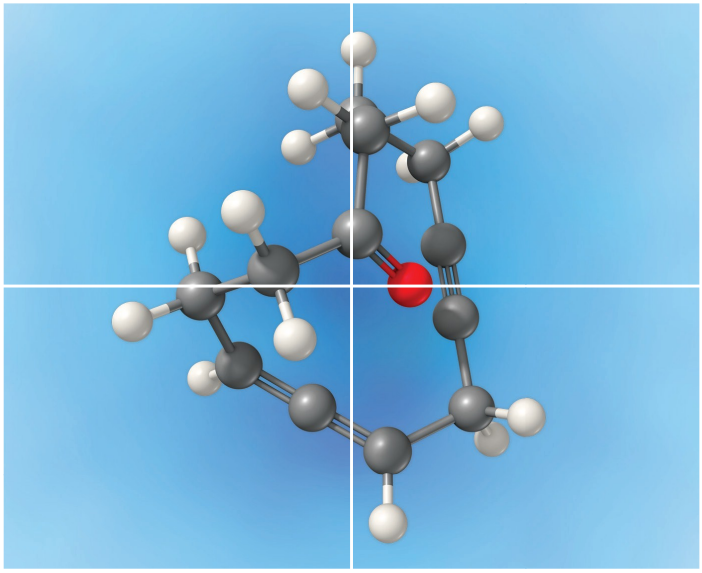
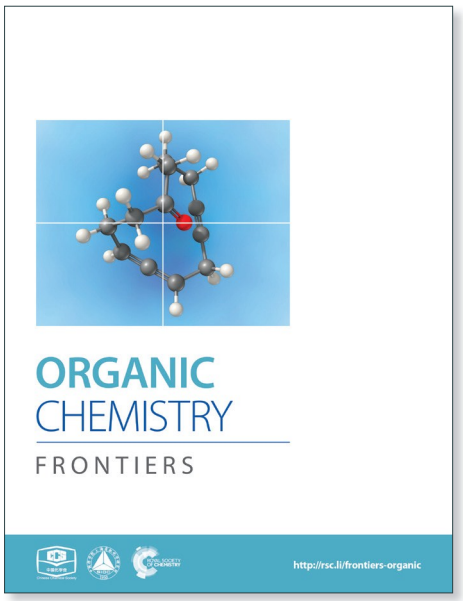
ORGANIC CHEMISTRY

FRONTIERS



Accepted Manuscript



This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this *Accepted Manuscript* with the edited and formatted *Advance Article* as soon as it is available.

You can find more information about *Accepted Manuscripts* in the **Information for Authors**.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard **Terms & Conditions** and the **Ethical guidelines** still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.

Journal Name

COMMUNICATION

C-H insertions in oxidative gold catalysis: Synthesis of polycyclic 2*H*-pyran-3(6*H*)-ones via a relay strategy

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

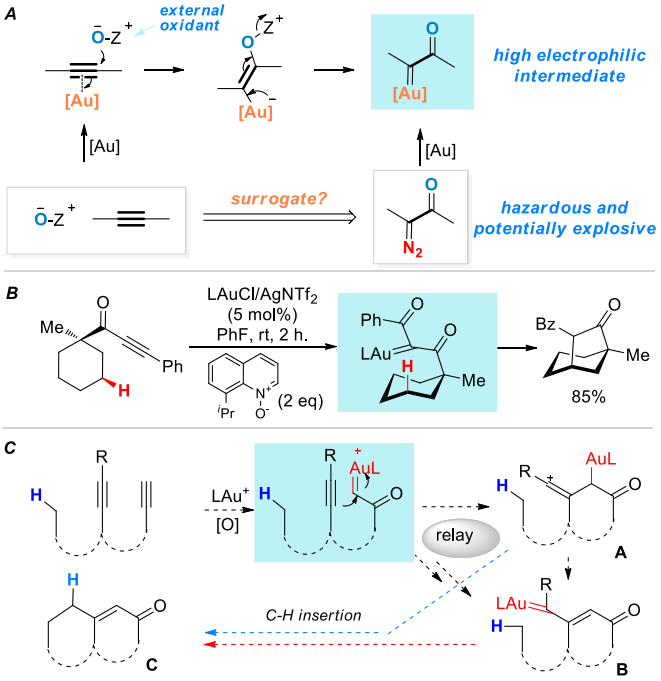
DOI: 10.1039/x0xx00000x

www.rsc.org/

Zhitong Zheng[a] and Liming Zhang[a]*

An expedient synthesis of bicyclic/polycyclic 2*H*-pyran-3(6*H*)-ones is realized in a cascade cyclization triggered by oxidative gold catalysis and terminated by streamlining C-H insertion. In this reaction, an α-oxo gold carbene intermediate, initially formed upon gold-catalyzed oxidation of alkyne, could be trapped by a tethered C-C triple bond, thereby resulting in the formation of a putative vinyl cation intermediate. This intermediate of highly electrophilicity is proposed to be responsible for the intramolecular C-H insertion, the mostly concerted nature of which is established by the reactions of chiral substrates. The reaction provides a rapid approach to the construction of functionalized polycyclic systems from easily accessible bispropargyl ethers and with minimal structural prefunctionalization.

Functionalization of unactivated C(sp^3)-H bonds is a topic of immense contemporary interest and of exceptional value in organic synthesis.[1] A time-honored strategy is C-H insertions by in situ-generated, highly reactive intermediates, among which are carbenes/carbenoids,[1c, d] vinylidenes[2] and their metal counterparts,[3] and vinyl cations.[4] In 2010, we[5] reported a general strategy of generating highly electrophilic α-oxo gold carbenes via gold-catalyzed intermolecular oxidation of alkynes (Scheme 1A). Despite the development of various versatile transformations based on these in situ-generated intermediates,[3d, 6,7] their highly reactive nature has sparsely lent themselves to the implementation of new C-H insertion strategies.[7d] Some time ago we initiated two parallel programs aiming to explore the utilities of these oxidatively generated gold carbenes in intramolecular C-H insertions, namely, direct C-H insertions (e.g., Scheme 1B), and transformations into other reactive species capable of C-H insertions (the relay approach). For the direct approach, we have very recently realized such insertions into unactivated C(sp^3)-H bonds by in situ-generated acceptor-/acceptor-substituted gold carbenes.[6g] For the relay approach,[8] as shown in Scheme 1C, our design anticipated that with a diyne substrate, a terminal α-oxo gold carbene could be selectively generated upon oxidation of the terminal C-C triple bond. Subsequently, the gold carbene would be attacked by the appropriately tethered internal alkyne to afford a reactive vinyl cation intermediate, i.e., A. **A** would either undergo reported C-H insertions[4] to afford the cyclic product **C**, or lead to the same product through the rearranged gold carbene intermediate **B**.[9] Hashmi and co-workers have reported a single example of this type of C-H insertion using an *O*-phenylenedialkyne substrate,[9] and another single case was recently reported.[10] We surmised that this little explored relay strategy, if realized with more flexible and readily accessible systems, would permit rapid access to cyclic products with no/little prior functionalization.



Scheme 1 α-Oxo gold carbenes: A) catalytic generation via oxidation of alkynes. B) An example of direct insertion into

[a] Department of Chemistry & Biochemistry, University of California, Santa Barbara, CA 93106.

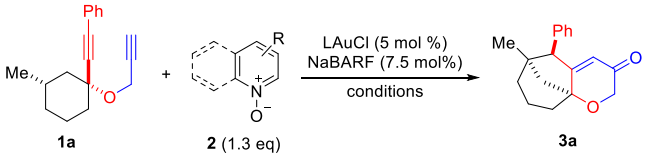
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See

Organic Chemistry Frontiers Accepted Manuscript

Please do not adjust margins

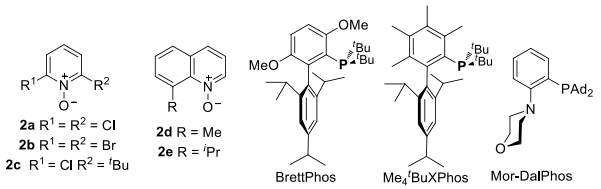
unactivated C-H bonds. C) A designed relay approach to C-H insertions.

Table 1 Initial reaction discovery and optimization[a]



entry	catalyst	*N*-oxide	conditions	yield
1	Ph_3PAuCl	**2a**	DCE, rt, 18 h	trace[b]
2	IPrAuCl	**2a**	DCE, rt, 18 h	trace[b]
3	JohnPhosAuCl	**2a**	DCE, rt, 18 h	trace[b]
4	BrettPhosAuCl	**2a**	DCE, rt, 3 h	24%
5	$Me_4{}^tBuXPhosAuCl$	**2a**	DCE, rt, 2 h	40%
6	Mor-DalPhosAuCl	**2a**	DCE, rt, 7 h	41%
7	$Me_4{}^tBuXPhosAuCl$	**2a**	PhMe, rt, 1 h	46%
8	$Me_4{}^tBuXPhosAuCl$	**2a**	PhF, rt, 1 h	50%
9	$Me_4{}^tBuXPhosAuCl$	**2b**	PhF, rt, 1 h	49%
10	$Me_4{}^tBuXPhosAuCl$	**2c**	PhF, rt, 1.5 h	60%
11	$Me_4{}^tBuXPhosAuCl$	**2d**	PhF, rt, 1 h	58%
12	**$Me_4{}^tBuXPhosAuCl$**	**2e**	**PhF, rt, 1 h**	**70%**
13	$Me_4{}^tBuXPhosAuCl$	**2e**	PhF, 50 °C, 5 min	70%[c]
14	$Me_4{}^tBuXPhosAuCl$	**2e**	PhF, 0 °C, 7 h	66%
15	$Me_4{}^tBuXPhosAuCl$	**2e**	PhF, -20 °C, 36 h	65%

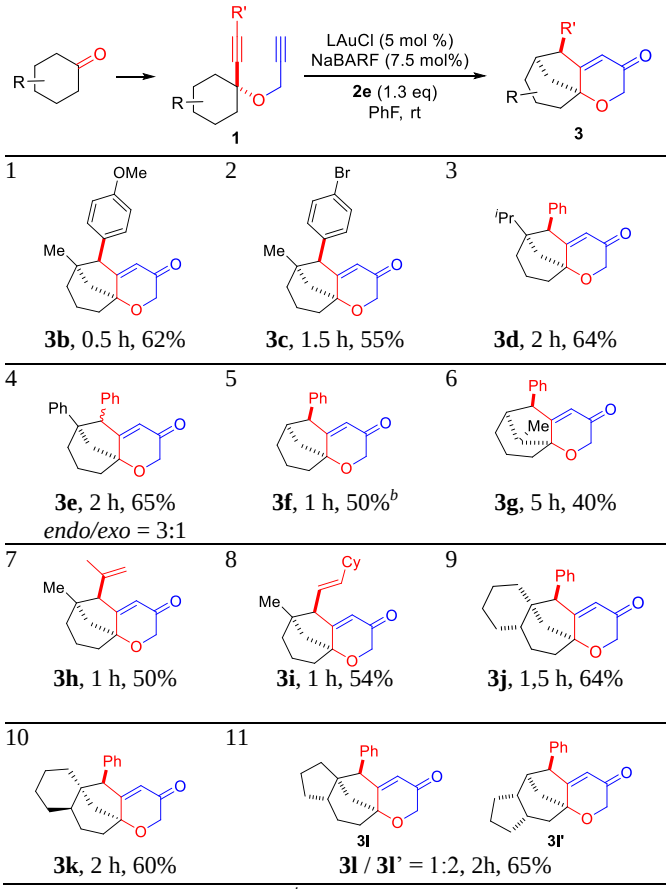
[a] Reaction is run in vial. [b] Complicated mixture formed, and no desired product detected. [c] Reaction was less clean.



We set out to explore the relay approach by using the bispropargyl ether **1a** as substrate, which was readily prepared from 3-methylcyclohexanone in two steps and 40% yield. Our unpublished results with another oxidative catalysis suggest that this type of ethereal diynes has a tendency to undergo oxidative cyclization.[10] While initial attempts with typical gold pre-catalysts including Ph_3PAuCl, IPrAuCl and JohnPhosAuCl led to complex mixtures (Table 1, entries 1-3), a combination of BrettPhosAuCl,[11] NaBARF and 2,6-dichloropyridine *N*-oxide (**2a**) yielded an encouraging 24% yield of the anticipated tricyclic 2*H*-pyran-3(6*H*)-one **3a** (entry 3). An improved yield (40%) was achieved with the sterically highly demanding $Me_4{}^tBuXPhos$ (entry 5) or the *P*,*N*-bidentate ligand Mor-DalPhos[12] (entry 6) as the metal ligand. Due to the faster reaction with $Me_4{}^tBuXPhosAuCl$, it was chosen for further condition optimization. A brief screening of solvents (entries 5 and 7-8) revealed that fluorobenzene was the solvent of chioce, and **3a** was formed in 50% yield (entry 5). A series of *N*-oxides with different steric and electronic properties were also examined (Table 1, entries 9-12). 8-Isopropylquinoline *N*-oxide (**2e**) turned out to be the most effective, and **3a** was formed in 70% yield (entry 12). To our surprise, the reaction effiency was somehow independent to the reaction temperature, despite the large span of reaction times (entries 13-15). It is notworthy that **3a** was formed regioselectively, indicating significant preference of the methine C-H bond over the methylene counterpart in the C-H insertion step; moreover, the reaction was highly diastereoselective, and 2D NMR studies revealed that the shown *endo*-Ph isomer was formed with >20:1 ratio over the unidentified *exo* isomer.

With the optimal reaction conditions (cf. Table 1, entry 12) in hand, the scope of this relay chemistry was explored with substrates derived from substituted cyclohexanones, and the results are shown in Table 2. First, the phenyl group of **1a** was varied by substitution of either an electron-donating 4-MeO (entry 1) or a slightly electron-withdrawing 4-Br (entry 2). In either case, the desired product was formed in a decent yield. The Me group on the cyclohexane ring of **1a** was then modified. With an isopropyl (entry 3) or a phenyl group (entry 4) instead, the oxidative relay gold catalysis worked smoothly, affording the tricyclic ketone **3d** or **3e** in 64% or 65% yield, respectively. When the Me group of **1a** was removed, the reaction still afforded **3f** in a serviceable 50% yield (entry 5). This lower efficiency, as compared to that of **3a**, is in accordance to the preference for tertiary C-H bonds over secondary ones in the insertion step (vide supra). With the substrate prepared from 2-methylcyclohexanone, the Isolated product **3g**, albeit in a moderate 40% yield, exhibits an

Table 2 Reaction scope with cyclohexanone-derived substrates[a]



[a] Isolated yield reported. [b] Product slightly decomposes on column.

This journal is © The Royal Society of Chemistry 20xx

Organic Chemistry Frontiers Accepted Manuscript

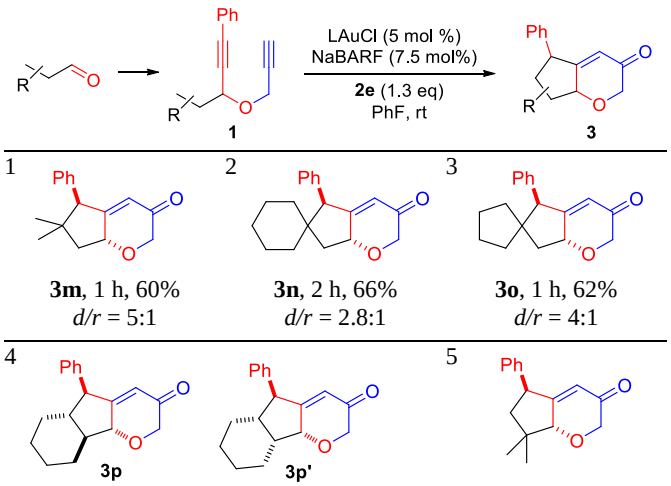
Please do not adjust margins

unexpected regiochemistry as the methylene C-H bond vicinal to the methyl group is selectively functionalized (entry 6). To our delight, the phenyl group at the alkyne terminus of **1a** could be replaced by alkenyl groups such as 2-propenyl (entry 7) and cyclohexylvinyl (entry 8), and the tricyclic 2*H*-pyran-3(6*H*)-ones **3h** and **3i** were isolated in fair yields.

To probe the feasibility of this oxidative gold catalysis in rapid access to even more complex polycyclic structures, we prepared substrates from readily available *cis*- and *trans*-2-decalones. Both reacted smoothly to afford the tetracyclic ketones **3j** and **3k** in satisfactory yields, respectively (entries 9-10). On the other hand, the substrate derived from *cis*-hexahydro-1*H*-inden-5(6*H*)-one was found to form two regioisomeric products, i.e., **3l** and **3l'**, with a combined yield of 65% (entry 11). The major isomer **3l'** is the result of insertion into a methylene C-H bond, while the minor isomer insertion into a typically more preferred methine C-H bond. This seemingly inconsistent result is attributable to the likely impact of the *cis*-fused 5-membered ring on the requisite reaction conformation(s) of the cyclohexane ring. The importance of achieving appropriate reaction conformation(s) is even more apparent as the reaction of the diastereoisomer of **1a**, where Me is cis to phenylethynyl, led to no desired product, despite full substrate consumption. In this case, the accessible insertion into the ring methylene C-H bond, as in the case of **3f**, is hampered by the necessity of a minor reactive conformation with an axial methyl group and the steric hindrance it poses.

With the exception of **3e**, all the other polycyclic pyranone products were formed as single diastereomers, in which the R' group is positioned on the *endo* side of the bicyclo[3.2.1]octane skeleton.

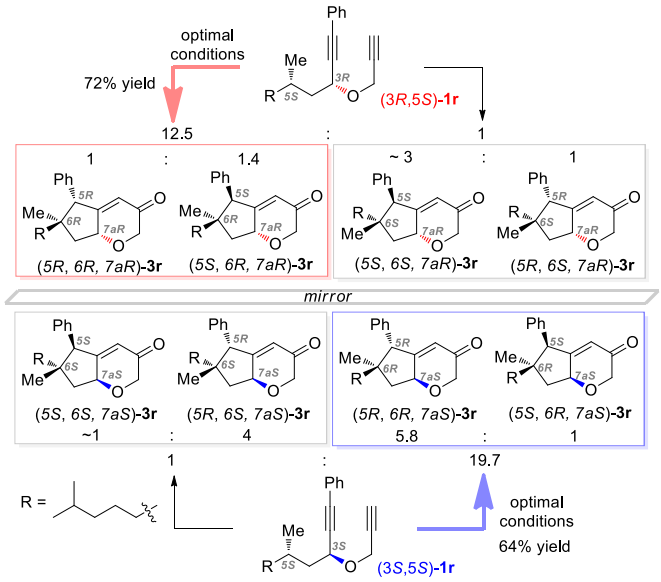
Table 3 Reaction scope with aldehyde-based substrates[a]



[a] Isolated yield reported.

With the success of cyclohexanone-based substrates, we then investigated substrates prepared in one step from various aldehydes. The C-H insertion reaction worked well on a series of substrates bearing properly positioned methine C-H bonds, affording the desired products in fairly good yields and with modest diastereoselectivities (Table 3, entries 1-3). Secondary C-H bonds on a cyclohexane ring could also be inserted under the same conditions, and the linearly-fused tricyclic diastereomers **3p** and **3p'** were formed in a good combined yield. Extensive 2D NMR spectroscopic studies revealed that their relative configurations differ at the ring fusion, where the *trans*-fused cyclohexane ring is moderately favored over the *cis* counterpart. At last, the insertion into methyl C-H bonds could also be achieved as the substrate prepared from pivalaldehyde underwent the oxidative gold catalysis smoothly, affording **3q** in a decent yield and with excellent diastereoselectivity. This last case highlights the high reactivity of the putative vinyl cation intermediate **A** or gold carbene **B**. In all these cases, the major diastereomers display *trans* relationships between the phenyl group and the ethereal oxygen.

Supported by DFT calculations, Metzger[4a] in 2006 suggested that vinyl cations insert into C-H bonds in a concerted manner. Later, Gaunt[4b] in his Cu-catalyzed cascades to carbocycles largely confirmed the concerted nature by the conversion of a substrate of 99% ee into a product of 95% ee. To probe whether the C-H insertions in our system are concerted or not and thereby to shed lights to the reaction mechanism, we prepared the separable disatereoisomers (3*R*, 5*S*)-**1r** and (3*S*, 5*S*)-**1r** from (*S*)-dihydrocitronellal (95% ee) and subjected each of them to the optimal conditions. As shown in Scheme 2, both reactions were efficient, and importantly in each case the diastereomers with unaltered configuration at the original dihydrocitronellal chiral center were formed predominantly. In the case of (3*R*, 5*S*)-**1r**, the ratio of diastereomeric pairs of 12.5/1 reflects that ~5% of the products experienced stereochemical inversion at the C-H insertion site, which are more significant than that reported by the Gaunt group (~2%);[4b] however, with (3*S*,5*S*)-**1r** as the substrate, the ratio of 19.5/1 reflects a comparable 2.3%



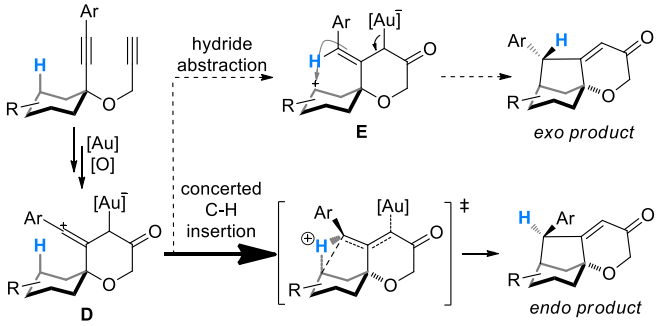
Scheme 2 Results supporting a mostly concerted C-H insertion mechanism

Organic Chemistry Frontiers Accepted Manuscript

Please do not adjust margins

stereochemical erosion. These results, indicative of mostly concerted C-H insertions in our system, are consistent with the intermediacy of vinyl cations of type **A**. While at this point the involvement of gold carbene intermediates of type **B** could not be ruled out, previous studies of related donor-/acceptor-substituted gold carbenes reveal their relative stability and little tendency of C-H insertion.[7a, b, 7q, 13] Hence, it is more likely that the C-H insertions are achieved by the vinyl cation intermediates.

As mentioned previously, almost all the reactions of cyclohexanone-derived substrates exhibited excellent *endo* diastereoselectivities (>20:1), and with the exception of **3e**, the thermodynamically more stable *exo*-products were not detectable. These stereoselectivities are consistent with the concerted C-H insertion mechanism by vinyl cation intermediates and can be readily rationalized. As shown in Scheme 3, the vinyl cation intermediate **D** formed upon the relay of the initially formed electrophilic gold carbene would have its linear vinyl cation moiety largely bisecting the cyclohexane ring. As such, a concerted C-H insertion would place the H atom away from the developing *endo* face of the bicyclo[3.2.1]octane system in the transition state,[4a] thereby affording the observed *endo* product. If a hydride abstract followed by cyclization were in operation, the carbenium intermediate **E**, with the expected double bond geometry, would lead to significant/preferred formation of the unobserved *exo* product due to the approach of the carbenium moiety to the back side of the alkene moiety. This rationale can also readily account for the observation of the thermodynamic isomer in the case of **3e**, where the benzylic hydrogen is much more prone to be abstracted as a hydride.



Scheme 3 Rationale for the observed diastereoselectivity

Conclusions

We have achieved an expedient synthesis of bicyclic/polycyclic 2*H*-pyran-3(6*H*)-ones from readily accessible bispropargyl ethers with minimal structural prefunctionalizations. This cascade cyclization is triggered by an oxidative gold catalysis and features a streamlining insertion into unactivated C-H bonds. In the reaction, an α-oxo gold carbene intermediate is initially formed upon gold-catalyzed regioselective oxidation of the terminal C-C triple bond and subsequently trapped by the tethered internal C-C triple bond, thereby affording a putative vinyl cation intermediate and realizing a relay of electrophilic site. This intermediate of highly electrophilicity is likely responsible for the intramolecular C-H insertions, the mostly concerted nature of which is established by the reactions of chiral substrates. This relay strategy opens a new venue for the application of oxidative gold catalysis in the development of novel and synthetically streamlining C-H insertions.

Notes and references

§ We acknowledge support from the NSF grant CHE-1301343 and the NIH shared instrument grant S10OD012077 for a 400 MHz NMR.

1. (a) Perez, P. J.; Editor, *Alkane C-H Activation by Single-Site Metal Catalysis. [In: Catal. Met. Complexes, 2012; 38]*. Springer: 2012; p 269 pp; (b) Yu, J.-Q.; Shi, Z.; Editors, *C-H Activation. [In: Top. Curr. Chem., 2010; 292]*. Springer GmbH: 2010; p 384 pp; (c) Doyle, M. P.; Liu, Y.; Ratnikov, M., *Org. React.* **2013,** *80*, 1-131; (d) Davies, H. M. L.; Dick, A. R., *Top. Curr. Chem.* **2010,** *292*, 303-345.
2. Kirmse, W., *Angew. Chem., Int. Ed.* **1997,** *36*, 1164-1170.
3. (a) Ye, L.; Wang, Y.; Aue, D. H.; Zhang, L., *J. Am. Chem. Soc.* **2012,** *134*, 31-34; (b) Wieteck, M.; Tokimizu, Y.; Rudolph, M.; Rominger, F.; Ohno, H.; Fujii, N.; Hashmi, A. S. K., *Chem. - Eur. J.* **2014,** *20*, 16331-16336; For related works, see: (c) Hashmi, A. S. K.; Braun, I.; Nösel, P.; Schädlich, J.; Wieteck, M.; Rudolph, M.; Rominger, F., *Angewandte Chemie International Edition* **2012,** *51*, 4456-4460; (d) Wang, T.; Shi, S.; Hansmann, M. M.; Rettenmeier, E.; Rudolph, M.; Hashmi, A. S. K., *Angewandte Chemie International Edition* **2014,** *53*, 3715-3719.
4. (a) Biermann, U.; Koch, R.; Metzger, J. O., *Angewandte Chemie International Edition* **2006,** *45*, 3076-3079; (b) Zhang, F.; Das, S.; Walkinshaw, A. J.; Casitas, A.; Taylor, M.; Suero, M. G.; Gaunt, M. J., *J. Am. Chem. Soc.* **2014,** *136*, 8851–8854; (c) Jin, T.; Himuro, M.; Yamamoto, Y., *J. Am. Chem. Soc.* **2010,** *132*, 5590-5591.
5. (a) Ye, L.; Cui, L.; Zhang, G.; Zhang, L., *J. Am. Chem. Soc.* **2010,** *132*, 3258-3259; (b) Ye, L.; He, W.; Zhang, L., *J. Am. Chem. Soc.* **2010,** *132*, 8550-8551; (c) Lu, B.; Li, C.; Zhang, L., *J. Am. Chem. Soc.* **2010,** *132*, 14070-14072.
6. (a) Zhang, L., *Acc. Chem. Res.* **2014,** *47*, 877–888; (b) Ji, K.; Zhao, Y.; Zhang, L., *Angewandte Chemie International Edition* **2013,** *52*, 6508-6512; (c) Wang, Y.; Ji, K.; Lan, S.; Zhang, L., *Angewandte Chemie International Edition* **2012,** *51*, 1915-1918; (d) Luo, Y.; Ji, K.; Li, Y.; Zhang, L., *J. Am. Chem. Soc.* **2012,** *134*, 17412-17415; (e) Ye, L.; He, W.; Zhang, L., *Angewandte Chemie International Edition* **2011,** *50*, 3236-3239; (f) He, W.; Li, C.; Zhang, L., *J. Am. Chem. Soc.* **2011,** *133*, 8482-8485; (g) Wang, Y.; Zheng, Z.; Zhang, L., *J. Am. Chem. Soc.* **2015,** *137*, 5316–5319; (h) Ji, K.; Zheng, Z.; Wang, Z.; Zhang, L., *Angewandte Chemie International Edition* **2015,** *54*, 1245-1249.
7. (a) Li, C.-W.; Lin, G.-Y.; Liu, R.-S., *Chem. Eur. J.* **2010,** *16*, 5803-5811; (b) Dateer, R. B.; Pati, K.; Liu, R.-S., *Chem. Commun.* **2012,** *48*, 7200-7202; (c) Ghorpade, S.; Su, M.-D.; Liu, R.-S., *Angewandte Chemie International Edition* **2013,** *52*, 4229-4234; (d) Bhunia, S.; Ghorpade, S.; Huple, D. B.; Liu, R.-S., *Angewandte Chemie International Edition* **2012,** *51*, 2939-2942; (e) Qian, D.; Zhang, J., *Chem. Commun.* **2012,** *48*, 7082-7084; (f) Qian, D.; Zhang, J., *Chem. Commun.* **2011,** *47*, 11152-11154; (g) Davies, P.

Organic Chemistry Frontiers Accepted Manuscript

This journal is © The Royal Society of Chemistry 20xx

Please do not adjust margins

W., *Pure Appl. Chem.* **2010,** *82*, 1537-1544; (h) Davies, P. W.; Cremonesi, A.; Martin, N., *Chem. Commun.* **2011,** *47*, 379-381; (i) Henrion, G.; Chavas, T. E. J.; Le Goff, X.; Gagosz, F., *Angewandte Chemie International Edition* **2013,** *52*, 6277-6282; (j) Xu, M.; Ren, T.-T.; Li, C.-Y., *Org. Lett.* **2012,** *14*, 4902-4905; (k) Shi, S.; Wang, T.; Yang, W.; Rudolph, M.; Hashmi, A. S. K., *Chem. Eur. J.* **2013,** *19*, 6576-6580; (l) Wang, T.; Shi, S.; Hansmann, M. M.; Rettenmeier, E.; Rudolph, M.; Hashmi, A. S. K., *Angewandte Chemie International Edition* **2014,** *53*, 3715–3719; (m) Wang, T.; Shi, S.; Rudolph, M.; Hashmi, A. S. K., *Advanced Synthesis & Catalysis* **2014,** *356*, 2337-2342; (n) Wang, T.; Huang, L.; Shi, S.; Rudolph, M.; Hashmi, A. S. K., *Chem. Eur. J.* **2014,** *20*, 14868-14871; (o) Pan, F.; Liu, S.; Shu, C.; Lin, R.-K.; Yu, Y.-F.; Zhou, J.-M.; Ye, L.-W., *Chem. Commun.* **2014,** *50*, 10726-10729; (p) Wang, L.; Xie, X.; Liu, Y. H., *Angewandte Chemie-International Edition* **2013,** *52*, 13302-13306; (q) Li, L.; Shu, C.; Zhou, B.; Yu, Y.-F.; Xiao, X.-Y.; Ye, L.-W., *Chem. Sci.* **2014,** *5*, 4057-4064; (r) Chen, M.; Chen, Y.; Sun, N.; Zhao, J.; Liu, Y.; Li, Y., *Angewandte Chemie International Edition* **2015**, 1200-1204.

8. For other diyne-relays in homogeneous gold catalysis, see: (a) Lauterbach, T.; Higuchi, T.; Hussong, M. W.; Rudolph, M.; Rominger, F.; Mashima, K.; Hashmi, A. S. K., *Advanced Synthesis & Catalysis* **2015,** *357*, 775-781; (b) Lauterbach, T.; Ganschow, M.; Hussong, M. W.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K., *Advanced Synthesis & Catalysis* **2014,** *356*, 680-686; (c) Lauterbach, T.; Gatzweiler, S.; Nösel, P.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K., *Advanced Synthesis & Catalysis* **2013,** *355*, 2481-2487; (d) Lauterbach, T.; Arndt, S.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K., *Advanced Synthesis & Catalysis* **2013,** *355*, 1755-1761.

9. Nösel, P.; dos Santos Comprido, L. N.; Lauterbach, T.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K., *J. Am. Chem. Soc.* **2013,** *135*, 15662-15666.

10. A related study using bispropargylic ethers was reported. For reference, see: Ji, K.; Liu, X.; Du, B.; Yang, F.; Gao, J., *Chem. Commun.* **2015,** *51*, 10318-10321.

11. Fors, B. P.; Watson, D. A.; Biscoe, M. R.; Buchwald, S. L., *J. Am. Chem. Soc.* **2008,** *130*, 13552-13554.

12. Lundgren, R. J.; Peters, B. D.; Alsabeh, P. G.; Stradiotto, M., *Angewandte Chemie International Edition* **2010,** *49*, 4071-4074.

13. (a) Xi, Y.; Su, Y.; Yu, Z.; Dong, B.; McClain, E. J.; Lan, Y.; Shi, X., *Angewandte Chemie International Edition* **2014,** *53*, 9817-9821; (b) Yu, Z.; Ma, B.; Chen, M.; Wu, H.-H.; Liu, L.; Zhang, J., *J. Am. Chem. Soc.* **2014,** *136*, 6904-6907.

Organic Chemistry Frontiers Accepted Manuscript

Please do not adjust margins