DOI: 10.1002/adsc.200900491

Reusable Gold(I) Catalysts with Unique Regioselectivity for Intermolecular Hydroamination of Alkynes

Antonio Leyva[a] and Avelino Corma[a,*]

[a] Instituto de Tecnología Química UPV-CSIC, Avda. de los Naranjos s/n, 46022 Valencia, Spain
Fax: (+34)-96-387-7809; phone: (+34)-96-387-7800; e-mail: acorma@itq.upv.es

Received: July 13, 2009; Revised: September 22, 2009; Published online: November 18, 2009

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200900491.

Abstract: Two gold(I) phosphine complexes bearing the low-coordinating bis(trifluoromethanesulfonyl)-imidate ligand, namely AuSPhosNTf$_2$ and AuPPh$_3$NTf$_2$, are active catalysts for the regioselective intermolecular hydroamination of both internal and terminal alkynes under mild reaction conditions. The catalysts show a regioselectivity based on electronic rather than steric factors, which allow the preferential synthesis of regioisomers opposite to those described previously. This subtle chemo- and regioselectivity depends on the catalyst, substrates and reaction conditions employed, and allows one to perform new tandem reactions. These gold(I) complexes operate under free-solvent conditions, without exclusion of air, without addition of acidic promoters and can be quantitatively recovered and reused by simple precipitation in hexane.

Keywords: alkynes; gold catalysis; hydroamination; imines; recoverable catalysts; regioselectivity

Introduction

The hydroamination of alkynes is a paradigmatic example of modern, sustainable organic reaction since it is catalytic and occurs with 100% atom economy.[1,2] This reaction allows the preparation of important nitrogen-containing compounds such as imines, enamines and hydrazones. However, there is not yet a simple method to achieve this transformation in a selective, efficient and environmentally friendly manner.

On one hand, a large number of catalysts has been reported to catalyse the *intra*molecular hydroamination of alkynes, including Brønsted acids and bases and metal salts and complexes.[1] Transition metal complexes, particularly those arising from palladium, are the most common catalyst for this transformation, leading to higher yields and allowing milder reactions conditions.[1] However, most of them need additional acidic promoters and/or heating to efficiently accelerate the process. On the other hand, examples of *inter*molecular hydroamination of alkynes are scarcer in the literature, and the catalysts reported, titanium,[3,4] lanthanide and actinide,[5] zirconium,[6] ruthenium,[7] and palladium[8] complexes have shown good activity, under moderate to high temperatures. Mercury salts[9] and the rhodium system [Rh(cod)$_2$]BF$_4$/PCy$_3$ reported by Beller[10] are active at room temperature for aromatic amines. However, most of the systems are unable to incorporate intermolecularly *alkyl*amines to alkynes except for the titanium complexes Cp*$_2$Ti reported by Doye[3,4] and some lanthanides and actinides complexes,[5] all of them working at temperatures between 60 and 110 °C. As remarked by the same authors, the high oxophilicity of those metals dwarfs the functional group tolerance, the use of late transition metals being a possible solution to this problem.

Gold compounds have shown high activity as catalysts for reactions involving the activation of unsaturated carbon-carbon bonds, especially triple bonds.[10] In the last years, a series of homogeneous[11] and heterogeneous[12] gold catalysts has surpassed, in some cases, the catalytic activity and/or selectivity of other metal catalysts. Among those, the hydroamination of alkynes has been reported.[13,14] The use of carbene-gold complexes as catalyst has proven to be particularly efficient.[14] Unfortunately, no regioselectivity has been described for internal alkynes in all the catalytic systems reported and the addition of alkylamines (or NH$_3$) is restricted to the carbene-gold catalysts.[14].

Concerning the reusability of the catalysts, few examples can be found in the literature for *inter*molecular hydroaminations. Sustainable chemistry demands

efficient catalytic process wherein the catalysts can be recovered and reused at the end of the reaction. To this respect, Lingaiah has reported cationic silver[15] and copper[16] exchanged tungstophosphoric acids as reusable catalysts for intermolecular hydroaminations. Recently, our group has reported two different gold-supported catalysts, on an Sn-containing MCM-41 support[17] and on a chitosan polymer,[18] which are able to catalyse the hydroamination of alkynes with aromatic amines with good conversions and selectivities. All these systems are based on the incorporation of the active species on insoluble solid supports, which often requires harder reaction conditions. The above catalysts work within a limited range of substrates (especially internal alkynes) and at $>70\,^{\circ}C$ reaction temperature. From all of the above, we can conclude that there is still a need for a general, efficient, selective and recoverable catalyst to perform the regioselective hydroamination of alkynes under mild conditions.

We have recently reported[19a] the hydration of alkynes at room temperature without acidic promoters by using easy-to-make, stable gold complexes such as $AuPR_3NTf_2$ (PR_3 = SPhos, PPh_3). We show here that these complexes are active for the *inter*molecular hydroamination of terminal alkynes with both alkyl- and arylamines at room temperature under solvent-free conditions, without requiring an inert atmosphere or the addition of external acidic promoters. The gold complexes are recovered at the end of the reaction by simple precipitation and filtration, and can be reused several times, while the corresponding products are obtained from the filtrates after removal of the solvent. This strategy constitutes a straightforward manner to isolate these acid-labile reaction products, since no chromatographic techniques are needed. Moreover, we will show that a subtle chemoselectivity operates depending on the catalyst and substrates employed. This will lead to transform internal alkynes to the corresponding imines with good to excellent regioselectivities, using aromatic amines under moderate conditions. The regioisomers produced have not been obtained in an efficient manner previously. Finally, we will show that the mildness of the conditions allows the inclusion of the gold-catalysed hydroamination into some new tandem reactions to obtain elaborated products in one-pot processes.

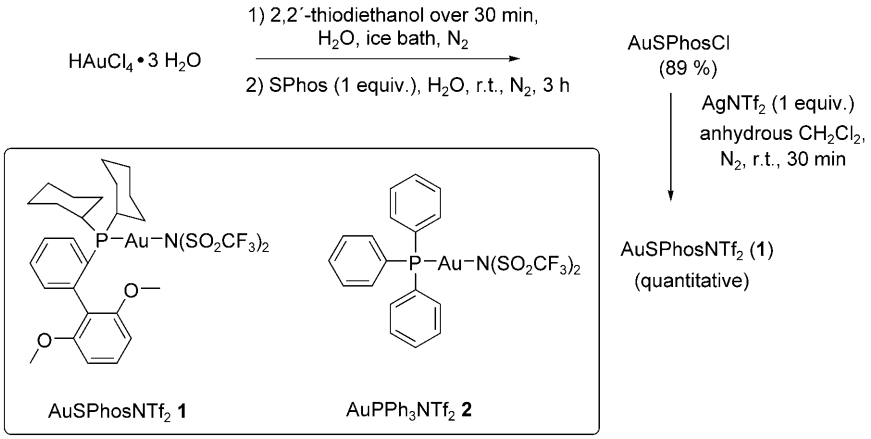
Results and Discusion

Synthesis and Characterisation of the $AuPR_3NTf_2$ Complexes

The catalysts employed in this work are our AuSPhosNTf$_2$ (**1**)[19a] [SPhos = 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl, NTf_2 = bis(trifluoromethanesulfonyl)imidate)] and the recently prepared by Gagosz and co-workers, commercially available $AuPPh_3NTf_2$ (**2**)[20] (Scheme 1).

The synthesis of this kind of complexes is easy and quantitative. Complex **1** is obtained as white crystals[19b] after recrystallisation in hexane-CH_2Cl_2, and it can be handled in open air. The activity is fully preserved after being stored in a dry box for 6 months. The crystal structure of complex catalyst **1** has been obtained here by DRX and it is shown in Figure 1 (see appendix in Supporting Information for data collection).

The presence of the ligand SPhos leads to a much more asymmetrical configuration compared to that of complex **2**,[20] observing how one side contains the polar motifs of the molecule (biphenyl, two SO_2, upper part in Figure 1) and the other side contains the apolar motifs (cyclohexyls, two CF_3, lower part in Figure 1). These structural differences between the two gold complexes could explain the different activities and selectivities that will be shown along this work.



Scheme 1. Preparative route for AuSPhosNTf$_2$ (**1**) and structures of complexes AuSPhosNTf$_2$ **1** and $AuPPh_3NTf_2$ **2**.

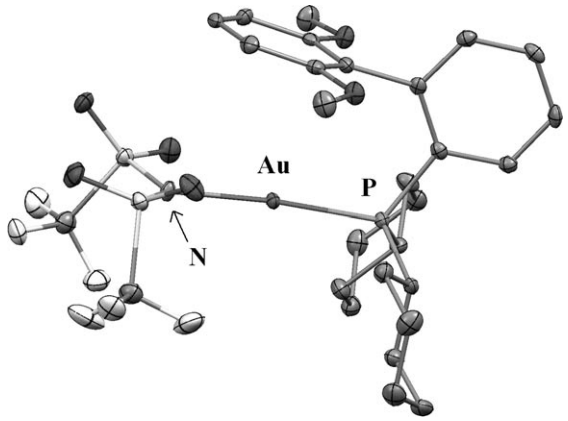


Figure 1. ORTEP structure of complex **1**. Ellipsoids account for 50% probability.[19b]

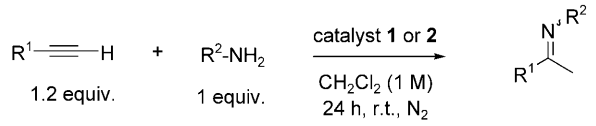
Hydroamination of Terminal Alkynes

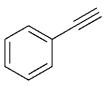
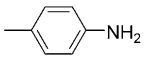
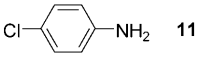
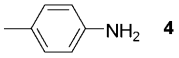
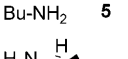
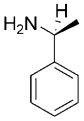
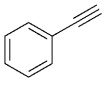
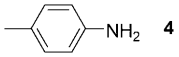
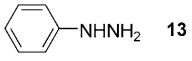
The first reactions tested were the hydroamination of 1-octyne **3** with *p*-toluidine **4** or *n*-butylamine **5**, using complex **2** as catalyst. Results are shown in Table S1 (see Supporting Information). It was found that hydration competes with hydroamination in non-freshly distilled solvents.[19a] However, the use of freshly distilled CH_2Cl_2 and dried CH_3CN solvents or, more conveniently, working under *solvent-free* conditions, minimises the formation of ketone (entries 8–10 and 13–15), **3** being converted to the corresponding imines **6** and **7** with good yields (entries 10 and 13) and selectivity. Inert atmosphere is not required to effectively perform the reaction (entry 10). In order to compare the activities of complexes **1** and **2** for the hydroamination of 1-octyne **3** with *p*-toluidine **4**, a kinetic study was accomplished (Supporting Information, Figure S1). The results showed that complex **1** gives a higher initial rate and final yield than complex **2**.

We have checked that the imine is formed by addition of the amine to the alkyne and not by condensation with the ketone that could arise from the hydration of the alkyne. Thus, experiments were carried out, (Supporting Information, Scheme S1) showing that 2-octanone **8** does not give imine **6** even in the presence of catalyst **1** (A). In fact, the reactivity of the amines towards **8** is opposite (B) to that observed for the hydroamination.

Different loadings of **1** were used for the reaction between phenylacetylene **9** and *p*-toluidine **4**, changing the corresponding solvent and reaction tempera-

Table 1. Hydroamination of terminal aromatic and alkyl alkynes with different aromatic and alkyl amines, using complexes **1** or **2** as catalysts.



Entry	Catalyst	Au [mol%]	Alkyne	Amine	Imine [%][a]
1	**1**	2.5	 **9**	 **4**	97 (94)
2	**1**	2.5		**4**	81 (68)
3	**1**	5		**4**	(74)
4	**1**	10	**3**	**4**	(92)[b]
5	**1**	5	**3**	 **11**	(74)
6	**2**	2	**3**	 **4**	70
7	**2**	5	**3**	 **5**	81
8	**2**	5	**3**	 **12**	95 (85)
9	**2**	5	 **9**	 **4**	57
10	**2**	5	**9**	 **13**	(71)

[a] GC yield. In brackets, isolated yield.
[b] 2 equiv. of **3**.

ture (Supporting Information, Table S2). The reaction was carried out in the presence of air and turnovers (TON) of *ca.* 2000 can be achieved by using CH_3CN as solvent at 80 °C (entry 1). The reaction can be performed at room temperature and 1 mol% of **1** is enough to give quantitatively the hydroamination of **9** after 24 h, using CH_3CN or CH_2Cl_2 as solvents (entries 12 and 13) or under free-solvent conditions (entry 14).

The scope of the reaction has been considered and the results are shown in Table 1. As it can be seen, both gold(I) complexes **1** and **2** are suitable catalysts for the hydroamination of aromatic and alkyl alkynes. Markovnikov addition was found in all cases.[19c] As previously assessed (see Supporting Information, Figure S1), complex **1** is in general more active than **2** when aromatic amines are involved. However, complex **1** was inactive for alkylamines. Interestingly, complex **2** was an excellent catalyst for the hydroamination of alkylalkynes with *alkyl*amines (entries 7 and 8), including phenylhydrazines (entry 10) to form hydrazones. Particularly interesting is the hydroamination with the chiral amine **12** (entry 8), since later hydrogenation and deprotection leads to enantiomerically pure primary amines,[4,21] if partial racemisation does not occur.[3c]

As highlighted in the introduction, recovery and reusability of the catalyst are important issues, and the results obtained here are shown in Figure 2.

Gold(I) complexes **1** and **2** can be precipitated quantitatively by adding hexane (10–20:1 *v:v*) at room temperature and stirring for 15–30 min. After sedimentation of the solid, the liquid is poured out and the remaining solid catalyst is washed with hexane, dried and reused. Complex **1** was used here six times without any decrease of the catalytic activity, either in solution (A) or under *free-solvent* conditions (B). Accordingly, the ^{31}P NMR spectra (Supporting Information, Figure S2) of the reused catalyst showed the presence of the phosphine ligands. Since the reaction is quantitative, imine **10** is easily obtained from the liquid phases after removal of the solvents. Furthermore, the analysis of gold by atomic absorption spectroscopy of imine **10** after isolation (reaction A in

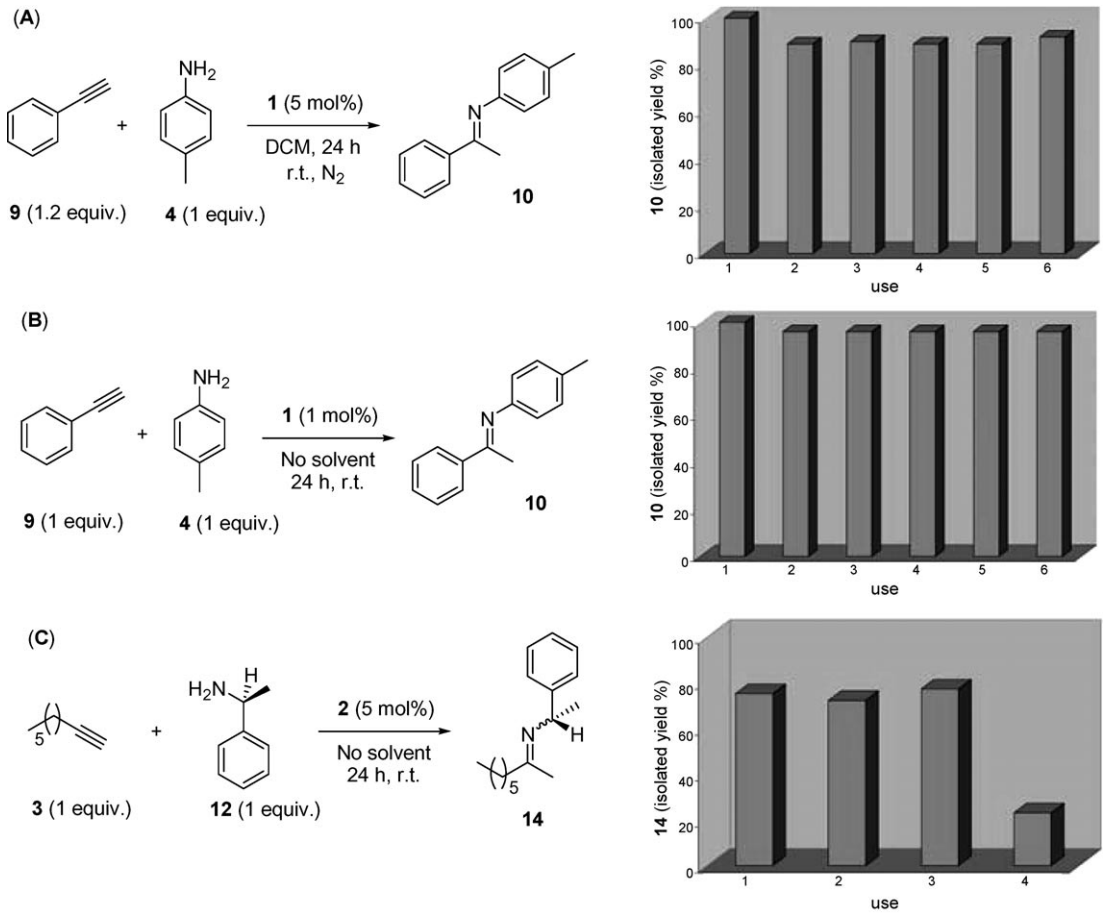


Figure 2. Reusability study for: (**A**) the hydroamination of phenylacetylene **9** with *p*-toluidine **4** catalysed by **1** (5 mol%) using DCM (2 M) as solvent under a nitrogen atmosphere; (**B**) the same reaction but using five times less catalyst, no protecting atmosphere and *solvent-free* conditions; (**C**) the hydroamination of 1-octyne **3** with *(S)*-1-phenylethylamine **12** catalysed by **2** (5 mol%) using the same experimental conditions as (B).

Table 2. Combinatorial study for the hydroamination of different terminal aromatic and alkyl alkynes with different aromatic and alkyl amines, using complexes **1** or **2** as catalysts. *Notation:* result for catalyst **1**/result for catalyst **2** (GC yield). For reaction conditions see Table 1.

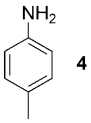
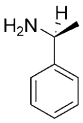
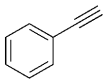
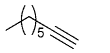
Entry	Alkyne \ Amine	A  **4**	B $Bu\text{-}NH_2$ **5**	*C*  **12**
1	 **9**	**97**/57	< 1/< 1	*19/7*
2	 **3**	***85/70***	*< 1/**81***	*2/**95***

Table 3. General catalytic behaviour of complexes **1** and **2** for the hydroamination reaction between different alkynes and amines, under the reaction conditions described in Table 1.

AuSPhosNTf$_2$ **1**			AuPPh$_3$NTf$_2$ **2**		
Alkyne \ Amine	Aromatic	*Alkylic*	Alkyne \ Amine	Aromatic	*Alkylic*
Aromatic	✓✓	*X*	Aromatic	✓	*X*
Alkylic	✓✓	*X*	*Alkylic*	✓	✓✓

Figure 2) gives a value of 0.41 ppm, which is below the limit authorised by the European Union for heavy metals in food.[22]

Mechanistic Studies: Towards a Predictable Regioselectivity for Internal Alkynes

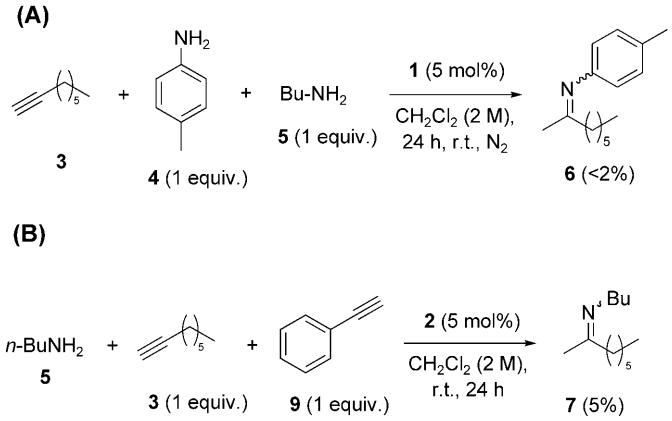
As indicated in Table 1, complex **1** is active only for aromatic amines. However, complex **2** is active for alkylamines, but only and exclusively with alkylalkynes. This curious behaviour has been further studied by performing a series of experiments where all the possible combinations between alkynes and amines have been tested under the same reaction conditions, using **1** or **2** as catalysts. Thus, phenylacetylene **9** and 1-octyne **3** were chosen as models for alkynes, and *p*-toluidine **4**, *n*-butylamine **5** and *S*-phenylethylamine **12** (as a benzylic partner) were chosen as amines (Table 2).

It can be clearly seen from Table 2 that complex **1** is highly active when the aromatic amine **4** (entries 1A and 2A) is the coupling partner, but completely inactive when the alkylamines **5** and **12** are used (entries 1B, 1C and 2B, 2C). In contrast, complex **2** is only moderately active for the aromatic amine **4** (entries 1A and 2A) but highly active for both alkylic amines (entries 2B, 2C). Surprisingly, complex **2** is mainly inactive to couple the aromatic phenylacetylene **9** with the alkylamines **5** and **12** (entries 1B, 1C). This dual catalytic behaviour of the complexes **1** and **2** towards alkynes and amines can be summarised as shown in Table 3.

The low reactivity of alkylamines compared to aromatic amines in metal-catalysed hydroaminations is well reported, and can be explained by the higher basicity and coordination ability of the former, that could lead to the poisoning of the catalyst. However, the excellent reactivity of alkylalkynes and the lack of reactivity of aromatic alkynes with alkylamines when complex **2** is used as catalyst is a surprising issue.

These dramatic differences in reactivity arising from subtle structural changes have been further studied. Then, two competitive reactions were firstly performed: (A) mixing both types of amines (aromatic and alkyl) with the alkylalkyne **3**; and (B) mixing both types of alkynes with the alkylamine **5** (Scheme 2).

The reactive amine **4** and the unreactive amine **5** were mixed with alkyne **3**, using **1** as catalyst (equation A). The presence of **5** completely inhibited the formation of **6**, which is formed in 74% isolated yield when **5** is not present (see Table 1, entry 3). Seemingly, the reactive alkyne **3** and the unreactive alkyne **9** were mixed with *n*-butylamine **5**, using **2** as catalyst (equation B). Again, the presence of **9** inhibited the formation of the imine **7**, which should be formed in 81% yield if **9** was not present (see Table 1, entry 7). To confirm this effect, a kinetic study was carried out, comparing the latter reaction (equation B in



Scheme 2. Competitive experiments: (**A**) between 1-octyne **3** and *p*-toluidine **4** and *n*-butylamine **5**, using **1** as catalyst; (**B**) between *n*-butylamine **5** and 1-octyne **3** and phenylacetylene **9**, using **2** as catalyst.

Scheme 2) without **9** and when one equivalent of **9** was added at 4 h reaction time (Figure 3).

The time-plot formation of imine **7** for both reactions clearly shows that just after the addition of phenylacetylene **9** the reaction stops. The little amount of **7** formed at this point is consumed, probably, by the nucleophilic attack of **9** to the imine in **7** to form the amine.[23] This inhibition by the aromatic alkyne **9** should come from electronic rather than steric effects, since the molecular size of **9** is even smaller than that of **3**. Two facts suggest that the attack of the amine does not occur in an outer-shell fashion but after coordination of both alkyne and amine to the gold

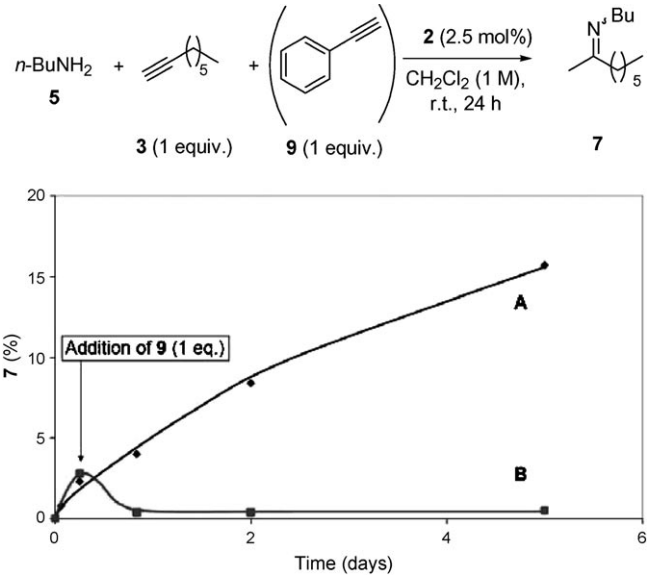


Figure 3. Kinetic study for the hydroamination between *n*-butylamine **5** with 1-octyne **3**, using **2** as catalyst under diluted conditions (**A**), and the same reaction conditions but adding phenylacetylene **9** at reaction time = 4 h (**B**).

centre: i) the more electrophilic alkynes (aromatics) and the more nucleophilic amines (alkyls) do not react between them and ii) aromatic alkynes are responsible for the inhibition of the reaction. To confirm these assumptions, the hydroamination of 1-octyne **3** with *n*-butylamine **5**, using **2** as catalyst, was followed by *in-situ* ^{1}H- and ^{31}P NMR spectroscopy. ^{1}H NMR will give information about the success of the reaction and ^{31}P NMR about the status of the catalyst. Two additional experiments were carried out, using phenylacetylene **9** as the alkyne or alkynes **3** and **9** together. The results and a plausible mechanism are shown in Figure 4.

Starting from the fresh catalyst **2**, the corresponding signal at 30 ppm shifts to 32 ppm when **3** is added (**I**). A similar intramolecular gold(I) complex has been isolated by Toste.[24] Subsequently, when **5** is added, a signal around 38 ppm predominates (**II**), which disappears after the reaction is nearly completed and imine **7** is formed, as assessed by ^{1}H NMR. As expected, the original signal of **2** at 30 ppm re-appears together with a minor signal at 32 ppm, corresponding to a small amount of alkyne **3** which is still interacting with the gold centre. Then, the catalyst is ready for a next run. When **9** is added to **2**, a signal shifted to 36 ppm is observed (**III**), which correlates with the higher electrophilicity of **9** compared to **3**. If **9** is added to intermediate **I** only the signal at 36 ppm is observed, the signal at 32 ppm disappearing. This can infer that **9** completely displaces **3** from the gold centre. Following the cycle anticlockwise, addition of **5** shifts the signal +6 ppm as observed for (**II**) (42 ppm, **IV**), indicating that **5** is able to coordinate to the gold centre. However, **IV** does not evolve to the imine. A control experiment showed that **5** does not change the signal of the fresh catalyst **2**, no interaction being produced.

The mechanism presented above correlates with the results obtained during the competitive experiment (Scheme 2, equation B) and the kinetic study (Figure 3). Phenylacetylene **9** clearly poisons the catalyst **2** for alkylalkynes such as **3**. All these effects can be rationalised in terms of *hard-soft* interactions. Gold(I) is a soft centre, that is coordinated in the original complex **2** to the soft, low-coordinating NTf_2 ligand. Then, a better soft donor ligand such as alkyne **3** displaces NTf_2. At this point, amine **5** is able to coordinate to the gold centre (not before, according to its nature as hard base), while the alkyne and the amine achieve the appropriate electronic nature to react and liberate the gold(I) centre for a new catalytic cycle. In contrast, the aromatic alkyne **9** is a softer donor ligand than alkylic **3**, due to the electron withdrawal action of the benzene ring, so it coordinates preferentially to form the intermediate **III**. However, in this particular case, intermediate **IV** is not active to perform the reaction.

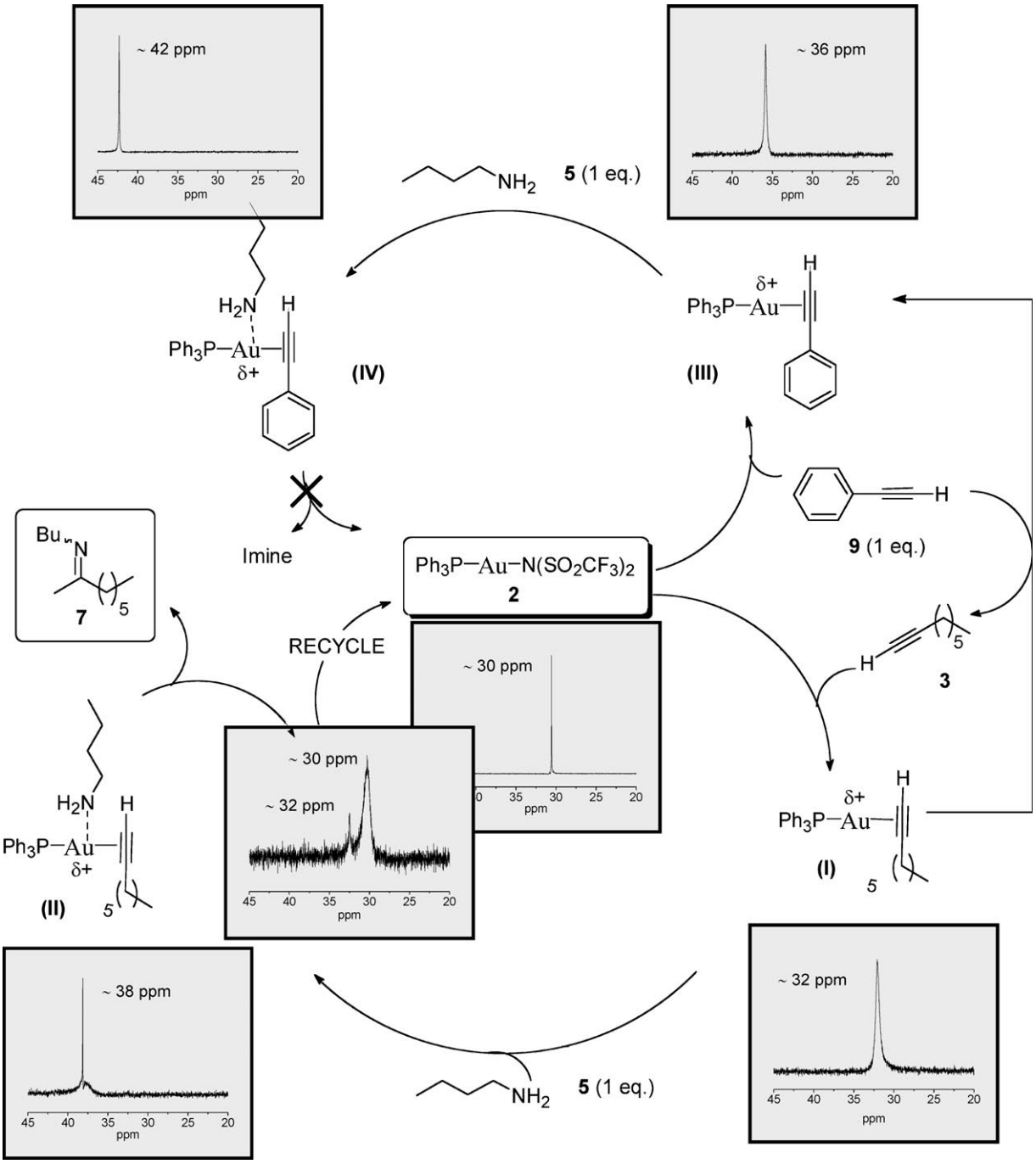


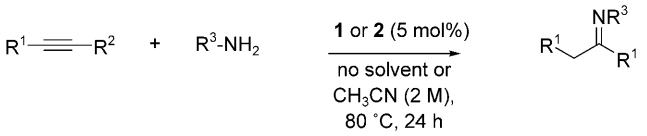
Figure 4. Plausible mechanism for the hydroamination of 1-octyne **3** and/or phenylacetylene **9** with *n*-butylamine **5**, using **2** as catalyst and $CDCl_3$ as solvent .^{31}P NMR spectra of complex **2** and the different intermediates are shown nearby.

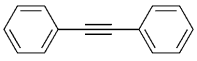
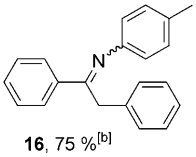
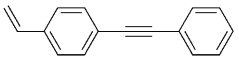
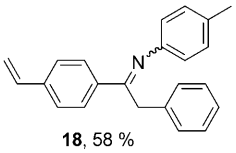
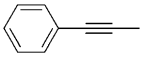
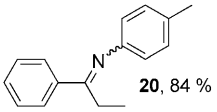
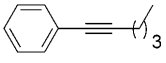
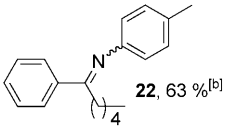
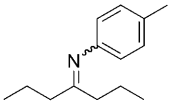
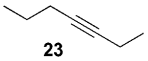
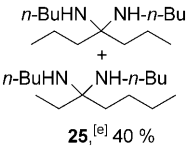
Hydroamination of Internal Alkynes: A Unique Regioselectivity

The mechanistic pathway proposed in Figure 4 prompted us to investigate a possible regioselectivity for internal alkynes where the electronic nature of the two substituents across the triple bond differs significantly (Table 4). Although catalysts **1** and **2** are inactive for the hydroamination of internal alkynes at room temperature, they showed good activity at 80 °C.

The results show that, indeed, catalysts **1** and **2** are *regioselective* catalysts for the hydroamination of internal alkynes (entries 3–5, 7 and 9). The reactivity pattern of the catalysts correlates with that observed for terminal alkynes (see Table 2 and Table 3), i.e., alkylamine **5** does not react with aromatic alkynes (entries 2, 6, 8, 10). Thus, the suitable catalyst, **1** or **2**, has

Table 4. Results obtained for the hydroamination of different internal alkynes with amines **4** and **5**, using **1** or **2** as catalysts (5 mol%), under free solvent conditions or in dry CH_3CN (2 M solution) after 24 h without exclusion of air.



Entry	Alkyne	Amine	Catalyst	Solvent	Major Product [Yield]	Regioselectivity[a]
1	 **15**	**4**	**1**	CH_3CN	 **16**, 75 %[b]	– (5:1)
2		**5**	**2**	CH_3CN	0%	–
3	 **17**	**4**	**1**	CH_3CN	 **18**, 58 %	90:10
4		**4**	**1**[c]	–	**18** (95%)	75:25
5		**4**	**1**[d]	–	**18** (88%)	75:25
6		**5**	**2**	CH_3CN	0%	–
7	 **19**	**4**	**1**	CH_3CN	 **20**, 84 %	57:43
8		**5**	**2**	CH_3CN	0%	–
9	 **21**	**4**	**1**	CH_3CN	 **22**, 63 %[b]	70:30 (8:1)
10		**5**	**2**	CH_3CN	0%	–
11		**4**	**1**	CH_3CN	 **24**, 74 %	50:50
12	 **23**	**5**	**1**[c]	CH_3CN	 **25**,[e] 40 %	–
13		**5**	**2**[f]	CH_3CN	**25**[e] 28%	–
14		**5**	**2**[c,f]	CH_3CN	**25**[e] 85%	–

[a] Major regioisomer : minor regioisomer (*E:Z* from the major).
[b] Isolated yield.
[c] 10 mol%.
[d] Reuse from entry 4.
[e] Mixture of compounds, tentatively assigned after control experiments and exhaustive characterisation, however, no regioselectivity can be differentiated.
[f] 2 equiv. of $BuNH_2$.

to be employed depending on the substrates. Importantly, internal alkynes where the differences between the two substituents are small (such as **17**) are hydroaminated with high regioselectivity (entry 3). The isolated yields that could be obtained after hydroamination of two internal alkynes are shown in Figure 5.

As a general pattern, the carbon attached to the more electron-withdrawing group is attacked by the

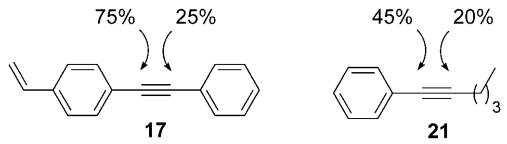


Figure 5. Final yields of the two regioisomers obtained for the hydroamination of selected internal alkynes (see Table 4 for details).

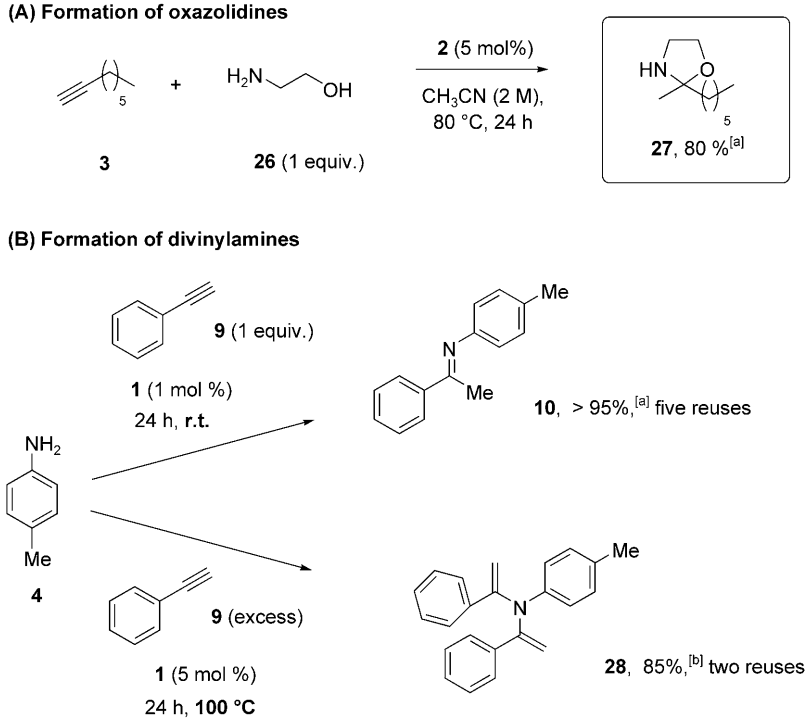
amine (styryl *vs.* phenyl, phenyl *vs.* alkyl). Therefore, although a larger number of substrates should be tested, we can infer a *predictable* regioselectivity during the hydroamination of internal alkynes catalysed by complexes **1** and **2**. As suggested above, the regioselectivity observed seems to come from electronic rather than steric effects. This "electronic" control is unusual in internal alkynes where the high steric constraints across the triple bond rule the reactivity.[2] In fact, the regioselectivity obtained for alkylarylalkynes is opposite and, therefore, complementary, to the one reported up to now.[5–7] Compound **25** might come from a first hydroamination to form the imine and later attack of the amine in excess.

In addition to this, the catalysts **1** and **2** are recoverable and reusable, being able to survive the conditions described in Table 4, including heating and solvent-free conditions: complex **1** is reused a second time (entries 4 and 5) without depletion in the yield or selectivity; the ^{31}P NMR spectrum of complex **2** after being used (entry 14) showed the signal corresponding to the phosphine ligands (Supporting Information, Figure S3).

Tandem Reactions

Process intensification by performing several synthesis steps in one pot is of importance from the point of view of sustainability and economy. Thus, the mildness of the reaction conditions with complexes **1** and **2** prompted us to look for domino reactions of interest in which the hydroamination is one of the steps involved. We have studied here two such cases (see Scheme 3).

Reactions (A) and (B) are novel. Firstly, the former takes advantage of the chemoselectivity of catalyst **1**, since it was previously checked that the hydroamination reaction prevails over the alkoxylation (see Supporting Information, Scheme S2). Thus, the one-pot formation of heterocycles such as oxazolidine **27** has been possible from the readily available alkyne and 1,2-amino alcohol (equation A). Moreover, during the direct formation of N-unprotected oxazolidines, advantage has been taken of the thermal stability of complex **2**, that it is able to act as catalyst at 100 °C under solvent-free conditions and be successfully reused. Secondly, the unexpected divinylamine **28** corresponds to a double hydroamination in cascade. This constitutes a novel pathway reaction under gold-cata-



Scheme 3. Different tandem reactions, where the hydroamination of alkynes catalysed by the complex **1** or **2** is one of the steps. [a] Isolated yield. [b] GC yield.

lysed conditions since it is well-reported that overreaction of imine **7** leads to polysubstituted 1,2-dihydroquinolines.[13c,25] Dienylamines have not been previously obtained in an efficient manner and further studies about the synthesis of these new products are being carried out.

Conclusions

Easy-to-make, stable gold(I) phosphine complexes **1** and **2** are regioselective catalysts for the intermolecular hydroamination of both internal and terminal alkynes with alkyl and aromatic amines. The obtained regioselectivity is based on electronic rather than steric factors, which act as descriptors of the reaction and allow the obtention of regiosiomers not previously observed for internal alkynes. The reaction procedure is simple, convenient and environmentally friendly. The complexes can be quantitatively recovered by simple precipitation in hexane and reused in a next run. A plausible mechanism has been proposed. Different tandem reactions which involve the gold-catalysed hydroamination have been shown. The catalytic system reported in this work is unique in terms of reusability, mildness and versatility, and could be useful in the synthesis of simple and more complex products.

Experimental Section

Typical Hydroamination Procedure for Terminal Alkynes (Table 1, entry 3)

Complex **1** (89 mg, 5 mol%) and *p*-toluidine **4** (216 mg, 2 mmol) were placed in a round-bottomed flask and air was evacuated. Nitrogen refilling was carried out, a rubber septum was rapidly fitted and a nitrogen balloon was coupled through a needle. Then, CH_2Cl_2 (2 mL) and 1-octyne **3** (355 μL, 2.4 mmol) were sequentially added and the mixture was magnetically stirred at room temperature for 24 h. *n*-Hexanes (100 mL) were added, observing the rapid precipitation of the solid. The mixture was magnetically stirred for 15–30 min (alternatively, in some cases, it was left into a fridge at −14 °C to assure a quantitative precipitation). The liquid was passed through a filter containing a Celite™ layer on top. The solid was washed with *n*-hexanes and the liquid was filtered again. The filtrates were concentrated under reduced pressure and, after drying under vacuum the resulting residue, (1-methylheptylidene)-*p*-tolylamine **6** (*E:Z* = 4:1) was obtained; yield: 321 mg (74%). GC/MS: major peaks found at *m/z* = 217 (M^+), 160, 148, 147, 132, 106, 91; ^{1}H NMR: δ = 7.10 (2H, d, *J* = 8 Hz), 6.60 (2H, d, *J* = 8 Hz), 2.40 (2H, t, *J* = 8 Hz), 2.35 (3H, s), 1.75 (3H, s), 1.65 (2H, quint), 1.45–1.3 (6H, mult), 0.95 (3H, t); ^{13}C NMR (signals corresponding to the minor isomer between brackets): δ = 171.9 (172.5), 149.0 (148.5), 132.0 (131.9), 129.2 (×2), 119.3 (×2), 41.7 (43.6), 31.6 (33.8), 28.9 (31.3), 26.3 (26.8), 22.4 (22.3), 20.6, 19.1, 13.9 (13.8).

Typical Hydroamination Procedure for Internal Alkynes (Table 4, entry 1)

Complex **1** (22 mg, 5 mol%), diphenylacetylene **14** (89 mg, 0.5 mmol) and *p*-toluidine **4** (53.5 mg, 0.5 mmol) were placed into a vial. Then, CH_3CN (0.25 mL) was added and the vial was sealed. The mixture was placed in a pre-heated oil bath at 80 °C and magnetically stirred for 24 h. Then, the mixture was concentrated under reduced pressure and *n*-hexanes (10 mL) added. The mixture was left into a fridge at −14 °C for 4 h. The liquid was passed through a filter containing a Celite™ layer on top. The solid was washed with *n*-hexanes and the liquid was filtered again. The filtrates were concentrated under reduced pressure and, after drying under vacuum the resulting residue, (1,2-diphenylethylidene)-*p*-tolylamine **16** (*E:Z* = 5:1) was obtained; yield: 106 mg (75%). GC/MS: major peaks found at *m/z* = 285 (M^+), 195, 194, 91, 65; ^{1}H NMR: δ = 7.80 (2H, dd, *J* = 8 Hz, 2 Hz), 7.35–6.90 (10H, mult), 6.64 (2H, d, *J* = 8 Hz), 3.97 (2H, s), 2.19 (3H, s); ^{13}C NMR (signals corresponding to the minor isomer between brackets): δ = 166.2 (165.7), 148.4, 138.4, 137.2, 133–126 (15 C), 36.0, 20.8.

Supporting Information

General methods, experimental procedures including syntheses and characterization of catalysts and substrates, kinetics and reaction procedures, additional Schemes, Figure and Tables, and data collection for the crystal structure of complex **1** for this article are available as Supporting Information.

Acknowledgements

A. L. thanks CSIC for a contract under JAE-doctors program. Financial support by MAT2006-14274-CC0201, PROMETEO from Generalitat Valenciana and Fundación Areces are acknowledged.

References

[1] For reviews see: a) F. Alonso, I. P. Beletskaya, M. Yus, *Chem. Rev.* **2004**, *104*, 3079; b) T. E. Müller, K. C. Hultzsch, M. Yus, F. Foubelo, M. Tada, *Chem. Rev.* **2008**, *108*, 3795.

[2] For additional reviews see: a) R. Severin, S. Doye, *Chem. Soc. Rev.* **2007**, *36*, 1407; b) F. Pohlki, S. Doye, *Chem. Soc. Rev.* **2003**, *32*, 104; c) I. Aillaud, J. Collin, J. Hannedouche, E. Schulz, *Dalton Trans.* **2007**, 5105. For a review about gold-catalysed hydroaminations, see: d) R. A. Widenhoefer, X. Han, *Eur. J. Org. Chem.* **2006**, 4555.

[3] a) A. Heutling, S. Doye, *J. Org. Chem.* **2002**, *67*, 1961; b) E. Haak, I. Bytschkov, S. Doye, *Angew. Chem.* **1999**, *111*, 3584; *Angew. Chem. Int. Ed.* **1999**, *38*, 3389; c) F. Pohlki, I. Bytschkov, H. Siebeneicher, A. Heutling, W. A. König, S. Doye, *Eur. J. Org. Chem.* **2004**, 1967.

[4] I. Bytschkov, S. Doye, *Eur. J. Org. Chem.* **2001**, 4411.
[5] Y. Li, T. J. Marks, *Organometallics* **1996**, *15*, 3770.
[6] A. M. Baranger, P. J. Walsh, R. G. Bergman, *J. Am. Chem. Soc.* **1993**, *115*, 2753.
[7] a) M. Tokunaga, M. Eckert, Y. Wakatsuki, *Angew. Chem.* **1999**, *111*, 3416; *Angew. Chem. Int. Ed.* **1999**, *38*, 3222; b) Y. Uchimaru, *Chem. Commun.* **1999**, 1133.
[8] T. Shimada, Y. Yamamoto, *J. Am. Chem. Soc.* **2002**, *124*, 12670.
[9] J. Barluenga, F. Aznar, R. Liz, R. Rodes, *J. Chem. Soc. Perkin Trans. 1* **1980**, 2732.
[10] a) A. Arcadi, *Chem. Rev.* **2008**, *108*, 3266; b) R. Skouta, C.-J. Li, *Tetrahedron* **2008**, *64*, 4917; c) E. Jimenez-Nuñez, A. M. Echavarren, *Chem. Commun.* **2007**, 333.
[11] a) D. J. Gorin, F. D. Toste, *Nature* **2007**, *446*, 395; b) A. S. K. Hashmi, G. J. Hutchings, *Angew. Chem.* **2006**, *118*, 8064; *Angew. Chem. Int. Ed.* **2006**, *45*, 7896.
[12] a) A. Grirrane, A. Corma, H. García, *Science* **2008**, *322*, 1661; b) A. Corma, H. Garcia, *Chem. Soc. Rev.* **2008**, *37*, 2096; c) A. Corma, C. Gonzalez-Arellano, M. Iglesias, F. Sanchez, *Angew. Chem.* **2007**, *119*, 7966; *Angew. Chem. Int. Ed.* **2007**, *46*, 7820; d) A, Corma, P. Serna, *Science* **2006**, *313*, 332.
[13] a) Y. Zhang, J. P. Donahue, C. J. Li, *Org. Lett.* **2007**, *9*, 627; b) C. Y. Zhou, P. W. H. Chan, C. M. Che, *Org. Lett.* 2006, 8, 325; c) Y. Luo, Z. Li, C.-J. Li, *Org. Lett.* **2005**, *7*, 2675; d) E. Mizushima, T. Hayashi, M. Tanaka, *Org. Lett.* **2003**, *5*, 3349.
[14] a) X. Zeng, G. D. Frey, R. Kinjo, B. Donnadieu, G. Bertrand, *J. Am. Chem. Soc.* **2009**, *131*, 8690; b) X. Zeng, G. D. Frey, S. Kousar, G. Bertrand, *Chem. Eur. J.* **2009**, *15*, 3056; c) V. Lavallo, G. D. Frey, B. Donnadieu, M. Soleilhavoup, G. Bertrand, *Angew. Chem.* **2008**, *120*, 5302; *Angew. Chem. Int. Ed.* **2008**, *47*, 5224.
[15] N. Lingaiah, N. S. Babu, K. M. Reddy, P. S. S. Prasad, I. Suryanarayana, *Chem. Commun.* **2007**, 278.
[16] N. Pasha, N. S. Babu, K. T. V. Rao, P. S. S. Prasad, N. Lingaiah, *Tetrahedron Lett.* **2009**, *50*, 239.
[17] A. Corma, C. Gonzalez-Arellano, M. Iglesias, M. T. Navarro, F. Sanchez, *Chem. Commun.* **2008**, *46*, 6218.
[18] A. Corma, P. Concepción, I. Domínguez, V. Fornés, M. J. Sabater, *J. Catal.* **2007**, *251*, 39.
[19] a) A. Leyva, A. Corma, *J. Org. Chem.* **2009**, *74*, 2067; b) CCDC 725960 contains the supplementary crystallographic data for compound **1** in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. c) As pointed out by one of the referees, the GC results were compared with the NMR spectra of the imines in order to avoid misinterpretation of the regioselectivities; see: Y. Shi, J. T. Ciszewski, A. L. Odom, *Organometallics* **2002**, *21* 5148.
[20] N. Mezailles, L. Ricard, F. Gagosz, *Org. Lett.* **2005**, *7*, 4133. Complex **2** $AuPPh_3NTf_2$ can be purchased from Aldrich Co. as the dimer-toluene adduct.
[21] a) E. Juaristi, J. L. León-Romo, A. Reyes, J. Escalante, *Tetrahedron: Asymmetry* **1999**, *10*, 2441; b) H.-J. Federsel, M. Hedberg, F. R. Qvarnström, M. P. T. Sjögren, W. Tian, *Acc. Chem. Res.* **2007**, *40*, 1377.
[22] Legal Commission Regulation (EC) No 1881/2006 of 19 Dec. 2006, http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:32006R1881:EN:NOT.
[23] X. Zhang, A. Corma, *Angew. Chem.* **2008**, *120*, 4430; *Angew. Chem. Int. Ed.* **2008**, *47*, 4358.
[24] N. D. Shapiro, F. D. Toste, *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 2779.
[25] X.-Y. Liu, P. Ding, J.-S. Huang, C.-M. Che, *Org. Lett.* **2007**, *9(14)*, 2645.

