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Gold(I)-Catalyzed Intramolecular Tandem Addition/Friedel−Crafts Reactions between Acyclic Enamides and 1-Arylalkynes

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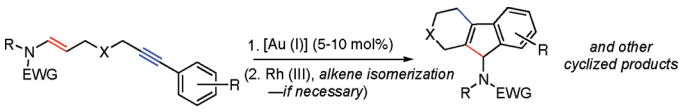

Electron-deficient acyclic enamine derivatives react with electron-rich 1-arylalkynes using cationic gold(I) species as catalysts in an intramolecular process to form annulated 1-amido-substituted indene derivatives as the major products. Yields for this process range between 21% and 98%. In some cases, a two-step process that includes a subsequent alkene isomerization is needed.

Introduction

Additions of carbon nucleophiles to activated C−C π systems are of fundamental importance in synthetic organic chemistry. The use of catalytic amounts of electrophilic metal salts to activate C−C π systems toward nucleophilic attack has been a topic of much scholarly interest.[1] Important examples of this reactivity paradigm forming C−C bonds include the addition of β-dicarbonyl compounds (Conia-ene),[2] enol silyl ethers,[3] allylsilanes or allylstannanes,[4] functionalized indoles,[5] and enamines generated in situ.[6] Our interest in this area stems from the use of electron-deficient enamine derivatives [*N*-arylsulfonyl enamines (enesulfonamides), *N*-carbamoyl enamines (enecarbamates), or *N*-acyl enamines (enamides)] serving as nucleophiles in order to form relatively complex nitrogen-containing ring systems.[7] For example, our group recently disclosed a cyclization in which a cyclic enamine derivative of general structure **1** reacted to produce largely compounds of type **2** within a mixture of isomers (Scheme 1, path a).[7a] An important question that we

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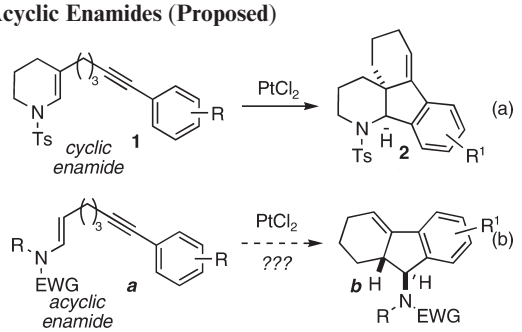
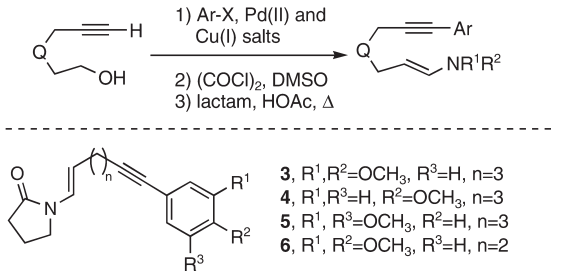
SCHEME 1. Pt(II)-Catalyzed Cyclization of Cyclic Enamides and Acyclic Enamides (Proposed)



SCHEME 2



have not yet addressed centers on the use of *acyclic enamine derivatives as nucleophiles* (Scheme 1, path b). A number of scientific questions would be addressed in such an investigation. The efficiency of the reaction of cyclic substrates was affected to a large extent by the substrate structure (i.e., ring size of enamine derivative, nature of electron-withdrawing group). Would the reactions of acyclic enamine derivatives in this study proceed as predictably (or even occur to any extent) as they had with cyclic enamine derivatives? A preference for an initial 6-*endo* cyclization event was observed previously—does the regioselectivity of the reaction change for acyclic enamine substrates? This report presents our initial work involving these questions.

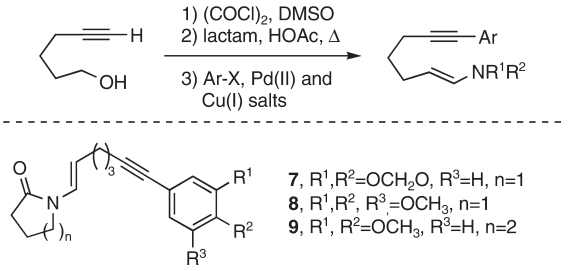
Results and Discussion

Substrate Construction. The substrates used in this study were synthesized in a straightforward manner with use of established synthetic technology. The key structural features within the substrates were (a) a 1-aryl-substituted alkyne and (b) an *acyclic* enamine functionalized by an electron-withdrawing group. In the end, three strategies were employed.

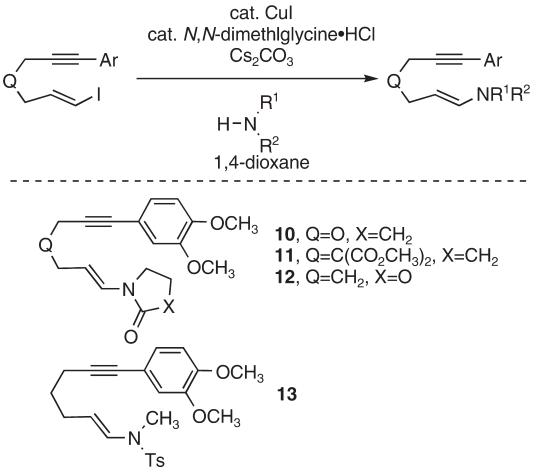
Readily available 1,*n*-alkynyl alcohols could be converted to substrates **3**−**6** by using a simple three-reaction sequence incorporating a Sonogashira coupling of a terminal alkyne function and a Swern oxidation followed by a carbonyl condensation reaction utilizing 2-pyrrolidinone with catalytic acetic acid in refluxing toluene (Scheme 2). Synthetically useful yields (>75%) were typically observed in these processes.[8]

(8) Substrates were constructed by using standard reactions with key steps including Sonogashira coupling, aldehyde-amide condensations, Takai olefination reactions, and copper(I)-catalyzed cross-coupling reactions between a vinyl iodide and amides. (a) Sonogashira coupling: Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett*. **1975**, *16*, 4467–4470. (b) Takai olefination: Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc*. **1986**, *108*, 7408–7410. (c) Copper(I)-catalyzed cross coupling: Pan, X.; Cai, Q.; Ma, D. *Org. Lett*. **2004**, *6*, 1809–1812.

SCHEME 3



SCHEME 4

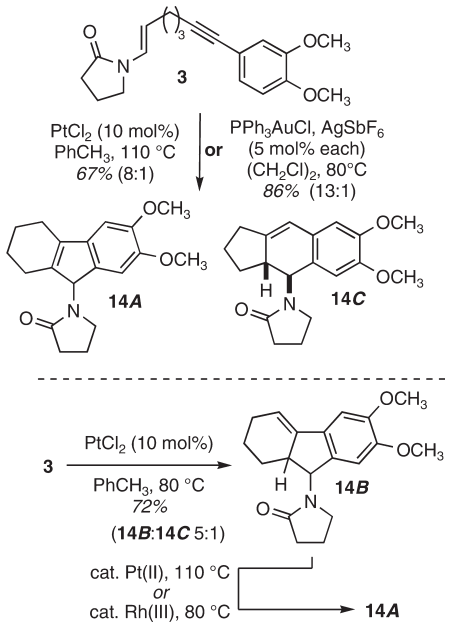


It was subsequently found that the Sonogashira coupling occurred smoothly in the presence of enamides. Consequently the oxidation and condensation processes could be carried out prior to the Sonogashira reaction (Scheme 3). This sequence was used to build enamides **7**−**9**.

A recently described Cu(I)-catalyzed coupling process between alkenyl iodides and amides, carbamates, and sulfonamides was used in a third synthetic approach to substrates **10**−**13** (Scheme 4). The functionalized alkenyl iodide starting materials were readily prepared. The copper(I)-catalyzed process was generally high-yielding. Efforts to produce a *Z*-configured enamide derivative by using a *Z*-alkenyl iodide as starting material with either catalytic or stoichiometric copper sources were uniformly unsuccessful due to extremely poor yields (<15%).

Cyclization Experiments. As a starting point, enamide **3** was treated with 10 mol % of platinum(II) chloride in toluene at 110 °C for 16 h (Scheme 5). Direct column chromatography of the crude reaction mixture on silica gel enabled the purification and isolation of cyclization products **14A** and **14C** in 67% yield in a 8:1 ratio. The major product was characterized by using ^{1}H, ^{13}C, and 2D NMR spectroscopy, specifically COSY and HMBC experiments. The major product **14A** apparently results from metal-catalyzed cyclization followed by alkene migration under the reaction conditions. Support for this conjecture derives from the following experiments. When compound **3** was subjected to the platinum catalyst at lower temperature (80 °C), an in situ alkene migration did not occur such that two diastereomeric compounds (1:1 ratio, represented as **14B**) were produced as well as **14C**. Importantly, exposure of **14B** either to

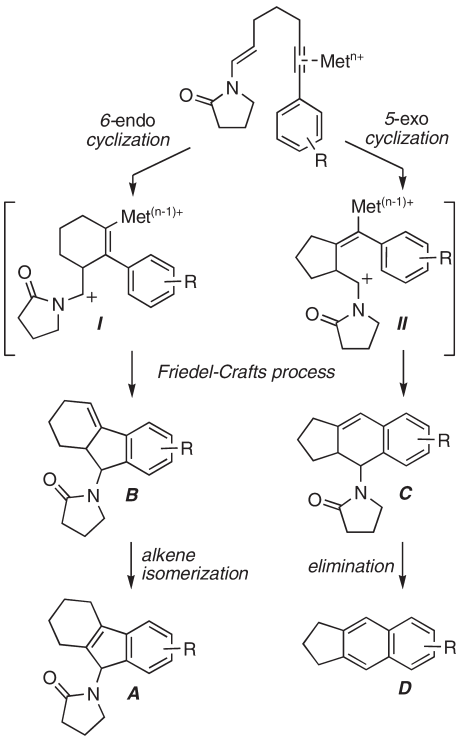
SCHEME 5. Initial Experiments



the original reaction conditions (10 mol % $PtCl_2$, toluene, 110 °C) or to rhodium(III) catalysis (10 mol % $RhCl_3 \cdot 3H_2O$, EtOH, 100 °C) generated **14A**. Further optimization experiments demonstrated that the catalyzed reaction of **3** with 5 mol % each of triphenylphosphine gold(I) chloride and silver hexafluoroantimonate in 1,2-dichloroethane at 80 °C provided **14A** and **14C** in 86% yield in a 13:1 ratio in only 1 h. As the cyclorearrangement of acyclic enamides using gold(I) catalysis proceeded with better selectivity at lower temperatures in less time compared to platinum(II) catalysis, catalyst systems based on gold(I) became the focus of further investigation. The standard catalyst conditions were the combination of triphenylphosphine gold(I) chloride and silver hexafluoroantimonate at 5 mol % load each in 1,2-dichloroethane. Compounds that were not particularly reactive with these catalyst conditions were reacted with $[(2\text{-biphenylbis-}tert\text{-butylphosphine})Au(I)\cdot NCCH_3]^+ SbF_6^-$ (**15**), a catalyst demonstrated to be particularly efficient in the activation of cycloisomerization reactions.[9]

Clearly, the product mixtures resulting from the reactions of acyclic enamide substrates are more complicated than

SCHEME 6. Four Distinct Products Could Be Formed



those from the reactions of cyclic enamides (Scheme 6). Putative coordination of the cationic metal catalyst to the alkyne initiates either a 6-*endo* (major pathway) or 5-*exo* (minor pathway) cyclization event to form intermediary azacarbenium ions **I** or **II**, and each of these undergoes subsequent Friedel–Crafts reaction.[10] After this cyclization, the initially formed product(s) of catalyst-induced 6-*endo* closure (possibly generated as a diastereomeric mixture, represented as **B**) can undergo alkene migration to form a 1-amidoindene derivative **A**. The product(s) **C** that derive from an initial 5-*exo* cyclization (again, the formation of diastereomers are possible) can also eliminate to give a substituted napthalene derivative **D** (vide infra). The diagnostic signals used in the NMR spectroscopic analysis of the product mixtures are presented later.

Each of the substrates **3**–**13** share the structural feature of electron-donating oxygen substituents on the aromatic ring, as these compounds were observed to undergo the tandem addition–Friedel–Crafts process with both reasonable efficiency and good regioselectivity (initial 6-*endo* vs 5-*exo* cyclization). These observations were in line with our previous results in which electron-rich aromatic systems were optimal in the cyclizations of cyclic enamides—reactions were both high-yielding and occurred with a good margin of 6-*endo* cyclization selectivity. Our experiments within the acyclic series using compounds having electron-withdrawing substituents on the aromatic ring (e.g., *p*-CF_3, *p*-NO_2) proceeded sluggishly or not at all. Electron-donating substituents on the aromatic ring would increase the electron density of the alkyne function, providing a rationale explaining the sluggish or nonreactivity of substrates having arene rings substituted by electron-withdrawing groups. A 1-aryl-substituted alkyne where the arene ring is substituted with electron-donating groups may also have electron density specifically localized on the carbon

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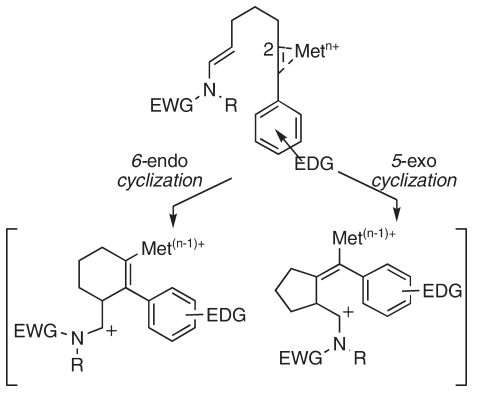
(10) For other examples of "coinage-metal"-catalyzed reactions that are sequenced with a Friedel–Crafts reaction, see: (a) Gourdet, B.; Lam, H. W. *J. Am. Chem. Soc.* **2009**, *131*, 3802–3803. (b) Leseurre, L.; Chao, C.-M.; Seki, T.; Genin, E.; Toullec, P. Y.; Genêt, J.-P.; Michelet, V. *Tetrahedron* **2009**, *65*, 1911–1918. (c) Odabachian, Y.; Gagosz, F. *Adv. Synth. Catal.* **2009**, *351*, 379–386. (d) Toullec, P. Y.; Chao, C.-M.; Chen, Q.; Gladiali, S.; Genêt, J.-P.; Michelet, V. *Adv. Synth. Catal.* **2008**, *350*, 2401–2408. (e) Nieto-Oberhuber, C.; Pérez-Galán, P.; Herrero-Gómez, E.; Lauterbach, T.; Rodríguez, C.; López, S.; Bour, C.; Rosellón, A.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2008**, *130*, 269–279. (f) Toullec, P. Y.; Genin, E.; Leseurre, L.; Genêt, J.-P.; Michelet, V. *Angew. Chem., Int. Ed.* **2006**, *45*, 7427–7430. (g) Nieto-Oberhuber, C.; López, S.; Echavarren, A. M. *J. Am. Chem. Soc.* **2005**, *127*, 6178–6179. (h) For an early example, see: Snider, B. B.; Kwon, T. *J. Org. Chem.* **1992**, *57*, 2399–2410.

SCHEME 7



distal (i.e., carbon 2) of the alkyne (Scheme 7). This electronic polarization may explain the preference for initial 6-*endo* cyclization rather than reaction through a 5-*exo* mode. The subsequent Friedel−Crafts process should also occur more readily with use of arene traps having electron-donating substituents. Despite the potential for the formation of a variety of products as outlined in Scheme 6, the outcomes of treatment of these substrates to gold(I) catalysis typically followed one of two scenarios.

The first cyclization scenario involves the production of compounds exemplified as products **A** and **C** in Scheme 6. The major isomer in the product mixture results from initial 6-*endo* cyclization followed by an alkene isomerization to produce a 1-substituted indene derivative (i.e., compound **A**). Products resulting from this cyclization path are presented in Figure 1. Some points merit comment. A minimum of one electron-donating alkoxy group was needed for adequate reactivity (entry 1). Indene derivative **17A** resulting from 5-*endo* cyclization of **6** could be obtained, although the yield was poor (entry 2). The yield could be improved to a less mediocre 34% by using catalyst **15** (5 mol % loading). Substrate **7** that contains a 1,3-dioxolane function was surprisingly sensitive to the presence of the gold(I) catalyst systems as it readily decomposed, revealing no indication that a useful reaction occurred (entry 3). However, the treatment of **7** with platinum(II) chloride in refluxing toluene did induce cyclization to produce 1-pyrrolidinoyl indene derivative **18A** as the major product in 69% yield. The regioselectivity of the initial alkyne addition reaction was typically high (12:1 to >95:5), although diester **11** was exceptional as it produced a mixture of products in a 2:1 isomeric ratio favoring initial 6-*endo* cyclization (entry 4). The reactions could also be run by using valerolactam or carbamate enamine derivatives, producing functionalized indenes **20A** and **21A** as the exclusive products (entries 5 and 6). A small amount (9%) of naphthalene derivative **21D** was isolated in the reaction forming **21A** (entry 6).

The second cyclization scenario involved the production of compounds exemplified as **B** and **C** in Scheme 6 (Figure 2). The alkene migration process did not take place in situ for five substrates that were examined, although the product derived via an initial 6-*endo* cyclization event was the major product. Interestingly—and fortunately in consideration of the practical difficulties of the analysis of the reaction mixture—the products of type **B** from 6-*endo* addition were observed as single diastereomers. In two instances a lower reaction temperature (25 °C) was used to prevent decomposition—alkene isomerization did

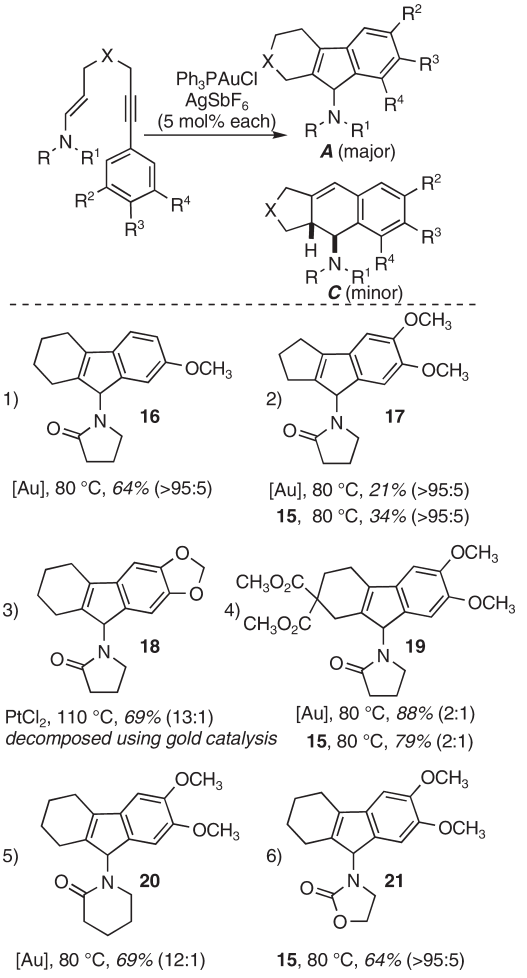
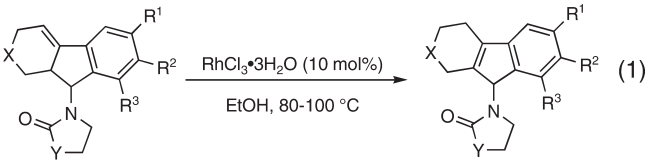


FIGURE 1. Acyclic enamide cyclizations producing indene derivatives as major products.

not take place at this lower temperature (entries 1 and 4). A small amount (4%) of naphthalene derivative **22D** was observed in the cyclization reaction of **5** to **22** (entry 1).

Importantly, a subsequent alkene isomerization of the products of Figure 2 could be smoothly promoted by using rhodium(III) catalysis in ethanol at 80−100 °C. In this manner, a construction of 1-substituted indene derivatives could be performed (eq 1). This isomerization process also assisted with the ultimate characterization of the reaction mixtures; it confirms that the substituted indene products are derived from a product of cyclization/Friedel−Crafts process.



22*B* to **22*A*** (X,Y=CH$_2$, R^1,R^3=OCH$_3$, R^2=H) *53%*

23*B* to **23*A*** (X,Y=CH$_2$, R^1,R^2,R^3=OCH$_3$) *77%*

24*B* to **24*A*** (X=O, Y=CH$_2$, R^1,R^2=OCH$_3$, R^3=H) *83%*

The reaction of 2-alkynyl indole **26** is interesting as the substrate in this case does not feature an oxygen-substituted aromatic ring, but rather a relatively electron-rich indole fragment (eq 2). The reactions of **26** with $PtCl_2$ were

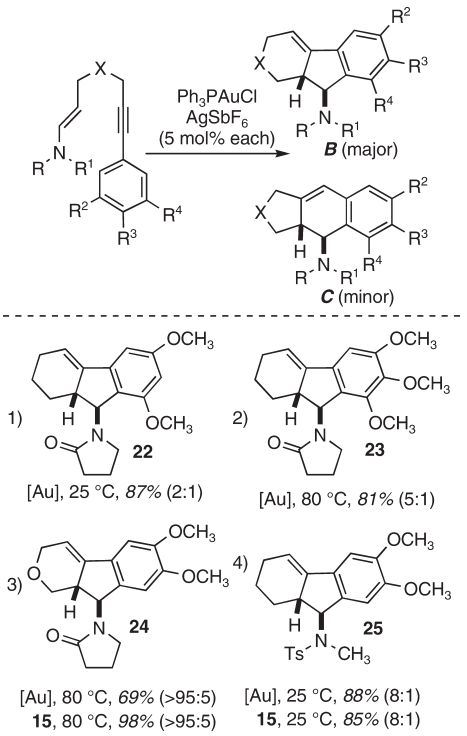
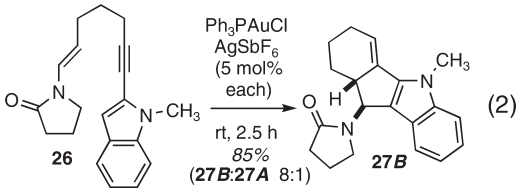


FIGURE 2. Acyclic enamide cyclizations producing tricycles as major products.

unsuccessful, but a cationic gold system initiated a tandem addition−Friedel−Crafts process to generate pentacycle **27B** as the major component in a product mixture obtained in 85% yield. Interestingly, products resulting from an initial 5-*exo* cyclization were not observed in the product mixture. The product mixture in this unusual case was composed of **27B** and **27A**, the 6-*endo* cyclization product that did not undergo alkene migration.[11]



Diagnostic signals for the spectroscopic analysis of two exemplary product mixtures are given in Figure 3. The key signal for products of type **A** (cyclization−isomerization) is a singlet between 5.6 and 5.8 ppm. For the products of 6-*endo* and 5-*exo* cyclization prior to alkene migration, key differences in the spectra are observed. The vinyl protons of **22C** and **23C** are found downfield relative to that of the major isomers, **22B** and **23B**. In addition, the coupling constants of the benzylic protons in each system are also diagnostic. The NMR spectra of products of 5-*exo* cyclization (**C**-series) have a diagnostic doublet with a relatively large (∼14 Hz) coupling constant, while the 6-*endo* regioisomers (**B**-series) are doublets having a smaller (∼7 Hz) *J* value.

In addition, the product characterization process was facilitated by X-ray crystallography. Specifically, compounds **25B**

(11) Attempts to isomerize this mixture to **27A** by using rhodium(III) chloride at 100 °C resulted in decomposition.

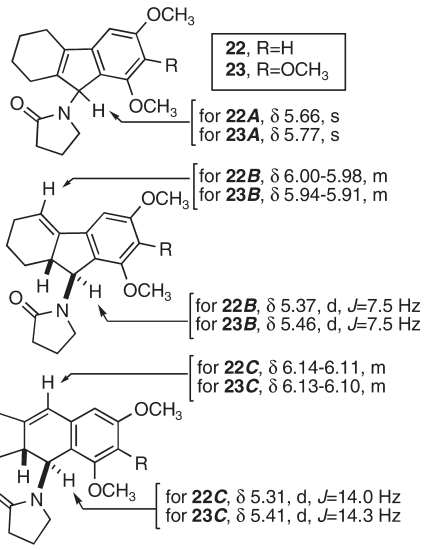


FIGURE 3. Diagnostic Spectral Characteristics of Products.

and **25C** formed a cocrystal suitable for analysis. This technique helped to establish the relative configuration of the stereogenic carbon atoms in the products. Single diastereomeric compounds in the **B** and **C** product series were observed. This observation is consistent with the original *E*-configuration in the enamide starting materials being relayed into the products. Unfortunately, a *Z*-configured enamide could not be synthesized in a practically useful yield, so the stereoselectivity of the gold-catalyzed process was not unequivocally determined.

In summary, the intramolecular reactions of acyclic enamine derivatives tethered to electron-rich aromatic rings to form 1-aza-substituted indene derivatives using a gold-catalyzed tandem alkyne addition/Friedel−Crafts process has been presented. Our understanding of the process at the present time does not enable prediction whether or not a subsequent alkene isomerization takes place during the course of the reaction. Future work will incorporate modification of the metal catalyst to generate products with a high level of enantiopurity and the further synthetic manipulation of these reaction products to generate compounds of interest in synthesis or biological studies. Efforts toward these goals will continue in our laboratory.

Experimental Section

Representative Procedure of an Enamide Condensation. (*E*)-1-(7-(3,5-Dimethoxyphenyl)hept-1-en-6-ynyl)pyrrolidin-2-one (5). A solution of 0.29 g of 7-(3,5-dimethoxyphenyl)hept-6-ynal (1.2 mmol), 0.4 mL of 2-pyrrolidinone (4.8 mmol), and 1.2 mL of acetic acid in 5 mL of toluene was heated to reflux within a Dean−Stark apparatus. The reaction mixture was stirred at reflux for 3 h before being cooled to rt. The solution was diluted with diethyl ether and washed carefully twice with a saturated solution of sodium bicarbonate. The aqueous fractions were then extracted twice with diethyl ether. The combined organic fractions were dried over sodium sulfate, filtered, and concentrated in vacuo to afford a brown oil. The crude oil was purified by column chromatography on triethylamine washed silica gel (3:1 to 1:1 to 1:3 hexanes:ethyl acetate) to afford 0.34 g (91%) of the title compound **5** as a pale yellow oil.

IR (neat): 2938, 2245, 1694, 1597, 835, 732 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.92 (d, J = 14.7 Hz, 1H), 6.54 (d, J = 2.4 Hz, 2H), 6.38 (t, J = 2.4 Hz, 1H), 4.93 (dt, J = 14.3, 7.2 Hz, 1H), 3.75 (s, 6H), 3.47 (t, J = 7.2 Hz, 2H), 2.47−2.43 (m, 2H),

2.40 (t, J = 7.2 Hz, 2H), 2.23 (q, J = 6.8 Hz, 2H), 2.06 (qt, J = 7.6 Hz, 2H), 1.68 (qt, J = 7.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.9, 160.6, 125.4, 124.5, 111.2, 109.5, 101.3, 89.6, 81.1, 55.5, 45.4, 31.4, 29.4, 29.2, 18.9, 17.6. HRMS (ESI) calcd for $C_{19}H_{23}NO_3Na$ $(M + Na)^+$ 336.1576, found 336.1584.

Representative Procedure for a Copper(I)-Catalyzed Coupling. (*E*)-1-(3-(3-(3,4-Dimethoxyphenyl)prop-2-ynyloxy)prop-1-enyl)pyrrolidin-2-one (10). A solution of 0.23 g of iodide, 0.058 mL of 2-pyrrolidinone (0.76 mmol), 0.018 g of copper(I) iodide (0.095 mmol), 0.027 g of *N*,*N*-dimethylglycine hydrochloride (0.19 mmol), and 0.41 g of cesium carbonate (1.3 mmol) in 1.5 mL of dioxane was prepared in a large test tube reaction flask in the absence of light. The reaction mixture was heated to 80 °C for 45 h. The resulting blue suspension was cooled to rt and filtered through a pipet of triethylamine washed silica gel. The solution was concentrated to afford a yellow oil. The crude oil was purified by column chromatography on triethylamine washed silica gel (3:1 to 1:1 to 0:1 hexanes:ethyl acetate) to afford 0.16 g (82%) of the title compound **10** as a clear, pale yellow oil.

IR (neat): 2937, 2247, 1702, 1662, 1514, 731 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 (d, J = 14.3 Hz, 1H), 7.03 (d, J = 8.2 Hz, 1H), 6.94 (s, 1H), 6.77 (d, J = 8.5 Hz, 1H), 5.04 (dt, J = 14.3, 7.0 Hz, 1H), 4.31 (s, 2H), 4.13 (d, J = 7.2 Hz, 2H), 3.84 (s, 6H), 3.50 (t, J = 7.0 Hz, 2H), 2.45 (t, J = 8.2 Hz, 2H), 2.07 (qt, J = 7.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.5, 149.7, 148.7, 128.1, 125.2, 114.9, 114.7, 111.1, 106.7, 86.5, 83.7, 68.7, 57.6, 56.0, 55.9, 45.2, 31.3, 17.6. HRMS (ESI) calcd for $C_{18}H_{21}NO_4Na$ $(M + Na)^+$ 338.1368, found 338.1364.

Representative Procedure for Cycloisomerization with Ph_3PAuCl and $AgSbF_6$. 1-(6,8-Dimethoxy-1,2,3,4,9-pentahydro-4*H*-fluoren-9-yl)-pyrrolidin-2-one (22A). A solution of 0.050 g of enamide **5** (0.16 mmol), 3.9 mg of [Ph_3PAuCl] complex (0.0079 mmol), and 2.7 mg of silver hexafluoroantimonate(V) (0.0079 mmol) in 0.75 mL of 1,2-dichloroethane was stirred in a large test tube reaction flask at rt for 8.5 h. The reaction mixture was cooled to rt and directly purified by column chromatography on triethylamine washed silica gel (1:1 to 1:3 hexanes:ethyl acetate) to afford 0.043 g (87%) of compound **22B** as a clear oil, along with 1.4 mg (4%) of elimination product 7-dimethoxy-2,3-dihydro-1*H*-cyclopenta[*b*]naphthalene (**22D**) as a off-white solid.

Isomerization of Alkene with Rhodium(III) Catalysis. A solution of 0.088 g of compound **22B** (0.28 mmol), 7.4 mg of rhodium-(III) chloride trihydrate (0.028 mmol), and 1 mL of ethanol was stirred in a sealed tube at 100 °C for 16 h. The reaction mixture was cooled to rt and directly purified by column chromatography on triethylamine washed silica gel (1:1 to 1:3 hexanes:ethyl acetate) to afford 0.047 g (53%) of the title compound **22A** as a clear oil, along with 0.020 g (31%) of the elimination product 5,7-dimethoxy-2,3-dihydro-1*H*-cyclopenta[*b*]naphthalene (**22D**) as a off-white solid (mp 85−88 °C).

IR (film): 2932, 1682, 821 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.38 (d, J = 1.7 Hz, 1H), 6.26 (d, J = 2.1 Hz, 1H), 5.66 (s, 1H), 3.83 (s, 3H), 3.78 (s, 3H), 2.78 (t, J = 7.0 Hz, 2H), 2.46 (t, J = 8.0 Hz, 2H), 2.36 (br s, 2H), 2.28−2.23 (m, 1H), 2.09−2.04 (m, 1H), 1.96−1.87 (m, 2H), 1.81−1..66 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.6, 162.2, 156.2, 147.9, 142.1, 137.8, 119.1, 96.8, 95.4, 57.8, 55.7, 55.6, 42.9, 31.3, 23.4, 22.9, 22.6, 22.3, 18.2. HRMS (ESI) calcd for $C_{19}H_{24}NO_3$ $(M + H)^+$ 314.1756, found 314.1749.

5,7-Dimethoxy-2,3-dihydro-1*H*-cyclopenta[*b*]naphthalene (**22D**): IR (film): 2956, 2843, 2252, 1615, 825 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (s, 1H), 7.52 (s, 1H), 6.69 (d, J = 2.1 Hz, 1H), 6.45 (d, J = 2.4 Hz, 1H), 4.00 (s, 3H), 3.94 (s, 3H), 3.03 (t, J = 7.3 Hz, 4H), 2.13 (qt, J = 7.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.6, 156.5, 144.7, 140.6, 134.6, 121.1, 121.0, 116.5, 98.1, 96.9, 55.6, 55.4, 32.8, 32.7, 26.3. HRMS (ESI) calcd for $C_{15}H_{17}O_2$ $(M + H)^+$ 229.1229, found 229.1231

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Supporting Information Available: Experimental procedures and characterization data for all previously unreported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.