

A Facile and Mild Synthesis of Enamides using a Gold-Catalyzed Nucleophilic Addition to Allenamides

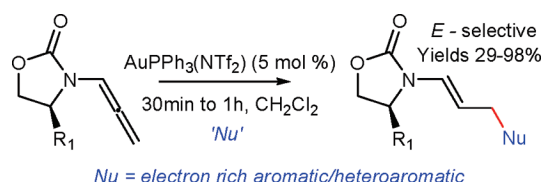
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ABSTRACT



A mild and facile synthesis of enamides has been developed, based on nucleophilic addition of electron-rich aromatic and heteroaromatics to an allenamide unit catalyzed by a gold salt. Yields for the transformation were 29–98%.

Enamides have become an increasingly valuable and hence topical functional group within the synthetic community.¹ They are contained in a number of natural product frameworks such as the chondriamides and salicylihalamides and within cyclic peptides. They have also been used as asymmetric synthetic precursors within the context of heterocyclic and amine synthesis.² The unique reactivity that enamides display has led to the development of a number of general and *E/Z* selective syntheses. To date the synthesis of enamides has often been centered around condensation of an amide equivalent with the corresponding carbonyl functionality.³ However more elaborate and novel methods such as organocuprate addition to isocyanates,⁴ acylation of *in situ* prepared imines⁵ and an *N*-acylation/Peterson elimination process⁶ have also been developed. Complementing

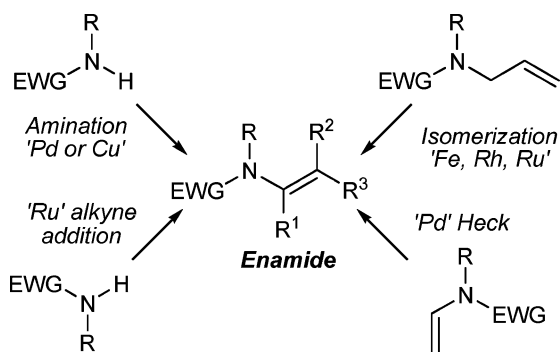
these methods, a number of transition-metal-catalyzed approaches based on C–N bond-forming reactions (Pd, Cu),⁷ isomerizations of allyl amides (Fe, Rh, Ru),⁸ addition of amides to alkynes (Ru), organometallic additions to ynamides (Rh),⁹ Heck couplings (Pd),¹⁰ co-oligomerization of *N*-vinyl amides (Ru),¹¹ and oxidative conjugate additions (Pd)¹² have also been reported (Scheme 1).

In the synthesis of enamides the relationship between enamides and allenamides, both of which contain the desired sp^2 carbon attached directly to the amide, has yet to be fully exploited. Allenamides represent a fascinating and versatile functional group whose chemical utility has been exploited

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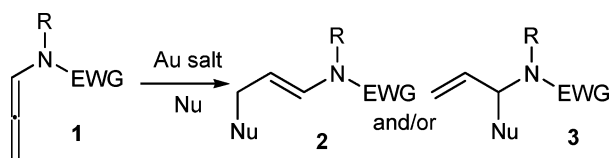
Scheme 1. Transition Metal Strategies in Enamide Synthesis



by a number of groups.¹³ The chemistry in which allenamides have participated include radical cyclizations,¹⁴ tandem epoxidation/cycloadditions,¹⁵ Pauson–Khand cyclizations,¹⁶ [4 + 2]¹⁷ and [4 + 3]¹⁸ cycloadditions, acid-catalyzed cyclizations/rearrangements,¹⁹ palladium-mediated transformations,²⁰ cyclopropanations,²¹ base-catalyzed CO₂ capture,²² and finally, gold-mediated transformations.²³

The use of gold salts for the activation of allenamides is an attractive concept as it would negate the use of acidic conditions for allenamide activation²⁴ and would therefore be more functional group tolerant.²⁵ It is in this class of reactions, catalyzed by gold salts, in which we thought we could make a contribution within the context of direct intermolecular arylations (Scheme 2).

Scheme 2. Intermolecular Gold Addition to Allenamides

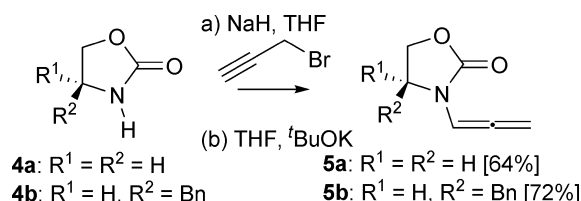


To date there have only been two reports of gold-catalyzed cyclization of allenamides, and in both cases the attacking nucleophile has been intramolecular and a heteroatom, forming either 2,5-disubstituted dihydrofurans^{23a} or

vinylimidazolidinones^{23b} via a 5-*exo-tet* mechanism in each case. However, for the intermolecular gold-catalyzed addition of nucleophiles to activated allenamides there have been no reports to our knowledge.²⁶

In the intermolecular addition there is an issue of regioselectivity (Scheme 2). Addition of the nucleophile to the terminal carbon of the gold-activated allenamide **1** would potentially deliver enamide **2**; alternatively, addition to the carbon adjacent to the nitrogen would deliver the allylic amine **3**. In this study we wished to explore this regioselectivity issue via the addition of carbon nucleophiles to an activated allenamide. To activate the allenamide we have chosen to utilize gold salts, and the attacking nucleophiles that we selected for the study would be electron-rich aromatics and heteroaromatics, which we expect to add to the activated allenamides via a Friedel–Crafts-type mechanism.

Scheme 3. Synthesis of Allenamides **5a,b**



Our test substrate for this study would be the allenamide **5a**, which was conveniently synthesized in 2 steps using the method of Wei *et al.* (Scheme 3).²⁷ With **5a** in hand, a trial reaction with 1-methylindole, **6a**, in the presence of 5 mol % of *in situ* prepared AuPPh₃OTf in CH₂Cl₂ was performed (Scheme 4).

To our delight the starting material was consumed within 30 min, and a new product was detected by TLC. This was subsequently isolated and shown to be the indole enamide **7a** by a combination of ¹H and ¹³C NMR and IR spectroscopy (Scheme 4). The spectroscopic data for **7a** show, *inter*

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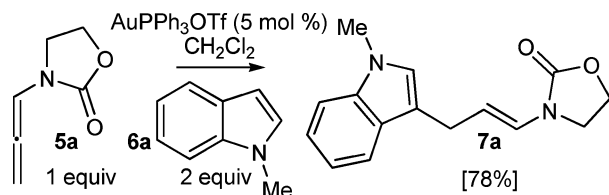
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alia, a doublet at 6.80 ($J = 14.4$ Hz), double triplets at 5.01 ($J = 14.4$ and 6.8), and a doublet at 3.51 ($J = 6.8$ Hz), as well as an absorbance at 1671 cm^{-1} in the IR spectrum, all indicative of an *E*-enamide. This result confirmed that addition of the indole nucleophile occurs at the terminus of the activated allenamide as opposed to the carbon adjacent to the nitrogen.

Scheme 4



While the yield for this transformation was adequate, we next set out to optimize our reaction conditions, the results of which are summarized in Table 1.

Table 1. Intermolecular Arylation of Allenamide **5a** with *N*-Methylindole **6a**^a

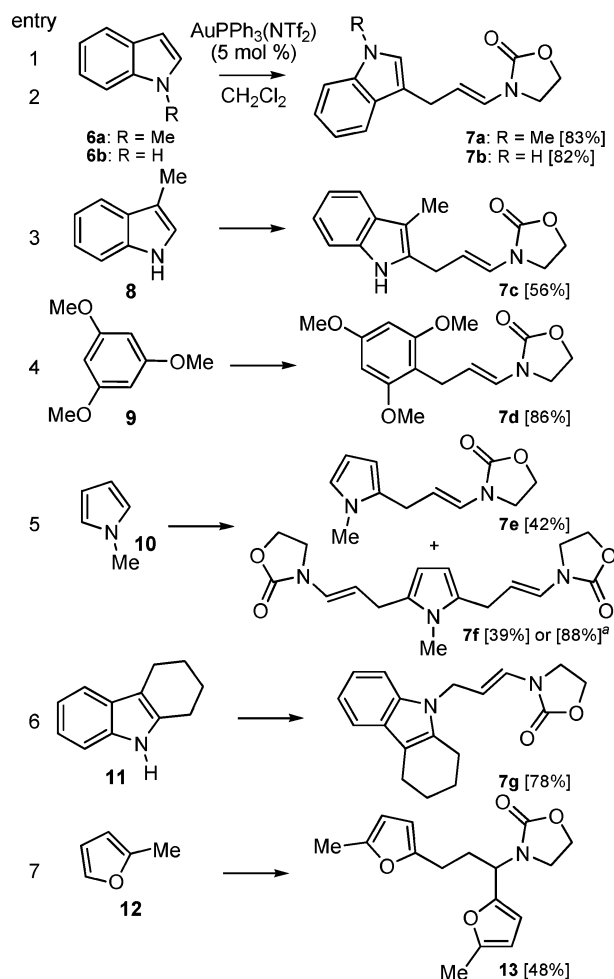
entry	catalyst	equivalents of 6a	time ^b (h)	conversion ^c [% yield]
1	PPh ₃ AuOTf	2.00	0.5	100 [82]
2	PPh ₃ AuOTf	1.50	0.5	100
3	PPh ₃ AuOTf	1.05	0.5	100
4 ^d	AgOTf	1.05	16	0
5 ^e	TFA	1.05	2.0	42
6	PPh ₃ Au(NTf ₂)	1.05	0.5	100 [83]
7 ^f	PPh ₃ Au(NTf ₂)	1.05	1.0	95

^a Reactions run with 5.0 mol % of catalyst in CH₂Cl₂ at room temperature unless otherwise stated. ^b Determined by disappearance of **5a** by TLC analysis unless otherwise stated. ^c Conversion was determined by ¹H NMR; isolated yield in brackets. ^d No consumption of starting material was seen after 16 h. ^e 1 equiv of acid relative to **5a**. ^f 1.0 mol % of catalyst.

Variation of the number of equivalents of **6a** from 2.0 to 1.05 had no effect on conversion to the desired product, indicating that the reaction could be essentially carried out with equimolar amounts of the two reactants (entries 1, 2, and 3, respectively). Conducting the reaction in the presence of only AgOTf had no effect on the reaction with starting material being recovered (entry 4). TFA did promote the reaction, as expected;²⁸ however, the conversion was low compared to the gold-catalyzed examples possibly due to product degradation, and significantly the rate of reaction was lower. Altering the gold source counterion from OTf to (NTf₂) had no effect on the reaction (entry 6); also, lowering the amount of gold catalyst from 5 to 1 mol % had little effect on conversion but did result in increased reaction times (entry 7).

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Scheme 5. Enamides Synthesized from **5a**



^a Yield is based on 2 equiv of **10**.

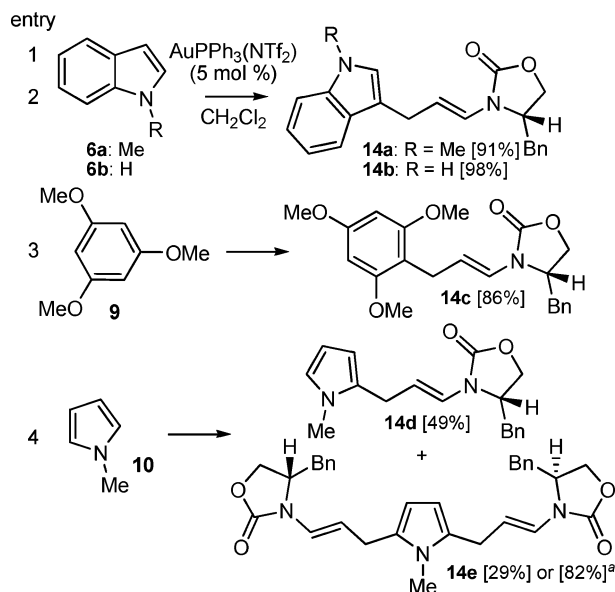
With optimized conditions for the arylation determined, the scope of this transformation was then explored (Scheme 5). *N*-Methylindole **6a** and indole **6b** reacted with allenamide **5a** to give the enamides **7a** and **7b** in good yields (entries 1 and 2). 3-Methylindole **8** gave the 2-substituted enamide **7c** in modest yield with the remaining mass balance being accounted for by the *N*-substituted enamide (entry 3).²⁹ This is where reaction has occurred through the indole NH and suggests that intermolecular enamide synthesis is attainable using heteroatoms. While anisole failed to add to allenamide **5a**, the more electron-rich 1,3,5-trimethoxy benzene **9** added in good yield to give **7d** (entry 4). *N*-Methyl pyrrole **10** gave a mixture of the mono- and disubstituted enamides **7e** and **7f** in modest yields (entry 5). Increasing the amount of **10** relative to allenamide **5a** to 2 equiv gave exclusively the disubstituted enamide **7f** in an excellent yield of 88%. Based on the result from using indole **8**, tetrahydrocarbazole **11** gave exclusively the *N*-substituted enamide **7g** in a yield of 78% (entry 6). Finally, addition of 2-methyl furan **12** gave

(29) See structure **22** in Supporting Information for physical data.

the amide **13** in a modest yield, presumably due to a second addition of **12** to the initially formed enamide (entry 7).³⁰

Chiral allenamide **5b** was coupled to **6a**, **6b**, **9**, and **10** under the same catalytic gold conditions (Scheme 6). The yields mirrored that of the achiral allenamide **5a**, and significantly, all enamides **14a–e** were delivered with no racemization of the stereogenic center (entries 1–4).

Scheme 6. Enamides Derived from Chiral **5b**

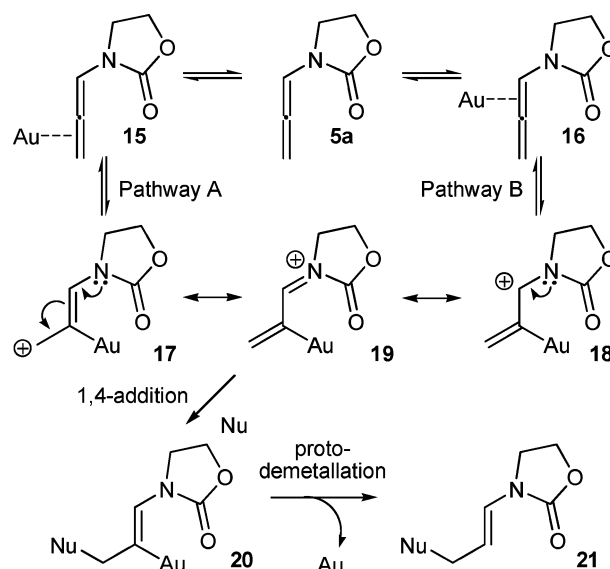


^a Yield is based on 2 equiv of **10**.

A plausible mechanism for this transformation is presented in Scheme 7. Initial Au complexation to **5a** could be *via* pathway A or B; however, pathway A could be energetically unfavorable as a result of the formation of a primary carbocation **17**. However, both pathways A and B deliver the key intermediate conjugated acyliminium **19** that can undergo 1,4-addition by a nucleophile giving **20**. This then subsequently undergoes protodemetalation giving the enamide **21**.

(30) The ¹H NMR spectra does indicate a small amount of the enamide is formed during the reaction; see Supporting Information.

Scheme 7. Plausible Mechanism



In summary, we have demonstrated for the first time that the intermolecular gold-catalyzed addition of electron-rich aromatics and heteroaromatics to activated allenamides is regioselective and high yielding. This method delivers the desired enamides under very mild conditions, with no exclusion of air during the reaction and in very short reaction times as compared to many of the Pd, Ru, Rh, and Cu coupling methods. The use of this transformation in further intermolecular transformations, multicomponent reactions, and natural product synthesis will be reported on in due course.

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Supporting Information Available: Experimental procedures, NMR spectra and characterization for all new materials. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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