CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.201103304

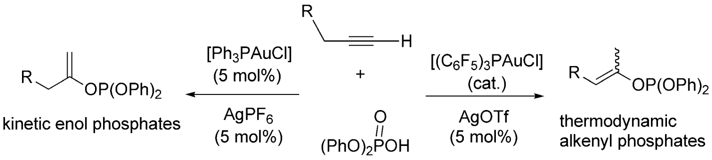
Gold(I)-Catalyzed Stereoselective Synthesis of Alkenyl Phosphates by Hydrophosphoryloxylation

Pierrick Nun,[a] Jonathan D. Egbert,[a] María-José Oliva-Madrid,[a, b] and Steven P. Nolan*[a]

In recent decades, late-transition-metal-mediated cross-coupling reactions have become one of the most important tools to create C–C bonds in organic synthesis.[1] Significant efforts have been devoted to developing catalytic systems, to expand the scope of useful substrates in these couplings. A significant goal is to develop systems that do not require aryl iodide or bromide, which represent the most common electrophilic moieties in Pd-catalyzed reactions.[2] Among the alternatives, we can cite the use of vinyl and aryl triflates[3] due to their excellent leaving group ability. Nevertheless, the synthesis of triflates is expensive and corrosive, making alternatives attractive. As a coupling partner, alkenyl phosphates have been proven reactive in most metal-catalyzed cross-coupling reactions, such as Stille,[4,8] Suzuki–Miyaura,[5] Negishi,[6] Kumada,[7] Sonogashira,[8] and Mizoroki–Heck.[9]

Alkenyl phosphate synthesis most often involves the conversion of carbonyl compounds into enolates by base-promoted proton extraction followed by reaction with dialkyl phosphorochloridates.[10] In addition to a simple synthesis, the selectivity between kinetic and thermodynamic alkenyl phosphates presents a significant challenge, which is difficult to solve using organic synthesis.[10b,11]

Gold complexes have emerged as powerful catalytic tools enabling numerous synthetic transformations.[12] Among a panoply of reagents, alkynes currently exist as the most prevalent substrates.[13] It is therefore not surprising that recently, Lee et al.[14] reported the gold(I)-catalyzed addition of diphenyl phosphates to terminal alkynes for the selective preparation of alkenyl phosphates using various phosphane-bearing gold centres in conjunction with silver salts as activators (Scheme 1). The choice of reaction conditions and catalytic system allow preparation of either the kinetic or thermodynamic product. Surprisingly, even though the reaction proved to be quite efficient with phosphane ligands, even at high catalyst loadings, the authors found no activity when *N*-heterocyclic carbenes[15] (NHC) were used as ligands.



Scheme 1. Previous protocols leading to the formation of kinetic and thermodynamic alkenyl phosphates.[14]

In the course of studies focusing on the chemistry of organogold complexes, we recently described the synthesis and characterization of an NHC-gold(I) hydroxide complex, [Au(IPr)(OH)] **1** (IPr = 1,3-bis-(2,6-diisopropylphenyl)imidazol-2-ylidene),[16] acting as a pre-catalyst and generating the corresponding active catalyst [Au(IPr)]$^+$ by protonolysis-activation using a Brønsted acid in situ. This procedure avoids the use of silver additives such as AgPF$_6$, AgBF$_4$, AgOTf, AgNTf$_2$, or AgSbF$_6$ that are known to be light- and moisture-sensitive, as well as expensive and toxic compounds. This pre-catalyst was previously applied to the hydration of alkynes at low catalyst loading.[17] Consequently, we decided to investigate this new catalytic system toward the hydrophosphoryloxylation of different terminal alkynes for the selective preparation of kinetic alkenyl phosphates (Markovnikov addition product).

To optimize the reactions conditions, 1-hexyne, with a short sterically unencumbered alkyl chain, was chosen as the model substrate to be reacted with diphenyl phosphate. Results of the catalyst generation protocol and subsequent transformation of 1-hexyne are summarized in Table 1. The reaction was carried out with [Au(IPr)(OH)] (**1**, 5 mol %) in toluene at 50 °C, using comparable conditions to those described by Lee et al. Unsurprisingly, without any acid activation, no reaction occurs and the starting material is isolated unchanged (Table 1, entry 1). When **1** is activated by a Brønsted acid (HX) to generate [Au(IPr)]X, relative conversion to either the kinetic or the thermodynamic alkenyl phosphate is dependent on the nature of X. With HNTf$_2$ no new product is observed (Table 1, entry 2), whereas with

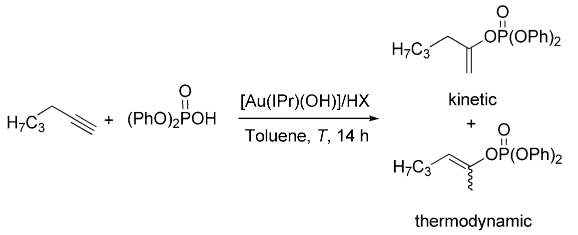
---

[a] Dr. P. Nun, Dr. J. D. Egbert, M.-J. Oliva-Madrid, Prof. S. P. Nolan
EaStCHEM School of Chemistry
University of St Andrews
St Andrews, KY 16 9ST (UK)
E-mail: snolan@st-andrews.ac.uk

[b] M.-J. Oliva-Madrid
Visiting researcher from:
Departamento de Química Inorgánica
Facultad de Química, Universidad de Murcia
Apartado 4021, 30071 Murcia (Spain)

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201103304.

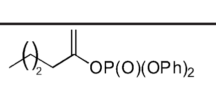
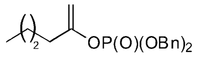
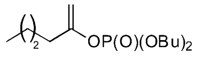
Table 1. Optimization of reaction conditions.



Entry	HX	[Au]/HX [mol %]	*T* [°C]	Conv. [%]	Kinetic/ Thermodynamic
1	–	5	50	0	–
2	HNTf$_2$	5	50	0	–
3	TfOH	5	50	100	8:92 (*E*/*Z* 1:0.3)
4	HBF$_4$	5	50	100	1:0
5	HBF$_4$	5	25	<20	1:0
6	HBF$_4$	1	50	100	1:0
7[a]	HBF$_4$	0.1	50	82	1:0
8[a]	HBF$_4$	0.1	70	100	1:0
9[a]	HBF$_4$	0.01	50	50	1:0
10	HBF$_4$	[Au] 0 HX 5	50	0	–

[a] Reaction time: 24 h.

Table 2. Gold(I) catalyzed synthesis of alkenyl phosphates.[a,b]

	Phosphate	*T* [°C]	Product	Yield [%]
1	diphenyl	50	 OP(O)(OPh)$_2$ **2a**	83[a]
2	dibenzyl	70	 OP(O)(OBn)$_2$ **2b**	76[a]
3	dibutyl	70	 OP(O)(OBu)$_2$ **2c**	68[a]

[a] Reaction time: 14 h; [b] 1 mol % catalyst loading.

HOTf and HBF$_4$ all the starting material is converted (Table 1, entries 3 and 4). However, the kinetic and thermodynamic products with HOTf form in an 8 to 92 mixture (Table 1, entry 3). Conversely, complete selectivity for the kinetic product is obtained with HBF$_4$ (Table 1, entry 4). Lowering the reaction temperature to 25 °C hinders the conversion significantly (Table 1, entry 5). A blank reaction without gold, in the presence of HBF$_4$ (5 mol %) gave no product and suggests that the reaction does not proceed by simple acid catalysis and that gold activation of the alkyne is necessary.

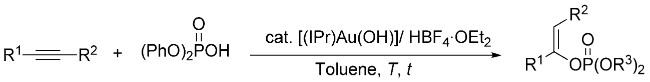
The minimal amount of **1** required was investigated to eliminate the use of excessive gold catalyst. In contrast to the [Au(PR$_3$)Cl] activated by silver system, which requires 5 mol % [Au], complex **1** gives full conversion with much lower loadings. With 1 mol % loading full conversion occurs within 14 h at 50 °C (Table 1, entry 6). With 0.1 mol % catalyst loading, full conversion occurs within 24 h, although a slight elevation in temperature to 70 °C is required (Table 1, entry 7). With extremely low catalyst loading (0.01 mol %) and the moderate temperature of 50 °C, a respectable 50 % conversion occurs in 24 h (Table 1, entry 9). Additional reactions were conducted with IPrAuCl (5 mol %) as catalyst and AgBF$_4$ or AgOTf (5 mol %) as co-catalyst and the best result using this protocol provided an 80 % conversion of the thermodynamic phosphate product after overnight stirring at 50 °C with 5 mol % each of IPrAuCl and AgOTf. These results highlight the higher reactivity of IPrAuOH in combination with acids and the superior selectivity of the protocol, allowing the preparation of either kinetic or thermodynamic alkenyl phosphates as a function of the nature of the activating acid.

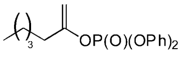
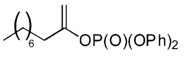
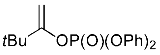
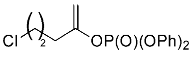
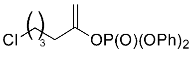
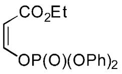
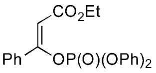
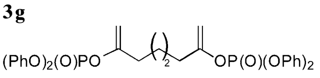
We next turned our attention to the direct preparation of various kinetic alkenyl phosphates through hydrophosphoryloxylation (Table 2). To further explore the scope of the reaction with respect to the phosphate selection, we carried out reactions with different phosphates and [Au(IPr)(OH)]/HBF$_4$ in toluene. As observed with our model substrate, when HBF$_4$ is used in combination with the catalyst [Au(IPr)(OH)] **1**, the kinetic alkenyl phosphates (Markovnikov products) form selectively in good yields (Table 2). 1-Hexyne, when reacted with diphenyl phosphate in the presence of [Au(IPr)(OH)]/HBF$_4$ (1 mol %) gave the desired product in 83 % isolated yield (Table 2, entry 1). The reactivity of both dibenzyl phosphate and dibutyl phosphate was examined using the same substrate. In both cases, the reactions required additional heating to 70 °C for comparable conversion in the same time as the less sterically demanding diphenyl phosphate (Table 2, entries 2 and 3).

Also explored, was the extent to which the alkyne could be varied. The reaction was conducted with several terminal alkynes with various length *n*-alkyl chains and diphenyl phosphate. Using 0.1 mol % loading the five-carbon derivative gives good but decreased reactivity compared with the four-carbon derivative (Table 3, entry 1). Transitioning to the much longer eight-carbon chain, results in more moderate reactivity (Table 2, entry 2). This reaction was also carried out at 70 °C with an extremely low catalyst loading, 0.01 mol %, and the desired product was isolated in 38 % yield. Using the much more sterically encumbered *tert*-butyl still gives the desired alkenyl phosphate, however 1 mol % catalyst loading is required for an efficient reaction. An 88 % yield was obtained after 14 h at 50 °C (Table 2, entry 3). The reaction still proceeds with 0.1 mol % catalyst loading but after 24 h at the same temperature only 20 % conversion is observed. Even at very low catalyst loading (0.01 mol %) the reaction between the *tert*-butyl substituted alkyne and diphenyl phosphate proceeds. Although sluggish, after 40 h 28 % conversion is achieved. Alkynes with electron-withdrawing halides have good conversion with 1 mol % catalyst loading. Treatment of 5-chloro-1-pentyne and 6-chloro-1-hexyne with diphenyl phosphate using 1 mol % of **1** in toluene at 50 °C (Table 3, entries 4 and 5), gave the corresponding alkenyl phosphates in 77 and 82 % yields respectively.

The addition of diphenyl phosphate to activated alkynes, such as ethyl propiolate and ethyl phenylpropiolate, gives *trans* addition in a regio- and stereoselective manner

Table 3. Gold(I) catalyzed synthesis of alkenyl phosphates.



	R^1; R^2	mol %	T [°C]	t [h]	Product	Yield [%]
1	n-C_5H_{11}; H	0.10	70	14	 **3a**	73
2	n-C_8H_{17}; H	0.1	70	18		64
		0.01	70	48	**3b**	38
3	tBu; H	1.0	50	14		88
		0.01	50	40	**3c**	28[a]
4	$Cl(CH_2)_3$; H	1.0	50	14	 **3d**	77
5	$Cl(CH_2)_4$; H	1.0	50	24	 **3e**	82
6	CO_2Et; H	1.0	50	14	 **3f**	74
7	CO_2Et; Ph	1.0	50	14	 **3g**	72
8	n-C_6H_9; H	0.01	50	20	 **3h**	96[a]

[a] % conversion from ^{31}P NMR spectroscopy.

(Table 3, entries 6 and 7).[18] Finally, a reaction was conducted using the di-terminal alkyne, 1,7-octadiyne. The reaction with phosphate occurs at both alkyne moieties. With extremely low (0.01 mol %) catalyst loading 1,7-octadiyne reacts nearly quantitatively with diphenyl phosphate in 20 h at 50 °C (Table 3, entry 8).

In conclusion, we have developed a straightforward silver-free method for the synthesis of alkenyl phosphates with high selectivity catalyzed by cationic gold(I) complexes generated in situ through the reaction between pre-catalyst [Au(IPr)(OH)] and HBF_4•OEt_2. The reaction requires low amounts of catalyst, and gives selectively the kinetic product. The reaction works with a variety of substrates. The main factor observed to require higher catalyst loading, increased temperature, or increased reaction time is sterics. In the case of sterically unencumbered substrates quantitative conversion can be realized with extremely low (0.01 mol %) catalyst loadings.

Experimental Section

General procedure for the synthesis of hex-1-en-2-yl diphenyl phosphate (2a): 1-hexyne (49.3 mg, 0.6 mmol) was added to a solution of [Au(IPr)(OH)], HBF_4•OEt_2, and phosphate (0.5 mmol) in toluene (2 mL) in a scintillation vial. The reaction was stirred at temperature, time, and catalyst loading as indicated in Table 2. The solvent was removed under vacuum and the crude product purified by silica-gel column chromatography (EtOAc/pentane 2:8) to afford hex-1-en-2-yl diphenyl phosphate (**2a**) as a colorless liquid (138 mg, 83 %). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.37$–7.33 (m, 4H, m-H), 7.25–7.18 (m, 6H, o-H+p-H), 4.94–4.92 (m, 1H, CH alkene), 4.60–4.59 (m, 1H, CH alkene), 2.22–2.18 (m, 2H, CH_2-C), 1.45–1.41 (m, 2H, CH_2), 1.33–1.26 (m, 2H, CH_2), 0.86 ppm (t, $^3J_{HH} = 7.2$ Hz, 3H, CH_3); ^{31}P NMR (162 Hz, $CDCl_3$): $\delta = -18.1$ ppm (s, OP(O)(OPh)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 156.1$ (s, C alkene), 150.7 (d, $^2J_{CP} = 10.2$ Hz, i-C, PhO), 129.9 (s, m-CH, PhO), 125.6 (s, p-CH, PhO), 120.2 (d, $^3J_{CP} = 6.6$ Hz, o-CH, PhO), 98.1 (d, $^3J_{CP} = 5.7$ Hz, CH_2 alkene), 34.1 (d, $^3J_{CP} = 7.4$ Hz, CH_2 aliphatic), 28.4 (s, CH_2 aliphatic), 22.0 (s, CH_2 aliphatic), 13.9 ppm (s, CH_3); HRMS (ESI): m/z: calcd for $C_{18}H_{21}O_4P$: 332.1177; found: 332.1170.

Acknowledgements

Support of this work by the ERC (Advanced Researcher Grant to S.P.N.) and EPSRC is gratefully acknowledged. We thank the Ministerio de Educación y Ciencia (Spain), FEDER (CTQ2007-60808/BQU), and Fundación Séneca (04539/GERM/06) for financial support to M.J.O.M. S.P.N. is a Royal Society Wolfson Research Merit Award holder.

Keywords: alkenyl phosphates • alkyne activation • gold • gold catalysis • homogeneous catalysis

---

[1] a) J. Tsuji, *Palladium Reagents and Catalysis: New Perspectives For the 21st Century*, Wiley, Chichester, **2004**; b) A. de Meijere, F. Diederich, *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed., Wiley-VCH, Weinheim, **2004**; c) E. Negishi, *Handbook of Organopalladium Chemistry for Organic Synthesis*, John Wiley&Sons, New York, **2002**; d) J. Tsuji, *Transition Metal Reagents and Catalysts: Innovations in Organic Synthesis*, John Wiley&Sons, Chichester, **2000**; e) *Advances in Metal-Organic Chemistry* (Ed.: L. S. Liebeskind), JAI Press, Greenwich, CT, **1996**; f) *Comprehensive Organic Synthesis* (Ed.: B. M. Trost), Pergamon Press, New York, **1991**; g) I. P. Beletskaya, A. V. Cheprakov, *Chem. Rev.* **2000**, *100*, 3009; h) W. A. Herrmann, V. P. W. Böhm, C.-P. Reisinger, *J. Organomet. Chem.* **1999**, *576*, 23; i) A. de Meijere, F. E. Meyer, *Angew. Chem.* **1994**, *106*, 2473; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2379.

[2] a) A. Zapf, M. Beller, *Chem. Commun.* **2005**, 431; b) A. F. Littke, G. F. Fu, *Angew. Chem.* **2002**, *114*, 4350; *Angew. Chem. Int. Ed.* **2002**, *41*, 4176; c) L. Ackermann, *Synlett* **2007**, *4*, 507; d) L. Ackermann, *Synthesis* **2006**, *10*, 1557; e) H. U. Blaser, A. Indolese, F. Naud, U. Nettekoven, A. Schnyder, *Adv. Synth. Catal.* **2004**, *346*, 1583; f) K. Selvakumar, A. Zapf, M. Beller, *Org. Lett.* **2002**, *4*, 3031; g) N. J. Whitcombe, K. K. M. Hii, S. E. Gibson, *Tetrahedron* **2001**, *57*, 7449; h) H. Ohta, M. Tokunaga, Y. Obora, T. Iwai, T. Iwasawa, T. Fujihara, Y. Tsuji, *Org. Lett.* **2007**, *9*, 89; i) A. Littke, M. Soumeillant, R. F. Kaltenbach, R. J. Cherney, C. M. Tarby, S. Kiau, *Org. Lett.* **2007**, *9*, 1711; j) L. Ackermann, R. Born, J. H. Spatz, D. Meyer, *Angew. Chem.* **2005**, *117*, 7382; *Angew. Chem. Int. Ed.* **2005**, *44*, 7216.

[3] a) K. Ritter, *Synthesis* **1993**, 735; b) T. Luker, H. Hiemstra, W. N. Speckamp, *J. Org. Chem.* **1997**, *62*, 8131; c) E. G. Occhiato, A. Trabocchi, A. Guarna, *J. Org. Chem.* **2001**, *66*, 2459.

[4] a) C. Buon, P. Bouyssou, G. Coudert, *Tetrahedron Lett.* **1999**, *40*, 701; b) K. C. Nicolaou, G.-Q. Shi, J. L. Gunzner, P. Gärtner, Z. Yang, *J. Am. Chem. Soc.* **1997**, *119*, 5467; c) H. Fuwa, M. Sasaki, *Org. Lett.* **2007**, *9*, 3347.

[5] a) A. L. Hansen, J.-P. Ebran, T. M. Gøgsig, T. Skrydstrup, *Chem. Commun.* **2006**, 4137; b) U. S. Larsen, L. Martiny, M. Begtrup, *Tetrahedron Lett.* **2005**, *46*, 4261; c) I. B. Campbell, J. Guo, E. Jones, P. G. Steel, *Org. Biomol. Chem.* **2004**, *2*, 2725; d) F. Lepifre, S. Clavier, P. Bouyssou, G. Coudert, *Tetrahedron* **2001**, *57*, 6969; e) Y. Nan, Z. Yang, *Tetrahedron Lett.* **1999**, *40*, 3321.

[6] a) J. Wu, Z. Yang, *J. Org. Chem.* **2001**, *66*, 7875; b) K. C. Nicolaou, G.-Q. Shi, K. Namoto, F. Bernal, *Chem. Commun.* **1998**, 1757; c) A. L. Lindhardt, T. M. Gogsig, T. Skrydstrup, *J. Org. Chem.* **2009**, *74*, 135.

[7] a) T. Hayashi, T. Fujiwa, Y. Okamoto, Y. Katsuro, M. Kumada, *Synthesis* **1981**, 1001; b) T. Hayashi, Y. Katsuro, Y. Okamoto, M. Kumada, *Tetrahedron Lett.* **1981**, *22*, 4449; c) B. C. Chary, S. Kim, D. Shin, P. H. Lee, *Chem. Commun.* **2011**, *47*, 7851.

[8] F. Lo Galbo, E. G. Occhiato, A. Guarna, C. Faggi, *J. Org. Chem.* **2003**, *68*, 6360.

[9] a) J. W. Coe, *Org. Lett.* **2000**, *2*, 4205; b) X. Fu, S. Zhang, Yin, J. T. L. McAllister, S. Jiang, A. T. Chou-Hong, K. Thiruvengadam, F. Zhang, *Tetrahedron Lett.* **2002**, *43*, 573; c) A. L. Hansen, T. Skrydstrup, *J. Org. Chem.* **2005**, *70*, 5997; d) A. L. Hansen, T. Skrydstrup, *Org. Lett.* **2005**, *7*, 5585; e) A. L. Hansen, J.-P. Ebran, M. Ahlquist, P.-O. Norrby, T. Skrydstrup, *Angew. Chem.* **2006**, *118*, 3427; *Angew. Chem. Int. Ed.* **2006**, *45*, 3349; f) J.-P. Ebran, A. L. Hansen, T. M. Gogsig, T. Skrydstrup, *J. Am. Chem. Soc.* **2007**, *129*, 6931.

[10] For examples of enolate formation, see: a) H. B. Mekelburger, C. S. Wilcox in *Comprehensive Organic Synthesis* Vol. 2 (Ed.: B. M. Trost), Pergamon, Oxford, **1991**, pp. 99–131; b) D. L. Boger in *Modern Organic Synthesis* TSRI, La Jolla, **1999**, pp. 147–206; c) W. Carruthers, I. Coldham, in *Modern Methods of Organic Synthesis* Cambridge University Press, Cambridge, **2004**, pp. 9–19; d) M. E. Limmert, A. H. Roy, J. F. Hartwig, *J. Org. Chem.* **2005**, *70*, 9364.

[11] M. E. Krafft, R. A. Holton, *Tetrahedron Lett.* **1983**, *24*, 1345.

[12] a) A. Arcadi, *Chem. Rev.* **2008**, *108*, 3266–3325; b) A. Fürstner, *Chem. Soc. Rev.* **2009**, *38*, 3208–3221; c) D. J. Gorin, F. D. Sherryand, F. D. Toste, *Chem. Rev.* **2008**, *108*, 3351; d) A. S. K. Hashmi, *Chem. Rev.* **2007**, *107*, 3180; e) E. Jiménez-Nuñez, A. M. Echavarren, *Chem. Rev.* **2008**, *108*, 3326; f) S. P. Nolan, *Acc. Chem. Res.* **2011**, *44*, 91; g) R. Skouta, C.-J. Li, *Tetrahedron* **2008**, *64*, 4917; h) T. W. Hudnall, A. G. Tennyson, C. W. Bielawski, *Organometallics* **2010**, *29*, 4569.

[13] a) A. Martínez, P. García-García, M. A. Fernández-Rodríguez, F. Rodríguez, R. Sanz, *Angew. Chem.* **2010**, *122*, 4737; *Angew. Chem. Int. Ed.* **2010**, *49*, 4633; b) E. Jímenez-Nuñez, A. M. Echavarren, *Chem. Commun.* **2007**, 333.

[14] P. H. Lee, S. Kim, A. Park, B. C. Chary, S. Kim, *Angew. Chem.* **2010**, *122*, 6958; *Angew. Chem. Int. Ed.* **2010**, *49*, 6806.

[15] For the use of NHCs in late-transition-metal catalysis, see; S. Díez-González, N. Marion, S. P. Nolan, *Chem. Rev.* **2009**, *109*, 3612.

[16] a) S. Gaillard, A. M. Z. Slawin, S. P. Nolan, *Chem. Commun.* **2010**, *46*, 2742–2744; b) S. Gaillard, J. Bosson, R. S. Ramon, P. Nun, A. M. Z. Slawin, S. P. Nolan, *Chem. Eur. J.* **2010**, *16*, 13729.

[17] P. Nun, R. S. Ramon, S. Gaillard, S. P. Nolan, *J. Organomet. Chem.* **2011**, *696*, 7.

[18] For reports dealing with the *trans*-selective addition to alkynes in gold catalysis, see: a) C. Krauter, A. S. K. Hashmi, M. Pempointer, *ChemCatChem* **2010**, *2*, 1226; b) A. S. K. Hashmi, *Angew. Chem.* **2010**, *122*, 5360; *Angew. Chem. Int. Ed.* **2010**, *49*, 5232.

Received: October 19, 2011