Gold(I)-Catalyzed Coupling Reactions for the Synthesis of Diverse Small Molecules Using the Build/Couple/Pair Strategy

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Abstract: The build/couple/pair strategy has yielded small molecules with stereochemical and skeletal diversity by using short reaction sequences. Subsequent screening has shown that these compounds can achieve biological tasks considered challenging if not impossible (‘undruggable’) for small molecules. We have developed gold(I)-catalyzed cascade reactions of easily prepared propargyl propiolates as a means to achieve effective intermolecular coupling reactions for this strategy. Sequential alkyne activation of propargyl propiolates by a cationic gold(I) catalyst yields an oxocarbenium ion that we previously showed is trapped by C-based nucleophiles at an extrannular site to yield α-pyrones. Here, we report O-based nucleophiles react by ring opening to afford a novel polyfunctional product. In addition, by coupling suitable building blocks, we subsequently performed intramolecular pairing reactions that yield diverse and complex skeletons. These pairing reactions include one based on a novel azawittig-6π-electrocyclization sequence and others based on ring-closing metathesis reactions.

Introduction

Small molecules are widely used for studying biology or treating diseases.1 Their discovery increasingly relies on small-molecule screening,2 although these studies have revealed the inadequacy of screening collections based on natural products and commercial vendor libraries.3 We have been exploring the build/couple/pair strategy for the synthesis of transformative small-molecule screening collections. These have properties that increase the probability of success in all facets of probe- and drug-discovery pipelines in which synthesis plays a role, including discovery of initial leads, optimization of them, and manufacturing of the optimized variant.4 The build/couple/pair strategy involves (1) the synthesis of building blocks having functionality suitable for subsequent “coupling” and “pairing” steps, (2) intermolecular coupling reactions that join the building blocks in all stereoechemisical combinations, and (3) intramolecular pairing reactions that join different combinations of functional groups yielding diverse skeletons. Compounds that have been made using this strategy of diversity-oriented synthesis have subsequently been identified as small-molecule probes of protein–DNA interactions,5 protein–protein interactions,6 transcription factors,7 multidrug-resistant pathogens,8 and many other processes often imagined to be difficult if not impossible tasks for small molecules.9

The build/couple/pair strategy facilitates the efficient synthesis of small molecules having diverse molecular skeletons, stereochemistry, and appendages,10 but also presents many challenges for methodology and planning, including the need for powerful coupling reactions linking the build and pair phases. Ideally, the intermolecular coupling reactions should be efficient and modular and have excellent functional group compatibility in order to minimize the use of protecting groups so as to facilitate subsequent intramolecular functional-group-pairing reactions.

In order to develop new coupling reactions that fulfill these criteria, we explored transition metal-catalyzed reactions of propargylic esters.11 By coordinating to the alkyne moiety of the propargylic ester, late-transition-metal catalysts induce a [3,3]-sigmatropic rearrangement that generates an allenyl ester poised for subsequent reactions.12 Among the alkyn-activating transition-metal catalysts, gold complexes are particularly promising by virtue of their superior π-acidity, air and moisture stability, functional group compatibility, and their associated
Elsewhere, several reactions have been investigated using propargyl propiolates, including intramolecular Diels–Alder reaction, cycloisomerization and cycloaddition. Here, we describe cationic gold(I)-catalyzed domino reactions of propargyl propiolates and report different modes of trapping of the presumed reactive intermediate by different nucleophiles (Figure 1). This novel transformation of propargyl propiolates as ligands of the reactivity of gold catalysts can be fine-tuned with different positions (pathway 2 and 3) yielding compounds 3 that diversify skeletons in the final products. To this end, we have reported the realization of pathway 1 in the absence of nucleophiles, and pathway 2 when electronic rich arenes are included as nucleophiles (eqs 1 and 2, Figure 1). We envisioned that pathway 3, which affords an unsaturated ketone without generating any new stereogenic elements, could expand the range of unique skeletons in the products of build/couple/pair syntheses using this unique system for coupling diverse building blocks.

Results and Discussion

Pathway 3: Alcohol Nucleophiles. When 2-bromobenzyl alcohol was used as a nucleophile in the gold(I)-catalyzed cascade reaction of the propargyl propiolate, products from both pathway 2 and pathway 3 were obtained (Scheme 1); however, ketoester 4ba was obtained as a single 2Z,4E olefin isomer as determined by NOE measurements (see the Supporting Information).

We determined that 3ba and 4ba were not interconvertible under the same reaction conditions, which suggests that the intermediate B underwent both pathways with comparable facility under the initial reaction conditions. We therefore undertook optimization studies in order to identify conditions that yield ring-opened products. For pathway 3, the C–O bond in the intermediate α-pyron ring is cleaved to yield the ketoester as the final product. We hypothesized that the readiness of B to undergo the ring-opening pathway correlates with the strength of the cleaving C–O bond, which is affected by the delocalization of the C–Au bonding electrons to the C–O antibonding orbital (B, Scheme 1). We envisioned that tuning the electron-density of the gold(I) catalyst by varying the ligand would adjust this hyperconjugation effect and hence the distribution of products.

To examine this proposal, we investigated the effect of various ligands on the ‘regioselectivity’ of the reaction (we use

![Figure 1](image-url)
We next investigated the influence of steric factors on the cascade reaction. The steric effects of different ligands do not influence the regioselectivity of the reaction, a result that is likely due to the linear coordinative pattern of the gold complex. In contrast, three substituents, R1, R2, and R3, dramatically affect the steric environment of the pyronylic position. Propargyl propiolate 1c produced more α-pyrene 3ca than ketoester 4ca under both condition A and B (Table 2, entries 1 and 2). In comparison, propargyl propiolates 1d and 1e, with the more hindered aryl group in R1 and R2, respectively, produced much more ketoester than did propargyl propiolate 1c under both conditions (entries 4, 5, 7, and 8). Although propargyl propiolate 1f produced 4fa exclusively under condition A (entry 10), it afforded a third product that results from a pathway other than pathways 2 and 3 under condition B (entry 11, the third product 5fa was isolated in 33% yield).

The regioselectivity of the reaction is also affected by the size of the nucleophile. The larger secondary (vs primary) alcohol preferentially attacks the carbonyl of intermediate B to afford the ketoester. For propargyl propiolates 1d-f, none of the α-pyrene products were isolated under condition A (entries 6, 9, and 12). The propargyl propiolate 1c also produced ketoester 4cb as the predominant product (entry 3).

A tertiary alcohol gave ketoester 4bb, albeit in a lower yield (eq 4, Scheme 2). When benzyl carbamate was used as a nucleophile in the reaction with propargyl propiolate 1g, α-pyrene 3g could be obtained in 65% yield under the optimized conditions (eq 5).

**Functional-Group Pairing: Ring-Closing Metathesis to Macrolactones.** The ring-closing metathesis (RCM) reaction is a powerful intramolecular coupling reaction that has been applied widely in the diversity-oriented syntheses. The modularity of the gold(I)-catalyzed coupling method facilitates efficient and convergent syntheses of RCM precursors (Table 3).

### Table 1. Optimization of Reaction Conditions for the Alcohol Nucleophile

<table>
<thead>
<tr>
<th>entry</th>
<th>cat.</th>
<th>conditions</th>
<th>3ba yield</th>
<th>4ba yield</th>
<th>ratio (3ba/4ba)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph2PAuCl/AgSbF6</td>
<td>CH2Cl2, rt, 4 h</td>
<td>30%</td>
<td>53%</td>
<td>1:1.8</td>
</tr>
<tr>
<td>2</td>
<td>Et2PAuCl/AgSbF6</td>
<td>CH2Cl2, rt, 1.5 h</td>
<td>13%</td>
<td>82%</td>
<td>1:6.3</td>
</tr>
<tr>
<td>3</td>
<td>(p-CF3C6H4)2PAuCl/AgSbF6</td>
<td>CH2Cl2, rt, 6 h</td>
<td>44%</td>
<td>37%</td>
<td>1:2.1</td>
</tr>
<tr>
<td>4</td>
<td>(IMes)AuCl/AgSbF6</td>
<td>CH2Cl2, rt, 1 h</td>
<td>10%</td>
<td>87%</td>
<td>1:8.7</td>
</tr>
<tr>
<td>5b</td>
<td>(IMes)AuCl/AgSbF6</td>
<td>CH2Cl2, rt, 1.5 h</td>
<td>7%</td>
<td>86%</td>
<td>1:12</td>
</tr>
<tr>
<td>6b</td>
<td>(tBu)3PAuCl/AgSbF6</td>
<td>CH2Cl2, rt, 2 h</td>
<td>3%</td>
<td>89%</td>
<td>1:30</td>
</tr>
<tr>
<td>7</td>
<td>Ph2PAuCl/AgSbF6</td>
<td>toluene, rt, 2 h</td>
<td>56%</td>
<td>23%</td>
<td>2.4:1</td>
</tr>
<tr>
<td>8</td>
<td>Ph2PAuCl/AgSbF6</td>
<td>CH2Cl2, 0 °C, 8 h</td>
<td>56%</td>
<td>36%</td>
<td>1.6:1</td>
</tr>
<tr>
<td>9b</td>
<td>(p-CF3C6H4)3PAuCl/AgSbF6</td>
<td>toluene, 0 °C, 8 h</td>
<td>61%</td>
<td>20%</td>
<td>3:1</td>
</tr>
</tbody>
</table>

*a* Isolated yield after column chromatography.  
*b* 2 equiv of alcohol was used.
When the coupling product 4h was subjected to Grubbs’ second-generation catalyst 6, the 12-membered macrolactone 5h was obtained in quantitative yield exclusively as the E isomer at $\Delta^{8,9}$ (entry 1). When a single-enantiomer alcohol was used as the nucleophile, the chiral RCM precursor 4ia was obtained. Under the same RCM reaction conditions, single-enantiomer macrolactone 5ia was provided in 70% yield as a predominate E isomer (10:1) as indicated by the coupling constant of the $\Delta^{8,9}$ olefin protons ($J = 15.1$ Hz, entry 2).

We next explored our ability to generate a variety of distinct macrolactone products. RCM substrate 4ib required the use of the Grubbs’ first-generation catalyst 7, affording the 14-membered macrolactone 5ib, as a mixture of E (29%) and Z isomers (21%). The Hoveyda—Grubbs’ first-generation catalyst 9 afforded 5ib in similar yield, but the ratio was increased slightly from 1.4:1 to 2.3:1 (entry 3).

Beginning with propargyl propiolate 1j bearing a stereogenic center, diastereomeric coupling products 4ja and 4jb, 4jc and 4jd were obtained using S or R alcohols (entries 4–7). In the presence of Hoveyda—Grubbs’ second-generation catalyst 8, 4ja underwent the RCM reaction to give the 14-membered macrolactone 5ja as an exclusive E isomer, whose structure was verified by X-ray crystallography (entry 4). The configuration of the newly formed olefin is dependent on the stereochemistry of the newly formed olefin is dependent on the stereochemistry of the newly formed olefin is dependent on the stereochemistry.
of the macrocycle. The coupling product 4jb, which is diastero-meric to 4ja, afforded macrolactone 5jb under the same RCM conditions, but as an inseparable 3:1 mixture of E/Z isomers (entry 5). The E/Z ratio of the newly formed olefin is also dependent on the ring size. The 15-membered macrolactones 5jc and 5jd were both obtained as inseparable E/Z isomers, whereas 5jd was formed with higher efficiency (entries 6 and 7).

Alternatively, placing the olefin moiety in a different building block leads to a different pairing pattern. To illustrate, beginning with propargyl propiolate 1k, 15-membered macrolactone 6k was produced in two steps with 1.7:1 E/Z ratio (entry 8).

On the basis of conformational analysis and the X-ray-derived structure of macrolactone 5ja, we anticipated that 5ja would expose one diastereotopic face preferentially to the periphery of the macrocycle. Indeed, the epoxidation 19 of the electronic-rich Δ10,11 olefin in 5ja yielded the epoxide 10 with 6.3:1 selectivity as determined by NOE experiments (eq 6, Scheme 3, also see Supporting Information). The newly formed olefin could also be selectively hydrogenated to give a single macro-lactone 11 (eq 7, Scheme 3).

**Functional-Group Pairing:** a Staudinger-aza-Wittig-6π-Electrocyclization Cascade Reaction and Efficient Syntheses of Substituted 2-Pyridones. Intramolecular pairing of distinct functional groups using the same molecular skeleton was next explored. Another cascade reaction was discovered when we subjected the coupling product 4bc to excess triphenylphosphine (18).
Table 3. Two-Step Syntheses of Macrolactones Based on the Cascade Coupling Reaction

<table>
<thead>
<tr>
<th>entry</th>
<th>propargyl propionate</th>
<th>alcohol</th>
<th>ketone: 4&lt;sup&gt;a&lt;/sup&gt;</th>
<th>RCM condition&lt;sup&gt;b&lt;/sup&gt;</th>
<th>macro lactone</th>
<th>yield&lt;sup&gt;c&lt;/sup&gt; (E/Z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="1.png" alt="Image" /></td>
<td><img src="2.png" alt="Image" /></td>
<td><img src="3.png" alt="Image" /></td>
<td><img src="4.png" alt="Image" /></td>
<td><img src="5.png" alt="Image" /></td>
<td>99% (&gt;20:1)</td>
</tr>
<tr>
<td>2</td>
<td><img src="6.png" alt="Image" /></td>
<td><img src="7.png" alt="Image" /></td>
<td><img src="8.png" alt="Image" /></td>
<td><img src="9.png" alt="Image" /></td>
<td><img src="10.png" alt="Image" /></td>
<td>70% (10:1)</td>
</tr>
<tr>
<td>3</td>
<td><img src="11.png" alt="Image" /></td>
<td><img src="12.png" alt="Image" /></td>
<td><img src="13.png" alt="Image" /></td>
<td><img src="14.png" alt="Image" /></td>
<td><img src="15.png" alt="Image" /></td>
<td>50% (1.4:1)</td>
</tr>
<tr>
<td>4</td>
<td><img src="16.png" alt="Image" /></td>
<td><img src="17.png" alt="Image" /></td>
<td><img src="18.png" alt="Image" /></td>
<td><img src="19.png" alt="Image" /></td>
<td><img src="20.png" alt="Image" /></td>
<td>74% (&gt;20:1)</td>
</tr>
<tr>
<td>5</td>
<td><img src="21.png" alt="Image" /></td>
<td><img src="22.png" alt="Image" /></td>
<td><img src="23.png" alt="Image" /></td>
<td><img src="24.png" alt="Image" /></td>
<td><img src="25.png" alt="Image" /></td>
<td>77% (3.3:1)</td>
</tr>
<tr>
<td>6</td>
<td><img src="26.png" alt="Image" /></td>
<td><img src="27.png" alt="Image" /></td>
<td><img src="28.png" alt="Image" /></td>
<td><img src="29.png" alt="Image" /></td>
<td><img src="30.png" alt="Image" /></td>
<td>96% (1.2:1)</td>
</tr>
<tr>
<td>7</td>
<td><img src="31.png" alt="Image" /></td>
<td><img src="32.png" alt="Image" /></td>
<td><img src="33.png" alt="Image" /></td>
<td><img src="34.png" alt="Image" /></td>
<td><img src="35.png" alt="Image" /></td>
<td>97% (1:1)</td>
</tr>
<tr>
<td>8</td>
<td><img src="36.png" alt="Image" /></td>
<td><img src="37.png" alt="Image" /></td>
<td><img src="38.png" alt="Image" /></td>
<td><img src="39.png" alt="Image" /></td>
<td><img src="40.png" alt="Image" /></td>
<td>69% (1.7:1)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conditions: 5% (Bu₃P)AuCl/AgSbF₆, CH₂Cl₂, rt.  
<sup>b</sup> RCM conditions A: 10% 6, CH₂Cl₂, rt, 4 h. B: 10% 7, CH₂Cl₂, reflux, 24 h. C: 10% 8, CH₂Cl₂, reflux, 6–24 h; D: 10% 9, CH₂Cl₂, reflux, 24 h.  
<sup>c</sup> Isolated yield.  
<sup>d</sup> Reaction conditions: 5% (IMes)AuCl/AgSbF₆, CH₂Cl₂, rt.  
<sup>e</sup> RCM conditions D.
We envision that the iminophosphorane generated by a Staudinger reaction initiated an intramolecular aza-Wittig reaction that, under the thermal conditions, underwent an aza-6π-electrocyclization\(^\text{(21)}\) in situ. Steric hindrance is avoided when the olefin approaches the dihydrooxazole ring from the face opposite the benzyl group. The 6π-disrotatory electrocyclization following the direction indicated by the arrows afforded the bicyclic compound 13b as the single product; the newly formed stereogenic center was determined by NOE measurements (see the Supporting Information).

Such ‘product equals substrate’ relationships enhance the ability of build/couple/pair pathways to afford diverse and complex products efficiently.\(^\text{(22)}\) Since cyclic ketene N,O-acetals undergo ring-opening reactions with acids yielding amidoesters,\(^\text{(23)}\) we envisioned that the cyclic ketene N,O-acetal of

\(^{12}\) refluxing toluene to give the dihydrooxazole 12 (Scheme 4).\(^\text{(20)}\)


the cascade reaction could induce another coupling reaction with carboxylic acids. To this end, bicyclic compound 13ic was synthesized following a similar sequence and subjected to excess 4-pentenoic acid (Scheme 5). This treatment yielded the 2-pyridone 14ica.

This 2-pyridone presumably arises from a dehydrogenation reaction of the expected dihydro-2-pyridone. To optimize the formation of the 2-pyridone, which is a substructure of numerous biologically active small molecules,24 we used polymer-supported triphenylphosphine to avoid the separation of the intermediate 13ic by chromatography.25 The best result was achieved by heating the crude product of Staudinger-aza-Wittig-6σ-electrocyclization with excess acid in toluene in the presence of 4 Å molecular sieves and oxygen (see Supporting Information). Using these conditions, 2-pyridone 14l was obtained in moderate yield after five sequential transformations from ketoester 4l (Scheme 6).

This modular approach to substituted 2-pyridones provides a novel scaffold for subsequent functional-group pairing to give polycyclic compounds. To illustrate, bicyclic 15ica was obtained from the RCM precursor 14ica (eq 10, Scheme 7). The use of cascade reactions enabling stereochemical diversity was highlighted by the syntheses of diastereomeric 2-pyridones 14icb and 14icc. In contrast to the macro lactones shown in Table 3, the 14-membered macro lactones 15icb and 15icc were obtained predominately as Z isomers (eqs 11 and 12, Scheme 7).

Summary and Conclusions

We have developed novel coupling and pairing reactions of readily available propargyl propiolates using cationic gold(I) catalysts. Sequential alkyne activation of the propargyl propiolate yields an oxocarbenium intermediate that can be induced to convert to distinct products. The coupling of building blocks and the pairing of pendant functionality using the novel reactions developed in this study yield products having stereochemical and skeletal diversity and complexity, properties valued in small-molecule screening collections that are used in assays involving complex biology.

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Supporting Information Available: Experimental details, condition optimization for the synthesis of 3ba, 4ba, and 14ica, spectral characterization data, crystallographic data of 5ja, and complete refs 8, 24c, and 24d. This material is available free of charge via the Internet at http://pubs.acs.org.

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