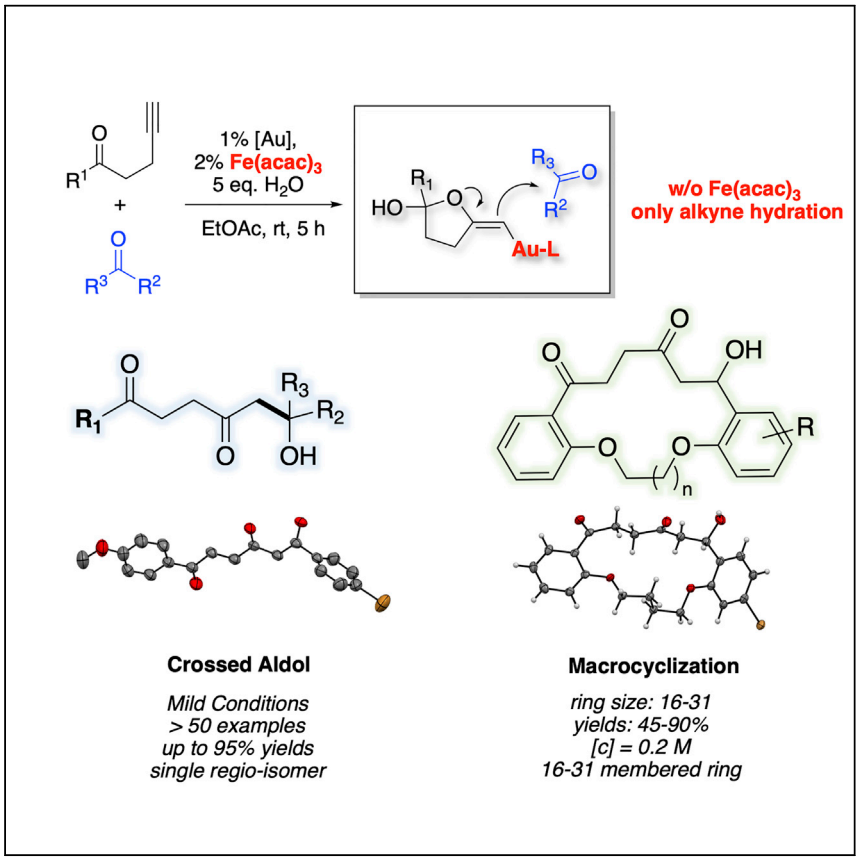
Chem

CellPress

Article

Regioselective Crossed Aldol Reactions under Mild Conditions via Synergistic Gold-Iron Catalysis



We report a synergistic gold-iron (Au-Fe) catalytic system to access vinyl Au reactivity by avoiding frequently occurring protodeauration. $Fe(acac)_3$ was identified as an essential co-catalyst, facilitating vinyl Au addition to aldehydes. A broad substrate scope was obtained under mild conditions (room temperature) with excellent regioselectivity and high efficiency (1% [Au], up to 95% yields). This protocol offers a practical solution for achieving macrocyclization (16–31 ring sizes, up to 90%, gram scale) without extended dilution, highlighting the synthetic utility in complex molecular synthesis.

Teng Yuan, Xiaohan Ye, Pengyi Zhao, ..., Jonathan Jean, Hao Chen, Xiaodong Shi

hao.chen.2@njit.edu (H.C.)
xmshi@usf.edu (X.S.)

HIGHLIGHTS

Synergistic gold-iron catalytic system toward C–C bond construction

Successful example of vinyl gold addition toward carbonyl compounds

$Fe(acac)_3$ as a new dynamic L-ligand suppresses the protodeauration of vinyl gold

A practical macrocyclization protocol without extended dilution (0.2 M)

Yuan et al., Chem 6, 1–12
June 11, 2020
https://doi.org/10.1016/j.chempr.2020.03.014

Please cite this article in press as: Yuan et al., Regioselective Crossed Aldol Reactions under Mild Conditions via Synergistic Gold-Iron Catalysis, Chem (2020), https://doi.org/10.1016/j.chempr.2020.03.014

Chem

CellPress

Article

Regioselective Crossed Aldol Reactions under Mild Conditions via Synergistic Gold-Iron Catalysis

Teng Yuan,[1] Xiaohan Ye,[1] Pengyi Zhao,[2] Shun Teng,[1] Yaping Yi,[3] Jin Wang,[1] Chuan Shan,[1] Lukasz Wojtas,[1] Jonathan Jean,[1] Hao Chen,[2,*] and Xiaodong Shi[1,4,*]

SUMMARY

A synergistic gold-iron (Au-Fe) catalytic system was developed for sequential alkyne hydration and vinyl Au addition to aldehydes or ketones. $Fe(acac)_3$ was identified as an essential co-catalyst in preventing vinyl Au protodeauration and facilitating nucleophilic additions. Effective C–C bond formation was achieved under mild conditions (room temperature) with excellent regioselectivity and high efficiency (1% [Au], up to 95% yields). The intramolecular reaction was also achieved, giving successful macrocyclization (16–31 ring sizes) with excellent yields (up to 90%, gram scale) without extended dilution (0.2 M), which highlights the great potential of this new crossed aldol strategy in challenging target molecule synthesis.

INTRODUCTION

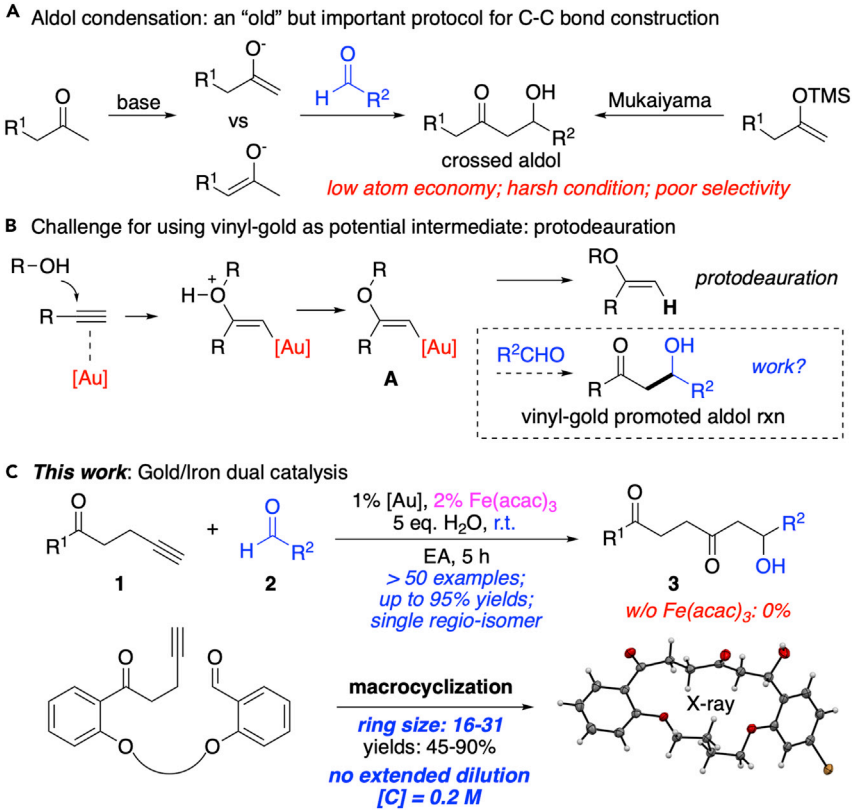
Aldol reaction is a classic C–C bond-forming transformation in organic synthesis.[1–5] Conventional aldol reactions often require strong bases to access the needed enolates, which limit the substrate scope. Moreover, when two different carbonyl groups are involved, the reactions often suffer from unsatisfactory chemoselectivity (self- versus crossed aldol) and regioselectivity (thermodynamic versus kinetic enolate). As an improved modification, Mukaiyama aldol used silyl enol ethers as nucleophiles.[6–11] However, the requirements of stoichiometric silyl reagents and harsh reaction conditions greatly reduced the atom economy of this method as practical synthesis, especially for challenging substrates (Scheme 1A). Although efforts have been made to improve reaction performance, such as applications of Lewis acids[2,12–15] and amine organo-catalysts,[16–23] challenges associated with regioselectivity and reaction efficiency remain for this fundamental but important transformation. Novel strategies with high efficiency are highly desirable.

Over the past two decades, homogeneous gold (Au) catalysis has drawn great attention because of its unique ability of activating alkynes and allenes under mild conditions.[24–32] As shown in Scheme 1B, one important intermediate involved is vinyl Au **A** upon nucleophilic addition toward Au-alkyne π-complexes. In most cases, a rapid protodeauration takes place, converting the C–Au bond into the C–H bond.[33–41] To date, alternative reactivity of vinyl Au intermediate **A** has been rarely explored.[42–51] Notably, the incorporation of electrophilic carbon atoms, such as carbonyl or carbonyl equivalents, in Au catalysis has been explored.[52–56] The pioneering work of Ito et al. has demonstrated the first Au-catalyzed asymmetric aldol reaction.[57,58] Here, we report the first successful example of vinyl Au addition toward carbonyl, giving formal crossed aldol products with high efficiency (1% Au loading,

The Bigger Picture

Effective construction of the C–C bond is one of the most important tasks in organic synthesis. Whereas aldol condensation is a classic C–C bond-forming transformation, it requires other chemical promoters, such as strong base and reactive acidic catalysts. As a result, the overall transformation is limited in terms of ideal atom economy and environmentally friendly operation. With the discovery of a gold-iron (Au-Fe) synergistic catalysis system, here we describe a new approach to facilitating alkyne hydration and sequential vinyl Au addition to carbonyls. This approach gives the C–C bond-forming products in excellent yields, wide substrate scope, and great functional-group compatibility under mild conditions. This protocol can also be applied to macrocyclization without extended dilution. This C–C bond-forming strategy could facilitate challenging molecule synthesis in chemical, biological, and medicinal research.

Please cite this article in press as: Yuan et al., Regioselective Crossed Aldol Reactions under Mild Conditions via Synergistic Gold-Iron Catalysis, Chem (2020), https://doi.org/10.1016/j.chempr.2020.03.014



Scheme 1. Formal Crossed Aldol Reaction with Au-Fe Dual Catalysis

(A) Aldol condensation: an "old" but important protocol for C–C bond construction.

(B) Challenge with using vinyl Au as potential intermediate: protodeauration.

(C) This work: Au-Fe dual catalysis.

up to 95% yields) and excellent regioselectivity (exclusively kinetic enolate addition). Moreover, intramolecular reaction gives successful synthesis of macrocyclic compounds with a ring size between 16 and 31 under mild conditions (room temperature [RT], up to 90% yields) with no need for extended dilution (Scheme 1C).

RESULTS AND DISCUSSION

Our interest in pursuing a vinyl Au intermediate as a nucleophile originated from the recent discovery of successful oxazolyl aldehydes synthesis via Au-iron (Fe) dual catalysis.[59–62] As shown in Figure 1A, treating alkyne **B** with a mixture of Au and Fe catalysts gave oxazolyl aldehydes **D**. Monitoring the reaction revealed interesting kinetic profiles: alkyne **B** under combined [Au] and [Fe] catalysis conditions gave a much faster reaction rate (formation of **D**) than the reaction of alkene **C** with [Fe] (k_1/k_2 > 10). Because **A** is the intermediate upon cyclization, these kinetic studies clearly suggested that vinyl Au **A** is more reactive than enol ether **C** toward Fe-activated oxygen radical. Considering that the oxygen radical is electron deficient, it is reasonable to conclude that vinyl Au **A** is more electron rich than vinyl ether. Therefore, we wondered whether intermediate **A** could be used to react with carbonyl as a new approach for C–C bond synthesis. To verify this hypothesis, we conducted reactions between aldehyde **2a** and phenylacetylene. Unfortunately, only Telle hydration was obtained, and no desired aldol products were observed under various conditions (Figure 1B).

[1]Department of Chemistry, University of South Florida, Tampa, FL, USA

[2]Department of Chemistry and Environmental Science, New Jersey Institute of Technology, Newark, NJ, USA

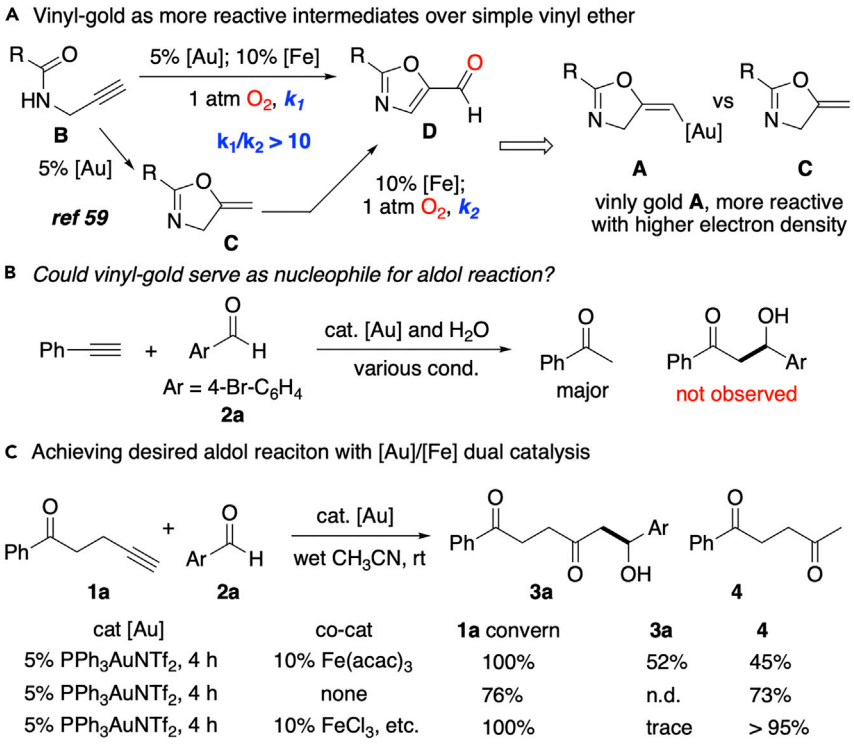
[3]Department of Chemistry, Tsinghua University, Beijing, China

[4]Lead Contact

*Correspondence: hao.chen.2@njit.edu (H.C.), xmshi@usf.edu (X.S.)

https://doi.org/10.1016/j.chempr.2020.03.014

Please cite this article in press as: Yuan et al., Regioselective Crossed Aldol Reactions under Mild Conditions via Synergistic Gold-Iron Catalysis, Chem (2020), https://doi.org/10.1016/j.chempr.2020.03.014



cat [Au]	co-cat	1a convern	3a	4
5% PPh_3AuNTf_2, 4 h	10% $Fe(acac)_3$	100%	52%	45%
5% PPh_3AuNTf_2, 4 h	none	76%	n.d.	73%
5% PPh_3AuNTf_2, 4 h	10% $FeCl_3$, etc.	100%	trace	> 95%

Figure 1. Electron-Rich Vinyl Au as a Potential Nucleophile

(A) Vinyl Au as a more reactive intermediate over simple vinyl ether.

(B) Could vinyl Au serve as a nucleophile for aldol reaction?

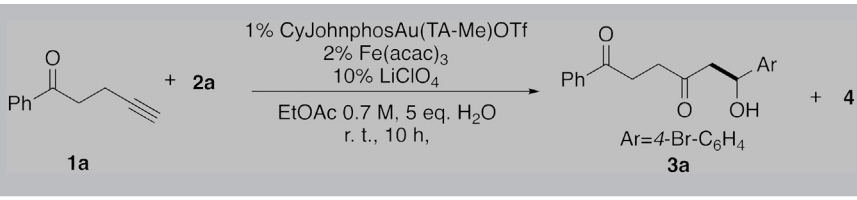
(C) Achieving desired aldol reaction with [Au]-[Fe] dual catalysis.

We also screened alkynes—including propargyl amides **B**, hydroxyl-alkynes, and keto-alkynes **1a**—but observed no desired crossed aldol products in any of the tested cases under Au catalytic conditions (see detailed screening conditions in Table S1). Notably, the hydration reaction rate for **1a** was faster than that for simple alkyne, most likely because of carbonyl-group neighboring-group participation toward Au-activated alkyne (5-exo-dig).[63] Alkyne hydration through vinyl Au protodeauration was a critical challenge in our attempt to apply vinyl Au as a nucleophile. To compete with undesired hydration, we applied various metal salts as co-catalysts for aldehyde **2a** activation, including $Sc(OTf)_3$, $Ga(OTf)_3$, and $FeCl_3$. Still, no desired product was observed. Interestingly, when $Fe(acac)_3$ was used as co-catalyst, the desired aldol product **3a** was received in 52% yield along with 45% hydration product **4** (Figure 1C). Notably, we observed slower hydration when we treated alkyne with a mixture of [Au] and $Fe(acac)_3$ (no aldehyde presented), suggesting the unique role of $Fe(acac)_3$ in preventing alkyne hydration side reactions. To improve reaction yields, we performed comprehensive condition screenings, including different Au catalysts, solvents, co-catalyst loadings, and amounts of water. Finally, the reaction reached 100% **1a** conversion with desired aldol product **3a** in 91% isolated yield under optimal conditions: 1% CyJohnPhosAu(TA-Me)OTf, 2% $Fe(acac)_3$, and 10% $LiClO_4$ in EtOAc with 5 equiv of water. The results of some representative conditions are summarized in Table 1.

According to condition screening, the primary ligand on Au is essential (entries 1–6). CyJohnPhos was revealed to give the best result. Triazoles, especially *N*-methyl benzotriazole (TA-Me), proved to be suitable dynamic ligands for suppressing hydration.[64–70] This could be explained by their good binding ability toward $[L–Au]^+$,

Please cite this article in press as: Yuan et al., Regioselective Crossed Aldol Reactions under Mild Conditions via Synergistic Gold-Iron Catalysis, Chem (2020), https://doi.org/10.1016/j.chempr.2020.03.014

Table 1. Reaction Optimization



	Variation from Standard Conditions	3a	4
1	none	95% (91%[a])	4%
2	[Au] = PPh_3AuNTf_2	55%	40%
3	[Au] = $IPrAuNTf_2$	60%	33%
4	[Au] = $JohnPhosAuNTf_2$	68%	30%
5	[Au] = $CyJohnPhosAuNTf_2$	70%	25%
6	[Au] = CyJohnPhosAu(TA-H)OTf	88%	10%
7	no $Fe(acac)_3$	0%	>95%
8	1% $Fe(acac)_3$	75%	20%
9	4% $Fe(acac)_3$	90%	6%
10	2% $Fe(dbm)_3$	28%	70%
11	2% $Fe(hfaa)_3$	0%	>95%
12	1 equiv H_2O	60%	35%
13	10 equiv H_2O	88%	8%
14	no $LiClO_4$	91%	8%
15	$M^{n+}(acac)_n$ instead of $Fe(acac)_3$ M = Co, Ni, Ga, Al, Sn, In, Sc, etc.	<42%	>50%
16	other solvents	<88%	>10%

Conversions and yields were determined by ^1H NMR using 1,3,5-trimethoxybenzene as the internal standard. Abbreviations are as follows: dbm, 1,3-diphenyl-1,3-propanedionate; hfaa, hexafluoroacetylacetone.
[a]Isolated yields.

preventing the formation of $[L–Au–H_2O]^+$, which leads to alkyne hydration under neutral conditions.[71] $Fe(acac)_3$ was crucial for optimal reactivity. Other Fe salts, such as $FeCl_2$, $FeCl_3$, and $Fe(OTf)_3$, were tested and gave exclusive hydration product **4**. Fe(III) salts with different acac-type ligands were also tested. With 1,3-diphenyl-1,3-propanedionate (dbm) ligand, reduced yield of **3a** was observed, most likely because of increased acidity. The more acidic hexafluoroacetylacetone (hfaa) ligand gave exclusive hydration product **4** (entries 10 and 11). Other metal $M(acac)_n$ complexes, such as Co^{2+}, Ga^{3+}, and Al^{3+}, led to reduced yields of **3a**, highlighting the unique role of $Fe(acac)_3$ in this dual-metal catalytic system. Notably, Li^+ could promote carbonyl activation with slightly improved yield (entry 14). Clearly, the amount of water is critical. Although water promotes undesired hydration, it is necessary to use water to trigger hemiacetal formation after carbonyl cyclization (formation of vinyl Au; Figure 4B). Detailed screening revealed that 5 equiv of water in ethyl acetate gave the optimal result of **3a** in 95% yield. With the optimal conditions in hand, we evaluated the substrate scope. The results are summarized in Figure 2.

Various aldehydes and ketones were tested to react with alkyne **1a**. The reaction generally worked well for various benzaldehydes, giving crossed aldol products **3** in good to excellent yields in almost all cases (**3a–3r**). Notably, with the unique vinyl Au mechanism, only kinetic enolate addition products were received in all cases. The

Please cite this article in press as: Yuan et al., Regioselective Crossed Aldol Reactions under Mild Conditions via Synergistic Gold-Iron Catalysis, Chem (2020), https://doi.org/10.1016/j.chempr.2020.03.014

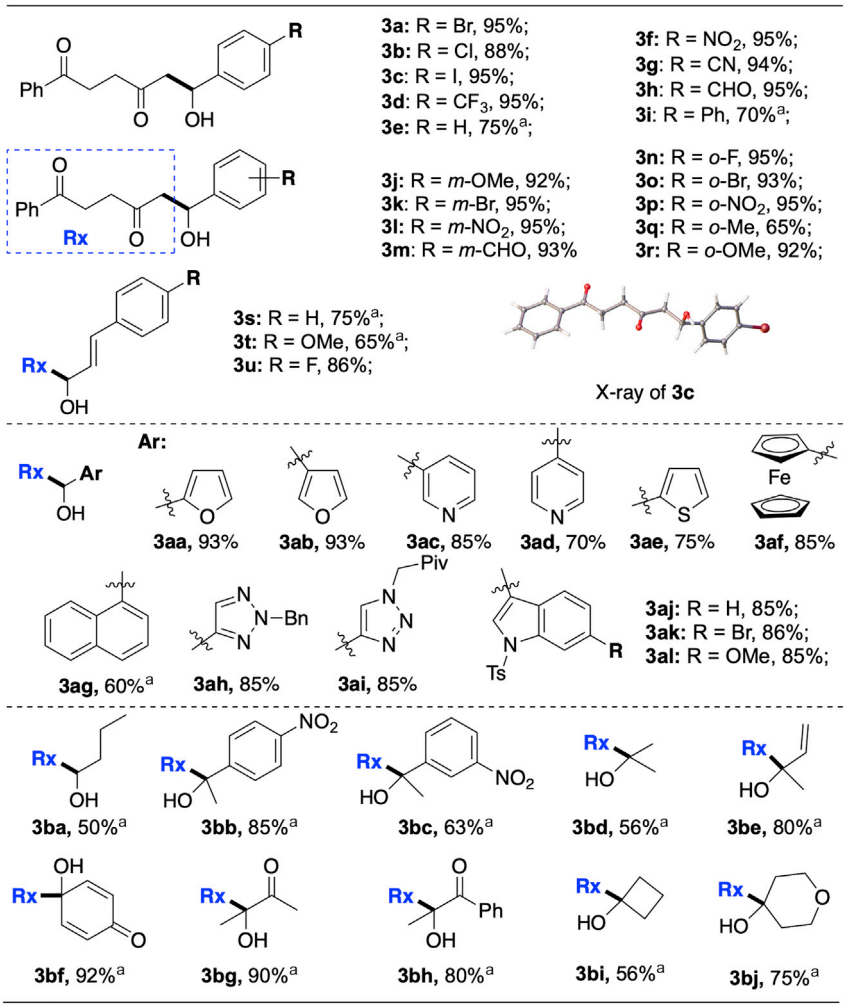


Figure 2. Reaction Scope of Aldehydes and Ketones

Standard conditions: 1% CyJohnPhosAu(TA-Me)OTf, 2% $Fe(acac)_3$, 10% $LiClO_4$, and 5 equiv water were added to an ethyl acetate (0.45 mL) solution of aldehyde **1** (0.6 mmol) and alkyne **2a** (0.3 mmol), and the reaction was run at RT for 12 h at isolated yield.

[a]5% CyJohnPhosAu(TA-Me)OTf, 10% $Fe(acac)_3$, 10% $LiClO_4$, and 0.9 mmol aldehyde and ketone were used.

structure of the resulting β-hydroxy-ketone was confirmed by X-ray crystallography (**3c**). Heteroaromatic aldehydes were also tolerated (**3aa–3al**). Particularly, substrates containing pyridine (**3ac** and **3ad**) and triazole (**3ah** and **3ai**) were all feasible despite their strong coordination effect with metal catalysts. According to the literature, with enone or enal electrophiles, Mukaiyama aldol dominantly goes through 1,4-addition.[72–76] With this Au-Fe system, exclusive 1,2-addition products were obtained (**3s–3u**), suggesting an orthogonal selectivity for synthetic applications. Moderate yield was achieved with aliphatic aldehyde (**3ba**) because of the reduced reactivity. Ketones are not good electrophiles under neutral conditions given that good to modest yields were obtained with various ketones (**3bb–3bj**). Notably, $LiClO_4$ was essential for this transformation. Only trace amounts of desired product (<5%) were obtained in the absence of $LiClO_4$, suggesting the important role of Li^+ in carbonyl activation. To the best of our knowledge, this was the first successful example of catalytic crossed aldol reaction with ketone under such mild and neutral conditions. We

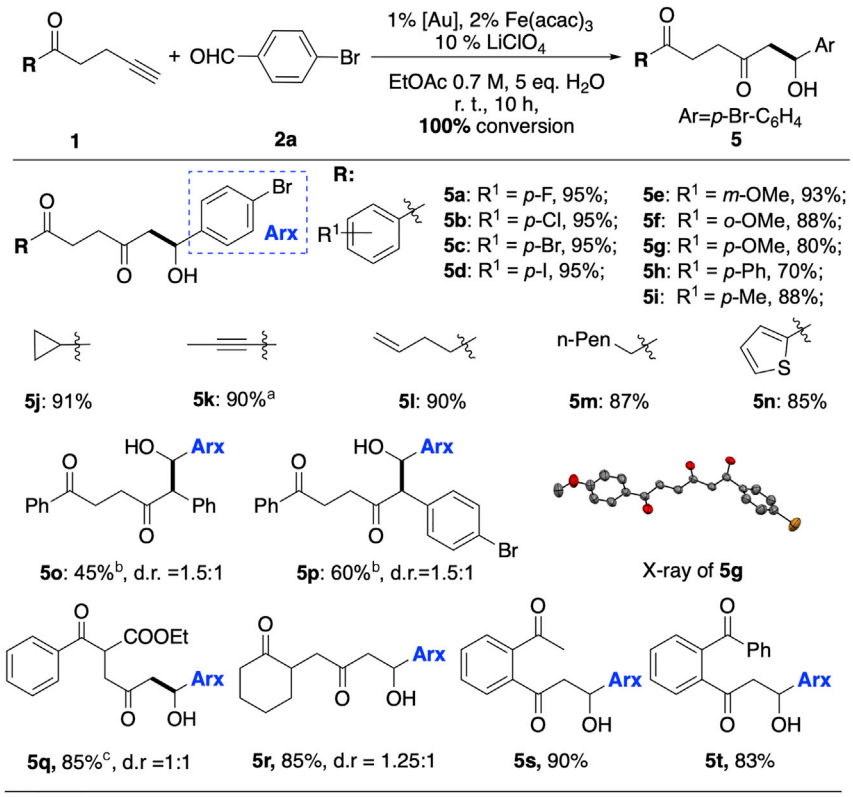


Figure 3. Reaction Substrate of Alkynes

Standard conditions: 1% CyJohnPhosAu(TA-Me)OTf, 2% $Fe(acac)_3$, 10% $LiClO_4$, and 5 equiv water were added to an ethyl acetate (0.45 mL) solution of aldehyde **1** (0.6 mmol) and alkyne **2a** (0.3 mmol), and the reaction was run at RT for 12 h at isolated yield. [a]45°C for 6 h. [b]50°C. [c]35°C for 24 h.

also evaluated the scope of alkyne by reacting with 4-bromo-benzylaldehyde **2a** under optimal conditions. A series of keto-substituted alkynes were prepared. The results are summarized in Figure 3.

Substituents on the carbonyl group showed a dramatic impact on this transformation. In general, electron-deficient aryl keto-alkynes (**5a–5d**) gave crossed aldol products in excellent yields. Slightly reduced yields were obtained with electron-rich aryl substrates (**5e–5i** and **5n**). Aliphatic substituted keto-alkynes were also suitable for this reaction (**5j–5m** and **5r**). Substituents such as cyclopropyl, a C≡C bond, and an allyl group remained intact in the reaction, indicating good function-group tolerance and mild conditions of this new Au-Fe catalytic system. Internal alkynes also worked well for this reaction by giving crossed aldol products in moderate yields and a low diastereomeric ratio (d.r.) (**5o** and **5p**). Compared with the activation of terminal alkynes, the activation of less reactive internal alkynes requires higher temperature (50°C), which adversely accelerates hydration. Substrates with different linkages between alkyne and carbonyl groups, including β-ester (**5q**) and α,β-aryl substituents (**5s** and **5t**), were tested. All of these substrates delivered the desired products in good yields. Overall, this new dual Au-Fe catalytic system showed superior regioselectivity and significantly improved reactivity for crossed aldol reaction under mild conditions.

To rationalize the role of $Fe(acac)_3$ in this transformation, we performed several experiments. First, conducting the reaction with Na(acac) instead of $Fe(acac)_3$ slowed

Please cite this article in press as: Yuan et al., Regioselective Crossed Aldol Reactions under Mild Conditions via Synergistic Gold-Iron Catalysis, Chem (2020), https://doi.org/10.1016/j.chempr.2020.03.014

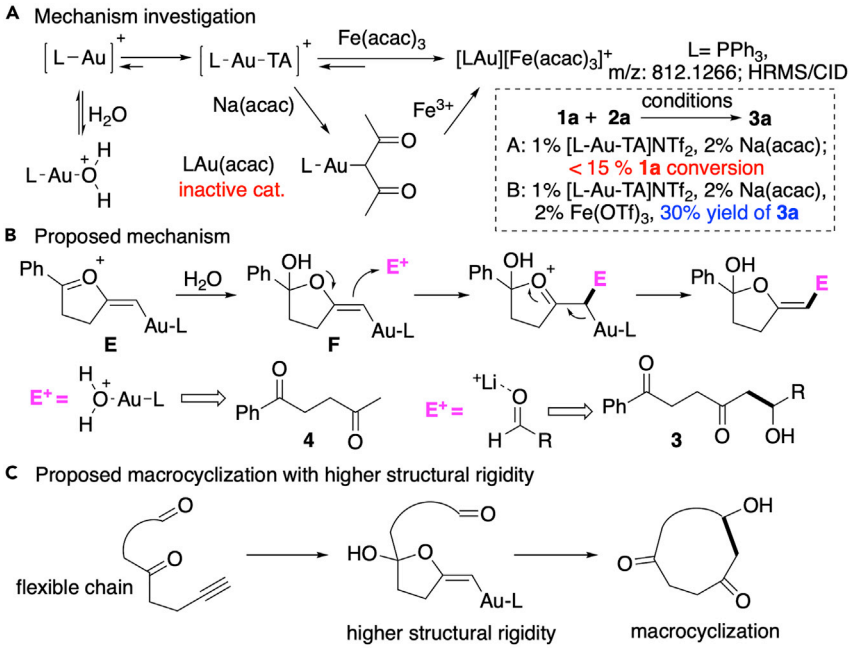


Figure 4. Au- and Fe-Catalyzed Cross-Aldol and Macrocyclization

(A) Mechanism investigation.

(B) Proposed mechanism.

(C) Proposed macrocyclization with higher structural rigidity.

down the reaction significantly (<15% **1a** conversion, 4 h; Figure 4A), and no desired product **3a** was formed. This was most likely due to a strong coordination of $acac^-$ anion toward $[L–Au]^+$.[77–80] As a precedent, an X-ray crystal structure of a corresponding C–Au(I) bond in an acetone complex has been reported.[81] Interestingly, the addition of a catalytic amount of $Fe(OTf)_3$ retriggered the system, giving **3a** in 30% yield. Monitoring the reaction with negative electrospray ionization mass spectrometry gave a diagnostic signal with *m/z* = 812.1266, corresponding to the formation of the Au-Fe complex (confirmed by collision-induced dissociation; see Figures S7–S9). On the basis of these results, a plausible reaction mechanism is proposed as shown in Figure 4B.

The important step of this reaction is the addition of vinyl Au **F** toward carbonyl electrophiles. To conform vinly Au **F** as the key intermediate, we treated hydration product **4** with aldehyde under the optimal reaction conditions (Au and Fe). No reaction was observed over an extended reaction time (48 h). This result clearly indicates the importance of combing Au and Fe for this transformation. Moreover, we monitored the reaction with reactive mass spectrometry. We observed no corresponding vinyl Fe complexes when we treated vinyl Au intermediate with Fe complexes, suggesting that vinyl Au transmetalation with Fe complexes is highly unlikely and that vinyl Au is most likely the nucleophile for the observed aldehyde addition (see Figure S10).[82] Because of the low concentration of H^+ under neutral conditions, the most reactive proton source is $[L–Au–H_2O]^+$, formed from the addition of water to $[L–Au]^+$. Therefore, reducing the overall concentration of free $[L–Au]^+$ is crucial for preventing protodeauration. As we have demonstrated previously, Au complexes with a dynamic L-ligand (DLL, such as 1,2,3-triazole) could activate alkyne through dynamic concerted coordination-dissociation without the formation of $[L–Au]^+$.[70] Although further evidence is needed, it is reasonable to rationalize that $Fe(acac)_3$ serves as another

Please cite this article in press as: Yuan et al., Regioselective Crossed Aldol Reactions under Mild Conditions via Synergistic Gold-Iron Catalysis, Chem (2020), https://doi.org/10.1016/j.chempr.2020.03.014

special DLL and reduces the amount of $[L–Au]^+$ in the system. Upon alkyne substitution, Au-alkyne π-complexes were formed for rapid nucleophilic addition (cyclization). As a result, the combination of $[L–Au]^+$ and $Fe(acac)_3$ achieved the needed slow protodeauration and allowed us to access vinyl Au reactivity (as a nucleophile) without severe hydration.

Encouraged by the success of achieving cross-aldol reaction under such mild conditions, we extended our attention to another challenging transformation: macrocyclization via C–C bond formation. Macrocycles are a group of important and valuable compounds in chemical, material, and biological fields.[83–86] However, protocols of macrocyclization using an irreversible C–C bond-forming approach are rarely reported.[87–93] In addition, to avoid undesired intermolecular polymerization, macrocyclization reactions are often performed under diluted conditions, which hinder their application in large-scale synthesis. Thus, conducting macrocyclization via irreversible C–C bond formation under conventional concentrations (with no extended dilution) is highly desirable.

One important factor in improving the macrocyclization performance, especially at high concentrations, is to effectively reduce the overall structure flexibility—having reaction units pre-organized under a favored conformation. As shown in Figure 4C, the formation of vinyl Au via a cyclic hemi-acetal moiety greatly increases overall structural rigidity, aligning C=O with vinyl Au at a favorable position. We postulated that this unique activation mechanism could be applied to challenging macrocyclization. To test this idea, we prepared substrates bearing alkyne and aldehyde. To our delight, macrocyclization was successfully achieved at RT (25°C). Impressively, no polymerization was observed even at a relatively high reaction concentration (0.2 M). Macrocyclization products with ring sizes from 16 to 24 atoms were prepared with yields between 65% and 90% at the gram scale (Figure 5A). Notably, besides intramolecular reaction, intermolecular condensation between diyne and di-aldehyde could also be achieved, giving the formation of a 31-membered ring structure with 45% yield (Figure 5B).

In summary, we report a novel Au-Fe dual catalytic system to promote alkyne hydration and sequential aldol addition under mild conditions. The key to this design is to access vinyl Au nucleophilicity by avoiding undesired protodeauration. The overall transformation is highly efficient with low catalyst loading, mild conditions, large substrate scope, and excellent aldol regioselectivity. Moreover, on the basis of the pre-cyclic conformational control, this strategy was further extended as a new macrocyclization method through irreversible C–C bond construction at high concentration. Clearly, this work greatly enriches cationic Au catalysis by allowing vinyl Au as an active intermediate for sequential transformations without undesired protodeauration. Other new transformations using this concept and applications of this method for the preparation of complex molecules are expected and currently ongoing in our lab.

EXPERIMENTAL PROCEDURES

Full experimental procedures are provided in the Supplemental Information.

DATA AND CODE AVAILABILITY

The structures of **3a**, **3d**, **5g**, **5s**, **7a′**, and **7e** reported in this article have been deposited in the Cambridge Crystallographic Data Centre under accession numbers CCDC: 1964770, 1964771, 1964772, 1964773, 1964774, and 1964775, respectively.

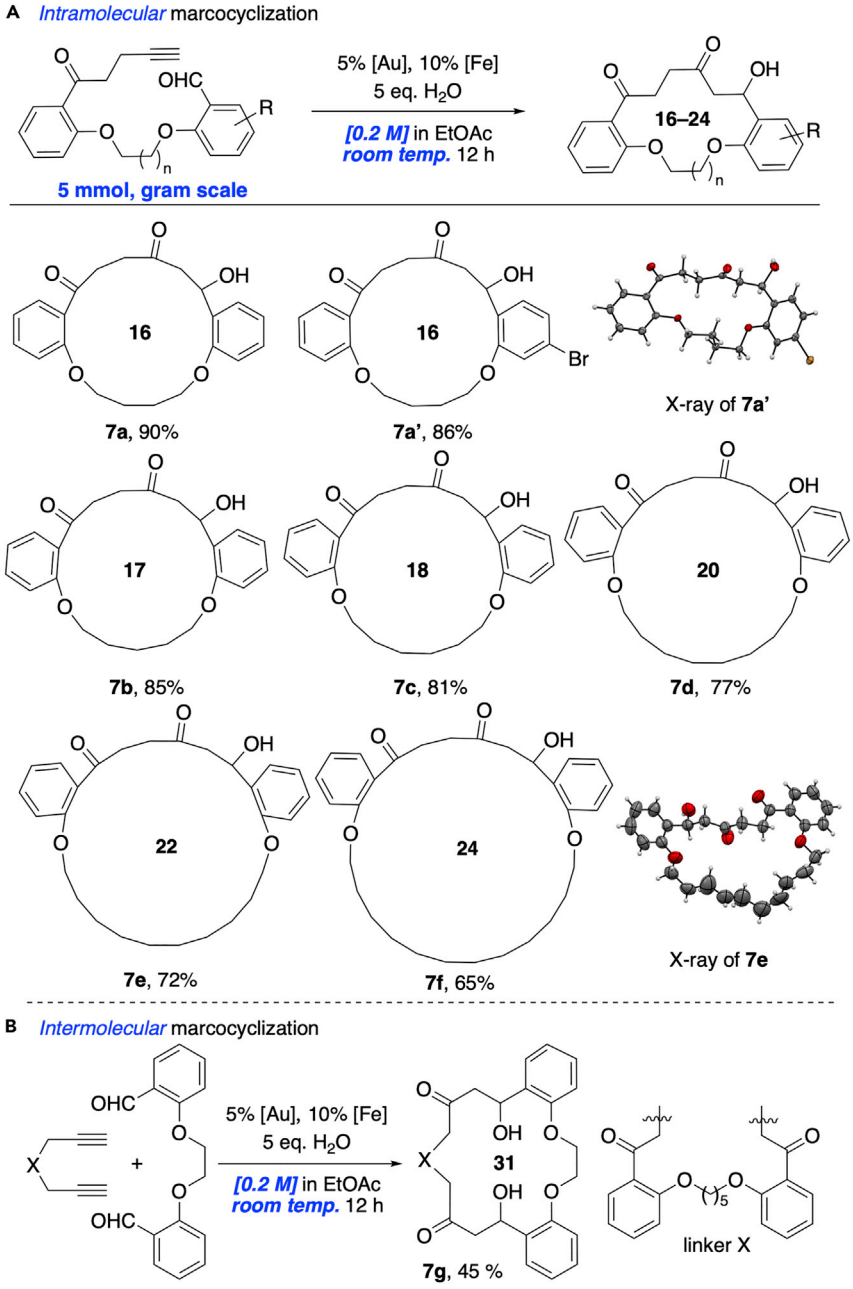


Figure 5. Macrocyclization via C–C Bond-Forming Reactions

(A) Intramolecular macrocyclization. Standard conditions: 5% CyJohnPhosAu(TA-Me)OTf, 10% $Fe(acac)_3$, and 5 equiv water were added to an ethyl acetate (25 mL) solution of substrates **6a–6f** (5 mmol), and the reaction was run at RT for 12 h at isolated yields.

(B) Intermolecular macrocyclization. Standard conditions: 5% CyJohnPhosAu(TA-Me)OTf, 10% $Fe(acac)_3$, and 5 equiv water were added to an ethyl acetate (1 mL) solution of diyne (0.2 mmol) and di-aldehyde (0.2 mmol), and the reaction was run at RT for 12 h at isolated yields.

SUPPLEMENTAL INFORMATION

Supplemental Information can be found online at https://doi.org/10.1016/j.chempr.2020.03.014.

ACKNOWLEDGMENTS

We are grateful to the NSF (CHE-1665122) and the NIH (1R01GM120240-01) for financial support. This work was supported in part by the University of South Florida Interdisciplinary NMR Facility and the Chemical Purification, Analysis, and Screening core facility, the Department of Chemistry, and the College of Arts and Sciences.

AUTHOR CONTRIBUTIONS

T.Y. discovered the reaction. T.Y. performed the optimization. P.Z. carried out the mass spectroscopy studies. T.Y., X.Y., S.T., Y.Y., J.W., and J.J. investigated the scope of the substrate and performed the application. C.S. and L.W. carried out the X-ray crystallography analysis. H.C. and X.S. directed the project and wrote the manuscript with input from all authors. All authors analyzed the results and commented on the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

Received: November 21, 2019
Revised: February 22, 2020
Accepted: March 19, 2020
Published: April 10, 2020

REFERENCES

1. Evans, D.A., Dart, M.J., Duffy, J.L., and Yang, M.G. (1996). A stereochemical model for merged 1,2- and 1,3-asymmetric induction in diastereoselective Mukaiyama aldol addition reactions and related processes. J. Am. Chem. Soc. *118*, 4322–4343.

2. Machajewski, T.D., and Wong, C.H. (2000). The catalytic asymmetric aldol reaction. Angew. Chem. Int. Ed. *39*, 1352–1375.

3. Mukaiyama, T. (1982). The directed aldol reaction. Org. React. *28*, 203–331.

4. Palomo, C., Oiarbide, M., and Garcia, J.M. (2002). The aldol addition reaction: an old transformation at constant rebirth. Chemistry *8*, 36–44.

5. Trost, B.M., and Brindle, C.S. (2010). The direct catalytic asymmetric aldol reaction. Chem. Soc. Rev. *39*, 1600–1632.

6. Beutner, G.L., and Denmark, S.E. (2013). Lewis base catalysis of the Mukaiyama directed aldol reaction: 40years of inspiration and advances. Angew. Chem. Int. Ed. *52*, 9086–9096.

7. Carreira, E.M., and Singer, R.A. (1994). Metal vesus Silyl triflate catalysis in the mukaiyama aldol addition-reaction. Tetrahedron Lett *35*, 4323–4326.

8. Kan, S.B.J., Ng, K.K.H., and Paterson, I. (2013). The impact of the Mukaiyama aldol reaction in total synthesis. Angew. Chem. Int. Ed. *52*, 9097–9108.

9. Kitanosono, T., and Kobayashi, S. (2013). Mukaiyama aldol reactions in aqueous media. Adv. Synth. Catal. *355*, 3095–3118.

10. Matsuo, J., and Murakami, M. (2013). The Mukaiyama aldol reaction: 40 years of continuous development. Angew. Chem. Int. Ed. *52*, 9109–9118.

11. Mikami, K., and Matsukawa, S. (1993). Enantioselective and diastereoselective catalysis of the mukaiyama aldol reaction: ene mechanism in titanium-catalyzed aldol reactions of silyl enol ethers. J. Am. Chem. Soc. *115*, 7039–7040.

12. Evans, D.A., Rieger, D.L., Bilodeau, M.T., and Urpi, F. (1991). Stereoselective aldol reactions of chlorotitanium enolates - an efficient method for the assemblage of polypropionate-related Synthons. J. Am. Chem. Soc. *113*, 1047–1049.

13. Johnson, J.S., and Evans, D.A. (2000). Chiral bis(oxazoline) copper(II) complexes: versatile catalysts for enantioselective cycloaddition, aldol, Michael, and carbonyl ene reactions. Acc. Chem. Res. *33*, 325–335.

14. Kobayashi, S., and Hachiya, I. (1994). Lanthanide triflates as water-tolerant lewis acids. activation of commercial formaldehyde solution and use in the aldol reaction of silyl enol ethers with aldehydes in aqueous media. J. Org. Chem. *59*, 3590–3596.

15. Trost, B.M., Ito, H., and Silcoff, E.R. (2001). Asymmetric aldol reaction via a dinuclear zinc catalyst: alpha-hydroxyketones as donors. J. Am. Chem. Soc. *123*, 3367–3368.

16. List, B., Lerner, R.A., and Barbas, C.F. (2000). Proline-catalyzed direct asymmetric aldol reactions. J. Am. Chem. Soc. *122*, 2395–2396.

17. Bahmanyar, S., and Houk, K.N. (2001). Transition states of amine-catalyzed aldol reactions involving enamine intermediates: theoretical studies of mechanism, reactivity, and stereoselectivity. J. Am. Chem. Soc. *123*, 11273–11283.

18. List, B., Pojarliev, P., and Castello, C. (2001). Proline-catalyzed asymmetric aldol reactions between ketones and alpha-unsubstituted aldehydes. Org. Lett. *3*, 573–575.

19. Sakthivel, K., Notz, W., Bui, T., and Barbas, C.F. (2001). Amino acid catalyzed direct asymmetric aldol reactions: a bioorganic approach to catalytic asymmetric carbon-carbon bond-forming reactions. J. Am. Chem. Soc. *123*, 5260–5267.

20. List, B., Hoang, L., and Martin, H.J. (2004). New mechanistic studies on the proline-catalyzed aldol reaction. Proc. Natl. Acad. Sci. USA *101*, 5839–5842.

21. Notz, W., Tanaka, F., and Barbas, C.F. (2004). Enamine-based organocatalysis with proline and diamines: the development of direct catalytic asymmetric aldol, mannich, Michael, and Diels-alder reactions. Acc. Chem. Res. *37*, 580–591.

22. Cobb, A.J.A., Shaw, D.M., Longbottom, D.A., Gold, J.B., and Ley, S.V. (2005). Organocatalysis with proline derivatives: improved catalysts for the asymmetric Mannich, nitro-Michael and aldol reactions. Org. Biomol. Chem. *3*, 84–96.

23. Tang, Z., Yang, Z.H., Chen, X.H., Cun, L.F., Mi, A.Q., Jiang, Y.Z., and Gong, L.Z. (2005). A highly efficient organocatalyst for direct aldol reactions of ketones with aldedydes. J. Am. Chem. Soc. *127*, 9285–9289.

24. Fürstner, A., and Davies, P.W. (2007). Catalytic carbophilic activation: catalysis by platinum and gold pi acids. Angew. Chem. Int. Ed. *46*, 3410–3449.

25. Gorin, D.J., and Toste, F.D. (2007). Relativistic effects in homogeneous gold catalysis. Nature *446*, 395–403.

26. Jiménez-Núñez, E., and Echavarren, A.M. (2007). Molecular diversity through gold catalysis with alkynes. Chem. Commun. 333–346.

27. Marion, N., and Nolan, S.P. (2008). N-heterocyclic carbenes in gold catalysis. Chem. Soc. Rev. *37*, 1776–1782.

28. Rudolph, M., and Hashmi, A.S.K. (2012). Gold catalysis in total synthesis–an update. Chem. Soc. Rev. *41*, 2448–2462.

29. Sengupta, S., and Shi, X.D. (2010). Recent advances in asymmetric gold catalysis. ChemCatChem *2*, 609–619.

30. Wang, Y.M., Lackner, A.D., and Toste, F.D. (2014). Development of catalysts and ligands for enantioselective gold catalysis. Acc. Chem. Res. *47*, 889–901.

31. Widenhoefer, R.A. (2008). Recent developments in enantioselective gold(I) catalysis. Chemistry *14*, 5382–5391.

32. Zhang, L.M., Sun, J.W., and Kozmin, S.A. (2006). Gold and platinum catalysis of enyne cycloisomerization. Adv. Synth. Catal. *348*, 2271–2296.

33. BabaAhmadi, R., Ghanbari, P., Rajabi, N.A., Hashmi, A.S.K., Yates, B.F., and Ariafard, A. (2015). A Theoretical study on the protodeauration step of the gold(I)-catalyzed organic reactions. Organometallics *34*, 3186–3195.

34. Gaggioli, C.A., Ciancaleoni, G., Zuccaccia, D., Bistoni, G., Belpassi, L., Tarantelli, F., and Belanzoni, P. (2016). Strong electron-donating ligands accelerate the protodeauration step in gold(I)-catalyzed reactions: a quantitative understanding of the ligand effect. Organometallics *35*, 2275–2285.

35. Richard, M.E., Ciccarelli, R.M., Garcia, K.J., Miller, E.J., Casino, S.L., Pike, R.D., and Stockland, R.A., Jr. (2018). Stereospecific protodeauration/transmetalation generating configurationally stable P-metalated nucleoside derivatives. Eur. J. Org. Chem. *2018*, 2167–2170.

36. Schafer, L.J., Garcia, K.J., Baggett, A.W., Lord, T.M., Findeis, P.M., Pike, R.D., and Stockland, R.A. (2018). Synthesis of spirocyclic Diphosphite-supported gold metallomacrocycles via a protodeauration/cyclization strategy: mechanistic and binding studies. Inorg. Chem. *57*, 11662–11672.

37. Brown, T.J., Weber, D., Gagné, M.R., and Widenhoefer, R.A. (2012). Mechanistic analysis of gold(I)-catalyzed intramolecular allene hydroalkoxylation reveals an off-cycle bis(gold) vinyl species and reversible C-O Bond formation. J. Am. Chem. Soc. *134*, 9134–9137.

38. Ciancaleoni, G., Belpassi, L., Zuccaccia, D., Tarantelli, F., and Belanzoni, P. (2015). Counterion effect in the reaction mechanism of NHC gold(I)-catalyzed alkoxylation of alkynes: computational insight into experiment. ACS Catal *5*, 803–814.

39. Hashmi, A.S.K., Ramamurthi, T.D., and Rominger, F. (2009). Synthesis, structure and reactivity of organogold compounds of relevance to homogeneous gold catalysis. J. Organomet. Chem. *694*, 592–597.

40. Malhotra, D., Hammond, G.B., and Xu, B. (2015). Ligand design in gold catalysis and chemistry of gold-oxonium intermediates. Top Curr Chem, L.M. Slaughter *357*, 1–23.

41. Zhdanko, A., and Maier, M.E. (2014). Mechanistic study of gold(I)-catalyzed hydroamination of alkynes: outer or inner sphere mechanism? Angew. Chem. Int. Ed. *53*, 7760–7764.

42. Boorman, T.C., and Larrosa, I. (2011). Gold-mediated C-H bond functionalisation. Chem. Soc. Rev. *40*, 1910–1925.

43. Hashmi, A.S.K. (2014). Dual gold catalysis. Acc. Chem. Res. *47*, 864–876.

44. Jiménez-Núñez, E., and Echavarren, A.M. (2008). Gold-catalyzed cycloisomerizations of enynes: a mechanistic perspective. Chem. Rev. *108*, 3326–3350.

45. LaLonde, R.L., Sherry, B.D., Kang, E.J., and Toste, F.D. (2007). Gold(I)-catalyzed enantioselective intramolecular hydroamination of allenes. J. Am. Chem. Soc. *129*, 2452–2453.

46. Suhre, M.H., Reif, M., and Kirsch, S.F. (2005). Gold(I)-catalyzed synthesis of highly substituted furans. Org. Lett. *7*, 3925–3927.

47. Harris, R.J., and Widenhoefer, R.A. (2016). Gold carbenes, gold-stabilized carbocations, and cationic intermediates relevant to gold-catalysed enyne cycloaddition. Chem. Soc. Rev. *45*, 4533–4551.

48. Huang, L., Rudolph, M., Rominger, F., and Hashmi, A.S.K. (2016). Photosensitizer-free visible-light-mediated gold-catalyzed 1,2-difunctionalization of alkynes. Angew. Chem. Int. Ed. *55*, 4808–4813.

49. Johnston, P., Carthey, N., and Hutchings, G.J. (2015). Discovery, development, and commercialization of gold catalysts for acetylene hydrochlorination. J. Am. Chem. Soc. *137*, 14548–14557.

50. Liu, L., and Zhang, J.L. (2016). Gold-catalyzed transformations of alpha-diazocarbonyl compounds: selectivity and diversity. Chem. Soc. Rev. *45*, 506–516.

51. Zhu, L., Yu, Y.H., Mao, Z.F., and Huang, X.L. (2015). Gold-catalyzed intermolecular nitrene transfer from 2H-azirines to ynamides: a direct approach to polysubstituted pyrroles. Org. Lett. *17*, 30–33.

52. Schelwies, M., Moser, R., Dempwolff, A.L., Rominger, F., and Helmchen, G. (2009). Gold-catalyzed intermolecular addition of carbonyl compounds to 1,6-enynes: reactivity, scope, and mechanistic aspects. Chemistry *15*, 10888–10900.

53. Barluenga, J., Diéguez, A., Fernández, A., Rodríguez, F., and Fañanás, F.J. (2006). Gold- or platinum-catalyzed tandem cycloisomerization/prins-type cyclization reactions. Angew. Chem. Int. Ed. *45*, 2091–2093.

54. Schelwies, M., Dempwolff, A.L., Rominger, F., and Helmchen, G. (2007). Gold-catalyzed intermolecular addition of carbonyl compounds to 1,6-enynes. Angew. Chem. Int. Ed. *46*, 5598–5601.

55. Yu, Y., Yang, W., Rominger, F., and Hashmi, A.S.K. (2013). In situ generation of nucleophilic allenes by the gold-catalyzed rearrangement of propargylic esters for the highly diastereoselective formation of intermolecular C(sp3)-C(sp2) bonds. Angew. Chem. Int. Ed. *52*, 7586–7589.

56. Zhang, M., Wang, Y., Yang, Y., and Hu, X. (2012). An alternative approach to direct aldol reaction based on gold-catalyzed methoxyl transfer. Adv. Synth. Catal. *354*, 981–985.

57. Ito, Y., Sawamura, M., and Hayashi, T. (1987). Asymmetric aldol reaction of an isocyanoacetate with aldehydes bychiral ferrocenylphosphine-gold(I) complexes: design and preparation of new efficient ferrocenylphosphine ligands. Tetrahedron Lett *28*, 6215–6218.

58. Hubbert, C. and Hashmi, A.S.K. Gold-catalyzed aldol and related reactions. In Modern Gold Catalyzed Synthesis, Hashmi, A.S.K. and Toste, F.D. eds. (John Wiley & Sons), pp. 237–261.

59. Peng, H.H., Akhmedov, N.G., Liang, Y.F., Jiao, N., and Shi, X.D. (2015). Synergistic gold and iron dual catalysis: preferred radical addition toward vinyl-gold intermediate over alkene. J. Am. Chem. Soc. *137*, 8912–8915.

60. Bay, S., Baumeister, T., Hashmi, A.S.K., and Röder, T. (2016). Safe and fast flow synthesis of functionalized oxazoles with molecular oxygen in a microstructured reactor. Org. Process Res. Dev. *20*, 1297–1304.

61. Hashmi, A.S.K., Blanco Jaimes, M.C., Schuster, A.M., and Rominger, F. (2012). From propargylic amides to functionalized oxazoles: domino gold catalysis/oxidation by dioxygen. J. Org. Chem. *77*, 6394–6408.

62. Hashmi, A.S.K., Weyrauch, J.P., Frey, W., and Bats, J.W. (2004). Gold catalysis: mild conditions for the synthesis of oxazoles from N-propargylcarboxamides and mechanistic aspects. Org. Lett. *6*, 4391–4394.

63. Chen, L., Chen, K., and Zhu, S. (2018). Transition-metal-catalyzed intramolecular nucleophilic addition of carbonyl groups to alkynes. Chem *4*, 1208–1262.

64. Chen, Y.F., Yan, W.M., Akhmedov, N.G., and Shi, X.D. (2010). 1,2,3-triazole as a special "X-factor" in promoting Hashmi phenol synthesis. Org. Lett. *12*, 344–347.

65. Duan, H.F., Sengupta, S., Petersen, J.L., Akhmedov, N.G., and Shi, X.D. (2009). Triazole-Au(I) complexes: a new class of catalysts with improved thermal stability and reactivity for intermolecular alkyne hydroamination. J. Am. Chem. Soc. *131*, 12100–12102.

66. Wang, D.W., Gautam, L.N.S., Bollinger, C., Harris, A., Li, M.Y., and Shi, X.D. (2011). 1,2,3-triazole bound Au(I) (TA-Au) as chemoselective catalysts in promoting asymmetric synthesis of substituted allenes. Org. Lett. *13*, 2618–2621.

67. Wang, D.W., Ye, X.H., and Shi, X.D. (2010). Efficient synthesis of E-alpha-haloenones through chemoselective alkyne activation over allene with triazole-Au catalysts. Org. Lett. *12*, 2088–2091.

68. Wang, D.W., Zhang, Y.W., Harris, A., Gautam, L.N.S., Chen, Y.F., and Shi, X.D. (2011). Triazole-gold-promoted, effective synthesis of enones from propargylic esters and alcohols: a catalyst offering chemoselectivity, acidity and ligand economy. Adv. Synth. Catal. *353*, 2584–2588.

69. Xi, Y.M., Dong, B.L., McClain, E.J., Wang, Q.Y., Gregg, T.L., Akhmedov, N.G., Petersen, J.L., and Shi, X.D. (2014). Gold-catalyzed intermolecular C-S bond formation: efficient synthesis of α-substituted vinyl sulfones. Angew. Chem. Int. Ed. *53*, 4657–4661.

70. Xi, Y.M., Wang, Q.Y., Su, Y.J., Li, M.Y., and Shi, X.D. (2014). Quantitative kinetic investigation of triazole-gold(I) complex catalyzed [3,3]-rearrangement of propargyl ester. Chem. Commun. *50*, 2158–2160.

71. Tang, Y., and Yu, B. (2012). Identification of (phosphine)gold(I) hydrates and their equilibria in wet solutions. RSC Adv *2*, 12686–12689.

72. Bernardi, A., Colombo, G., and Scolastico, C. (1996). Enantioselective Mukaiyama-Michael reactions of 2-carbomethoxy cyclopentenone catalyzed by chiral bis(oxazoline)-Cu(II) complexes. Tetrahedron Lett *37*, 8921–8924.

73. Brown, S.P., Goodwin, N.C., and MacMillan, D.W.C. (2003). The first enantioselective organocatalytic Mukaiyama- Michael reaction: a direct method for the synthesis of enantioenriched gamma-butenolide architecture. J. Am. Chem. Soc. *125*, 1192–1194.

74. Desimoni, G., Faita, G., Filippone, S., Mella, M., Zampori, M.G., and Zema, M. (2001). A new and highly efficient catalyst for the enantioselective Mukaiyama-Michael reaction between (E)-3-crotonoyl-1,3-oxazolidin-2-one and 2-trimethylsilyloxyfuran. Tetrahedron *57*, 10203–10212.

75. Evans, D.A., Scheidt, K.A., Johnston, J.N., and Willis, M.C. (2001). Enantioselective and diastereoselective mukaiyama-Michael reactions catalyzed by bis(oxazoline) copper(II) complexes. J. Am. Chem. Soc. *123*, 4480–4491.

76. Wang, W., Li, H., and Wang, J. (2005). Enantioselective organocatalytic Mukaiyama-Michael addition of silyl enol ethers to α,β-unsaturated aldehydes. Org. Lett. *7*, 1637–1639.

77. Fornies, J., Navarro, R., Tomas, M., and Urriolabeitia, E.P. (1993). Different behavior of (NBu4)[M(C6F5)2(acac)] (M = Pd, Pt) toward AgClO4. X-ray crystal structures of (NBu4)[M2Ag(C6F5)4(acac)2] (M = Pd, Pt). Organometallics *12*, 940–943.

78. Swift, C.A., and Gronert, S. (2014). Formation and reactivity of gold carbene complexes in the gas phase. Organometallics *33*, 7135–7140.

79. Gibson, D. (1969). Carbon-bonded beta-diketone complexes. Coord. Chem. Rev. *4*, 225–240.

80. Forniés, J., Martínez, F., Navarro, R., and Urriolabeitia, E.P. (1996). Reactivity of (NBu 4) [Pt(C 6 F 5) 2 (acac)] toward electrophilic metal centers: metal−metal vs metal−C γ (acac) bond formation. crystal structure of [PtAg(C 6 F 5) 2 (acac)(CH 2 Cl 2)] 2, a complex containing a μ 2 -acac- O, O ′bridging ligand and a coordinated dichloromethane. Organometallics *15*, 1813–1819.

81. Hashmi, A.S.K., Schäfer, S., Wölfle, M., Diez Gil, C., Fischer, P., Laguna, A., Blanco, M.C., and Gimeno, M.C. (2007). Gold-catalyzed benzylic C-H activation at room temperature. Angew. Chem. Int. Ed. *46*, 6184–6187.

82. Hashmi, A.S.K., and Molinari, L. (2011). Effective transmetalation from gold to iron or ruthenium. Organometallics *30*, 3457–3460.

83. Qi, Z., and Schalley, C.A. (2014). Exploring macrocycles in functional supramolecular gels: from stimuli responsiveness to systems chemistry. Acc. Chem. Res. *47*, 2222–2233.

84. Marsault, E., and Peterson, M.L. (2011). Macrocycles are great cycles: applications, opportunities, and challenges of synthetic macrocycles in drug discovery. J. Med. Chem. *54*, 1961–2004.

85. Iyoda, M., Yamakawa, J., and Rahman, M.J. (2011). Conjugated macrocycles: concepts and applications. Angew. Chem. Int. Ed. *50*, 10522–10553.

86. Driggers, E.M., Hale, S.P., Lee, J., and Terrett, N.K. (2008). The exploration of macrocycles for drug discovery—an underexploited structural class. Nat. Rev. Drug Discov. *7*, 608–624.

87. Ye, X., Peng, H., Wei, C., Yuan, T., Wojtas, L., and Shi, X. (2018). Gold-catalyzed oxidative coupling of alkynes toward the synthesis of cyclic conjugated diynes. Chem *4*, 1983–1993.

88. Blankenstein, J., and Zhu, J.P. (2005). Conformation-directed macrocyclization reactions. Eur. J. Org. Chem. *2005*, 1949–1964.

89. Hansen, J.G., Feeder, N., Hamilton, D.G., Gunter, M.J., Becher, J., and Sanders, J.K.M. (2000). Macrocyclization and molecular interlocking via Mitsunobu alkylation: highlighting the role of C-H···O interactions in templating. Org. Lett. *2*, 449–452.

90. Martí-Centelles, V., Pandey, M.D., Burguete, M.I., and Luis, S.V. (2015). Macrocyclization reactions: the importance of conformational, configurational, and template-induced preorganization. Chem. Rev. *115*, 8736–8834.

91. Mohr, P.J., and Halcomb, R.L. (2003). Total synthesis of (+)-phomactin A using a B-alkyl Suzuki macrocyclization. J. Am. Chem. Soc. *125*, 1712–1713.

92. Romo, D., Rzasa, R.M., Shea, H.A., Park, K., Langenhan, J.M., Sun, L., Akhiezer, A., and Liu, J.O. (1998). Total synthesis and immunosuppressive activity of (-)-pateamine A and related compounds: implementation of a β-lactam-based macrocyclization. J. Am. Chem. Soc. *120*, 12237–12254.

93. Turner, R.A., Oliver, A.G., and Lokey, R.S. (2007). Click chemistry as a macrocyclization tool in the solid-phase synthesis of small cyclic peptides. Org. Lett. *9*, 5011–5014.