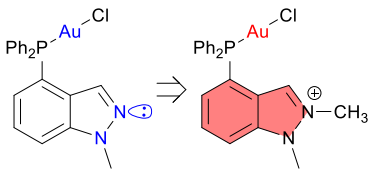
Synthesis of an Indazole/Indazolium Phosphine Ligand Scaffold and its Application in Gold(I) Catalysis

Asima Munawar, Logan T. Maltz, Wei-Chun Liu, and François P. Gabbaï*

ABSTRACT: Advances in ligand development have allowed for fine-tuning of gold catalysis. To contribute to this field, we designed a new indazole phosphine ligand scaffold that allows facile introduction of cationic charge through methylation. With minimal changes to the structure upon methylation, we could assess the importance of the electronic effects of insertion of a positive charge on the catalytic activity of the resulting gold(I) complexes. Using the benchmark reactions of propargyl amide cyclization and enyne cyclization with and without hexafluoroisopropanol (HFIP), we observed marked differences in the catalytic activities of the neutral and cationic gold species.



Phosphines are common ancillary ligands in gold catalysis. These ligands' properties are easily tuned by chemical modification, allowing for simple yet impactful changes to catalytic activity.[1] One method for modification that has seen increasing use is the insertion of a positive charge in the ligand backbone.[2] This positive charge has differing impacts on the coordinated metal depending on its position. Over the past few years, the Gabbaï group has synthesized a group of acridinium- (**A**) and xanthylium-based (**B**) γ-cationic phosphines that position the cationic charge at a remote position to withdraw electron density orthogonally from gold while minimizing the reduction in σ-donation from the phosphine (**Figure 1**).[3] Positioning the cationic charge α to P, many groups have contributed to the development of α-cationic phosphines—including phosphines of types **C**[4] and **D**[5]—wherein electron density is withdrawn directly from P, thereby weakening σ-donation to the attached gold (**Figure 1**).

This method produces a phosphine that is as poor of a donor as PF_3, $P(CF_3)_3$, and PCl_3 while avoiding the air- and moisture-sensitivity typical of the phosphorus-halogen bond.[2c] Due to their electron-poor nature, these cationic phosphines have been commonly used to promote reactions catalyzed by electron-rich transition metals where the catalytic step benefits from a more Lewis acidic metal center, a common example being the gold(I) activation of alkenes, allenes, and alkynes.[6] Because of the minimal backbonding from gold, a balance must be found between maximizing the Lewis acidity of gold through reduction of σ-donation from the phosphine while avoiding decomposition of the catalyst.

Adding to the collection of cationic phosphines, we report the synthesis of a new phosphine ligand containing an indazole group directly bound to the phosphorus which allows for facile insertion of a positive charge through methylation of the indazole backbone. A similar approach was taken in 2008 by Debono *et al.* for modifying a bisphosphine for application in palladium catalysis.[7] This simple method for positive-charge insertion allows us to easily modulate donicity and directly compare newly synthesized neutral and cationic phosphine gold(I) complexes. We look to the common benchmark reactions of propargyl amide cyclization and enyne cyclization to assess the differences in their reactivity.

Building on our recent efforts in the chemistry of indazole-based ligands,[8] we decided to investigate the introduction of a phosphine functionality at the 4-position of this compound. To this end, ^{n}BuLi was added to a solution of 4-bromo-1-methyl-*1H*-indazole (**1**) in dry THF at -78 °C. After stirring for 30 min, Ph_2PCl was added as a phosphorus source. The resulting mixture was warmed to room temperature and stirred overnight to obtain **2** as a pale-yellow solid (**Figure 2**). The formation of **2** is easily followed by ^{31}P NMR spectroscopy, which shows a single peak at -11.84 ppm. ^{1}H NMR spectroscopy further evinces the phosphine's formation with a diagnostic singlet for the indazole C-*H* at 7.62 ppm in addition to a distinct methyl peak at 4.02 ppm. Layering of hexanes over a dichloromethane (DCM) solution of **2** yielded clear block crystals, and single-crystal X-ray diffraction (SCXRD) further established the identity of **2** (**Figure S1**).

We combined **2** with 1.1 eq. of (tht)AuCl (tht = tetrahydrothiophene) in DCM at room temperature. After stirring for 30 min, the resulting solution was concentrated to 1 mL before hexanes were added to precipitate **3** as a white powder. A peak at 26.06 ppm in the ^{31}P NMR—downfield of the peak corresponding to the free ligand—confirmed the formation of **3**. Slow diffusion of hexanes into a concentrated solution of **3** in DCM gave clear plate crystals which were analyzed by SCXRD (**Figure 2**).

With the phosphine now protected by gold, we were able to methylate the indazole nitrogen by reacting **3** with 1.1 eq. of methyl trifluoromethanesulfonate (MeOTf) in dry DCM in the glovebox. The mixture was stirred overnight, and light yellow [**4**][OTf] was

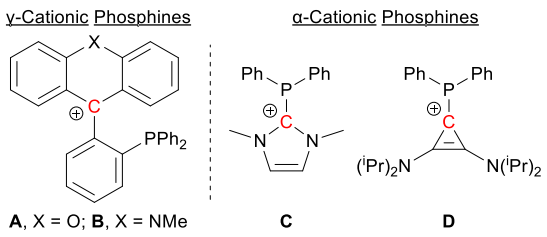


Figure 1. Examples of γ- and α-cationic phosphines.

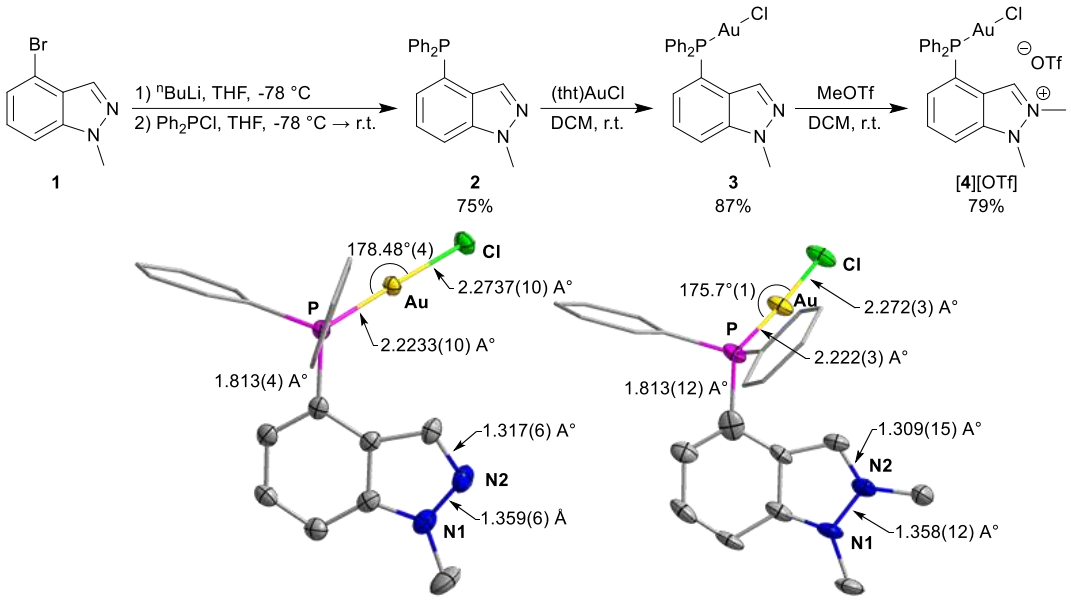


Figure 2: Top: Reaction scheme for synthetic procedures. Bottom: Crystal structures of **3** (left) and [**4**][OTf] (right) in the solid-state showing selected bond lengths and angles. Hydrogen atoms and anions omitted for clarity. Thermal ellipsoids drawn at 50% probability, and phenyl groups drawn as thin lines.

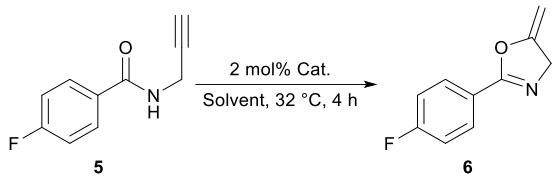
precipitated using hexanes. The formation of this cationic species was readily verified by NMR spectroscopy which showed an upfield shift in the ^{31}P NMR spectrum from 26.06 to 24.97 ppm. In the ^{1}H NMR spectrum, the indazolium proton singlet saw a significant downfield shift from 7.83 to 8.70 ppm, accompanied by an increase in the integral of the methyl peak by three protons due to merging of the new methyl peak with the previous one. X-ray quality clear block crystals were obtained by slow diffusion of Et_2O into a concentrated solution of [**4**][OTf] in acetonitrile (**Figure 2**).

Comparing the crystal structures of **3** and [**4**][OTf] in **Figure 2**, there is not a significant difference in either the bond lengths or the bond angles. This minimal perturbation of the structure upon introduction of positive charge has been previously observed in the case of pyridine/pyridinium phosphine gold(I) complexes.[9] Despite this lack of structural change, we expected to see more significant differences in their catalytic activities, so we turned to the benchmark reactions of propargyl amide cyclization and enyne cyclization.

We started our catalytic investigations with the cyclization of *N*-propargyl-4-fluorobenzamide, a reaction commonly used to gauge the activity of gold catalysts.[3b, 10] Silver salts are often used to activate the otherwise stable Au-Cl bond to access the cationic gold species that serves as the active catalyst. This activation promotes substrate binding not only by opening a coordination site on gold but also by increasing the metal center's Lewis acidity.[11] Aside from the drawbacks of adding silver salts to the reaction mixture,[11] the already increased Lewis acidity of the gold center in our cationic system due to the weakly donating phosphine led us to consider a milder activator—hexafluoroisopropanol (HFIP).

HFIP as a solvent has been increasingly employed to facilitate a range of catalyses[12] and has even found its way into the field of gold catalysis.[13] Many of these gold catalyses use HFIP simply as a polar protic solvent with the catalyst being activated by a silver salt. Some of the more recent examples, however, use HFIP not only to solubilize the catalyst but also to activate the Au-Cl bond by hydrogen bonding with chloride.[13c, 13d, 13f-h] While these groups favored HFIP as the primary solvent for their reactions, due to solubility, we decided to use HFIP more as an additive with $CDCl_3$ being the solvent.

Table 1. Propargyl amide cyclization



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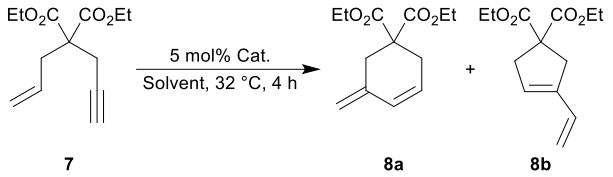
Entry	Cat.	Solvent	Conversion (%)[a]
1	Ph_3PAuCl	1:11 HFIP/$CDCl_3$[b]	13
2	**3**	1:11 HFIP/$CDCl_3$[b]	22
3	[**4**][OTf]	1:11 HFIP/$CDCl_3$[b]	89
4	Ph_3PAuCl	$CDCl_3$	0
5	**3**	$CDCl_3$	100[c]
6	[**4**][OTf]	$CDCl_3$	—[d]

[a]Conversion determined by ^{1}H NMR. [b]vol/vol ratio [c]Reaction complete after 2 h. [d][**4**][OTf] insoluble in $CDCl_3$.

Using a 1:11 HFIP/$CDCl_3$ solution, 2 mol% catalyst loading yielded decent conversion of **5** within a reasonable amount of time. The progress of the reaction was monitored by ^{1}H NMR spectroscopy and the results are summarized in **Table 1**.

Under these conditions, the reaction sees only a 13% conversion within 4 hours using Ph_3PAuCl (entry 1), a significant drop compared to Tzouras *et al.*'s complete conversion of *N*-propargyl benzamide within 3 hours using pure HFIP and a 1 mol% catalyst loading.[13g] This result suggests that increasing the ratio of HFIP to $CDCl_3$ increases catalytic activity. Even so, cationic [**4**][OTf] achieves 89% conversion under these same conditions (entry 3). The reaction only proceeds to 22% conversion in the presence of **3** which is expected given the similar structures of **3** and Ph_3PAuCl around the P (entry 2). Taken together, this data illustrates that by decreasing the σ-donation from the phosphine, the Lewis acidity of gold—and thus the catalytic activity—increases. As is typical for any catalytic study, we needed to verify that the additive, HFIP, does indeed promote

Table 2. Enyne cyclization



7 8a 8b

Entry	Cat.	Solvent	Conversion (%)[a]
1	Ph_3PAuCl	1:2 HFIP:$CDCl_3$[b]	0
2	**3**	1:2 HFIP:$CDCl_3$[b]	0
3	[**4**][OTf]	1:2 HFIP:$CDCl_3$[b]	86[c]
4	Ph_3PAuCl	$CDCl_3$	0
5	**3**	$CDCl_3$	0
6	[**4**][OTf]	$CDCl_3$	—[d]

[a]Conversion determined by ^{1}H NMR. [b]vol/vol ratio. [c]**8a:8b** = 6:1 [d][**4**][OTf] insoluble in $CDCl_3$.

this reaction.

Therefore, we performed the reaction without the addition of HFIP under the same experimental conditions. Because Au-Cl species are typically seen as pre-catalysts requiring activation, we expected to see no reactivity without HFIP. To our surprise, while the reaction no longer proceeded with Ph_3PAuCl (entry 4), complete conversion was observed within 2 hours using neutral **3** as the catalyst (entry 5). This substantial increase in catalytic activity without HFIP indicates a different process at work than we initially assumed. A notable difference between PPh_3 and **2** as ligands is the presence of a free lone pair on the nitrogen of the indazole of **2**. It appears that this nitrogen acts as a Brønsted base during the reaction, perhaps promoting the deprotonation of the propargyl amide starting material—producing a stronger nucleophile—or assisting the protodeauration step. In the presence of HFIP, this hydrogen bond accepting site is likely quenched, resulting in decreased catalytic activity as **2** becomes like PPh_3 again, only contacting the catalytic cycle through the P atom. Unfortunately, we were unable to directly compare the activities of **3** and [**4**][OTf] without HFIP due to the insolubility of the cation in pure $CDCl_3$ (entry 6), highlighting HFIP's role as not only an activator but also a solubilizing agent for polar catalysts. We did attempt the catalysis in CD_3CN—which dissolved [**4**][OTf]—but the reactivity was minimal even in the presence of HFIP.

With this understanding of the reactivity of **3**, we wanted to test a reaction in which there are no acidic protons, allowing us to focus our comparison on the change in electron donation to the gold upon introducing a positive charge. As such, we turned to the cyclization of 2-allyl-2-(2-propynyl)malonate which lacks an acidic proton. As this reaction is known to be more challenging, we increased the HFIP concentration to 1:2 HFIP/$CDCl_3$ and the catalyst loading to 5 mol% (**Table 2**). Even under these conditions, neither Ph_3PAuCl nor neutral **3** promote cyclization (entries 1 and 2). Catalyst [**4**][OTf], on the other hand, facilitated 86% conversion within four hours as indicated by ^{1}H NMR spectroscopy (entry 3). Without HFIP, the reaction did not proceed with any of the catalysts, indicating the necessity of this additive to the success of this reaction (entries 4-6). The higher activity of [**4**][OTf] can be attributed to the weaker σ-donation of the phosphine enhancing the electrophilic character of the gold center.

In summary, we synthesized a new phosphine ligand containing an indazole group. After complexation with gold, the lone pair on nitrogen allowed for easy introduction of a positive charge through methylation, thereby permitting the straightforward comparison of a neutral and cationic gold phosphine complex with minimal structural changes. We used the common reporter reactions of propargyl amide cyclization and enyne cyclization to assess the differences between these two new complexes. In both reactions, the cationic species outperforms the neutral one in solutions containing HFIP as an additive, demonstrating the benefits of decreasing σ-donation as a way to increase the Lewis acidity of gold. In pure $CDCl_3$, however, the neutral complex performed even better in the propargyl amide cyclization than the cationic one in the HFIP/$CDCl_3$ solution, suggesting that in this particular reaction, the Brønsted basic nitrogen of the neutral catalyst also participates. This result reminds us that HFIP is still an additive and, like silver, can engage the reactive species productively or counterproductively, depending on the specifics of the reaction mixture.

ASSOCIATED CONTENT

Supporting Information.

The supporting information is available free of charge via the Internet at http://pubs.acs.org.

Synthetic methods, NMR spectra, and details and NMR spectra for catalytic studies (PDF)

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Author Contributions

A.M. conducted the experimental and analytical work. A.M. and L.T.M. designed the experiments and analyzed the data. W.-C. L. performed the initial study of HFIP as an additive in various reactions with Ph_3PAuCl. F.P.G. oversaw the study. A.M., L.T.M., and F.P.G. wrote the manuscript.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This work was performed at Texas A&M University with support of the National Science Foundation (CHE-2154972), the Welch Foundation (A-1423), and Texas A&M University (Arthur E. Martell Chair of Chemistry).

REFERENCES

1. (a) Tolman, C. A., Steric effects of phosphorus ligands in organometallic chemistry and homogeneous catalysis. *Chem. Rev.* **1977,** *77,* 313-348; (b) Klahn, P.; Kirsch, S. F., Electronic Fine-Tuning of Carbene Ligands and its Impact on Gold Catalysis. *ChemCatChem* **2011,** *3,* 649-652.
2. (a) Canac, Y.; Maaliki, C.; Abdellah, I.; Chauvin, R., Carbeniophosphanes and their carbon → phosphorus → metal ternary complexes. *New J. Chem.* **2012,** *36,* 17-27; (b) Alcarazo, M., α-Cationic Phosphines: Synthesis and Applications. *Chem. Eur. J.* **2014,** *20,* 7868-7877; (c) Alcarazo, M., Synthesis, Structure, and Applications of α-Cationic Phosphines. *Acc. Chem. Res.* **2016,** *49,* 1797-1805; (d) Schwedtmann, K.; Zanoni, G.; Weigand, J. J., Recent Advances in Imidazoliumyl-Substituted Phosphorus Compounds. *Chem. - Asian J.* **2018,** *13,* 1388-1405; (e) Canac, Y., Carbeniophosphines versus Phosphoniocarbenes: The Role of the Positive Charge. *Chem. - Asian J.* **2018,** *13,* 1872-1887; (f) Rugen, C. J.; Alcarazo, M., α-Cationic Phosphines: from Curiosities to Powerful Ancillary Ligands. *Synlett* **2021,** *33,* 16-26.
3. (a) Wilkins, L. C.; Kim, Y.; Litle, E. D.; Gabbaï, F. P., Stabilized Carbenium Ions as Latent, Z-type Ligands. *Angew. Chem. Int. Ed.* **2019,** *58,* 18266-18270; (b) Litle, E. D.; Wilkins, L. C.; Gabbaï, F. P., Ligand-enforced intimacy between a gold cation and a carbenium ion: Impact on stability and reactivity. *Chem. Sci.* **2021,** *12,* 3929-3936.
4. (a) Kuhn, N.; Fahl, J.; Bläser, D.; Boese, R., Synthese und Eigenschaften von [Ph2(Carb)P]AlCl4 (Carb=2,3-Dihydro-1,3-diisopropyl-4,5-dimethylimidazol-2-yliden) – ein stabiler Carben-Komplex des dreiwertigen Phosphors [1]. *Zeitschrift für anorganische und allgemeine Chemie* **1999,** *625,* 729-734; (b) Brauer, D. J.; Kottsieper, K. W.; Liek, C.; Stelzer, O.; Waffenschmidt, H.; Wasserscheid, P., Phosphines with 2-imidazolium and para-phenyl-2-imidazolium moieties—synthesis and application in two-phase catalysis. *Journal of Organometallic Chemistry* **2001,** *630,* 177-184; (c) Azouri, M.; Andrieu, J.; Picquet, M.; Richard, P.; Hanquet, B.; Tkatchenko, I., Straightforward Synthesis of Donor-Stabilised Phosphenium Adducts from Imidazolium-2-carboxylate and Their Electronic Properties. *European Journal of Inorganic Chemistry* **2007,** *2007,* 4877-4883.
5. (a) Petuškova, J.; Bruns, H.; Alcarazo, M., Cyclopropenylylidene-Stabilized Diaryl and Dialkyl Phosphenium Cations: Applications in Homogeneous Gold Catalysis. *Angew. Chem. Int. Ed.* **2011,** *50,* 3799-3802; (b) Carreras, J.; Gopakumar, G.; Gu, L.; Gimeno, A.; Linowski, P.; Petuškova, J.; Thiel, W.; Alcarazo, M., Polycationic Ligands in Gold Catalysis: Synthesis and Applications of Extremely π-Acidic Catalysts. *J. Am. Chem. Soc.* **2013,** *135,* 18815-18823; (c) Mboyi, C. D.; Maaliki, C.; Mankou Makaya, A.; Canac, Y.; Duhayon, C.; Chauvin, R., Phosphenium Versus Pro-Phosphide Character of P-tert-butyl-dicyclopropeniophosphine: Zwitterionic Palladate Complexes of a Dicationic Phosphido Ligand. *Inorg. Chem.* **2016,** *55,* 11018-11027; (d) Tinnermann, H.; Nicholls, L. D. M.; Johannsen, T.; Wille, C.; Golz, C.; Goddard, R.; Alcarazo, M., N-Arylpyridiniophosphines: Synthesis, Structure, and Applications in Au(I) Catalysis. *ACS Catal.* **2018,** *8,* 10457-10463.
6. Shahzad, S. A.; Sajid, M. A.; Khan, Z. A.; Canseco-Gonzalez, D., Gold catalysis in organic transformations: A review. *Synth. Commun.* **2017,** *47,* 735-755.
7. Debono, N.; Canac, Y.; Duhayon, C.; Chauvin, R., An Atropo-Stereogenic Diphosphane Ligand with a Proximal Cationic Charge: Specific Catalytic Properties of a Palladium Complex Thereof. *European Journal of Inorganic Chemistry* **2008,** *2008,* 2991-2999.
8. Park, G.; Gabbaï, F. P., The Elusive Au(I)···H–O Hydrogen Bond: Experimental Verification. *J. Am. Chem. Soc.* **2021,** *143,* 12494-12498.
9. (a) Tinnermann, H.; Wille, C.; Alcarazo, M., Synthesis, Structure, and Applications of Pyridiniophosphines. *Angew. Chem. Int. Ed.* **2014,** *53,* 8732-8736; (b) Hobbollahi, E.; List, M.; Hupp, B.; Mohr, F.; Berger, R. J. F.; Steffen, A.; Monkowius, U., Highly efficient cold-white light emission in a $[Au_2CuCl_2(P\cap N)_2]PF_6$ type salt. *Dalton Trans.* **2017,** *46,* 3438-3442.
10. Hashmi, A. S. K.; Weyrauch, J. P.; Frey, W.; Bats, J. W., Gold Catalysis: Mild Conditions for the Synthesis of Oxazoles from N-Propargylcarboxamides and Mechanistic Aspects. *Org. Lett.* **2004,** *6,* 4391-4394.
11. Lu, Z.; Hammond, G. B.; Xu, B., Improving Homogeneous Cationic Gold Catalysis through a Mechanism-Based Approach. *Acc. Chem. Res.* **2019,** *52,* 1275-1288.
12. Pozhydaiev, V.; Power, M.; Gandon, V.; Moran, J.; Lebœuf, D., Exploiting hexafluoroisopropanol (HFIP) in Lewis and Brønsted acid-catalyzed reactions. *Chem. Commun.* **2020,** *56,* 11548-11564.
13. (a) Hamada, N.; Yamaguchi, A.; Inuki, S.; Oishi, S.; Ohno, H., Gold(I)-Catalyzed Oxidative Cascade Cyclization of 1,4-Diyn-3-ones for the Construction of Tropone-Fused Furan Scaffolds. *Org. Lett.* **2018,** *20,* 4401-4405; (b) Zhai, R. L.; Xue, Y. S.; Liang, T.; Mi, J. J.; Xu, Z., Regioselective Arene and Heteroarene Functionalization: N-Alkenoxypyridinium Salts as Electrophilic Alkylating Agents for the Synthesis of α-Aryl/α-Heteroaryl Ketones. *J. Org. Chem.* **2018,** *83,* 10051-10059; (c) Xu, C.; Feng, Y.; Li, F.; Han, J.; He, Y.-M.; Fan, Q.-H., A Synthetic Route to Chiral Benzo-Fused N-Heterocycles via Sequential Intramolecular Hydroamination and Asymmetric Hydrogenation of Anilino-Alkynes. *Organometallics* **2019,** *38,* 3979-3990; (d) Wang, W.; Cao, X.; Xiao, W.; Shi, X.; Zuo, X.; Liu, L.; Chang, W.; Li, J., Stereospecific Synthesis of cis-2,5-Disubstituted Pyrrolidines via N,O-Acetals Formed by Hydroamination Cyclization–Hydroalkoxylation of Homopropargylic Sulfonamides in HFIP. *J. Org. Chem.* **2020,** *85,* 7045-7059; (e) Xiao, J.; Cui, Y.; Li, C.; Xu, H.; Zhai, Y.; Zhang, X.; Ma, S., Room Temperature Allenation of Terminal Alkynes with Aldehydes. *Angew. Chem. Int. Ed.* **2021,** *60,* 25708-25713; (f) Li, W.; Shi, R.; Chen, S.; Zhang, X.; Peng, W.; Chen, S.; Li, J.; Xu, X.-M.; Zhu, Y.-P.; Wang, X., Synthesis of Diverse Pentasubstituted Pyrroles by a Gold(I)-Catalyzed Cascade Rearrangement-Cyclization of Tertiary Enamide. *J. Org. Chem.* **2022,** *87,* 3014-3024; (g) Tzouras, N. V.; Gobbo, A.; Pozsoni, N. B.; Chalkidis, S. G.; Bhandary, S.; Van Hecke, K.; Vougioukalakis, G. C.; Nolan, S. P., Hydrogen bonding-enabled gold catalysis: ligand effects in gold-catalyzed cycloisomerizations in hexafluoroisopropanol (HFIP). *Chem. Commun.* **2022,** *58,* 8516-8519; (h) Tzouras, N. V.; Zorba, L. P.; Kaplanai, E.; Tsoureas, N.; Nelson, D. J.; Nolan, S. P.; Vougioukalakis, G. C., Hexafluoroisopropanol (HFIP) as a Multifunctional Agent in Gold-Catalyzed Cycloisomerizations and Sequential Transformations. *ACS Catal.* **2023,** *13,* 8845-8860; (i) Truchon, A.; Dupeux, A.; Olivero, S.; Michelet, V., Gold-Catalyzed One-Pot Cycloisomerization/Nucleophilic Addition/Rearrangement of Acenaphthylene Carbaldehyde Derivatives. *Advanced Synthesis & Catalysis* **2023,** *365,* 2006-2012.

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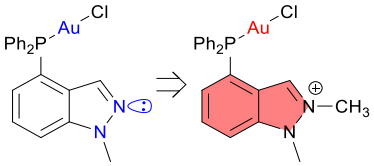

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