

# Hydroamination reactions by metal triflates: Brønsted acid vs. metal catalysis?

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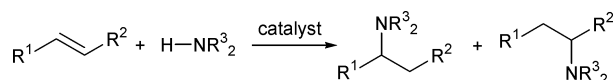
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Catalytic hydroamination reactions involving the addition of carboxamides (X = CO), carbamates (X = CO<sub>2</sub>) and sulfonamides (X = SO<sub>2</sub>) to unactivated C=C bonds are briefly reviewed. Development in this field of catalytic research is briefly charted, followed by a discussion of possible mechanisms, including arguments to support the operation of both metal and Brønsted acid catalysis in these systems. Future developments in the area are summarised.

## Introduction

Direct addition of N–H bonds across a C=C bond, also known as the hydroamination reaction, produces highly valuable nitrogen-containing compounds from readily available precursors (Scheme 1). As the reaction does not generate any waste, research in this area of catalytic chemistry has intensified over the last decade,<sup>1</sup> driven by the increasing demand for more efficient and green processes, particularly for the production of fine chemicals and pharmaceutical compounds.<sup>2</sup>



Scheme 1 Hydroamination reactions.

With the exception of *aza*-Michael reactions, where amines add spontaneously to electron-deficient alkenes in protic solvents,<sup>3</sup> most hydroamination reactions have very high activation energies,

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particularly if it involves reactions of unactivated alkenes. In these cases, unfavourable kinetic barriers can be overcome by the use of catalysts.

Strictly speaking, ‘unactivated’ alkenes refer to unfunctionalised C=C bonds, *i.e.* cyclic or acyclic alkenes with H or alkyl substituents, although more reactive systems such as the strained norbornene and conjugated alkenes (vinylarenes and 1,3-dienes) are often included in this category (Fig. 1).<sup>4</sup>

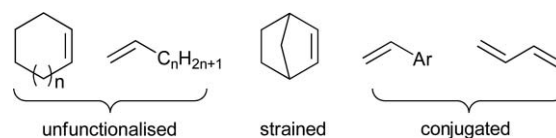


Fig. 1 Types of ‘unactivated’ alkene substrates.

Certain hydroamination reactions, particularly intramolecular cyclisation of aminoalkenes, can be catalysed by using alkali (earth) metal complexes such as *n*-BuLi and metal amides.<sup>5,6</sup> As the application of such highly basic entities is not always desirable or practical, much research in the area has been directed towards the development of transition metal catalysts. Two mechanisms are often suggested for these, where C–N formation is triggered by the activation of either the N–H or C=C moiety



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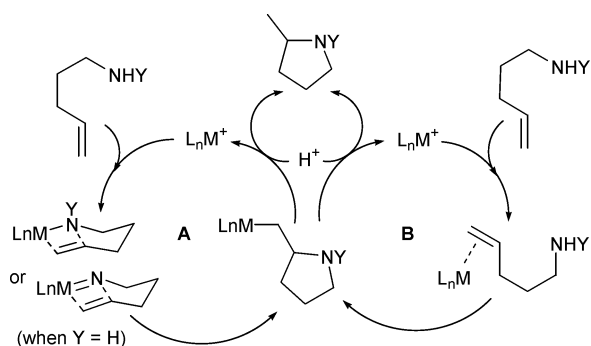
Jason Guy Taylor completed his MChem (Hons) degree at Nottingham Trent University, subsequently a PhD degree at Imperial College London in the group of Dr Mimi Hii, on the development of hydroamination catalysts. He is presently working as a postdoctoral research fellow with Professor Carlos Roque D. Correia at the Universidade Estadual de Campinas (UNICAMP) in Brazil.



Luis Angel Adrio

Luis Angel Adrio studied chemistry at the University of Santiago de Compostela, where he gained his PhD degree under the joint supervision of Dr's J. M. Vila and M<sup>o</sup> T. Lorenzo in 2006. Since then he has been working as a postdoctoral fellow with Mimi Hii at Imperial College London in UK, supported by Fundación Caixa Galicia and Xunta de Galicia (programme ‘Angeles Alvariño’).

(Scheme 2). Lanthanides/early metal complexes generally favour route A, where reactions proceed by activation of the N–H bond, followed by insertion of the C=C across the resultant M–N bond (when M = Ln)<sup>7</sup> or, if a primary amine is used, a metal-imido complex can be formed (when M = group 4 transition metal),<sup>8,9</sup> in which case, bond formation between M=N and C=C can occur *via* a [2+2] cycloaddition. Conversely, late transition metal catalysts (e.g. Rh, Pd, Pt) favour  $\pi$ -coordination of the C=C bond, activating it towards *exo*-metallic attack of the nucleophilic amine (Scheme 2, route B).<sup>10–12</sup> In both of these routes, the turnover step requires the protonolysis of the alkyl–M bond. For most addition of nucleophilic primary or secondary alkylamines and anilines, reaction mechanisms are fairly well established, including the isolation of catalytically-viable intermediates, theoretical studies<sup>13</sup> and enantioselective examples, which have been described in a previous *Perspective*.<sup>14</sup>

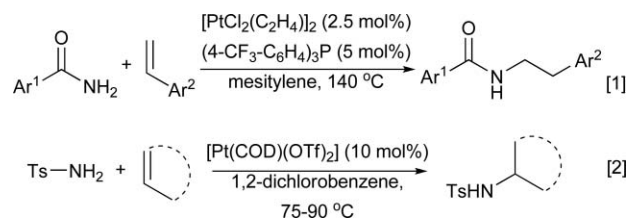


**Scheme 2** General mechanisms for metal-catalysed hydroamination reactions (illustrated for intramolecular reactions).

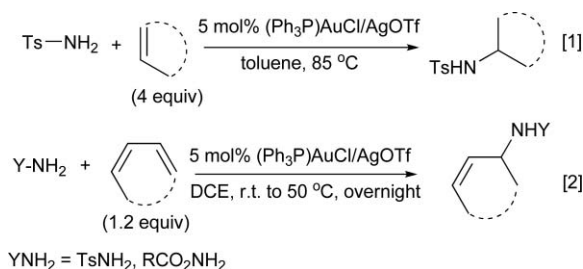
In recent years, there has been significant debate over the existence of alternative reaction mechanisms, particularly for the addition of non-nucleophilic (also referred as ‘non-basic’) amines, exemplified by carboxamides, sulfonamides and carbamates, to unactivated alkenes. This type of hydroamination reaction was first reported in 2005 by Qian and Widenhoefer,<sup>15</sup> where the addition of carboxamides to vinylarenes proceeded in mesitylene at 140 °C, by using a platinum catalyst generated from a mixture

of  $[\text{PtCl}_2(\text{H}_2\text{C}=\text{CH}_2)]_2$  (2.5 mol%) and  $(4\text{-CF}_3\text{C}_6\text{H}_4)_3\text{P}$  (5 mol%). This was followed closely by a report by Tilley and co-workers, where  $(\text{COD})\text{Pt}(\text{OTf})_2$  at 10 mol% effected the addition of sulfonamides and aromatic amines to cyclic and acyclic alkenes at a much lower reaction temperature (75–90 °C).<sup>16</sup>

The use of group 11 coinage metal complexes for these reactions emerged shortly (Scheme 4), with reports of inter- and intramolecular addition of sulfonamides and carbamates to alkenes<sup>17</sup> and 1,3-dienes<sup>18</sup> under mild reaction conditions, using a cationic gold(i) complex generated from 5 mol% of  $\text{Ph}_3\text{PAuCl}/\text{AgOTf}$ .<sup>19</sup> In these studies, catalytic activity was attributed to  $\pi$ -activation of the C=C bond by the metal (as shown by route B in Scheme 2).

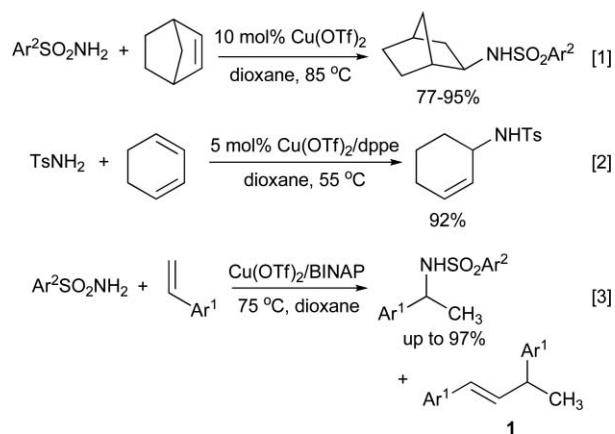


**Scheme 3** Pt-catalysed hydroamination of unactivated alkenes by non-nucleophilic N–H bonds.



**Scheme 4** Hydroamination of unactivated alkenes catalysed by cationic gold(i) complexes.

Around the same time, work from our laboratory discovered the use of  $\text{Cu}(\text{OTf})_2$  for the O–H addition of acids and alcohols to norbornene,<sup>20</sup> which was later extended to the addition of sulfonamides. Furthermore, in the presence of a diphosphine ligand, addition to vinylarenes and 1,3-dienes can also be effected under similar reaction conditions (Scheme 5).<sup>21</sup>



**Scheme 5** Copper(II) catalysed addition of  $\text{TsNH}_2$  to unactivated alkenes.



**King Kuok (Mimi) Hii**

Dr. Mimi Hii graduated from the University of Leeds with BSc (Hons) and PhD degrees (supervisor: Prof. Bernard L. Shaw, FRS), before conducting postdoctoral research (1994–7) at Oxford University with Dr. John M. Brown, FRS. She was briefly a Ramsay Research Fellow back at Leeds, before her appointment as a Lecturer in organic chemistry at King's College London (1998). She moved to a Senior Lectureship in inorganic chemistry at Imperial College London (2003), where she was recently promoted to Reader of Catalysis (July 2009).

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Given that copper(II) is not as  $\pi$ -acidic as gold(I),<sup>22</sup> we speculated that an alternative mechanism was in operation. This was supported by a series of observations made during the study (reactions between TsNH<sub>2</sub> and styrene):

1. The product yield was enhanced by increasing the amount of sulfonamide, but not by increasing the amount of styrene. Thus, the alkene is unlikely to be involved in the rate-limiting step.

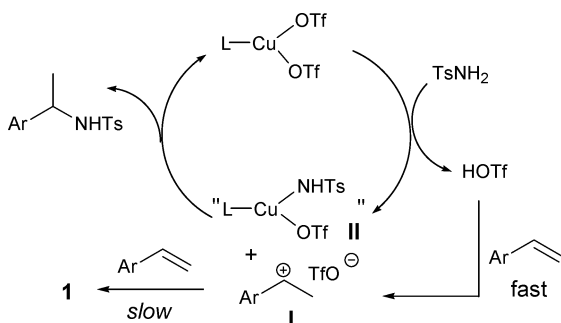
2. In cases where the reaction is slow, the major byproduct of the reaction is compound **1**, a styrene dimer.

3. The reaction was suppressed by the presence of non-coordinating bases such as CuCO<sub>3</sub> and K<sub>2</sub>CO<sub>3</sub> (10 mol%), suggesting the involvement of Brønsted acid.

4. In the absence of sulfonamide, Cu(OTf)<sub>2</sub> or triflic acid catalysed the conversion of styrene to the dimer **1** at 75 and 85 °C, respectively.

5. Using 20 mol% of TfOH as catalyst, the reaction between TsNH<sub>2</sub> and styrene led to a very low yield of the expected product and **1** (14% and 15%, respectively), the rest of the reaction mixture is composed of styrene oligomer/polymer.

Based on these observations, we postulated a catalytic cycle where ligand metathesis between the metal complex and sulfonamide generates triflic acid. This protonates the alkene to produce a stable carbocation intermediate (**I**), which undergoes C–N bond formation with the copper-amide complex **II** to give the product (Scheme 6). Where the reaction between **I** and **II** is slow, competitive reaction of the carbocation and styrene occurs to give the dimer **1**. Subsequently, similar reaction mechanisms have been proposed for addition of toluenesulfonamide to norbornene catalysed by [(COD)Pt(OTf)<sub>2</sub>] (Scheme 3, equation 2),<sup>23</sup> and also for the addition of aniline to norbornene by non-triflate based Lewis acids.<sup>24</sup>



**Scheme 6** Proposed mechanism for Cu(OTf)<sub>2</sub>-diphosphine catalysed hydroamination reaction.<sup>21</sup>

Following our publication, separate reports by Hartwig<sup>25</sup> and He<sup>26</sup> demonstrated that the use of triflic acid alone is effective for intermolecular addition of sulfonamides and carbamates to norbornene, vinylarenes and 1,3-dienes. The key to success is to employ a low catalyst loading (1–5 mol%). In agreement with our earlier results, low yields of the product were obtained at a higher loading of the acid (10–20 mol%), due to competitive reactions to yield unspecified products (described as a series of isomeric products from the combination of two alkenes). By drawing parallels between product yields and distribution afforded by HOTf and metal triflate complexes, it was suggested that the latter are merely serving as precatalysts for the formation of a protic acid catalyst.<sup>25</sup>

**Table 1** Comparison of catalytic activity of triflic acid, Au and Cu catalysts<sup>a</sup>

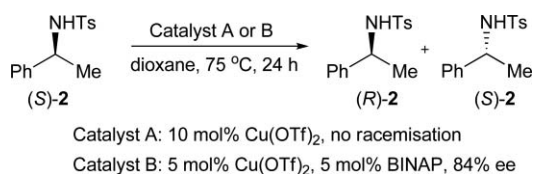
Entry	Reactants	Product	Catalyst <sup>b</sup>	Yield (%)
1	BzNH <sub>2</sub>		TfOH	88 <sup>25</sup>
2	TsNH <sub>2</sub>		Cu(OTf) <sub>2</sub> /dppe	NR
3			TfOH	58 <sup>25</sup>
4	TsNH <sub>2</sub>		Ph <sub>3</sub> PAuOTf	90 <sup>17</sup>
5			Cu(OTf) <sub>2</sub> /dppe	NR
6			TfOH	88
7	TsNH <sub>2</sub>		Ph <sub>3</sub> PAuOTf	83 <sup>17</sup>
8			Cu(OTf) <sub>2</sub> /dppe	NR
9			TfOH	63 <sup>25</sup>
10			Cu(OTf) <sub>2</sub> /dppe	92
11			Cu(OTf) <sub>2</sub>	3

<sup>a</sup> Reaction conditions: Dioxane, 100 °C, 24 h (Entries 1 and 2); toluene, 80–85 °C, 18 h (entries 3–8); Dioxane, 50–55 °C, 18 h (entries 9–11). <sup>b</sup> 1 mol% TfOH or 5 mol% Cu(OTf)<sub>2</sub>/dppe or 10 mol% Cu(OTf)<sub>2</sub>, or 5 mol% Ph<sub>3</sub>PAuOTf, generated from a mixture of Ph<sub>3</sub>PAuCl/AgOTf.

Formation of Brønsted acids by cation hydrolysis is a well-documented process.<sup>27</sup> However, there remained substantial differences in the observed catalyst activity between cationic gold(I) complexes and HOTf, which cannot be explained by a single mechanism.<sup>26</sup> Also, the formation of (Ph<sub>3</sub>P)AuNHTs and triflic acid was not observed by NMR experiments.<sup>17</sup> For reactions catalysed by copper(II) complexes, there are several instances where differences can be observed (Table 1).<sup>28</sup> For example, while triflic acid catalysed the addition of benzamide to styrene (entry 1) and toluenesulfonamide to cyclohexene and cyclooctene (entries 3 and 6), Au catalyst has been shown to be better (entry 4) or comparable (entry 7) in two of these cases. In comparison, Cu(OTf)<sub>2</sub>-dppe was not productive under the same conditions (entries 2, 5 and 8). On the other hand, a higher product yield was afforded by the copper catalyst than triflic acid, for the addition of TsNH<sub>2</sub> to 1,3-cyclohexadiene, but only in the presence of dppe ligand (entries 9–11).

The ligand effect was further supported by an experiment, whereby the configurational stability of optically pure (*S*)-*N*-(1-phenylethyl)toluenesulfonamide, (*S*)-**2**, was monitored in the presence of Cu(OTf)<sub>2</sub>, with and without added *rac*-BINAP (Scheme 7).<sup>21</sup> In the absence of added phosphine, the presence of 10 mol% Cu(OTf)<sub>2</sub> did not lead to any observable changes in the stereochemical integrity of the sulfonamide. In contrast, an erosion of the enantiopurity to 84% ee was observed at 5 mol% of Cu(OTf)<sub>2</sub>-BINAP, clearly indicating a lower energy barrier in the presence of the ligand.

Furthermore, catalytic activity is not exclusive to metal triflate complexes; as shown by reports of other Lewis acidic metal catalysts for these processes, *e.g.* InBr<sub>3</sub><sup>29</sup> and FeCl<sub>3</sub>,<sup>30</sup> although

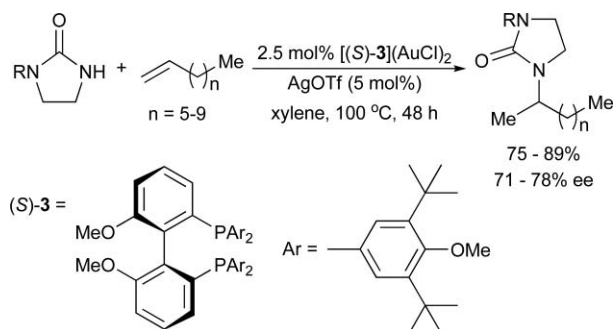


**Scheme 7** Ligand effect in the Cu-mediated racemisation of an optically pure toluenesulfonamide.

they were employed at higher catalytic loadings (10–20 mol%) and reaction temperatures (120 °C). Conversely, solid acids *e.g.* H<sup>+</sup> exchanged montmorillonite<sup>31</sup> and silicotungstic acid<sup>32</sup> have also been reported to catalyse the addition of amides, sulfonamides and carbamates to cyclic and acyclic alkenes, vinylarenes and 1,3-hexadiene.

Undoubtedly, Brønsted acid catalysis can be effective for the hydroamination reactions of unactivated alkenes. However, there is a growing body of evidence to suggest that metal-catalysed processes cannot be ruled out completely. For example, recent theoretical calculations support the participation of the metal in the gold(I)-phosphine-catalysed hydroamination of 1,3-dienes.<sup>33</sup> In this study, DFT calculations suggest that the generation of a triflic acid by the coordination of carbamate to the cationic gold(I) complex is energetically less favourable than the coordination of diene (the counteranion was found to have an important effect in the protonolysis step by acting as a proton shuffle).

Perhaps a more convincing case for metal-catalysed process is the attainment of enantioselectivity. Asymmetric hydroamination reactions of unactivated alkenes have been limited almost exclusively to intramolecular cyclisation of aminoalkenes,<sup>1,14</sup> with some limited intermolecular examples involving the addition of anilines to norbornene and styrene, catalysed by iridium<sup>34</sup> and palladium,<sup>35</sup> respectively. Reactions involving non-nucleophilic amines are particularly challenging, as several of these reactions can be reversible,<sup>15,21,36</sup> so the attainment of high ee's is disfavoured by thermodynamics.<sup>34</sup> In this respect, a significant breakthrough has been achieved recently by Widenhofer:<sup>37</sup> using a mixture of [(*S*)-**3**](AuCl)<sub>2</sub> (2.5 mol%) and AgOTf (5 mol%), reactions of 1-alkenes with imidazolidin-2-ones proceeded selectively at 100 °C (Scheme 8). Although the ee's were modest, it nevertheless proves that enantioselective reactions can be realised with group 11 metal triflates, corroborating the operation of metal-catalysed processes for these reactions.



**Scheme 8** Enantioselective hydroamination of unactivated alkenes.

## Outlook

The addition of non-nucleophilic amines to unactivated alkenes converts bulk material into valuable fine chemicals (amines, amides, sulfonamides and carbamate); not only does this confer much added-value to the process, it does so with great atom-economy, satisfying numerous criteria of a green chemical process.<sup>38</sup> To date, several metal complexes have been reported to be catalytically active for these reactions under mild reaction conditions. Concurrently, strong Brønsted acids can also effect these reactions under very similar reaction conditions. Evidence for both H<sup>+</sup> and metal-catalysed mechanisms exist; it is therefore important for researchers to perform the requisite control experiments and analyse their results carefully to avoid misinterpretation.

In terms of synthetic utility of these reactions, the choice of catalyst is often dependent on cost, practicality and the desired reaction outcome. For most applications, Brønsted acids may be perfectly adequate, provided that the catalytic conditions can be controlled to avoid competitive side reactions. In certain cases, the conditions offered by metal catalysts may be preferred, particularly for compounds containing acid-labile groups.

With the discovery of enantioselective processes, the attainment of optically active material from inactive alkenes by the hydroamination reaction is a distinct possibility. However, the scope, enantioselectivity (ee's >90% are rare) and turnover number are presently modest. For these reasons, hydroamination reactions of unactivated alkenes will remain a highly topical area of catalytic research for the foreseeable future.

## Acknowledgements

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## Notes and references

- 1 T. E. Müller, K. C. Hultsch, M. Yus, F. Foubelo and M. Tada, *Chem. Rev.*, 2008, **108**, 3795.
- 2 D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, J. L. Leazer, R. J. Linderman, K. Lorenz, J. Manley, B. A. Pearlman, A. Wells, A. Zaks and T. Y. Zhang, *Green Chem.*, 2007, **9**, 411.
- 3 For example, see: (a) B. C. Ranu and S. Banerjee, *Tetrahedron Lett.*, 2007, **48**, 141; (b) R. Kumar, P. Chaudhary, S. Nimesh and R. Chandra, *Green Chem.*, 2006, **8**, 356.
- 4 U. Dzhemilev, G. Tolstikov and R. Khusnutdinov, *Russ. J. Org. Chem.*, 2009, **45**, 957.
- 5 See for example: (a) C. Quinet, P. Jourdain, C. Hermans, A. Atest, I. Lucas and I. E. Marko, *Tetrahedron*, 2008, **64**, 1077; (b) P. Horrillo-Martinez, K. C. Hultsch, A. Gil and V. Branchadell, *Eur. J. Org. Chem.*, 2007, 3311, and references therein.
- 6 M. R. Crimmin, M. Arrowsmith, A. G. M. Barrett, I. J. Casely, M. S. Hill and P. A. Procopiou, *J. Am. Chem. Soc.*, 2009, **131**, 9670.
- 7 S. Hong and T. J. Marks, *Acc. Chem. Res.*, 2004, **37**, 673.
- 8 P. J. Walsh, A. M. Baranger and R. G. Bergman, *J. Am. Chem. Soc.*, 1992, **114**, 1708.
- 9 C. Müller, R. Koch and S. Doye, *Chem.–Eur. J.*, 2008, **14**, 10430.
- 10 M. Beller, H. Trauthwein, M. Eichberger, C. Breindl, J. Herwig, T. E. Müller and O. R. Thiel, *Chem.–Eur. J.*, 1999, **5**, 1306.
- 11 M. Rodríguez-Zubiri, S. Anguille and J. J. Brunet, *J. Mol. Catal. A: Chem.*, 2007, **271**, 145.
- 12 J. E. Bäckvall, B. Åkermark and S. O. Ljunggren, *J. Am. Chem. Soc.*, 1979, **101**, 2411.

- 13 See for example: (a) C. Hahn, *Chem.–Eur. J.*, 2004, **10**, 5888; (b) A. Motta, I. L. Fragala and T. J. Marks, *Organometallics*, 2006, **25**, 5533; (c) S. Tobisch, *Chem.–Eur. J.*, 2008, **14**, 8590.
- 14 I. Aillaud, J. Collin, J. Hannedouche and E. Schulz, *Dalton Trans.*, 2007, 5105.
- 15 H. Qian and R. A. Widenhoefer, *Org. Lett.*, 2005, **7**, 2635.
- 16 D. Karshedt, A. T. Bell and T. D. Tilley, *J. Am. Chem. Soc.*, 2005, **127**, 12640.
- 17 J. Zhang, C. Yang and C. He, *J. Am. Chem. Soc.*, 2006, **128**, 1798.
- 18 C. Brouwer and C. He, *Angew. Chem., Int. Ed.*, 2006, **45**, 1744.
- 19 X. Giner and C. Najera, *Org. Lett.*, 2008, **10**, 2919.
- 20 J. G. Taylor, N. Whittall and K. K. Hii, *Chem. Commun.*, 2005, 5103.
- 21 J. G. Taylor, N. Whittall and K. K. Hii, *Org. Lett.*, 2006, **8**, 3561.
- 22 For a discussion of ethylene complexes of Cu(I), Ag(I) and Au(I), see: H. V. R. Dias and J. Wu, *Eur. J. Inorg. Chem.*, 2008, 509.
- 23 J. L. McBee, A. T. Bell and T. D. Tilley, *J. Am. Chem. Soc.*, 2008, **130**, 16562.
- 24 X. J. Cheng, Y. Z. Xia, H. Wei, B. Xu, C. G. Zhang, Y. H. Li, G. M. Qian, X. H. Zhang, K. Li and W. Li, *Eur. J. Org. Chem.*, 2008, 1929.
- 25 D. C. Rosenfeld, S. Shekhar, A. Takemiya, M. Utsunomiya and J. F. Hartwig, *Org. Lett.*, 2006, **8**, 4179.
- 26 Z. Li, J. Zhang, C. Brouwer, C.-G. Yang, N. W. Reich and C. He, *Org. Lett.*, 2006, **8**, 4175.
- 27 T. C. Wabnitz, J. Q. Yu and J. B. Spencer, *Chem.–Eur. J.*, 2004, **10**, 484.
- 28 Jason G. Taylor, PhD Thesis, Imperial College London, 2008.
- 29 J. M. Huang, C. M. Wong, F. X. Xu and T. P. Loh, *Tetrahedron Lett.*, 2007, **48**, 3375.
- 30 J. Michaux, V. Terrasson, S. Marque, J. Wehbe, D. Prim and J. M. Campagne, *Eur. J. Org. Chem.*, 2007, 2601.
- 31 K. Motokura, N. Nakagiri, K. Mori, T. Mizugaki, K. Ebitani, K. Jitsukawa and K. Kaneda, *Org. Lett.*, 2006, **8**, 4617.
- 32 L. Yang, L. W. Xu and C. G. Xia, *Tetrahedron Lett.*, 2008, **49**, 2882.
- 33 G. Kovacs, G. Ujaque and A. Lledos, *J. Am. Chem. Soc.*, 2008, **130**, 853.
- 34 R. Dorta, P. Egli, F. Zurcher and A. Togni, *J. Am. Chem. Soc.*, 1997, **119**, 10857.
- 35 These were shown to proceed via allylpalladium(II) intermediates, see: J. F. Hartwig, *Pure Appl. Chem.*, 2004, **76**, 507 and references therein.
- 36 A. M. Johns, N. Sakai, A. Ridder and J. F. Hartwig, *J. Am. Chem. Soc.*, 2006, **128**, 9306.
- 37 Z. Zhang, S. D. Lee and R. A. Widenhoefer, *J. Am. Chem. Soc.*, 2009, **131**, 5372.
- 38 P. Anastas and J. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, New York, 1998.