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1,6-Carbene Transfer: Gold-Catalyzed Oxidative Diyne Cyclizations

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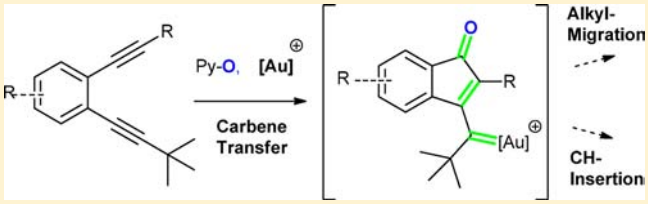
Supporting Information

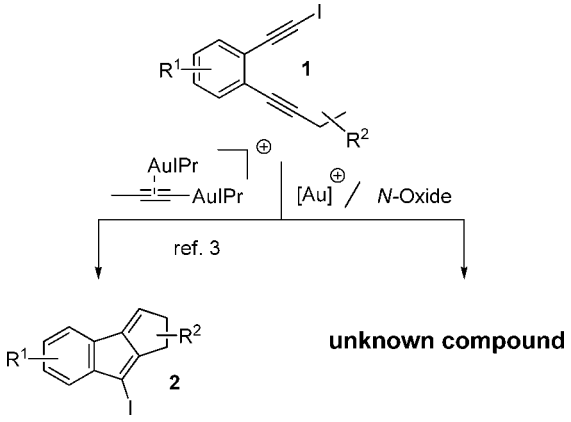
ABSTRACT: In the presence of a gold catalyst an unprecedented oxidative cyclization of diynes takes place. The reaction cascade is initiated by an oxygen transfer from a *N*-oxide onto a gold-activated alkyne. The formed α-oxo carbene is transferred across the second alkyne yielding a stabilized vinyl carbene/cation. Alkyl migration or sp^3-CH insertion then terminates the catalytic cycle by formation of highly substituted functionalized indenones. A 1,6-carbene shift could be supported by the oxidation of the vinyl carbene. This protocol represents an attractive alternative to procedures which are based on the metal-catalyzed decomposition of hazardous, not easily accessible, diazo compounds.



INTRODUCTION

Driven by the ongoing explorations of new types of reactivities, the contribution of homogeneous gold catalysis to the field of organic synthesis is still emerging.[1] Only recently a new type of reactivity was discovered by Zhang's group and our group. The mode of reaction is based on a dual activation opening up new pathways for diyne systems. After activation of a terminal alkyne, via the formation of a gold acetylide, the second alkyne can be activated via π-coordination of a second gold ion. This then initiates the formation of highly reactive carbene/vinylidene intermediates that enable a range of fruitful transformations.[2] Besides the use of terminal alkynes for the generation of the gold acetylide, iodoalkynes can also be applied as starting materials (Scheme 1, left).[3]

Scheme 1. Unexpected Product Formation for the Gold-Catalyzed Conversion of Iodoalkyne 1 in the Presence of an *N*-Oxide



For this kind of substrate organo-gold additives are crucial, and the best catalysts turned out to be the well-defined σ-/π-dinuclear propyne-based gold acetylides[4] (DAC = dual activation catalysts). Among the additives that were applied, in order to find the optimum reaction conditions for this transformation, *N*-oxides were also tested as these were reported to be suitable additives for acetylide formation as well.[2a] To our surprise not even traces of the expected iodofulvene were observed, and instead a different product was formed in significant amounts (Scheme 1, right). Our efforts to explore this unexpected reaction pathway are presented in this contribution.

RESULTS AND DISCUSSION

The initial reaction was performed with 2,6-lutidine *N*-oxide together with IPrAuCl/$AgNTf_2$ as the catalyst system. After 16 h at 55 °C we were able to obtain 20% of a solid unknown compound **3a**. In order to obtain a concrete picture of the obtained product, crystals suitable for X-ray analysis were grown; the solid-state molecular structure is depicted in Figure 1. The obtained structure contains an iodo-indenone skeleton. In addition, a transformation of the former *tert*-butylalkynyl group into a tetra-substituted alkene moiety takes place.

In order to obtain higher yields of the iodo-indenone, we subsequently performed an intensive screening for the best reaction conditions. First we set out to investigate solvent effects (see SI). All tested solvents allowed for the reaction to occur, MeCN gave the best result (24%). This evidence was then followed, and a screening of different ligands at the Au-center was carried out (Table 1). We initially varied the NHC ligand to SIPr which led to a small decrease in yield (entry 2).

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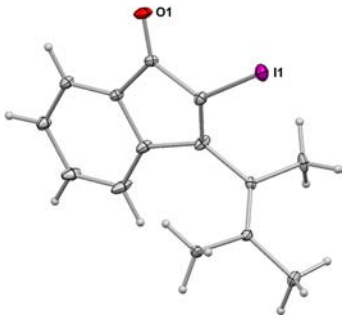
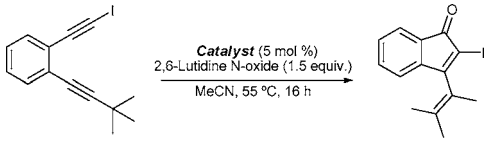


Figure 1. Solid-state molecular structure of the unexpected product.

Table 1. Ligand Sceening

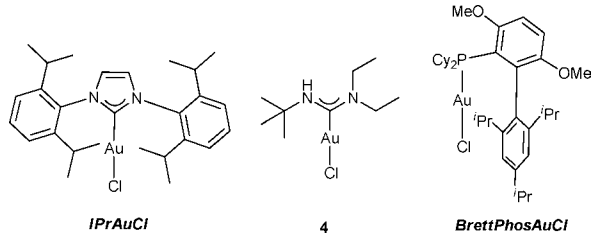


entry	catalyst	GC yield[a]
1	IPrAuCl/$AgNTf_2$	24%
2	SIPrAuCl/$AgNTf_2$	17%
3	IPrAuCl/$AgNTf_2$ with 4 Å MS	20%
4	**4**/$AgNTf_2$	42%[c]
5	$Ph_3PAuCl/AgNTf_2$	63%
6	BrettPhosAuCl/$AgNTf_2$	61%
7	*t*-ButylXPhosAuCl/$AgNTf_2$	51%
8	$Ph_3PAuNTf_2$	60%[b]
9	**$Ph_3PAuNTf_2$**	**94%**[b,d]

[a]GC yields are averaged over a minimum of two runs using *n*-dodecane as an internal standard. [b]Isolated yield. [c]Reaction time is 1 h. [d]Reaction run at room temperature with 3,5-dibromopyridine *N*-oxide as oxidant.

Equally inefficient was the addition of 4 Å molecular sieves (entry 3). Interestingly, an increase in yield was observed when gold complex **4** was used carrying an acyclic carbene ligand resulting in 42% GC yield (entry 4).[5] To our delight we found that changing to phosphine ligands led to a drastic increase in yield. Simple Ph_3PAuCl combined with $AgNTf_2$ gave 63% GC yield (entry 5). We also tested the commonly used Buchwald ligands, which are often reported to be superior to PPh_3 in gold-catalyzed reactions. Both BrettPhos (entry 6) and *t*-BuXPhos (entry 7) only gave comparable yields, hence all following reactions were carried out using much cheaper PPh_3 complexes. As reactions of diynes are potentially catalyzed by Ag-salts, we also tested $AgNTf_2$ in the absence of gold. For this control experiment no reaction was observed. In addition, synergistic effects of Au and Ag have been reported,[6] therefore, we prepared $Ph_3PAuNTf_2$ and tested it in the absence of the Ag salt used to liberate the cationic Au species. The desired product was isolated in 60% yield. This shows that there is no involvement of the Ag salt in this particular catalytic reaction.

Although the yields are improved by using a phosphine-based catalyst, the reactions usually do not go to completion and residual starting material is observed. In order to drive the reactions to completion we tested a number of *N*-oxides (see SI). While 8-isopropylquinoline *N*-oxide gave a slightly increased yield, pyridine and 4-picoline *N*-oxides resulted in diminished yields of 41% and 31%, respectively. Again, unreacted starting material was observed in all cases which is



most probably based on blocking of the catalyst by the released pyridine. In order to decrease the donor abilities of the pyridine, we applied electron-deficient 2,6-dibromopyridine *N*-oxide as oxygen donor, and indeed TLC analysis showed full conversion of the starting material at 55 °C after only 20 min. However, we were only able to isolate 49% product by column chromatography along with several mixed fractions containing an unidentified side product. The significantly increased reactivity could easily be controlled by lowering the temperature from 55 °C to room temperature, allowing isolation of the desired product in excellent 97% yield after 1 h. 3,5-Dibromopyridine *N*-oxide (Table 1, entry 9) was similarly effective and has been used in the exploration of different substrates, as separation of the formed 2,6-dibromopyridine proved to be difficult in some cases (see below). It is noteworthy that diphenyl sulfoxide may also serve as an oxidant in this reaction, albeit in a slightly reduced yield.

We finally set out to investigate the scope of this reaction briefly (Table 2). Variation of the halide was carried out first. Both the iodo- and bromo-precursor resulted in the desired products **3a** and **3b** in excellent 94% and 90% isolated yields, respectively. However, the chloro-compound **3c** was only isolated in 57% yield. Electron-rich substituents were greatly tolerated under the reaction conditions giving products **3d**−**i** in 73−85% isolated yield. Substrates containing electron-withdrawing groups gave slightly reduced yields. The nitro-containing product **3j** was obtained in 63% isolated yield. This was similarly the case for the fluorine containing product **3k** which was isolated in 66% when using 5 mol % Au catalyst. In this case we also tested an increased catalyst loading of 7.5 mol %, resulting in 75% isolated yield. The thiophene-containing product **3l** could also be obtained, although only in a rather modest 45% yield requiring 10 mol % catalyst. If a cyclopentyl substituted alkyne was transformed, a 2:1 mixture of two products was obtained in good overall yield. Besides the ring expansion product **3mb**, the product of a competing hydride shift **3ma** was also obtained (Scheme 2). The reaction of a substrate containing a hexyne moiety turned out to be unselective. An aryl substituted alkyne was also tested (Scheme 3). In this case a second oxygen atom was incorporated in the final molecule. As no hydride shift or alkyl migration can take place with the aryl substituent, oxidation of the intermediate carbenoid by another molecule of *N*-oxide seems to be the main pathway. It should be noted that the yield of the reaction could not be improved by an increase of the amount of *N*-oxide. Nevertheless, the product gives a clear indication that 1,6-carbene transfer takes place. Figure 2 shows the molecular solid-state structure of the obtained product **5**.

Our next efforts were concentrated on a further expansion of the subtrate scope. It turned out that not only haloalkynes are suitable substrates. By using substrate **6**, bearing two *tert*-butyl acetylene moieties, desymetrization of the molecule took place. As the reaction only proceeded at elevated temperatures, we used $IPrAuNTf_2$ as a catalyst which showed the best results in

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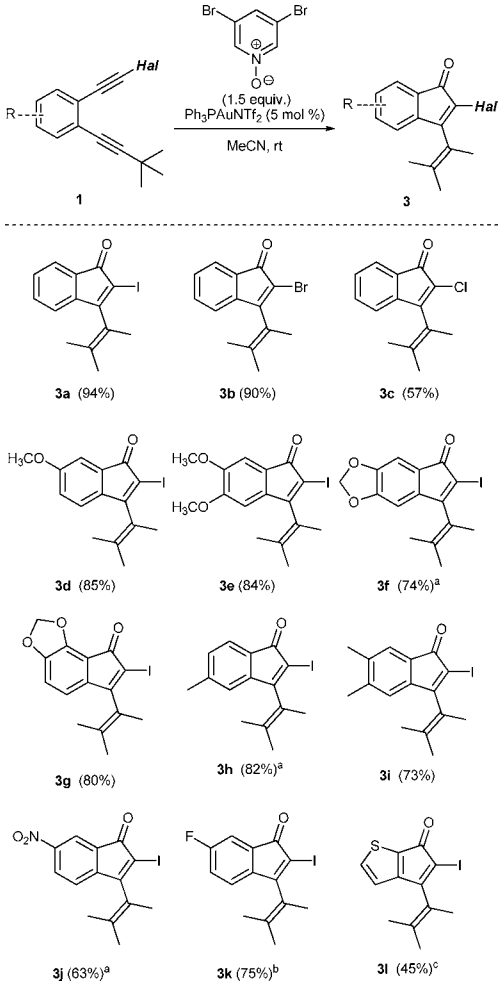
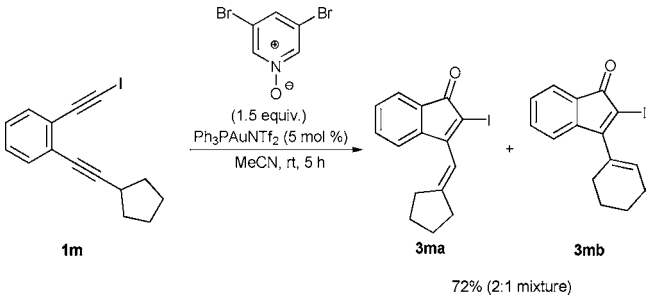
Table 2. Subtrate Scope

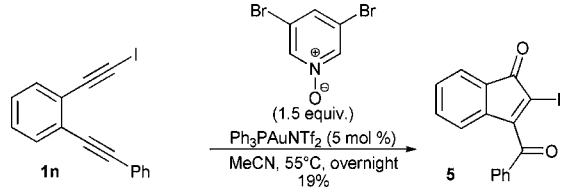


[a]Contains traces of 3,5-dibromo pyridine. [b]7.5 mol % catalyst used. [c]10 mol % catalyst used.

Scheme 2. Conversion of Substrate 1m



Scheme 3. Oxidation of the Intermediate Carbenoid



combination with a quinoline *N*-oxide derivative. Instead of a 1,2-shift of a methyl group, sp^3-CH-insertion takes place, delivering a tricyclic product **7** in moderate yield (Scheme 4).

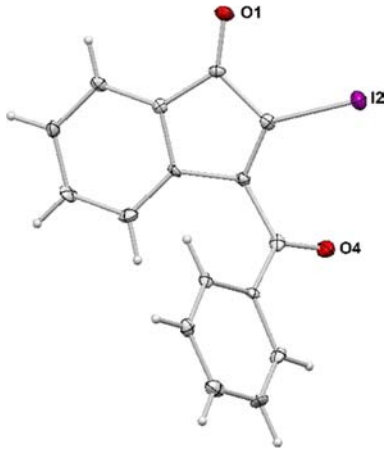
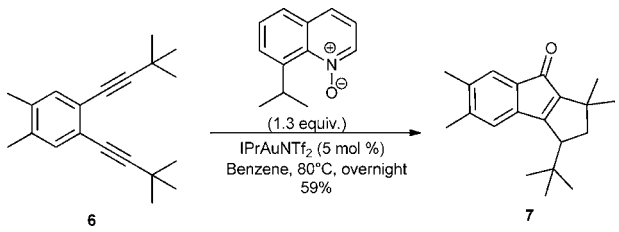


Figure 2. Solid-state molecular structure of diketone **5**.

The assigment of the product could be verified by X-ray crystallography (Figure 3).

Scheme 4. Desymetrization of 6 via Carbene Transfer Followed by CH Insertion



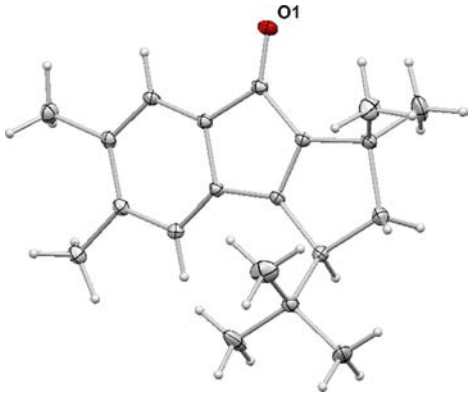


Figure 3. Solid-state molecular structure of indenone **7**.

If one of the *tert*-butyl alkynes was changed to a phenyl acetylene, a completely different picture was obtained. For this subtrate the less hindered aryl alkyne reacts with the *N*-oxide in the first step and then, in analogy to the iodoalkynes, a 1,2-methyl shift terminates the reaction cascade which finally delivers product **9** in moderate yield (Scheme 5). Our attempts to use silyl-protected alkynes or nonaromatic tethers failed (Scheme 6).

The products of the iodoalkyne cyclizations are suitable substrates for further functionalization via cross coupling strategies (Scheme 7). This was demonstrated by a Sonogashira reaction with substrate **3a** delivering product **12** in excellent yield. A Suzuki coupling was also possible, however, in a moderate yield. *p*-Methoxy boronic acid was chosen as coupling

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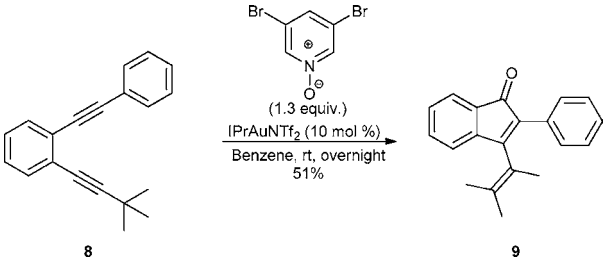
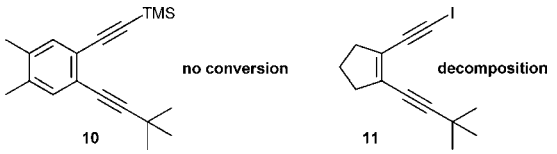
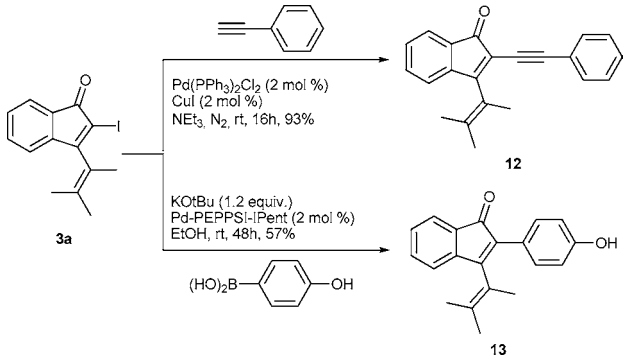
Scheme 5. Transformation of Aryl/Alkyl Diyne 8



Scheme 6. Limitations of the Oxidative Cyclization



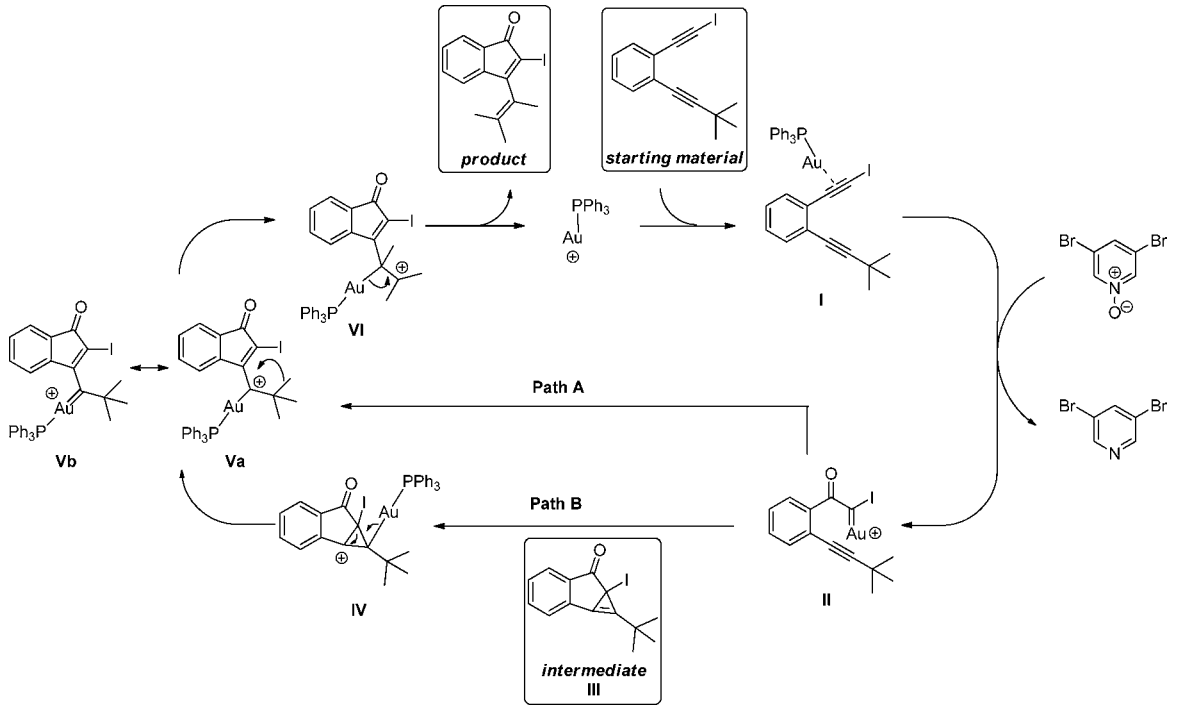
Scheme 7. Cross-Coupling Reactions with Subtrate 3a



partner as the obtained target **13** contains a substructure which has already been reported as efficient estrogen receptor ligand.[7]

Our mechanistic idea of the transformation is depicted in Scheme 8. Due to the oxygen transfer into the final molecule, it seems that in this case the *N*-oxide does not play the role of a base like in the case of the dual catalyzed reactions.[2a] Instead a selective oxidation of a π-activated alkyne takes place. The oxidation of alkynes with *N*-oxides in the presence of a Au catalyst generating an α-keto Au carbenoid is a well-established reaction.[8] Subsequent cyclopropenation is a conceivable scenario. A gold-catalyzed cyclopropenation of an alkyne by a gold carbenoid derived from the decomposition of a diazo compound was recently published by the Davies group.[9] It remains unclear whether a cyclopropene intermediate **III** is formed (Path B) or a concerted process directly delivers cation/carbene intermediate **V** (Path A). The carbene transfer over a pendant alkyne is a well-known process for Rh catalysts, but for all of these substrates hazardous diazo precursors are used for the generation of the carbenoids.[10] It has been demonstrated by Toste's group that a gold carbene can be transferred across an alkyne and similarly to the case of the mentioned Rh examples, a diazo compound was used as carbene precursor.[11] During preparation of the manuscript the groups of Hirao and Chan reported a carbenoid transfer reaction based on a 1,2-acetoxy migration as initiating step.[12] In analogy with Toste's contribution, the last step of the reaction cascade is a 1,2-migration of the methyl group onto the electrophilic carbenoid center which might also be regarded as a gold-stabilized carbocation, elimination of the gold catalyst delivers the iodo-indenone products. As demonstrated in this manuscript, other pathways based on carbene reactivity are also possible with intermediates of type **V**, namly CH insertions or the oxidation of the carbenoid by a second molecule of *N*-oxide.

Scheme 8. Mechanistic Picture



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CONCLUSION

In summary, we could demonstrate that gold carbenoids generated by oxygen transfer from *N*-oxides can be transferred over a tethered alkyne. The formed highly electrophilic vinyl carbenoid can then be exploited for further transformations like Wagner−Meerwein chemistry, CH insertions or oxidation of the carbenoids. The easy availability of the starting materials combined with the safer reactions conditions should establish this protocol as a perfect expansion toward related reactions that are based on metal-catalyzed decomposition of diazo compounds. Currently we are working on the expansion of this methodology for the invention of new synthetically useful transformations.

ASSOCIATED CONTENT

Supporting Information

Complete experimental procedures and characterization data for the prepared compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) For representative reviews on gold catalysis, see: (a) Dyker, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 4237−4239. (b) Hashmi, A. S. K. *Gold Bull.* **2003**, *36*, 3−9. (c) Hashmi, A. S. K. *Gold Bull.* **2004**, *37*, 51−65. (d) Krause, N.; Hoffmann-Röder, A. *Org. Biomol. Chem.* **2005**, *3*, 387−391. (e) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2005**, *44*, 6990−6993. (f) Hashmi, A. S. K.; Hutchings, G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7896−7936. (g) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395−403. (h) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410−3449. (i) Jimenez-Nunez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333−346. (j) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180−3211. (k) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239−3265. (l) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266−3325. (m) Shen, H. C. *Tetrahedron* **2008**, *64*, 3885−3909. (n) Shen, H. C. *Tetrahedron* **2008**, *64*, 7847−7870. (o) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2010**, *49*, 5232−5241. (p) Corma, A.; Leyva-Pérez, A.; Sabater, M. J. *Chem. Rev.* **2011**, *111*, 1657−1712.

(2) (a) Ye, L.; Wang, Y.; Aue, D. H.; Zhang, L. *J. Am. Chem. Soc.* **2012**, *134*, 31−34. (b) Hashmi, A. S. K.; Braun, I.; Rudolph, M.; Rominger, F. *Organometallics* **2012**, *31*, 644−661. (c) Hashmi, A. S. K.; Wieteck, M.; Braun, I.; Nösel, P.; Jongbloed, L.; Rudolph, M.; Rominger, F. *Adv. Synth. Catal.* **2012**, *354*, 555−562. (d) Hashmi, A. S. K.; Braun, I.; Nösel, P.; Schädlich, J.; Wieteck, M.; Rudolph, M.; Rominger, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 4456−4460. (e) Hashmi, A. S. K.; Wieteck, M.; Braun, I.; Rudolph, M.; Rominger, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 10633−10637. (f) Hansmann, M. M.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2013**, *52*, 2593−2598.

(3) Nösel, P.; Lauterbach, T.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. *Chem.—Eur. J.* **2013**, *19*, 8634−8641.

(4) Hashmi, A. S. K.; Lauterbach, T.; Nösel, P.; Vilhelmsen, M. H.; Rudolph, M.; Rominger, F. *Chem.—Eur. J.* **2013**, *19*, 1058−1065.

(5) Hashmi, A. S. K.; Hengst, T.; Lothschütz, C.; Rominger, F. *Adv. Synth. Catal.* **2010**, *352*, 1315−1337.

(6) Wang, D.; Cai, R.; Sharma, S.; Jirak, J.; Thummanapelli, S. K.; Akhmedov, N. G.; Zhang, H.; Liu, X.; Petersen, L. J.; Shi, X. *J. Am. Chem. Soc.* **2012**, *134*, 9012−9019.

(7) McDevitt, R. E.; Malamas, M. S.; Manas, E. S.; Unwalla, R. J.; Xu, Z. B.; Miller, C. P.; Harris, H. A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3137−3142.

(8) (a) Xiao, J.; Li, X. *Angew. Chem., Int. Ed.* **2011**, *50*, 7226−7236. (b) Blanco, M. C.; Hashmi, A. S. K. *Modern Gold Catalyzed Synthesis*; Hashmi, A. S. K., Toste, F. D., Eds.; Wiley-VCH: Weinheim, 2012; Chapter 11, pp 273−295.

(9) Briones, J. F.; Davies, H. M. *J. Am. Chem. Soc.* **2012**, *134*, 11916−11919.

(10) For selected publications see: (a) Padwa, A. *Molecules* **2001**, *6*, 1−12. (b) Padwa, A. *J. Organomet. Chem.* **2000**, *610*, 88−101. (c) Jansone-Popova, S.; May, J. A. *J. Am. Chem. Soc.* **2012**, *134*, 17877−17880. (d) Le Paih, J.; Bray, C. V-L.; Dérien, S.; Dixneuf, P. H. *J. Am. Chem. Soc.* **2010**, *132*, 7391−7397. Panne, P.; Fox, J. M. *J. Am. Chem. Soc.* **2007**, *129*, 22−23. Mueller, P. H.; Kassir, J. M.; Semones, M. A.; Weingarten, M. D.; Padwa, A. *Tetrahedron Lett.* **1993**, *34*, 4285−4288. Padwa, A.; Krumpe, K. E.; Kassie, J. M. *J. Org. Chem.* **1992**, *57*, 4940−4948.

(11) Witham, C. A.; Mauleón, P.; Shapiro, N. D.; Sherry, B. D.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 5838−5839.

(12) Rao, W.; Koh, M. J.; Li, D.; Hirao, H.; Chan, P. W. H. *J. Am. Chem. Soc.* **2013**, *135*, 7926. See also: Lauterbach, T.; Gatzweiler, S.; Nösel, P.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. *Adv. Synth. Catal.* **2013**, *355*, 2481−2487.