Gold-Catalyzed *N*-Alkenylation of Isoxazolines and the Use of Alkenyl Gold Intermediates in the Synthesis of 2-Amino-1-Pyrrolines

Abdullah S. Alshreimi[a], Guanqun Zhang[a†], Esther J. Shim[a], Donald J. Wink[a], and Laura L. Anderson[a]*

[a]Department of Chemistry, University of Illinois Chicago, 845 W. Taylor St., Chicago, IL 60607

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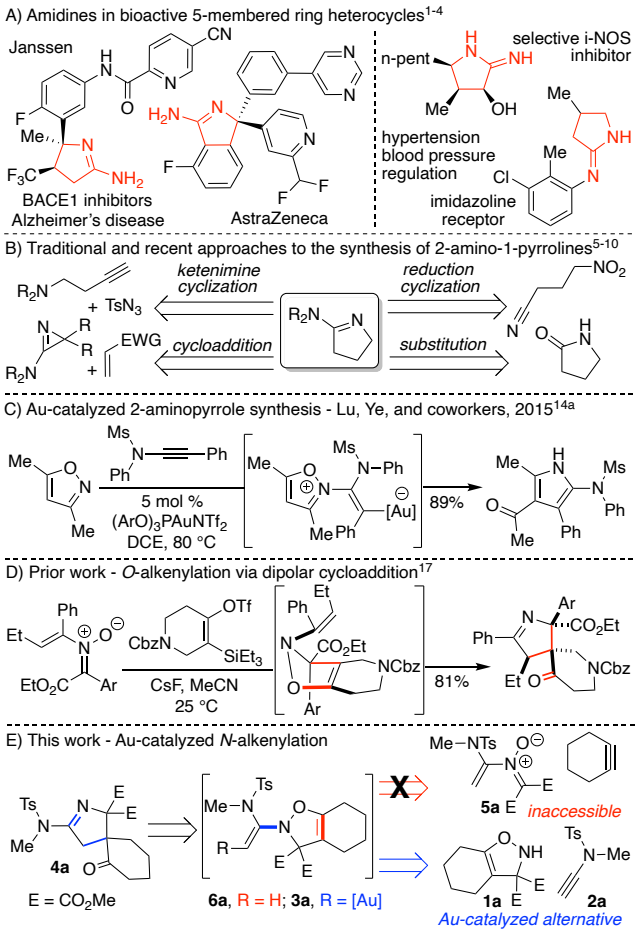
ABSTRACT: A gold-catalyzed method for *N*-alkenylation has been developed for N*H*-isoxazolines, which are challenging substrates for alternative transition metal-catalyzed *N*-functionalization reactions. Generation of a vinyl gold intermediate from the addition of N*H*-isoxazolines to gold-activated ynamides initiates a diastereoselective [3,3']-sigmatropic rearrangement to give 2-amino-1-pyrrolines. Optimization of this transformation is described in addition to reaction scope, the use of chiral auxiliaries for the preparation of chiral non-racemic 2-amino-1-pyrrolines, and mechanistic insight. This method prepares heterocycles that are difficult to access through traditional approaches with an enabling gold-catalyzed disconnection.

Heterocycles with imbedded amidine functional groups are common motifs in biologically active molecules.[1] As shown in Scheme 1A, 2-amino-1-pyrrolines and 2-imino-pyrrolidines have been shown to be active BACE1 inhibitors in Alzheimer disease studies, selective nitric oxide synthase (NOS) inhibitors in therapeutic NOS regulation, and selective imidazoline receptor ligands for the management of blood pressure, hypertension and metabolic disorders.[2-4] Traditional methods for the synthesis of these small molecules primarily rely on reduction and cyclization of nitrile- and nitro-functionalized precursors and/or substitution of γ-lactams (Scheme 1B).[3,5,6] While proven to be effective, these approaches require pre-installation of stereocenters and have limited tolerance of functional groups susceptible to reduction or acyl substitution. As alternative routes to 2-amino-1-pyrrolines, conjugate additions of 2-aminoazirines, cyclizations of ketenimine intermediates, and three-component coupling reactions have been reported; however, while providing complementary disconnections from traditional methods and greater structural complexity, these transformations can be inhibited by competing reaction pathways for substrates with reactive functional groups.[5c,7-10] Given the importance of 2-amino-1-pyrrolines and the current synthetic limitations surrounding these compounds, we wondered if construction of these scaffolds from *N*-alkenylisoxazolines through a [3,3']-sigmatropic rearrangement could provide a milder functional group compatible alternative with stereochemical control. Achieving this transformation, necessitated the development of an isoxazoline *N*-alkenylation reaction.

While palladium- and copper-catalyzed *N*-arylation reactions of pyrrazoles and isoxazolidines have been reported, to the best of our knowledge *N*-alkenylations of N*H*-isoxazolines are unknown.[11-13] Addition of an isoxazole to an ynamide to give a vinyl gold intermediate followed by fragmentation and recombination was proposed by Lu, Ye, and coworkers as a pathway for pyrrole synthesis (Scheme 1C).[14a,b] Similar transformations have been reported to access other α-imino gold carbene intermediates.[14] We were curious if addition of N*H*-isoxazolines **1** to gold-activated ynamides **2** could access related *N*-alkenyl-

Scheme 1. Synthesis of 2-Amino-1-Pyrrolines and Complementary Routes to *N*-Alkenylisoxazolines

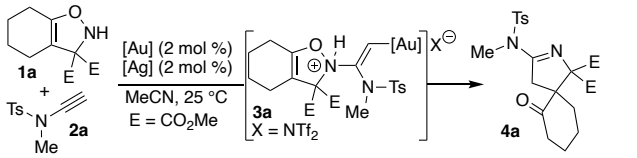


isoxazoline intermediates **3** and trigger a diastereoselective [3,3']-sigmatropic rearrangement to give 2-amino-1-pyrrolines **4** (Scheme 1E).[15,16] In previous work, we reported that *O*-functionalization of *N*-alkenylnitrones via dipolar cycloaddition can generate analogous intermediates that undergo rearrangement to give 1-pyrrolines (Scheme 1D).[17] Unfortunately, enamine-substituted nitrones such **5a** are unavailable and this route cannot be used for the synthesis of 2-amino-1-pyrrolines **4** (Scheme 1E, red). Considering an alternative disconnection, we envisioned accessing **3a** by gold-catalyzed *N*-alkenylation of **1a** (Scheme 1E, blue). Herein we describe the development of a gold-catalyzed method for the synthesis of 2-amino-1-pyrrolines **4** from ynamides **2** and N*H*-isoxazolines **1** via formation of vinyl gold complex **3** followed by rearrangement.[18] This new reaction overcomes limitations associated with established synthetic routes for the synthesis of 2-amino-1-pyrrolines and showcases the unique ability of gold-catalysis to access the intermediate needed to initiate C–C bond formation.

When initial investigations of copper- and palladium-catalyzed methods for the *N*-alkenylation of N*H*-isoxazolines such as **1a** were unproductive (see Supporting Information), we turned our attention to the development of a gold-catalyzed reaction.[11-13] As shown in Table 1, entry 1, when a mixture N*H*-isoxazoline **1a** and ynamide **2a** were treated with (Johnphos)AuCl and $AgNTf_2$, pyrroline **4a** was observed in high yield. Removal of both the Au(I) catalyst and the Ag additive showed that there is no metal-free background reaction (Table 1, entry 2). Treatment of a mixture of **1a** and **2a** with either (JohnPhos)AuCl or $AgNTf_2$ indicated that both components of the catalyst mixture are required to achieve high yield (Table 1, entry 3 – 4). Consistent results between Table 1, entry 1 and entry 5, where (JohnPhos)AuCl was pretreated with $AgNTf_2$ and filtered through celite, supports the role of $AgNTf_2$ for counterion exchange but indicates no additional silver effect.[19] While a mixture of (JohnPhos)AuCl and $AgNTf_2$ in MeCN was ultimately determined to be optimal for the conversion of **1a** to **4a**, the reaction was also shown to tolerate several other common Au(I) catalysts and Ag(I) additives in good yield (Table 1, entries 6 – 8 and 11 – 12). Au(III) and Pt(II) catalysts were also effective, albeit in slightly lower yields (Table 1, entries 9 – 10). Solvents such as toluene and DCE performed similarly to MeCN (Table 1, entries 13 – 14). With the optimal conditions shown in Table 1, entry 1 in hand, the scope of the synthesis of pyrrolines **4** from isoxazolines **1** was explored.

Investigation of the scope of the gold-catalyzed addition of isoxazolines to ynamides followed by rearrangement to 2-amino-1-pyrrolines initially focused on the structure of the N*H*-isoxazoline reagent **1** (Scheme 2). Isoxazolines with styrenyl and related conjugated aromatic groups smoothly converted to pyrrolines **4b** – **4d**. Linear alkyl- and cyclic alkyl-substituted isoxazolines were also tolerated giving pyrroline **4e** and spirocycles **4a** and **4f** – **4h**. Racemic isoxazolines with chiral quaternary carbon centers were shown to control the diastereoselectivity of the rearrangement to give pyrrolines **4i** and **4j** as single diastereomers. When isoxazolines generated from enynes via a procedure developed by Zhang and coworkers were tested under the reaction conditions, *gem*-dione products **4k** – **4o** were isolated in good yield and high diastereoselectivity.[20] The relative configuration of **4** was determined by NMR spectroscopy and confirmed by X-ray crystal structure analysis of **4o** and **4t** (see reference 17b for X-ray crystal structure analysis of related compounds generated from similar intermediates). The observed *cis*- and *trans*-relationships of the substituents can be explained by a boat transition state conformation (see **TS1** Scheme 2) for the [3,3']-sigmatropic rearrangement in analogy to our previous work with related thermal rearrangements.[17] Having established the generality of the gold-catalyzed reaction for the synthesis of novel 1-pyrrolines **4** from isoxazolines **1**, we next turned our attention to the ynamide reaction partner.

Table 1. Optimization of Au-Catalyzed *N*-Alkenylation and Rearrangement

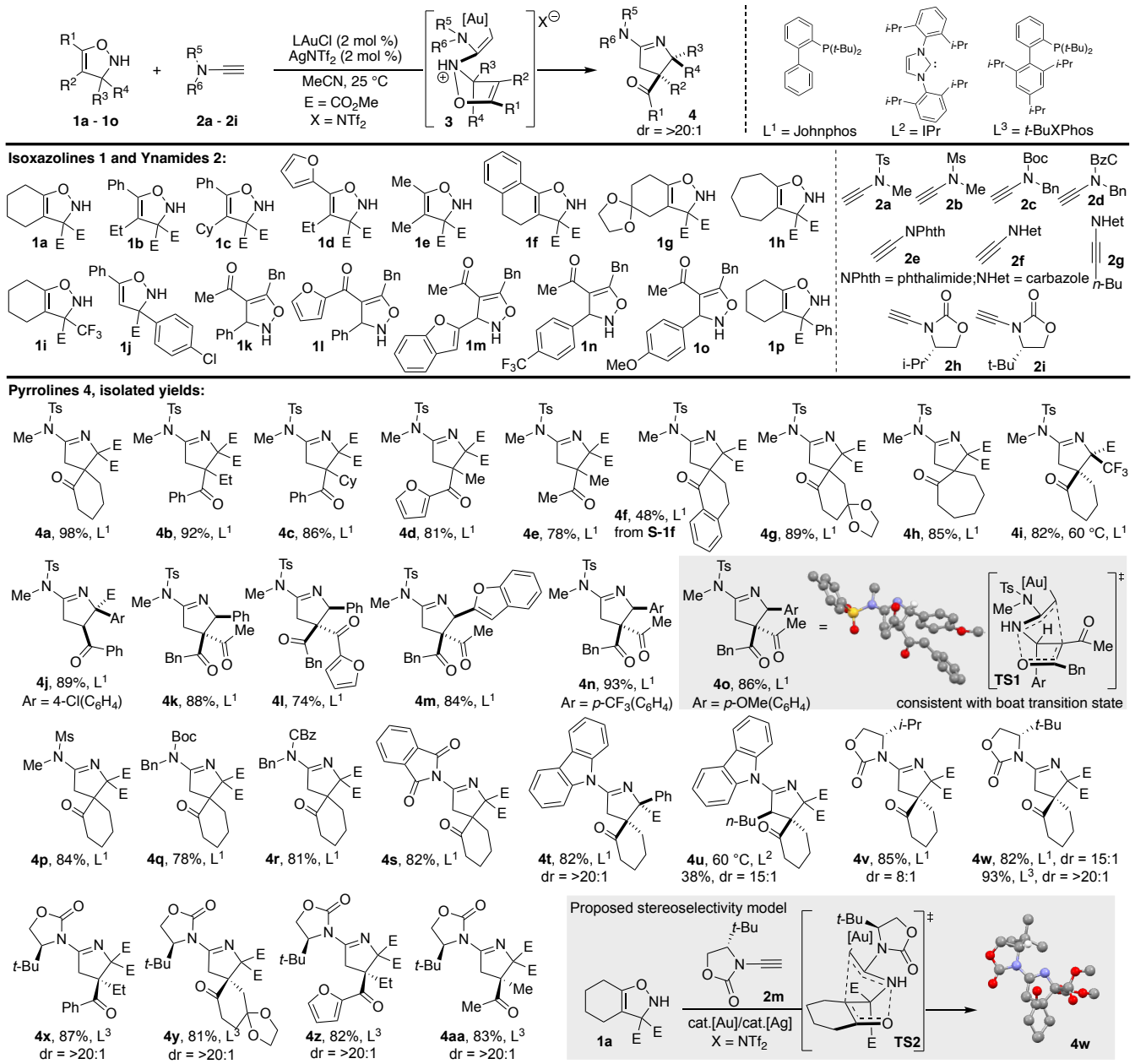


Entry[a]	[Au] (2 mol %)	[Ag] (2 mol %)	% Yield[b]
1	(JohnPhos)AuCl	$AgNTf_2$	>95
2	--	--	0
3	(JohnPhos)AuCl	--	58
4	--	$AgNTf_2$	29
5[c]	(JohnPhos)AuCl	$AgNTf_2$	93
6	(IPr)AuCl	$AgNTf_2$	89
7[d]	$(ArO)_3PAuCl$	$AgNTf_2$	81
8	(*t*-BuXPhos)AuCl	$AgNTf_2$	94
9	$PicAuCl_2$	--	80
10[d,e]	$PtCl_2/P(OAr)_3$	--	81
11	(JohnPhos)AuCl	AgOTf	87
12	(JohnPhos)AuCl	$AgBF_4$	91
13[e]	(JohnPhos)AuCl	$AgNTf_2$	88
14[f]	(JohnPhos)AuCl	$AgNTf_2$	83

[a]Conditions: **1a** (1 equiv), **2a** (1.1 equiv), 0.025 M, 25 °C, 18 h. [b]Determined by ^1H NMR spectroscopy using CH_2Br_2 as an internal standard. [c][Au] and [Ag] mixed for 30 min in MeCN and filtered through celite prior to mixing with **1a** and **2a**. [d]Ar = 2,4-(*t*-Bu)$_2$C$_6$H$_3$. [e]DCE used as solvent. [f]Toluene used as solvent.

As shown in Scheme 2, ynamides and ynamines with mesyl, carbamate, tosyl, and heterocyclic functionalities smoothly underwent the gold-catalyzed addition and rearrangement reaction with isoxazoline **1a** to give pyrrolines **4p** – **4t**. Isoxazolines with racemic quaternary chiral carbon centers continued to give the corresponding pyrrolines in high diastereoselectivity as observed for **4t**. An X-ray crystal structure of **4t** confirmed the relative configuration to be consistent with **4o**. In contrast, isoxazolines **1k** – **1o** required ynamides with sulfonamide substituents to undergo conversion to pyrrolines **4** and were unreactive with ynamides and ynamines (**2c** – **2i**). Due to the steric interactions involved with nucleophilic attack, internal ynamides were more challenging substrates for the gold-catalyzed addition and rearrangement reaction. Surprisingly, while carbamate- and sulfonamide-substituted internal ynamides were unreactive with isoxazoline **1a**, a mixture of **1a** and **2g** gave **4u** in moderate yield and good diastereoselectivity at elevated temperature with IPrAuCl as the catalyst. Use of a stronger electron-donating *N*-functional group may be required to electronically-favor ynamide coordination to the gold catalyst for sterically-demanding substrates.

Scheme 2. Scope of N*H*-Isoxazoline *N*-Alkenylation and Rearrangement.

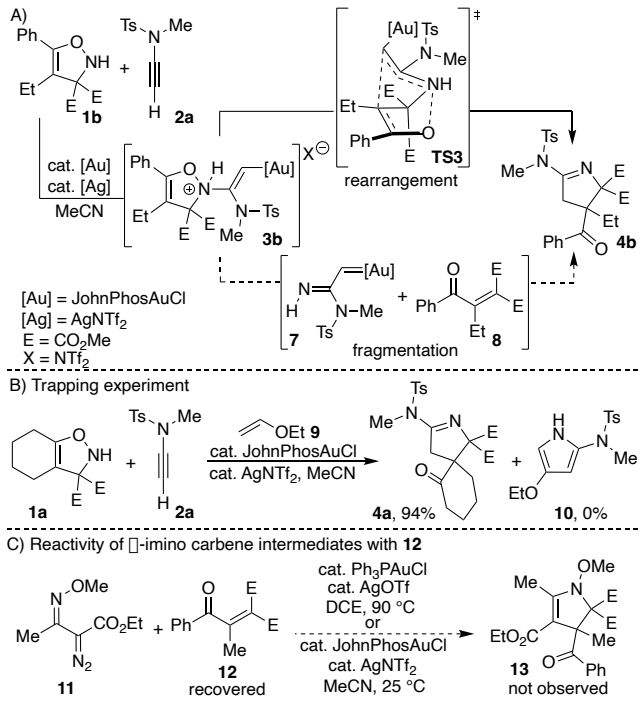


Investigation of ynamides with chiral auxiliaries under the gold-catalyzed conditions for pyrroline synthesis described above showed that remote stereocenters can be used to control the approach of an N*H*-isoxazoline towards an activated ynamide and the diastereoselectivity of the subsequent sigmatropic rearrangement (Scheme 2, **4v** – **4aa**). Ynamide **2h** initially gave pyrroline **4v** as an 8:1 diastereomeric mixture. Changing the size of the oxazolidinone substituent effected the selectivity of the process with *t*-butyl-oxazolidinone ynamide **2i** resulting in a higher distereomeric ratio for pyrroline **4w**. A complementary change in catalyst structure to *t*-BuXPhosAuCl further optimized the transfer of the stereochemical information giving **4w** with dr = >20:1. Having established that oxazolidinone ynamide substituents could control the synthesis of pyrrolines **4** from **1**, this diastereoselective synthesis was investigated with other substrates. Compounds **4x** – **4aa**, with both acyclic and spirocyclic quaternary carbon stereocenters, were isolated in good yield and high diastereoselectivity as enantioenriched products. An X-ray crystal structure of **4w** prepared from the *S*-oxazolidinone-substituted ynamide **2i** suggests that **TS2** is the preferred transition state minimizing steric interactions between the chiral auxiliary and the gold-catalyst.

The gold-catalyzed *N*-alkenylation of **1** and rearrangement to pyrroline **4** was initially proposed to proceed through either: 1) [3,3']-sigmatropic rearrangement of gold-coordinated addition product **3** via transition state **TS3**,[16] or 2) fragmentation of gold-coordinated addition product **3** to gold carbene **7** and α,β-unsaturated ketone **8**, followed by recombination via cycloaddition (Scheme 3A).[14] To determine whether fragmentation to a carbene intermediate was occurring, vinyl ether **9** was added to the reaction mixture of **1a** and **2a** (Scheme 3B).[21] This reagent has previously been reported to trap α-imino gold carbene intermediates to give pyrroles such as **10** but no evidence of trapping was observed and pyrroline **4a** was the only product. To

further probe the possibility of an α-imino gold carbene intermediate, diazoester **11** was prepared and treated with α,β-unsaturated ketone **12** under gold-catalyzed conditions previously reported to convert **11** to an α-imino gold carbene, and with our optimized reaction conditions, but no evidence of **13** was observed and **12** was recovered (Scheme 3C).[21] These experiments are inconsistent with the proposed fragmentation pathway for gold-catalyzed conversion of **1** and **2** to pyrrolines **4**; however, they do not rule out cyclization by C–H insertion of a potential α-imino carbene intermediate.[22] The relative configuration of **4i** – **4o** and **4t** are consistent with the proposed boat-like rearrangement of intermediate **3**. This suggests that a pathway through **TS3**, or an analogous transition state after protodeauration, is likely for the synthesis of **4** and consistent with our previous reports on the reactivity of related intermediates generated by alternative routes.

Scheme 3. Proposed pathways and trapping experiments.



A new method for the synthesis of 2-amino-1-pyrrolines has been developed that provides access to novel examples of this heterocycle, which is a common scaffold in a variety of biologically active molecules. Gold-catalysis conditions were developed to access *N*-alkenylisoxazoline intermediates **3** that rearrange to form the desired pyrrolines **4**. Studies towards accessing these rearrangement precursors identified the gold-catalyzed addition of isoxazolines to ynamides to be uniquely productive, while alternative transition metal-catalyzed *N*-alkenylation strategies were unsuccessful with N*H*-isoxazolines **1**. Trapping studies support the proposed gold-catalyzed addition and rearrangement pathway, indicating that α-imino gold carbene intermediates are unlikely to play a role in the reaction mechanism. This study expands chemical space around known privileged structures, showcases the utility of *N*-alkenylisoxazolines as versatile intermediates for the synthesis of stereodefined 1-pyrrolines, and identifies gold-catalysis as distinctively effective for the *N*-alkenylation of N*H*-isoxazolines.

ASSOCIATED CONTENT

AUTHOR INFORMATION

Corresponding Author

* Laura L. Anderson, Department of Chemistry, University of Illinois Chicago, 845 W. Taylor St. Chicago, IL 60607, USA, lauralin@uic.edu.

Present Addresses

†BroadPharm, 6625 Top Gun St. Suite 103, San Diego, CA 92121.

Author Contributions

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Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details, spectral data, expanded Table 1, synthesis of **1**, deprotection of **4r**, and hydrolysis of **4w** (PDF). X-ray crystal structure data (cif).

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ABBREVIATIONS

BrettPhos Pd G3, [(2-di-cyclohexylphosphino-3,6-dimethoxy-2′,4′,6′-triisopropyl-1,1′-biphenyl)-2-(2′-amino-1,1′-biphenyl)] palladium(II) methanesulfonate methanesulfonate; dba, dibenzylideneacetone; XPhos, 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl; Johnphos, (2-biphenyl)di-*t*-butylphosphine; IPr, 1,3-bis(2,6-diisopropylphenyl)imidazole-2-ylidene; *t*-BuXPhos = 2-di-*t*-butylphosphine-2’,4’,6’-triisopropylbiphenyl; Pic, 2-picolylamine.

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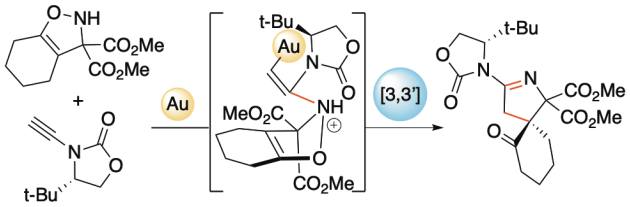
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