Communication

Utility of Ligand Effect in Homogenous Gold Catalysis: Enabling Regiodivergent #-bond-activated Cyclization

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Utility of Ligand Effect in Homogenous Gold Catalysis: Enabling Regiodivergent π-bond-activated Cyclization

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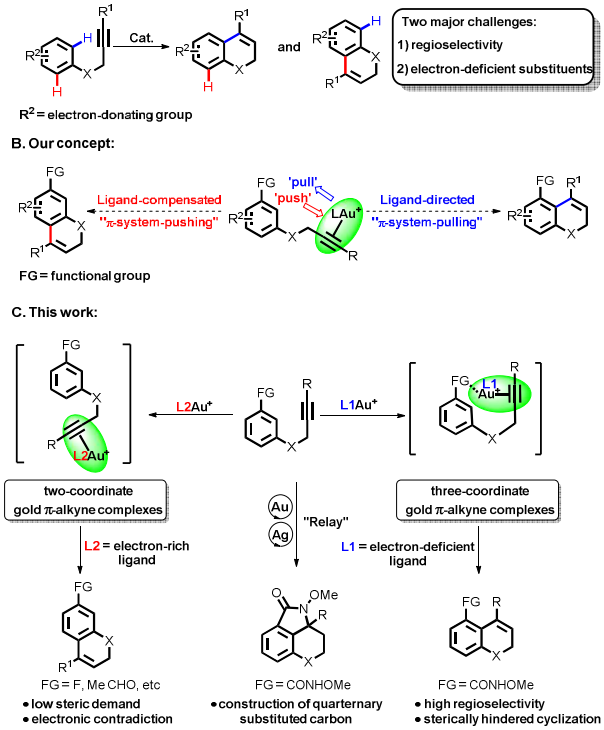
Supporting Information Placeholder

ABSTRACT: A comprehensive utilization of both electronic and steric properties from the ligands in homogenous gold catalysis is achieved through being applied to regiodivergent intramolecular hydroarylation of alkynes reactions. Flexible electron-deficient phosphite ligand, combining with readily transformable directing group methoxyl amide, is attached to cationic gold(I) center in three-coordinate mode affording sterically hindered *ortho*-position cyclization. Meanwhile, *para*-position cyclization is exclusively achieved by the assistance of a rigid electron-abundant phosphine ligand based gold(I) catalyst, in which ligands manifest the compensating effect for cyclization through steric hinderance and electronic properties. Combining gold with silver catalysts, tetrahydropyrroloquinolinones possessing congested tricyclic structure are obtained, which is proved to be Au/Ag relay catalytic process.

Homogenous gold catalysis underwent a flourishing development in the past decade and emerged as an efficient and powerful tool for constructing complex molecules, largely due to its preponderant function as carbophilic π-acid activating carbon-carbon multiple bonds.[1] Ligands play a crucial role in boosting the progress of homogenous gold catalysis for steering properties of catalysts, leading to the variation of reactions.[2-3] Intramolecular hydroarylation of alkyne reactions catalyzed by gold have been useful methods for obtaining fused heteroarenes in virtue of its highly efficient atom economy.[4] In 2005, Echavarren group reported the first gold(I) catalyzed regioselective version of intramolecular hydroarylation with one substrate bearing electron-rich hydroxyl group.[4c] Then regiocontrol of intramolecular hydroarylation on indole scaffolds was achieved by switching gold(I) and gold(III) catalyst that also disclosed by Echavarren et al.[4d] Although massive attention has been paid to gold-catalyzed alkyne hydroarylation processes from then on,[4e-4k] regioselectivity of substituted aromatics and utilization of electron-deficient substrates still remains stubborn challenges (Scheme 1, **A**). Following the understanding of ligand effect[5] in our research and combiningwith directing concept in C-H activation,[6] solution for problems mentioned above is envisioned. Electrophilic gold complexes, tuned by electron-deficient ligands, will permit another coordination with directing group which simultaneously "pull" gold-coordinated π-system to sterically hindered *ortho* position on aromatic rings for further cyclization.[7]

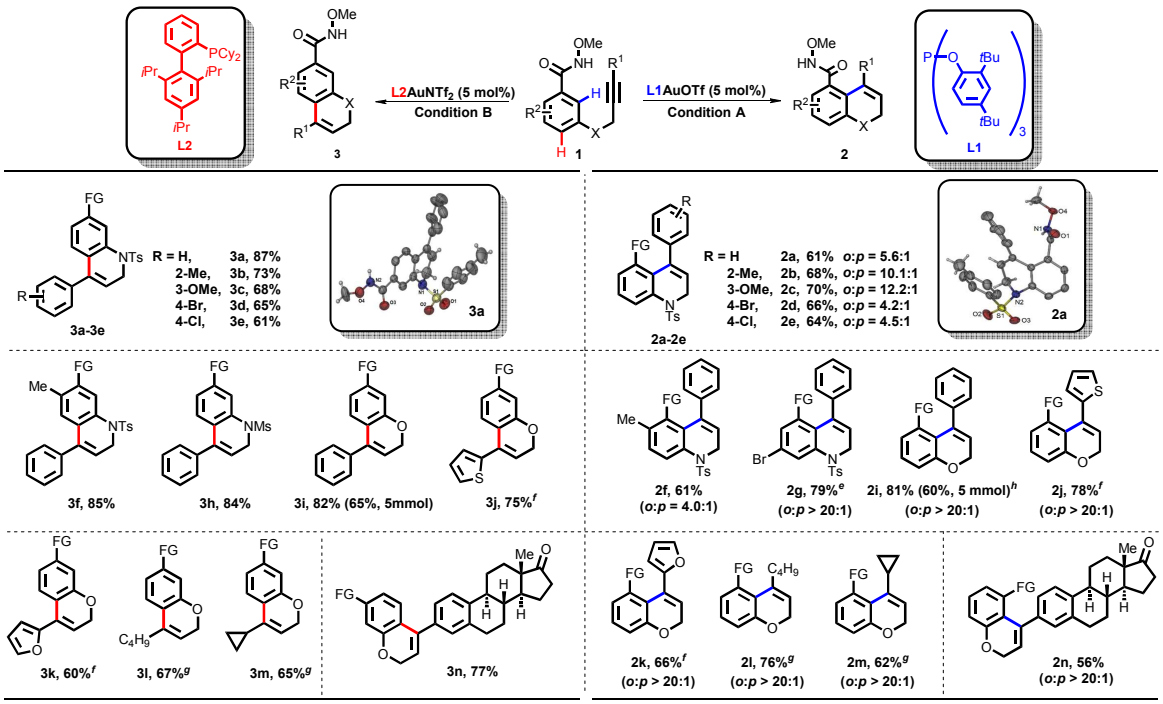
Scheme 1. Gold-Catalyzed Intramolecular Hydroarylation of Alkynes and Cascade Cyclization.



Alternatively, the rigid bulky electron-rich ligands supplement steric hinderance and electronic properties, which eventually "push" π-system to *para* position (Scheme 1, **B**). Herein, we report the gold(I)-catalyzed regiodivergent intramolecular hydroarylation of alkynes, in which sterically hindered *ortho*-position cyclization is governed by the electron-deficient ligand via three-coordinate gold and bulky electron-rich ligand surmounts the defect of electronic and steric requirement.

We commenced the study with the model substrate **1a** equipped with methoxyl amide which was unfolded as the best directing group[8] to test gold(I) catalysts with diverse electronic and steric properties (Table S1).[9] As assumed, electron-deficient tris(2,4-di-*tert*-butylphenyl) phosphite ligand resulted in smooth *ortho*-position cyclization, generating dihydroquinoline **2a** in 61% isolated yield. The ligand compensating effect was demonstrated

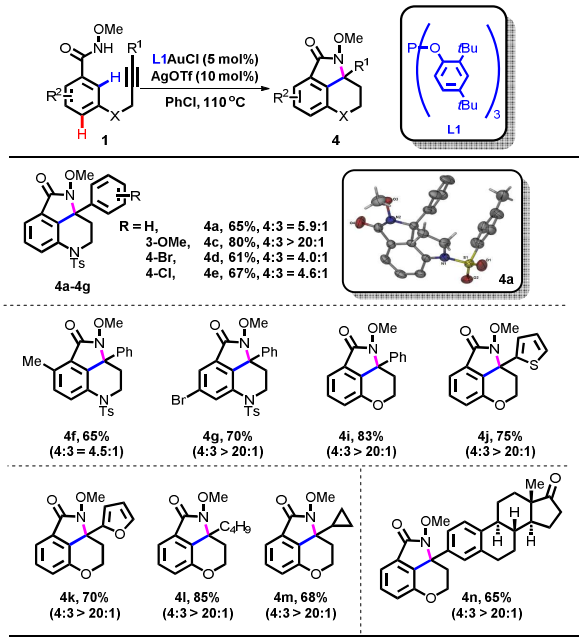
Table 1. Scope of Both *Ortho*- and *Para*-Position Cyclization[a, b, c, d]



[a]FG = CONHOMe. [b]Condition A: **1a** (0.1 mmol), (2,4-*t*Bu$_2$PhO)$_3$PAuOTf (5 mol%) in DCE (1.0 mL) at 80 °C for 8 h. Condition B: **1a** (0.1 mmol), XphosAuNf$_2$ (5 mol%) in DCE at 80 °C for 8 h. [c] Isolated yields of pure product, in the right table isolated yields refer to the yields of *ortho*-cyclized products.. [d] The ratio was determined by ^{1}HNMR. [e](2,4-*t*Bu$_2$PhO)$_3$PAuNTf$_2$ was used and 1 equivalent of acetic acid was added. [f]3 h. [g]5 h. [h]*o*:*p* = 10.8:1

when gold(I) complexes coordinated with rigid bulky electron-rich Xphos ligand, leading to the exclusive formation of dihydroquinoline **3a** in 87% yield via *para*-position cyclization. As shown on the right section of Table 1, R^1 substituted with electron-donating groups, provided better yields and higher regioselectivity than substituted with electron-withdrawing groups, probably owing to the poorer coordination of electron-deficient alkynes with gold catalyst (Table 1, **2b-2e**). Particularly, when the aromatic ring contained *meta*-substituted bromine group, *ortho*-position cyclization occurred with great regioselectivity (>20:1) (Table 1, **2g**). In addition, when oxygen atom employed as linker in substrate, the selectivity was attained with over 20:1 for *ortho*-position cyclization, since oxygen linkage gave open and flexible space for facile coordination of ligand. (Table 1, **2i-2n**). Furthermore, substrates bearing heterocycles such as thiophene and furan also worked well for *ortho*-position cyclization (Table 1, **2j-2k**). In particular, alkyne substituted with three-membered ring was compatible and the strained ring remained intact (Table 1, **2m**). Remarkably, natural product estrone could be equipped with alkynes and proceeded *ortho*-position cyclization well with moderate yield and excellent regioselectivity (Table 1, **2n**). The corresponding *para*-position cyclization is shown on the left section of Table 1. In general, both electron-rich and electron-deficient substituents of R^1 and R^2 successfully achieved this transformation, generating the desired products with sole regioisomers (Table 1, **3b-3f**). Notably, *para*-position cyclization was equally tolerated with heterocycles, aliphatic groups and complex steroids as well (Table 1, **3i-3n**). Gratifyingly, gram-scale operations were feasible in both *ortho*- and *para*-cyclization, affording **2i** and **3i** in moderate yields. Moreover, to demostrate the facile removal of the directing group, dihydroquinolines **2a** and **3a** were readily transformed into corresponding aldehyde and ketone with high yields.[11] With attempt to explore the catalyst efficiencies, turnover numbers

Table 2. Au/Ag relay cascade cyclization.[a,b]



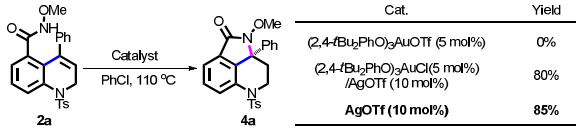
[a]Reaction conditions: **1a** (0.1 mmol), (2,4-*t*Bu$_2$PhO)$_3$PAuCl (5 mol%), AgOTf (10 mol%), PhCl (1.0 mL), 110 °C, 12 h. [b]Isolated yields.

(TON) were studied. When 0.5 mol% phosphite gold(I) catalyst was applied, TON is 60 for *ortho*-cyclization. While Xphos based gold(I) catalyst for *para*-cyclization gave a higher TON of 164. However, regioselectivity of corresponding products were decreased dramaically in both cyclizations when lowering the catalyst loading.

Interestingly, tetrahydropyrrolo[2,3,4-*de*]quinolin-5(*1H*)-one **4a** was obtained directly by subjecting **1a** to the mixture of gold and silver (Table S1, Entry 10), which was further confirmed by X-ray analysis(Table 2, **4a**).[10] After testing the ratio of gold(I) catalyst with silver additive, 5 mol% of gold(I) catalyst and 10 mol% of silver salt were identified as the best proportions. Substrate scope of this cascade cyclization was consequently evaluated under optimized conditions (Table 2). Both electron-donating and electron-withdrawing substituents of R^1 and R^2 accomplished this transformation efficiently, affording products with quaternary substituted carbon center in good to excellent yields (Table 2, **4c-4g**). Comparatively, the cyclization of substrates with oxygen atom linker, delivered the oxygenated product **4i-4n** in excellent yields and over 20:1 (*o*:*p*) regioselectivity (Table 2, **4i-4n**).

Control experiments were conducted subsequently (Scheme 2). There was no formation of **4a** resulting in 77% yield of **2a** recovered, when cationic gold catalyst $(2,4\text{-}t\text{Bu}_2\text{PhO})_3\text{PAuOTf}$ was solely utilized. Combination of $(2,4\text{-}t\text{Bu}_2\text{PhO})_3\text{PAuCl}$ with excess catalytic amount of AgOTf afforded the desired product in 80% yield. **4a** could be obtained in 85% yield with complete consumption of **2a**, even when silver triflate was applied alone, demonstrating that silver was the authentic catalyst in the second cyclization step. These results showed the different phenomenon in gold chemistry, which indicated the exclusive catalytic effect of silver towards double bonds rather than simple additive for precipitating halide anions. [12]

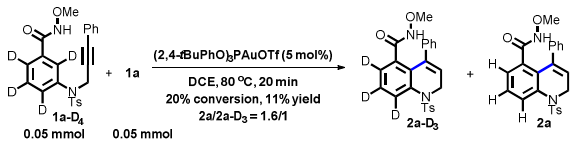
Scheme 2. Control experiments of Au/Ag relay cyclization.



Cat.	Yield
$(2,4\text{-}t\text{Bu}_2\text{PhO})_3\text{AuOTf}$ (5 mol%)	0%
$(2,4\text{-}t\text{Bu}_2\text{PhO})_3\text{AuCl}$(5 mol%) /AgOTf (10 mol%)	80%
AgOTf (10 mol%)	**85%**

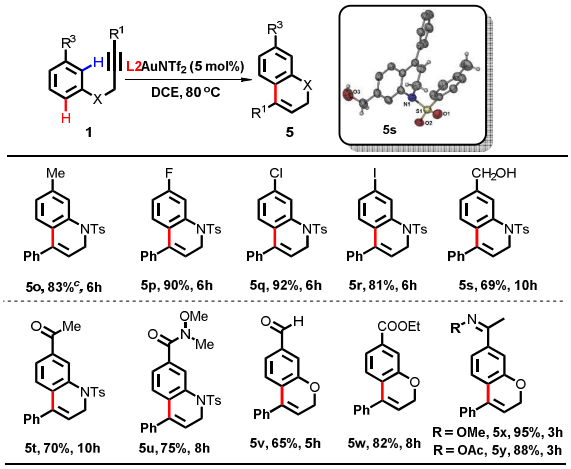
To further demonstrate the ligand compensating effect, we investigated the aromatic nucleophiles bearing electron-deficient and substituted functional groups with subtle steric hinderance (Table 3). Notably, dihydroquinoline **5o** could be exclusively obtained only with methyl group substituted on meta-position, which was assisted by tBuXphos-based gold(I) catalyst (Table 3, **5o**). Furthermore, substrate bearing fluoro atom, which barely possesses steric hinderance, also afforded corresponding product solely in high yield (Table 3, **5p**). Moreover, this transformation could be compatible with hydrogen-bond containing hydroxyl group generating corresponding product **5s** (Table 3, **5s**).[10] Delightedly, electron-withdrawing substituents, such as ketone (**5t**), Weinreb amide (**5u**), aldehyde (**5v**), ester (**5w**) and sensitive imines (**5x**, **5y**) were all well tolerated in good to excellent yields.

Scheme 3. KIE Experiments.



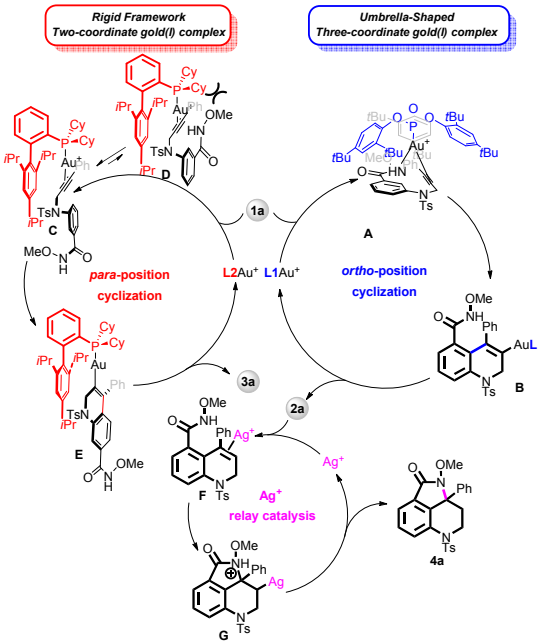
Intermolecular kinetic isotope effect (KIE) experiment was conducted at *ortho*-position cyclization resulted in the value of 1.6:1. This demonstrated the secondary kinetic isotope effect for this transformation, which indicated the cleavage of carbon-hydrogen bond was not rate-determining step (Scheme 3). Based on these results, the tunable pathway mechanisms by ligand effect are shown in Scheme 4. Both flexible electron-deficient tris(2,4-di-tert-butylphenyl) phosphite (**L1**) and weakly coordinating OTf anion would increase the electrophilicity of

Table 3. *Para*-position cyclization of subtle steric hindered and electron-deficient aromatic nucleophiles.[a,b]



[a]Reaction conditions: **1a** (0.1 mmol), XphosAuNTf_2 (5 mol%), DCE (1.0 mL), 80 °C. [b]Isolated yields. [c]*t*BuXphosAuNTf$_2$ was used instead of XphosAuNTf_2.

Scheme 4 Proposed Mechanism



gold center. Then gold(I) catalyst demands to be trapped by lone pair electrons on amide group, allowing for the formation of three-coordinate gold(I) π-alkyne intermediate **A**.[7] Additionally, flexibly bulky aryl moieties on phosphite ligand offers umbrella-shaped protection, further stabilizing intermediate **A**. Through Friedel-Crafts type addition, intermediate **B** is generated and subsequently followed by protonation, affording sterically hindered *ortho*-position cyclization forming dihydroquinoline product **2a**. Subsequently, the carbon-carbon double bond in **2a** is activated by silver catalyst, giving rise to intermediate **F**, which undergoes nucleophilic addition to obtain the congested tricyclic product **4a**. Moreover, rigid and bulky electron-abundant Xphos ligand (**L2**) and a bit stronger coordinated NTf_2^- could jointly lower the electrophilicity of gold center to increase the stability of intermediate **C** and minimizes the conformation leading to *ortho*-position cyclization. The electron-rich *tri*-isopropylphenyl ring on ligand compensates for electron-deficient phenyl moiety of substrate through π-π interaction, which affords the smooth

cyclization of electron-deficient aromatics. Finally, *para*-position selective cyclization is successfully achieved after the sequential cyclization and protonation.

In conclusion, we have developed a ligand controlled gold(I)-catalyzed regiodivergent intramolecular hydroarylation of alkynes reaction. *Ortho*- and *para*-position cyclization are successfully established respectively through fine-tuning electronic and steric effects of the ligands derived from gold complexes. Altering three-coordinate gold(I) complexes is the key in the adjacent cyclization. And rigid electron-rich ligand allows *para*-position cyclization exclusively, in which aromatic nucleophiles bearing electron-deficient functional groups and subtle steric difference could afford the cyclization highly selectively. Moreover, silver instead of gold catalyst was proved to be the prior activator of double bonds in the second cyclization of cascade cyclization. Further synthetic applications of these tunable transformations are currently under investigation in our group.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, NMR spectral, X-Ray, and analytical data for all new compounds. The Supporting Information 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 selected leading reviews, please see (a) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem. Int. Ed.* **2006**, *45*, 7896. (b) Gorin, D. J.; Toste, F. D. *Nature*. **2007**, *446*, 395. (c) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (d) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266. (e) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351. (f) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326. (g) Widenhoefer, R. A. *Chem. Eur. J.* **2008**, *108*, 3351. (h) Abu Sohel, S. M. Liu, R. *Chem. Soc. Rev*. **2009**, *38*, 2269. (i) Díez-González, S.; Marion, N.; Nolan, S. P. *Chem. Rev.* **2009**, *109*, 3612. (j) Nolan, S. P. *Acc. Chem. Res*. **2011**, *44*, 91. (k) Liu, L.; Hammond, G. B. *Chem. Soc. Rev.* **2012**, *41*, 3129. (l) Hashmi, A. S. K. *Acc. Chem. Res*. **2014**, *47*, 864. (m) Zhang, L. *Acc. Chem. Res*. **2014**, *47*, 877. (n) Wang, Y.; Lackner, A. D.; Toste, F. D. *Acc. Chem. Res*. **2014**, *47*, 889. (o) Obradors, C.; Echavarren, A. M. *Acc. Chem. Res*. **2014**, *47*, 902. (p) Fensterbank, L.; Malacria, M. *Acc. Chem. Res*. **2014**, *47*, 953. (q) Dorel, R.; Echavarren, A. M. *Chem. Rev.* **2015**, *115*, 9028. (r) Jia, M.; Bandini, M. *ACS Catal.* **2015**, *5*, 1638.

(2) For selected ligand-controlled gold-catalyzed reactions, please see: (a) Fructos, M. R.; Belderrain, T. R.; de Frémont, P.; Scott, N. M.; Nolan, S. P.; Díaz-Requejo, M. M.; Pérez, P. J. *Angew. Chem. Int. Ed.* **2005**, *44*, 5284.(b) López, S.; Herrero-Gómez, E.; Pérez-Galán, P.; Nieto-Oberhuber, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 6029. (c) Lemière, G.; Gandon, V.; Agenet, N.; Goddard, J.; Kozak, A.; Aubert, C.; Fensterbank, L.; Malacria, M. *Angew. Chem. Int. Ed.* **2006**, *45*, 7596. (d) Gorin, D. J.; Watson, I. D. G.; Toste, F. D. *J. Am. Chem. Soc.* **2008**, *130*, 3736. (e) Xi, Y.; Su, Y.; Yu, Z.; Dong, B.; McClain, E. J.; Lan, Y.; Shi, X. *Angew. Chem. Int. Ed.* **2014**, *53*, 9817.

(3) For selected examples of elegant ligand-controlled regiodivergent gold-catalyzed reactions, please see: (a) Sromek, A. W.; Rubina, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2005**, *127*, 10500. (b) Fructos, M. R.; de Frémont, P.; Nolan, S. P.; Díaz-Requejo, M. M.; Pérez, P. J. *Organometallics.* **2006**, *25*, 2237. (c) Xia,Y.; Dudnik, A. S.; Gevorgyan, V.; Li, Y. *J. Am. Chem. Soc.* **2008**, *130*, 6940. (d) Mauleón, P.; Zeldin, R. M.; González, A. Z.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 6348. (e) Alonso, I.; Trillo, B.; López, F.; Montserrat, S.; Ujaque, G.; Castedo, L.; Lledós, A.; Mascareñas, J. L. *J. Am. Chem. Soc.* **2009**, *131*, 13020. (f) Alcarazo, M.; Stork, T.; Anoop, A.; Thiel, W.; Fürstner, A. *Angew. Chem. Int. Ed.* **2010**, *49*, 2542. (g) Barabé, F.; Levesque, P.; Korobkov, l.; Barriault, L. *Org. Lett.* **2011**, *13*, 5580. (h) Haro, T.; Gómez-Bengoa, E.; Cribiú, R.; Huang, X.; Nevado, C. *Chem. Eur. J.* **2012**, *18*, 6811. (i) Li, W.; Li, Y.; Zhou, G.; Wu, X.; Zhang, J. *Chem. Eur. J.* **2012**, *18*, 15113. (j) Wang, Z.; Wang, Y.; Zhang, L. *J. Am. Chem. Soc.* **2014**, *136*, 8887. (k) Shiroodi, R. K.; Koleda, O.; Gevorgyan, V. *J. Am. Chem. Soc.* **2014**, *136*, 13146. (l) Rao, W.; Susanti, D.; Ayers, B. J.; Chan, P. W. *J. Am. Chem. Soc.* **2015**, *137*, 6350. (m) Mei, L.; Wei, Y.; Tang, X.; Shi, M. *J. Am. Chem. Soc.* **2015**, *137*, 8131.

(4) (a) Nieto-Oberhuber, C.; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 2402. (b) Shi, Z.; He, C. *J. Org. Chem.* **2004**, *69*, 3669. (c) Nevado, C.; Echavarren, A. M. *Chem. Eur. J.* **2005**, *11*, 3155. (d) Ferrer, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 1105. (e) Wegner, H. A.; Ahles, S.; Neuburger, M. *Chem. Eur. J.* **2008**, *14*, 11310. (f) Menon, R. S.; Findlay, A. D.; Bissember, A. C.; Banwell, M. G. *J. Org. Chem.* **2009**, *74*, 8901. (g) Do, H. J.; Kim, N. H.; Yoon, J.; Kim, J. S.; Kim, H. J. *Org. Lett.* **2010**, *12*, 932. (h) Morán-Poladura, P.; Suárez-Pantiga, S.; Piedrafita, M.; Rubio, E.; González, J. *J. Organomet. Chem.* **2011**, *696*, 12. (i) Vadola, P. A.; Sames, D. *J. Org. Chem.* **2012**, *77*, 7804. (j) Cervi, A.; Aillard, P.; Hazeri, N.; Petit, L.; Chai, C.; Willis, A. C.; Banwell, M. G.; *J. Org. Chem.* **2013**, *78,* 9876. (k) Aparece, M. D.; Vadola, P. A. *Org. Lett.* **2014**, *16*, 6008. (l) Nösel, P.; Müller, V.; Mader, S.; Moghimi, S.; Rudolph, M.; Braun, I.; Rominger, F.; Hashmi, A. S. K. *Adv. Synth. Catal.* **2015**, *357*, 500. (m) For the first gold-catalyzed hydroarylation reactions, please see: Hashmi, A. S. K.; Schwarz, L.; Choi, J.; Frost, T. M. *Angew. Chem. Int. Ed*. **2000**, *39*, 2285.

(5) (a) Feng, M.; Tang, B.; Wang, N.; Xu, H.; Jiang, X. *Angew. Chem. Int. Ed.* **2015**, *54*, 14960. (b) Qiao, Z.; Jiang, X. *Org. Lett.* **2016**, *18*, 1550.(c) Liu, H.; Wei, J.; Qiao, Z.; Fu, Y.; Jiang, X. *Chem. Eur. J.* **2014**, *30*, 8308. (d) Li, Y.; Pu, J.; Jiang, X. *Org. Lett.* **2014**, *16*, 2692. (e) Qiao, Z.; Wei, J.; Jiang, X. *Org. Lett.* **2014**, *16*, 1212.

(6) For selected recent reviews on directing concept, please see: (a) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307. (b) Guari, Y.; Sabo-Etienne, S.; Chaudret, B. *Eur. J. Inorg. Chem*. **1999**, 1047. (c) Kakiuchi, F.; Murai, S. *Acc. Chem. Res*. **2002**, *35*, 826. (c) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077. (d) Chen, X.; Engle, K. M.; Wang, D.; Yu, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 5094. (e) Li, B.; Shi, Z. *Chem. Soc. Rev.* **2012**, *41*, 5588. (f) Engle, K. M.; Mei, T.; Wasa, M.; Yu, J. *Acc. Chem. Res*. **2012**, *45*, 788.

(7) For tricoordinated gold(I) complexes, please see: (a) Gimeno, M. C.; Laguna, A. *Chem. Rev.* **1997**, *97*, 511. (b) Teles, J. H.; Brode, S.; Chabanas, M. *Angew. Chem. Int. Ed.* **1998**, *37*, 1415. (c) Ito, H.; Saito,T.; Miyahara, T.; Zhong, C.; Sawamura, M. *Organometallics.* **2009**, *28*, 4829. (d) Zeng, X.; Kinjo, R.; Donnadieu, B.; Bertrand, G. *Angew. Chem. Int. Ed.* **2010**, *49*, 942. (e) Khin, C.; Hashmi, A. S. K.; Rominger, F. *Eur. J. Inorg. Chem.* **2010**, 1063. (f) Zhan, J.; Lv, H.; Yu, Y.; Zhang, J. *Adv. Synth. Catal.* **2012**, *354*, 1529. (g) Luo, Y.; Ji, K.; Li, Y.; Zhang, L. *J. Am. Chem. Soc.* **2012**, *134*, 17412. (h) Gualco, P.; Mallet-Ladeira, S.; Kameo, H.; Nakazawa, H.; Mercy, M.; Maron, L.; Amgoune, A.; Bourissou, D. *Organometallics*. **2015**, *34*, 1449. (i) Yang, H.; Gabbaï, F. P. *J. Am. Chem. Soc.* **2015**, *137*, 13425.

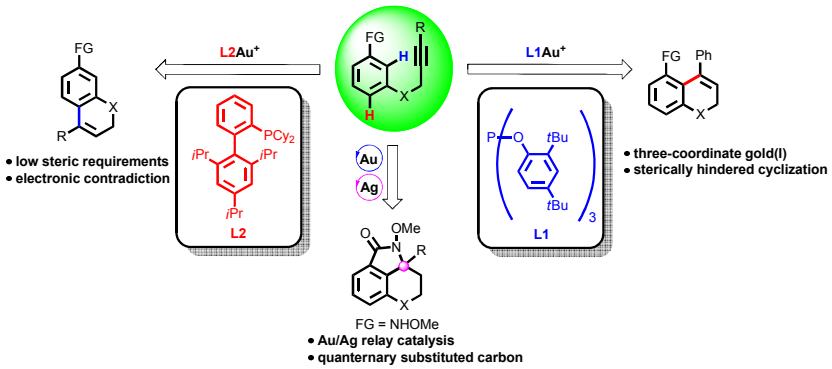
(8) For effect of other directing groups, please see SI-S4 for details.

(9) For details of optimization, please see SI-S3.

(10) CCDC-1058363 (**2a**), CCDC-1058364 (**3a**), CCDC-1058366 (**4a**), CCDC-1058362 (**5s**), for CIF data, please see SI-S41.

(11) For details of transformation, please see SI-S32.

(12) (a) Ramón, R. S.; Bosson, J.; Díez-González, S.; Marion, N.; Nolan, S.; *J. Org. Chem.* **2010**, *75*, 1197; (b) Wang, H.; Denton, J. R.; Davies, H. M. L. *Org. Lett.* **2011**, *13*, 4316. (c) Wang, D.; Cai, R.; Sharma, S.; Jirak, J.; Thummanapelli, S. K.; Akhmedov, N. G.; Zhang, H.; Liu, X.; Petersen, J. L.; Shi, X. *J. Am. Chem. Soc.* **2012**, *134*, 9012; (d) Robertson, B. D.; Brooner, R. E. M.; Widenhoefer, R. A. *Chem. Eur. J.* **2015**, *21*, 5714.


FG
X
R
• low steric requirements
• electronic contradiction
L2Au+
PCy2
iPr
iPr
iPr
L2
FG
R
H
X
H
Au
Ag
OMe
O
N
R
X
FG = NHOMe
• Au/Ag relay catalysis
• quanternary substituted carbon
L1Au+
P
O
tBu
tBu
3
L1
FG
Ph
X
• three-coordinate gold(I)
• sterically hindered cyclization