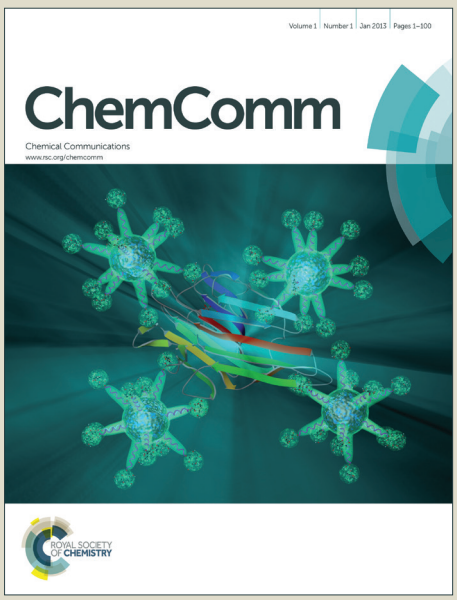
ChemComm

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: L. Wang, L. Kong, Y. Li, G. Rakesh and R. Kinjo, *Chem. Commun.*, 2015, DOI: 10.1039/C5CC04091D.



View Article Online
DOI: 10.1039/C5CC04091D

Journal Name

ARTICLE

Anti-Markovnikov Hydroimination of Terminal Alkynes in Gold-Catalyzed Pyridine Construction using Ammonia†

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Liliang Wang,[‡a] Lingbing Kong,[‡a] Yongxin Li,[b] Rakesh Ganguly[b] and Rei Kinjo*[a]

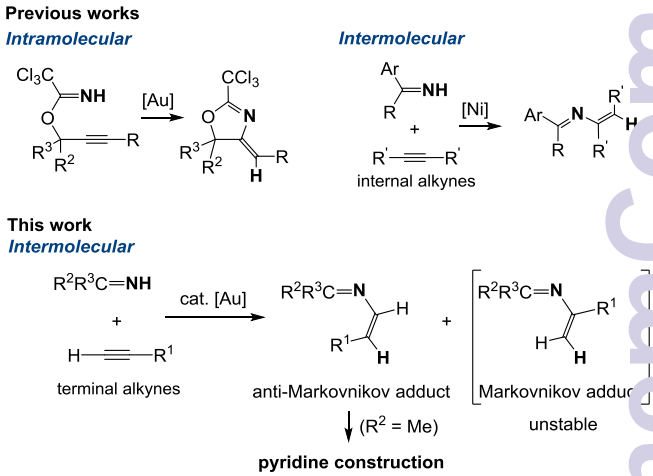
A gold-catalyzed hydroimination of terminal alkynes, giving rise to anti-Markovnikov adducts concomitant with unstable Markovnikov adducts is described. The elementary step can be applied for construction of pyridine derivatives from ammonia and alkynes.

Acyclic and heterocyclic nitrogen-containing skeletons are ubiquitous in a myriad of naturally occurring compounds as well as in industrial products involving agrochemicals, pharmaceuticals, cosmetics, and fine chemicals.[1] Hence, efficient methodology for the formation of carbon-nitrogen bonds has been a subject of considerable interest in synthetic chemistry. In recent years, metal-catalyzed hydroamination, which forms C-N bonds by direct addition of a nitrogen-hydrogen bond across carbon-carbon multiple bonds, has represented a powerful atom-economic tool for the synthesis of nitrogen-containing compounds.[2] However, control of the regioselectivity is a major problem to be addressed. Thus, as classical textbooks state that the proton forms a bond with the carbon bearing fewer substituents in accordance with Markovnikov's rule, archetypal hydroamination products are also dominated by Markovnikov adducts with branched skeleton.[3] Accordingly, preparation of nitrogen-containing compounds with linear skeleton by direct anti-Markovnikov hydroamination remains highly challenging.[4]

Since Beller and co-workers' pioneering work on the first metal-catalyzed anti-Markovnikov hydroamination of olefins in 1999,[5] various methodologies for intermolecular anti-Markovnikov hydroamination with metal catalysts involving alkali metals,[6] alkaline earth metals,[7] organolanthanide,[8] Ti,[9] Re,[10] Ru,[11] Rh,[12] Pd,[13] Cu,[14] Au[15] have been reported to this date. Although such seminal approaches have led to solid progresses, these strategies often involve disadvantages such as limiting the substrate scope, harsh reaction condition, the use of strong bases, or stepwise indirect processes.

In marked contrast to recent advances in the field of hydroamination, addition of an N-H bond of primary imines $HN=CR_2$ to alkenes and alkynes, namely hydroimination, has rarely been achieved thus far despite the significance of the predicted products, 2-aza-1,3-dienes, as synthetic intermediates for N-heterocycles.[16] The use of primary imines as nucleophilic substrates is hampered by several difficulties, mainly because of the propensity to behave as electrophiles rather than nucleophiles due to the polarized C=N bonds, especially in the presence of Brønsted/Lewis acids. Primary imines are known to act as directing groups by coordinating to metals which induces intramolecular C-H activation.[17] In addition, oxidative homo coupling of primary imines also undergoes to form an N-N bond in the presence of metals.[18] To prevent such undesired processes, hydroimination has mainly been limited to intramolecular reaction with the geometrically pre-organized substrates (Scheme 1).[19] Very recently, Zhao *et al*. first reported nickel-catalyzed intermolecular coupling between internal alkynes and aromatic N–H ketimines.[20] However, employment of terminal alkynes in their system led to alkyne oligomerization instead of the desired hydroimination. Thus, to the best of our knowledge, hydroimination of terminal alkynes is still unknown to date.

Given the importance of C-N bonds in synthetic chemistry, the development of general means for the selective formation is imperative. Here, we report gold-catalyzed hydroimination of



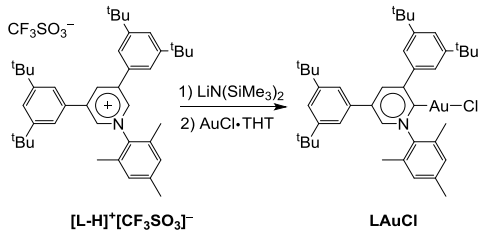
Scheme 1 Metal-catalyzed intramolecular and intermolecular hydroimination.

[a] *Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Nanyang Link 21,Singapore 637371 (Singapore). E-mail rkinjo@ntu.edu.sg*
[b] *NTU-CBC Crystallography Facility, Nanyang Technological University Nanyang Link 21, Singapore 637371 (Singapore).*
‡ These authors contributed equally.

†Electronic supplementary information (ESI) available: Experimental and calculation details, and crystallographic information for LAuCl, **3h**, **3i**, **5b**, **5g** and **6d**. CCDC 1051367, 1051368, 1051369, 1051370, 1051371 and 1051372. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/x0xx00000x.

terminal alkynes, which afforded both anti-Markovnikov and Markovnikov products. We also describe the first example for construction of pyridine derivatives from ammonia and alkynes.

Our protocol for intermolecular hydroimination of terminal alkynes is based on gold catalysis employing primary ketimines $HN{=}CR_2$. We envisaged that (a) soft π-acidity of gold allows interacting with alkynes effectively prior to ketimines, and (b) the presence of two R-substituents at the imine carbon of ketimines suppresses the attack by nucleophiles kinetically. We also reasoned that incorporation of a bulky ligand into gold might minimise the interaction with ketimines by steric repulsion, which will induce selective activation of terminal alkynes rather than undesired reaction pathway. Among various ligands available, pyrid-2-ylidenes ligands are considered as good candidates because substitutions at 1- and 3-positions maximize the steric impact at the gold center due to the six-membered ring skeleton.[21] Pyrid-2-ylidenes are also recognized as strong σ-donor ligands, which will contribute to promote substrate exchange, necessary for high turnover in catalysis, as well as the stability of the complex.[22] Hence, to commence our studies, we designed a novel gold chloride complex supported by a pyrid-2-ylidene ligand L bearing a 1,3,5-trimethylphenyl group and 3,5-di-tert-butylphenyl groups. When the deprotonation of a pyridinium salt $[L\text{-}H]^+[CF_3SO_3]^-$ was performed with lithium hexamethyldisilazide (LiHMDS)(3eq), which is followed by the addition of chloro(tetrahydrothiophene)gold(I), a clean reaction occurred with a characteristic signal for the carbene carbon at 187.8 ppm in the $^{13}C\{^1H\}$ NMR spectrum. After the products were worked up, LAuCl was obtained as a white solid in 49% yield (Scheme 2). LAuCl was fully characterized by standard spectroscopic methods, including a single crystal X-ray diffraction study.[23] LAuCl is air-stable, and can be stored for several months without significant decomposition, both in solution and in the solid state (m.p.; 220 °C).



Scheme 2 Synthesis of the gold complex **LAuCl**.

With the precatalyst LAuCl in hand, we next examined its catalytic activity in hydroimination of terminal alkynes. Recently, Toste and co-workers reported that gold-catalyzed reaction of phenylacetylene **1a** with N,1-diphenylmethanimine PhN=CHPh afforded a propargyl amine.[24] In marked contrast, the reaction between two equivalents of **1a** and benzophenone imine **2a** with a catalytic amount of LAuCl produced a mixture of (Z)-1,1-diphenyl-N-styrylmethanimine **3a** and 1,1-diphenyl-N-(1-phenylvinyl) methanimine **4a** after 1 hour at 150 °C, and unexpectedly, the yield of the anti-Markovnikov adduct **3a** was nearly identical to that of Markovnikov adduct **4a** (**3a**:**4a** ≈ 1:1). We also observed that **4a** gradually decomposed to unidentified mixture under the reaction condition (see the ESI). Therefore, in order to substantiate the apparent regioselectivity, reaction was repeated, and monitored by NMR spectroscopy. Among the screened reaction conditions, the highest production of anti-Markovnikov adduct **3a** (51%) was confirmed after 6 hours (Table 1-entry 1).

To further probe the formation of anti-Markovnikov product, we performed a ^{13}C-labeling experiment with a ^{13}C-labeled phenylacetylene **1a***, which decisively afforded **3a*** (Fig. 2a). Control reactions revealed the innocence of potassium tetrakis(pentafluorophenyl)borate $KB(C_6F_5)_4$, demonstrating the essential role of a gold complex LAuCl in this reaction. In fact, the reaction was shut down in the absence of the Au precatalyst. With AgOTf instead of $KB(C_6F_5)_4$ under similar reaction conditions, the product **3a** was obtained in lower yield (20%). When 1-bromo-4-ethynylbenezene **1b** was used (entry 2), the formation of anti-Markovnikov product **3b** was prior to Markovnikov product **4b** even at the early stage of the reaction (after 1 h; **3b**:**4b** = 12:1), and the highest yield (54%) of **3b** was obtained after 6 hours when **4b** decomposed completely. Treatment of **1a** and 4-ethynyltoluene **1c** afforded the similar result in which anti-Markovnikov adduct **3c** was formed in 43% after 6 hours (entry 3). These results indicate that the *apparent* anti-Markovnikov regioselectivity is concomitant with the decomposition of Markovnikov product in addition to the formation of a mixture of other unidentified products, whereas the stability of anti-Markovnikov products encouraged us for further exploration. Reaction of **2a** and an internal alkyne, diphenylacetylene, was also tested, which afforded *N*-(1,2-diphenylvinyl)-1,1-diphenylmethanimine in 78% after 22h (see the ESI).

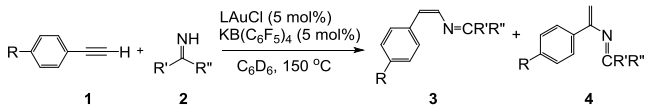
To test the scope of the hydroimination with respect to imines, we employed various imine substrates. Each reaction was monitored by NMR spectroscopy, and the results with anti-Markovnikov adduct **3** in the highest yield are summarized in Table 1. Standard functional groups are tolerated, including diaryl imines featuring p-methylphenyl groups **2b**, p-fluorophenyl group **2c**, as well as methyl benzimidate **2d**. All imine substrates **2a**-**d** examined in this study reacted well with alkynes **1a**-**c**, and provided 2-aza-1,3-dienes **3a**-**l** in moderate yields. Note that catalytic formation of 2-aza-1,3-dienes such as **3** and **4** from *terminal* alkynes and imines has never reported before. It is also noteworthy to mention that under similar conditions, employment of other gold catalysts such as $(Ph_3P)AuCl$ and (IPr)AuCl afforded no and a few (< 10%) products, respectively. We also examined the reaction of a bis-aliphatic imine, 2,2,4,4-tetramethylpentan-3-imine ($^tBu_2C{=}NH$) with **1a**, which gave a complex mixture.

Reaction of **1a** with 1-phenylethan-1-imine **2e** also proceeded under similar conditions. However, neither **3m** nor **4m** was detected. Instead, only unidentified self-decomposed products of **2e** were observed after the reaction. To our surprise, when a large excess amount of **1a** was used, we obtained 2-benzyl-4,6-diphenylpyridine **5** in 51% yield after 5 hours indicating that three equivalents of **1a** were involved in the reaction (Table 1, entry 13). Although we attempted to confirm the reaction intermediates by varying reaction temperature, time, and substrate ratio, **5a** was also only detectable product under any conditions.[25] Presumably instability of the corresponding 2-aza-1,3-diene intermediate caused the fast cyclization with a second alkyne. High reactivity of the intermediates may be due to the presence of the sterically less demanding methyl group at the imine carbon, which also could

induce tautomerization to transient enamine intermediates. It has already been shown that less-hindered 2-aza-1,3-diene derivatives react with unsaturated molecules to generate cyclic products.[16,26]

Bertrand and co-workers have reported that a catalytic amount of cyclic (alkyl)(amino)carbene gold complexes effectively promotes the addition of ammonia (NH_3) across alkynes and allenes.[27] In their study, hydroamination of a terminal arylalkyne, 4-ethynyltoluene, proceeded with Markovnikov regioselectivity, which afforded a 1-arylethan-1-imine. On the basis of these results, we attempted the direct synthesis of pyridine skeletons, common components of natural products and pharmaceuticals,[28] from alkynes and NH_3 through anti-Markovnikov hydroimination ~

Table 1 Au-catalyzed hydroimination of terminal arylalkynes.[a]



1 2 3 4

Entry	1	2	T (°C)	Time (h)	Yield[b,c] (3)	Products ratio (3 : 4)[b]
1	**1a** (R = H)		150	6	51(47)%	**3a** : **4a** = 6.2 : 1
2	**1b** (R = Br)		150	6	54(50)%	**3b** : **4b** = 100 : 0
3	**1c** (R = Me)	**2a**	150	6	43(39)%	**3c** : **4c** = 100 : 0
4	**1a** (R = H)		150	6	40(37)%	**3d** : **4d** = 100 : 0
5	**1b** (R = Br)		150	6	48(44)%	**3e** : **4e** = 100 : 0
6	**1c** (R = Me)	**2b**	150	6	42(37)%	**3f** : **4f** = 100 : 0
7	**1a** (R = H)		150	5	50(47)%	**3g** : **4g** = 100 : 0
8	**1b** (R = Br)		150	6	48(42)%	**3h** : **4h** = 100 : 0
9	**1c** (R = Me)	**2c**	150	5	36(32)%	**3i** : **4i** = 100 : 0
10	**1a** (R = H)		150	4	51(47)%	**3j** : **4j** = 4.3 : 1
11	**1b** (R = Br)		150	3	55(51)%	**3k** : **4k** = 6.1 : 1
12	**1c** (R = Me)	**2d**	150	3	43(39)%	**3l** : **4l** = 6.1 : 1
13	**1a** (R = H)	**2e**	150	5	–	**3m** : **4m** = – **5a**, 51%

a) Reaction conditions: **1** (0.4 mmol), **2** (0.2 mmol), LAuCl (5 mol%) and $KB(C_6F_5)_4$ (5 mol%), C_6D_6 (0.5 mL), 150 °C. b) Yields and selectivity were determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. c) Isolated yields are given in parentheses.

cyclization sequence. We postulate that treatment of terminal arylalkynes **1** and NH_3 in the presence of our gold catalyst LAuCl also would generate 1-arylethan-1-imines **2** via Markovnikov hydroamination rather than anti-Markovnikov selectivity due to the less bulkiness of ammonia molecule. The imines formed in situ would further react with a second alkyne in an anti-Markovnikov fashion to give 2-aza-1,3-diene intermediates **3** which would isomerize to **3A** and **3B** followed by cyclization with an additional alkyne. Finally, dehydrogenative aromatization from intermediates **C** would afford pyridine derivatives **5** (Fig. 2b).

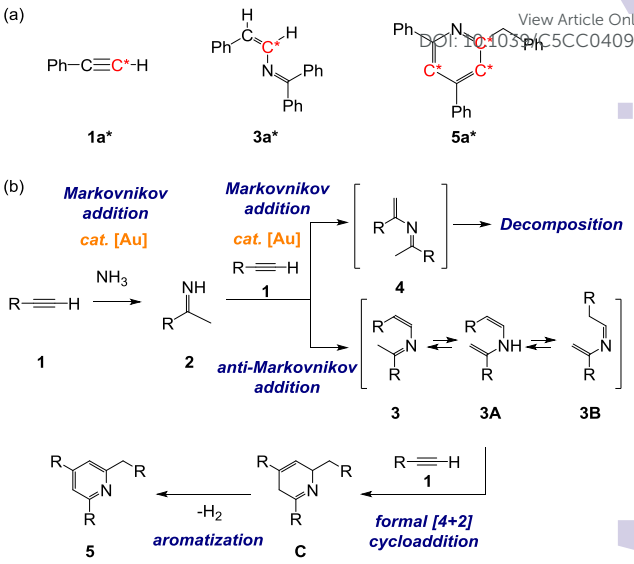


Fig. 2 (a) Representations of ^{13}C-labeled phenylacetylene **1a***, (Z)-1,1-diphenyl-N-styrylmethanimine **3a***, and 2-benzyl-4,6-dipheny lpyridine **5a***. (b) Proposed reaction pathway for construction o pyridine **5** from alkynes **1** and ammonia.

To bear out this hypothesis, 2.5 equivalents of **1a** we treated with NH_3 in the presence of the gold complex LAuCl (1 mol%). To our delight, after 12 hours at 150 °C **5a** was obtained in 43% yield (Table 2a, entry 1). Interestingly, the spontaneou aromatization by dehydrogenation was induced even without a oxidant. To gain insight into the reaction pathway, we performe further experiments. Reaction of **1a** with a large excess of NH_3 exclusively afforded 1-phenylethan-1-imine **2e**, confirming th the initial step is a Markovnikov hydroamination of alkyne, affording an enamine which may subsequently tautomerize t imine **2e**. Next, a ^{13}C-labeling experiment was conducted wit **1a***. When **1a*** was employed under the same reaction condition **5a*** was produced which supports the proposed reaction path (Fig. 2a). The scope of the catalytic reaction was briefly examined with a variety of alkynes **1** (Table 2a). Terminal alkynes with electron-donating as well as electron-withdrawing aromat groups were well tolerated (Table 2a, entries 2-7, 9, 1 Relatively low yield with **1h** was probably due to the extreme strong electron-withdrawing CF_3-group adopted (Table 2a, ent 8). 2-ethynylthiophene and 3-ethynylthiophene also exhibite tolerance to the reaction conditions (Table 2a, entries 11 and 12 Finally, our preliminary test showed that this strategy can b extended to three-component coupling reaction employing tw different terminal alkynes and NH_3, which afforded rather complex pyridine derivatives **6** (Table 2b). This result illustrates the potential application for the preparation of various heterocycl although the co-products **5** assembled from the mono-compone alkyne were also formed in this reaction.

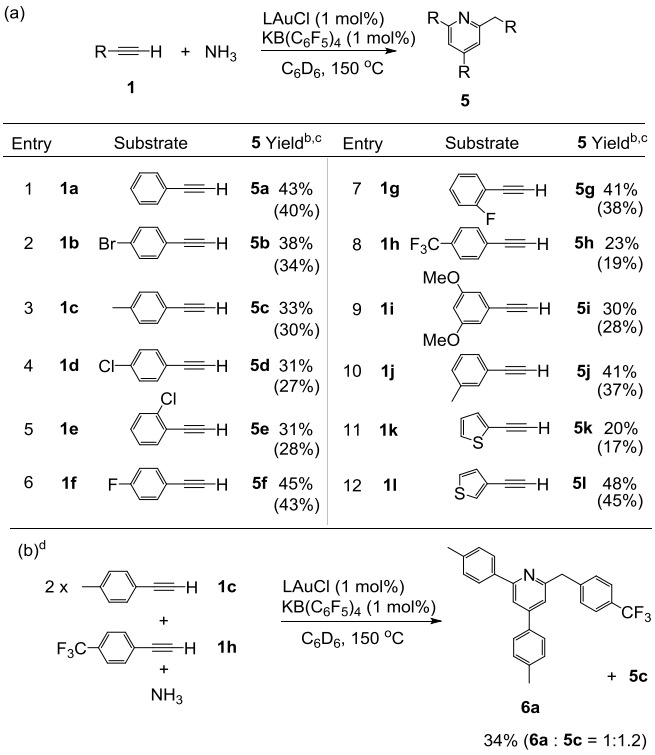
To investigate the reaction mechanism, we tested the reactio of **3a** and **1c** in the presence of LAuCl/KBArf (5mol%) under the similar reaction conditions. However, products corresponding to were not detected, and only a complex mixture was obtained. We postulated that Me-group at the imine carbon in **3** is necessary fo the formal [4+2] cycloaddition because it could isomerize to

transient **3B**, to which alkyne **1** readily approaches due to the less steric hindrance. Meanwhile, it has been reported that the formal [4+2] cycloaddition between azadienes and unsaturated compounds proceeds without any catalysts.[29]

In summary, we have developed the first gold-catalyzed intermolecular hydroimination of terminal alkynes, which afforded anti-Markovnikov adduct in moderate yields, concomitant with unstable Markovnikov adducts. Further study on the relevant gold ctalysis[30] with LAuCl is currently under investigation.

The authors gratefully acknowledge financial support from Nanyang Technological University and PSF/A*STAR (SERC 1321202066) of Singapore.

Table 2 (a) Au-catalyzed pyridine construction from alkynes and ammonia. (b) Au-catalyzed three-component coupling reaction.[a]



Entry	Substrate	5 Yield[b,c]	Entry	Substrate	5 Yield[b,c]
1	1a	5a 43% (40%)	7	1g	5g 41% (38%)
2	1b	5b 38% (34%)	8	1h	5h 23% (19%)
3	1c	5c 33% (30%)	9	1i	5i 30% (28%)
4	1d	5d 31% (27%)	10	1j	5j 41% (37%)
5	1e	5e 31% (28%)	11	1k	5k 20% (17%)
6	1f	5f 45% (43%)	12	1l	5l 48% (45%)

a) Reaction conditions: **1** (1 mmol), NH_3 (0.25 mmol), LAuCl (1 mol%) and $KB(C_6F_5)_4$ (1 mol%), C_6D_6 (0.7 mL), 150 °C. b) Yields and selectivity were determined by ^1H NMR spectroscopy using 1,4-di-t-butylbenzene as an internal standard. c) Isolated yields are given in parentheses. d) For other examples, see ESI (Scheme S4).

Notes and references

1 (a) S. A. Lawrence, Amines: Synthesis, Properties, and Applications, Cambridge University Press, New York, 2004; (b) D. O'Hagan, *Nat. Prod. Rep.*, 2000, **17**, 435.

2 (a) A. L. Reznichenko, K. C. Hultzsch, *Top. Organomet. Chem.*, 2013, **43**, 51; (b) J. F. Hartwig, *Organotransition Metal Chemistry*. University Science Books, Mill Valley, CA. 2010, ch. 16.5, p. 700; (c) T. E. Müller, K. C. Hultzsch, M. Yus, F. Foubelo, M. Tada, *Chem. Rev.*, 2008, **108**, 3795; (d) R. Severin, S. Doye, *Chem. Soc. Rev.*, 2007, **36**, 1407; (e) E. Mizushima, T. Hayashi, M. Tanaka, *Org. Lett.,* 2003, **5**, 3349.

3 M. B. Smith, J. March, *March's Advanced Organic Chemistry*. Wiley, New York, 2001, ed. 5.

4 J. Haggin, *Chem. Eng. News.*, 1993, **71**, 23.

5 M. Beller, H. Trauthwein, M. Eichberger, C. Breindl, J. Herwig, T. E. Müller, O. R. Thiel, *Chem. Eur. J.*, 1999, **5**, 1306.

6 (a) P. Horrillo-Martínez, K. C. Hultzsch, A. Gil, V. Branchadell, *Eur. J. Org. Chem.*, 2007, 3311; (b) K. Kumar, D. Michalik, I. Garcia Castra, A. Tillack, A. Zapf, M. Arlt, T. Heinrich, I. Böttcher, M. Beller, *Chem. Eur. J.*, 2004, **10**, 746.

7 (a) C. Brinkmann, A. G. M. Barrett, M. S. Hill, P. A. Procopiou, *J. Am. Chem. Soc.*, 2012, **134**, 2193; (b) A. G. M. Barrett, C. Brinkmann, M. R. Crimmin, M. S. Hill, P. Hunt, P. A. Procopiou, *J. Am. Chem. Soc.*, 2009, **131**, 12906.

8 J.-S. Ryu, G. Y. Li, T. J. Marks, *J. Am. Chem. Soc.*, 2003, **125**, 12584.

9 A. Tillack, I. G. Castro,C. G. Hartung, M. Beller, *Angew. Chem. Int. Ed.*, 2002, **41**, 2541.

10 S. S. Yudha, Y. Kuninobu, Takai. K, *Org. Lett.*, 2007, **9**, 5609.

11 (a) M. Arndt, K. S. M. Salih, A. Fromm, L. J. Goossen, F. Menges, G. Niedner-Schatteburg, *J. Am. Chem. Soc.*, 2011, **133**, 7428; (b) M. Utsunomiya, J. F. Hartwig, *J. Am. Chem. Soc.*, 2004, **12** 2702.

12 M. Utsunomiya, R. Kuwano, M. Kawatsura, J. F. Hartwig, *J. Am. Chem. Soc.*, 2003, **125**, 5608.

13 S. M. Bronner, R. H. Grubbs, *Chem. Sci.*, 2014, **5**, 101.

14 R. P. Rucker, A. M. Whittaker, H. Dang, G. Lalic, *J. Am. Chem. Soc.*, 2012, **134**, 6571.

15 J. C. Timmerman, B. D. Robertson, R. A. Widenhoefer, *Angew. Chem., Int. Ed.*, 2015, **54**, 2251.+

16 F. Palacios, C. Alonso, M. Rodríguez, E. M. d. Marigorta, G. Rubiales, *Eur. J. Org. Chem.*, 2005, 1795.

17 (a) R. He, Z.-T. Huang, Q.-Y. Zheng, C. Wang, *Angew. Chem., Int. Ed.*, 2014, **53**, 4950; (b) S. Gupta, J. Han, Y. Kim, S. W. Lee, Y. T. Rhee, J. Park, *J. Org. Chem.*, 2014, **79**, 9094; (c) D. N. Tran, N. Cramer, *Angew. Chem., Int. Ed.*, 2013, **52**, 10630; (d) J. Zhang, A. Ugrinov, P. Zhao, *Angew. Chem., Int. Ed.*, 2013, **52**, 6681.

18 A. Laouiti, M. M. Rammah, M. B. Rammah, J. Marrot, F. Couty, G. Evano, *Org. Lett.*, 2012, **14**, 6.

19 (a) D. Pflästerer, P. Dolbundalchok, S. Rafique, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Adv. Synth. Catal.*, 2013, **355**, 138. (b) V. H. L. Wong, T. S. A. Hor, K. K. Hii, *Chem. Commun.*, 2013, **49**, 9272; (c) A. S. K. Hashmi, M. Rudolph, S. Schymura, J. Visus, W. Frey, *Eur. J. Org. Chem.*, 2006, 4905; (d) J.-E. Kang, H.-B. Kim, J.-W. Lee, S. Shin, *Org. Lett.*, 2006, **8**, 3537.

20 R. S. Manan, P. Kilaru, P. Zhao, *J. Am. Chem. Soc.* [doi: 10.1021/jacs.5b02272.

21 K. Hata, Y. Segawa, K. Itami, *Chem. Commun.*, 2012, **48**, 6642.

22 (a) A. A. Tukov, A. T. Normand, M. S. Nechaev, *Dalton. Trans.* 2009, 7015. For further examples of catalyst stabilization by bulky ligands, see: (b) M. C. B. Jaimes, F. Rominger, M. M. Pereira, R. M. B. Carrilho, S. A. C. Carabineiro, A. S. K. Hashmi, *Chem. Commun.*, 2014, **50**, 4937; (c) M. C. B. Jaimes, C. R. N. Böhling, J. M. Serra-Becerra, A. S. K. Hashmi, *Angew. Chem. Int. Ed.*, 2013, **52**, 7963.

23 Experimental data for $[L\text{-}H]^+[CF_3SO_3]^-$, LAuCl, and products **3**, and **6** are available in the ESI.

24 M. J. Campbell, F. D. Toste, *Chem. Sci.*, 2011, **2**, 1369.

25 A. S. K. Hashmi, *Angew. Chem., Int. Ed.*, 2010, **49**, 5232.

26 F. Palacios, C. Alonso, C. Tobillas, G. Rubiales. *Heterocycles*, 2004, **64**, 229.

27 V. Lavallo, G. D. Frey, B. Donnadieu, M. Soleilhavoup, G. Bertrand, *Angew. Chem., Int. Ed.*, 2008, **47**, 5224.

28 A. Brossi, The Alkaloids: *Chemistry and Pharmacology*, Ed.: G. A. Cordell, Academic Press, San Diego, 1993, vol. 43, p. 119.

29 (a) S. Jayakumar, M. P. S. Ishar, M. P. Mahajan, *Tetrahedron*, 2002, **58**, 379; (b) S. M. Weinreb, P. M. Scola, *Chem. Rev.*, 1989, **89**, 1525.

30 (a) A. Corma, A. Leyva-Pérez, M. J. Sabater, *Chem. Rev.*, 2011, **111**, 1657; (b) A. Arcadi, *Chem. Rev.*, 2008, **108**, 3266; (c) Z. Li, C. Brouwer, C. He, *Chem. Rev.*, 2008, **108**, 3239.