khrustalev, K. Morokuma, D. G. Musaev, *J. Am. Chem. Soc.* **2012**, *134*, 6637; b) H. Kuniyasu, A. Ogawa, K. I. Sato, I. Ryu, N. Kambe, N. Sonoda, *J. Am. Chem. Soc.* **1992**, *114*, 5902.

[15] For homogeneous gold catalysis, see, a) M. Bandini, *Chem. Soc. Rev.* **2011**, *40*, 1358; b) A. S. K. Hashmi, M. Bührle, *Alrdichim. Acta* **2010**, *43*, 27; c) N. D. Shapiro, F. D. Toste, *Synlett* **2010**, 675; d) M. Lein, M. Rudolph, S. K. Hashmi, P. Schwerdtfeger, *Organometallics* **2010**, *29*, 2206; e) N. Bongers, N. Krause, *Angew. Chem.* **2008**, *120*, 2208; *Angew. Chem. Int. Ed.* **2008**, *47*, 2178; f) D. J. Gorin, B. D. Sherry, F. D. Toste, *Chem. Rev.* **2008**, *108*, 3351; g) R. A. Widenhoefer, *Chem. Eur. J.* **2008**, *14*, 5382; h) A. S. K. Hashmi, M. Rudolph, *Chem. Soc. Rev.* **2008**, *37*, 1766; i) D. J. Gorin, F. D. Toste, *Nature* **2007**, *446*, 395; j) A. S. K. Hashmi, *Chem. Rev.* **2007**, *107*, 3180; k) A. S. K. Hashmi, G. J. Hutchings, *Angew. Chem.* **2006**, *118*, 8064; *Angew. Chem. Int. Ed.* **2006**, *45*, 7896; l) A. Hoffmann-Röder, N. Krause, *Org. Biomol. Chem.* **2005**, *3*, 387; m) M. M. Hansmann, A. S. K. Hashmi, M. Lautens, *Org. Lett.* **2013**, *15*, 3226.

Received: October 21, 2013
Published online on January 29, 2014