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

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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 aza-Wittig-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 stereochemical 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 posed for subsequent reactions.[12] Among the alkyne-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

(1) (a) Schreiber, S. L. *Nat. Chem. Biol.* **2005**, *1*, 64–66. (b) Stockwell, B. R. *Nature* **2004**, *432*, 846–854.
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(3) Payne, D. J.; Gwynn, M. N.; Holmes, D. J.; Pompliano, D. L. *Nat. Rev. Drug Discov.* **2007**, *6*, 29–40.
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mild reaction conditions.[13] Furthermore, it has been shown that the reactivity of gold catalysts can be fine-tuned with different ligands.[14]

Elsewhere, several reactions have been investigated using propargyl propiolates, including intramolecular Diels−Alder reaction, cycloisomerization and cycloaddition.[15] 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).[11] This novel transformation of propargyl propiolates assembles building blocks (R^1, R^2, R^3, and Nu, Figure 1) into either α-pyrones, which are present in many biologically active compounds,[16] or unsaturated ketones, which are substrates for many useful reactions. The cationic gold(I)-catalyzed [3,3]-sigmatropic rearrangement of the propargyl propiolate **1** affords the corresponding enyne allene **A**. With the coordination of the remaining alkyne, a 6-endodig cyclization yields the oxocarbenium **B**.[17] Elimination of a proton (pathway 1) and demetalation gives rise to a vinyl α-pyrone **2**. Trapping of the intermediate **B** by a variety of nucleophiles at two distinct positions (pathway 2 and 3) yields compounds **3** and **4**.

Strategic placement of suitable functionality in the building blocks allows intramolecular functional group-pairing reactions that diversify skeletons in the final products.[4] 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).[11] 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.

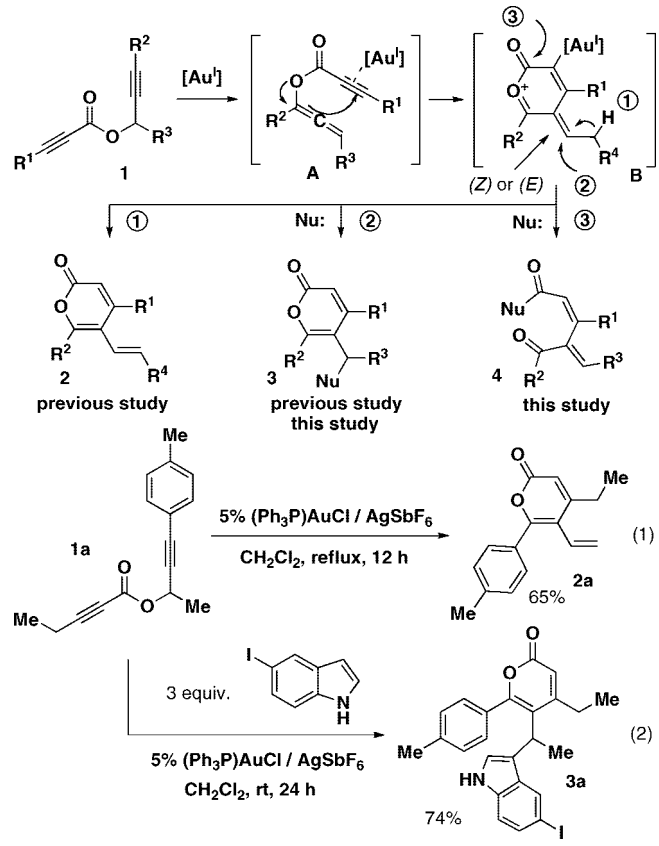

Figure 1. Gold(I)-catalyzed cascade reactions of propargyl propiolates.

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 2*Z*,4*E* 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-pyrone 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

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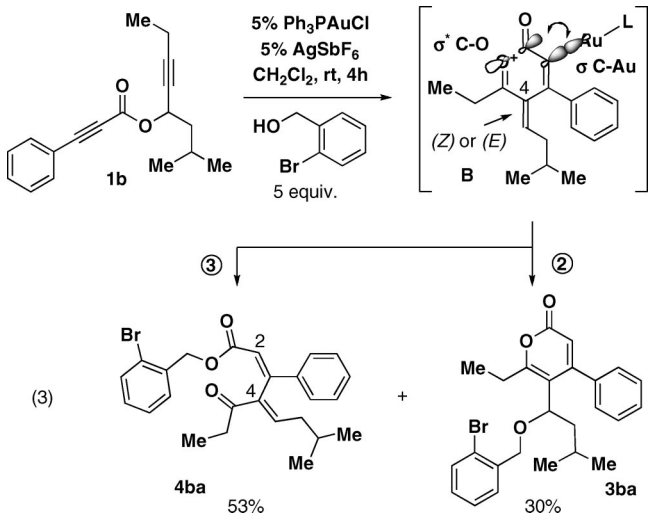
Scheme 1



this term to refer to the site of nucleophilic trapping of the extended π system; **B** in Scheme 1) (Table 1 and Supporting Information Table S1). As expected, more ketoester **4ba** was produced with the more electron-donating ligand triethylphosphine (entry 2 vs entry 1). On the contrary, more α-pyrone **3ba** was produced with the less electron-donating ligand, tris(para-trifluoromethylphenyl)phosphine (entry 3 vs entry 1). The ratio of **4ba** to **3ba** was increased to more than 10:1 with the best electron-donating ligands, the carbene ligand or tritert-butylphosphine (entries 5 and 6), whereas the stoichiometry of the alcohol had no significant consequence (entries 4 vs entry 5). Using the nonpolar solvent toluene or lowering the temperature both disfavored pathway 3 and afforded more α-pyrone **3ba** (entries 7 and 8). With 5% cationic tris(*para*-trifluoromethylphenyl)phosphine gold(I) catalyst, α-pyrone **3ba** was obtained with 61% yield in toluene at 0 °C (entry 9).

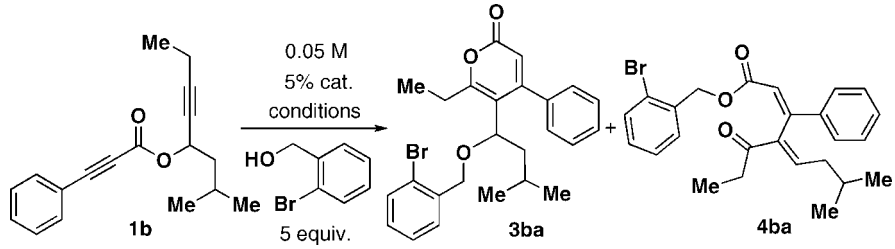
We next investigated the influence of steric factors on the cascade reaction. The steric effects of different ligands do not influence the regioselectivity of the reaction, a result that is likely due to the linear coordinative pattern of the gold complex. In contrast, three substitutents, R^1, R^2, and R^3, dramatically affect the steric environment of the pyronylic position. Propargyl propiolate **1c** produced more α-pyrone **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 R^1 and R^2, 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-pyrone 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).

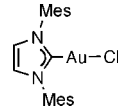
A tertiary alcohol gave ketoester **4bb**, albeit in a lower yield (eq 4, Scheme 2). When benzyl carbamate was used as a nucleophile in the reaction with propargyl propiolate **1g**, α-pyrone **3g** could be obtained in 65% yield under the optimized conditions (eq 5).

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.[4,9,18] 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



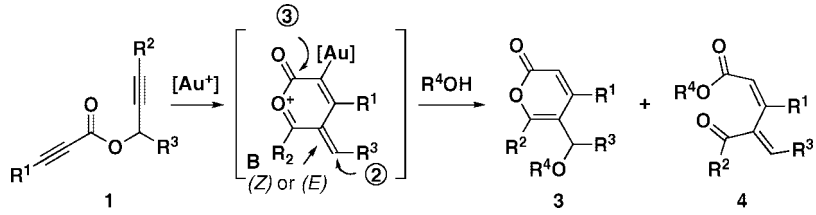
entry	cat.	conditions	yield[a] 3ba	yield[a] 4ba	ratio (3ba/4ba)
1	$Ph_3PAuCl/AgSbF_6$	CH_2Cl_2, rt, 4 h	30%	53%	1:1.8
2	$Et_3PAuCl/AgSbF_6$	CH_2Cl_2, rt, 1.5 h	13%	82%	1:6.3
3	$(p\text{-}CF_3\text{-}C_6H_4)_3PAuCl/AgSbF_6$	CH_2Cl_2, rt, 6 h	44%	37%	1.2:1
4	(IMes)$AuCl/AgSbF_6$	CH_2Cl_2, rt, 1 h	10%	87%	1:8.7
5[b]	(IMes)$AuCl/AgSbF_6$	CH_2Cl_2, rt, 1.5 h	7%	86%	1:12
6[b]	$(^t\text{Bu})_3PAuCl/AgSbF_6$	CH_2Cl_2, rt, 2 h	3%	89%	1:30
7	$Ph_3PAuCl/AgSbF_6$	toluene, rt, 2 h	56%	23%	2.4:1
8	$Ph_3PAuCl/AgSbF_6$	CH_2Cl_2, 0 °C, 8 h	56%	36%	1.6:1
9[b]	$(p\text{-}CF_3\text{-}C_6H_4)_3PAuCl/AgSbF_6$	toluene, 0 °C, 8 h	61%	20%	3:1

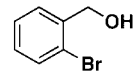
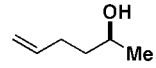
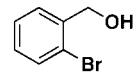
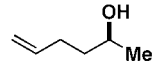
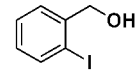
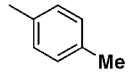
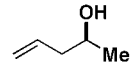
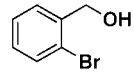
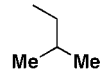
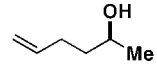


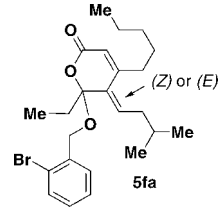
(IMes)AuCl

[a] Isolated yield after column chromatography. [b] 2 equiv of alcohol was used.

Table 2. Steric Factors Determining the Distribution of **3** and **4**



entry	R^1	R^2	R^3	R^4OH	conditions[a]	yield[b] 3	yield[b] 4	ratio (3/4)
1	**1c**				A[c]	54%	42%	1.3 : 1
2					B[c]	67%	8%	8.4 : 1
3					A[d]	7%[e]	75%	1 : 11
4	**1d**				A[c]	4%	83%	1 : 20
5					B[c]	62%	11%	5.6 : 1
6					A[d]	0%	80%	-
7	**1e**				A[c]	0%	85%	-
8					B[c]	47%	32%	1.5 : 1
9					A[d]	0%	77%	-
10	**1f**				A[c]	0%	75%	-
11					B[c]	43%	9%	4.8 : 1[f]
12					A[d]	0%	73%	-



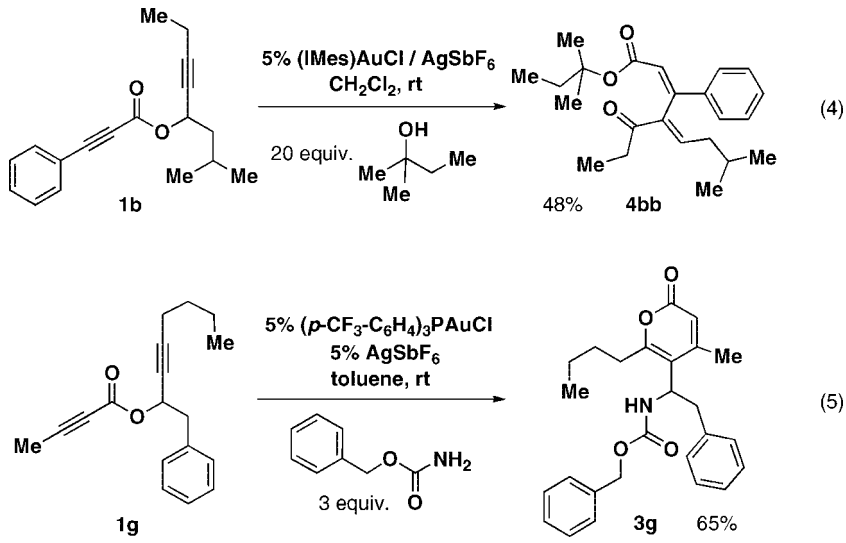
[a] Method A: 5% (IMes)AuCl/$AgSbF_6$, CH_2Cl_2, rt. Method B: 5% (p-CF_3−C_6H_4)$_3$PAuCl/ $AgSbF_6$, toluene, 0 °C. [b] Isolated yield after column chromatography. [c] 2 equiv of alcohol was used. [d] 4 equiv of alcohol was used. [e] dr = 1.3:1. [f] See the text.

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 $\Delta^{8,9}$ (Table 3, 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).

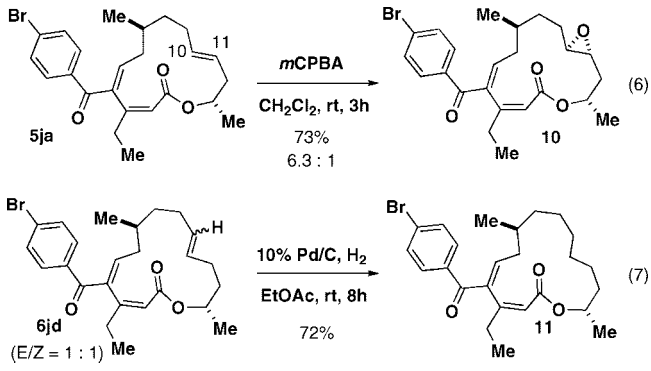
We next explored our ability to generate a variety of distinct macrolactone products. RCM substrate **4ib** required the use of the Grubbs' first-generation catalyst **7**, affording the 14-membered macrolactone **5ib**, as a mixture of *E* (29%) and *Z* isomers (21%). The Hoveyda−Grubbs' first-generation 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

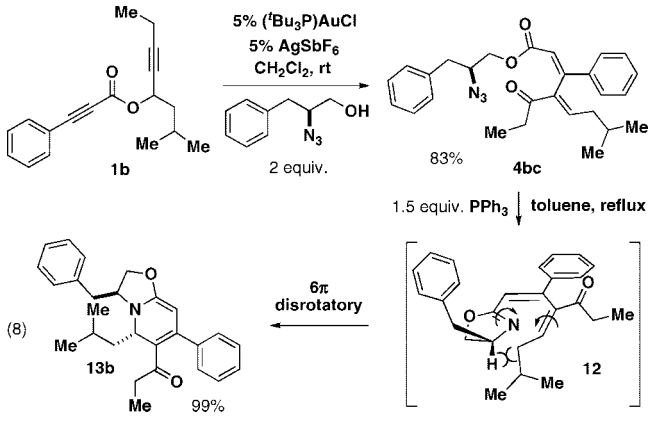
Scheme 2



Scheme 3



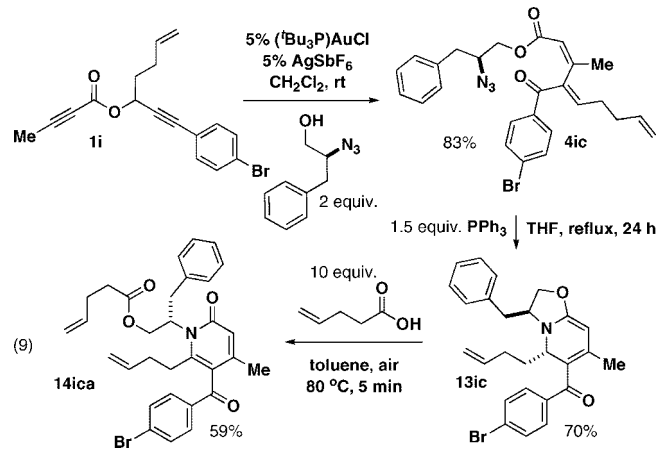
Scheme 4



of the macrocycle. The coupling product **4jb**, which is diastereomeric 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).

Scheme 5



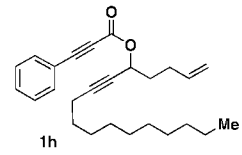
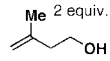
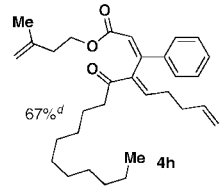
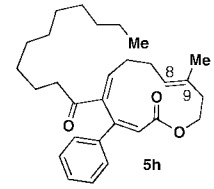
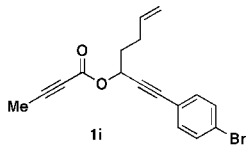
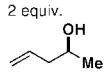
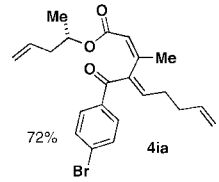
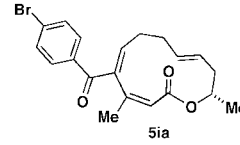
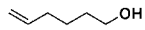
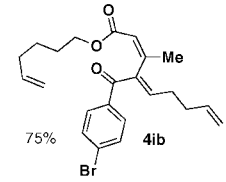
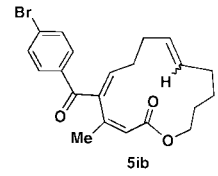
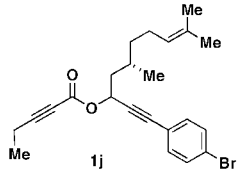
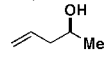
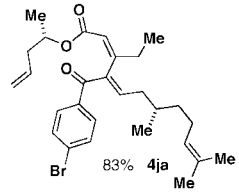
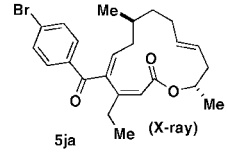
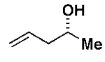
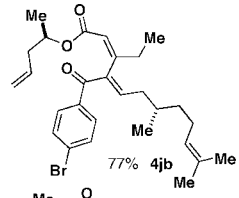
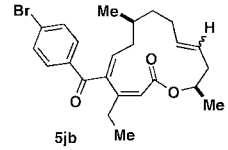
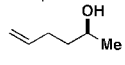
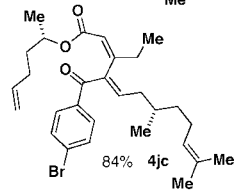
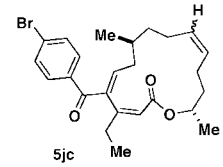
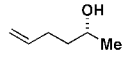
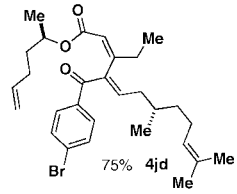
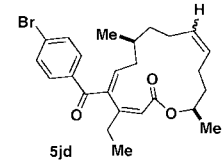
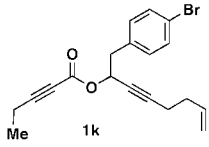
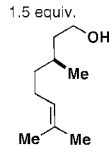
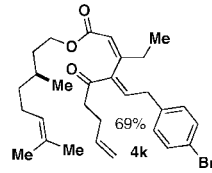
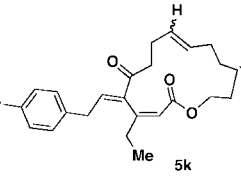
On the basis of conformational analysis and the X-ray-derived structure of macrolactone **5ja**, we anticipated that **5ja** would expose one diastereotopic face preferentially to the periphery of the macrocycle. Indeed, the epoxidation[19] of the electronic-rich $\Delta^{10,11}$ olefin in **5ja** yielded 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 macrolactone **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

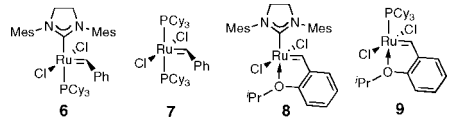
(18) (a) Micalizio, G. C.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2002**, *41*, 152–154. (b) Kim, Y. k.; Arai, M. A.; Arai, T.; Lamenzo, J. O.; Dean, E. F.; Patterson, N.; Clemons, P. A.; Schreiber, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 14740–14745. (c) Spiegel, D. A.; Schroeder, F. C.; Duvall, J. R.; Schreiber, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 14766–14767. (d) Morton, D.; Leach, S.; Cordier, C.; Warriner, S.; Nelson, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 104–109.

(19) (a) Vedejs, E.; Gapinski, D. M. *J. Am. Chem. Soc.* **1983**, *105*, 5058–5061. (b) Still, W. C.; Novack, V. *J. Am. Chem. Soc.* **1984**, *106*, 1148–1149. (c) Schreiber, S. L.; Sammakia, T.; Hulin, B.; Schulte, G. *J. Am. Chem. Soc.* **1986**, *108*, 2106–2108.

Table 3. Two-Step Syntheses of Macrolactones Based on the Cascade Coupling Reaction

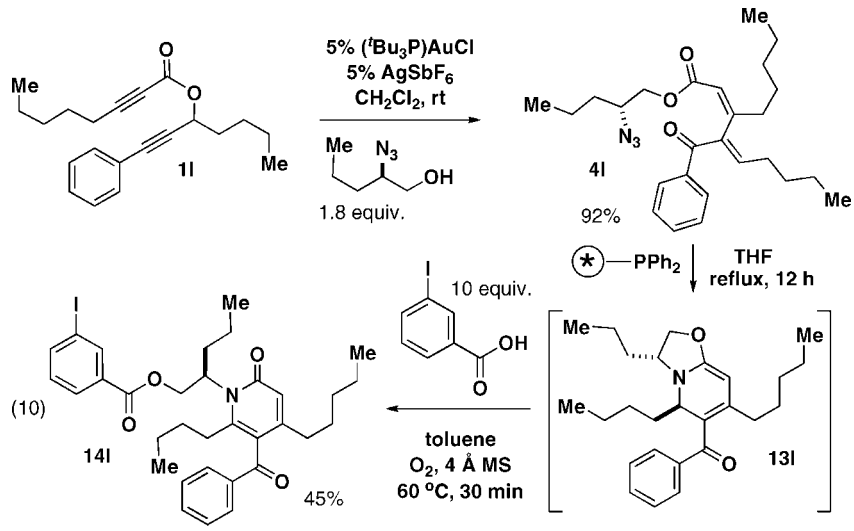
entry	propargyl propiolate	alcohol	ketoester 4[a]	RCM condition[b]	macrolactone	yield[c] (*E*:*Z*)
1	 **1h**	 2 equiv.	 67%[d] **4h**	A	 **5h**	99% (>20:1)
2	 **1i**	 2 equiv.	 72% **4ia**	A	 **5ia**	70% (10:1)
3	**1i**	 2 equiv.	 75% **4ib**	B	 **5ib**	50% (1.4:1) 53% (2.3:1)[e]
4	 **1j**	 2 equiv.	 83% **4ja**	C	 **5ja** (X-ray)	74% (>20:1)
5	**1j**	 2.5 equiv.	 77% **4jb**	C	 **5jb**	77% (3.3:1)
6	**1j**	 2 equiv.	 84% **4jc**	C	 **5jc**	86% (1:2.1)
7	**1j**	 2 equiv.	 75% **4jd**	C	 **5jd**	97% (1:1)
8	 **1k**	 1.5 equiv.	 69% **4k**	C	 **5k**	69% (1.7:1)

[a] Reaction conditions: 5% (^{t}Bu$_3$P)AuCl/AgSbF$_6$, CH_2Cl_2, rt. [b] RCM conditions A: 10% **6**, CH_2Cl_2, rt, 4 h. B: 10% **7**, CH_2Cl_2, reflux, 24 h. C: 10% **8**, CH_2Cl_2, reflux, 6−24 h; D: 10% **9**, CH_2Cl_2, reflux, 24 h. [c] Isolated yield. [d] Reaction conditions: 5% (IMes)AuCl/AgSbF$_6$, CH_2Cl_2, rt. [e] RCM conditions D.

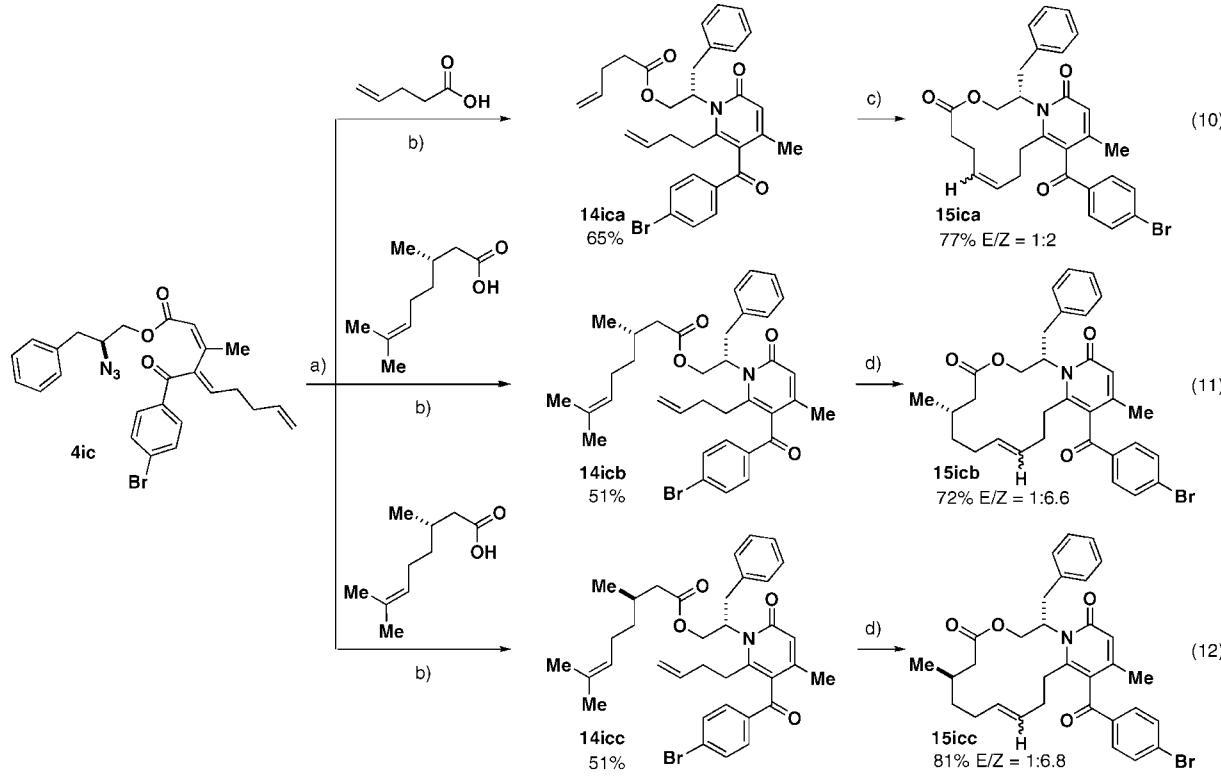


6 **7** **8** **9**

Scheme 6



Scheme 7



a) 1.5 equiv. $(*)$–PPh_2,THF, reflux. b) toluene, O_2, 4 Å MS, 60 °C, 30 min, 10 equiv. acid. c) 10% **8**, CH_2Cl_2, rt, 24h. d) 10% **8**, toluene, 60 °C, 11h.

in refluxing toluene to give the dihydrooxazole **12** (Scheme 4).[20] 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[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.[22] Since cyclic ketene N,O-acetals undergo ring-opening reactions with acids yielding amidoesters,[23] we envisioned that the cyclic ketene N,O-acetal of

(20) Riedrich, M; Harkal, S.; Arndt, H.-D. *Angew. Chem., Int. Ed.* **2007**, *46*, 2701–2703.
(21) (a) Okamura, W. H.; De Lera, A. R.; Reischl, W. *J. Am. Chem. Soc.* **1988**, *110*, 4462–4464. (b) Nedolya, N. A.; Brandsma, L.; van der Kerk, A. H. T. M.; Vvedensky, V. Y.; Trofimov, B. A. *Tetrahedron Lett.* **1998**, *39*, 1995–1996.
(22) Lee, D.; Sello, J. K.; Schreiber, S. L. *Org. Lett.* **2000**, *2*, 709–712.

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-6π-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 macrolactones shown in Table 3, the 14-membered macrolactones **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.

Acknowledgment. The NIGMS-sponsored Center of Excellence in Chemical Methodology and Library Design (Broad Institute CMLD; P50 GM069721) sponsored this research. We thank Ben Stanton and Drs. Weiping Tang, Arturo Vegas, Thomas Nielsen, and Xiang Wang for helpful discussions. S.L.S. is a Howard Hughes Medical Institute Investigator.

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.

JA900414S

(23) (a) Elliott, M. C.; Kruiswijk, E.; Willock, D. J. *Tetrahedron* **2001**, *57*, 10139–10146. (b) Fustero, S.; Salavert, E.; Sanz-Cervera, J. F.; Piera, J.; Asensio, A. *Chem. Commun.* **2003**, 844–845. (c) Zhou, A.; Pittman, C. U. *J. Comb. Chem.* **2006**, *8*, 262–267.

(24) For recent examples, see: (a) Wagenaar, M. M.; Gibson, D. M.; Clardy, J. *Org. Lett.* **2002**, *4*, 671–673. (b) Pinkner, J. S.; Remaut, H.; Buelens, F.; Miller, E.; Åberg, V.; Pemberton, N.; Hedenström, M.; Larsson, A.; Seed, P.; Waksman, G.; Hultgren, S. J.; Almqvist, F. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 17897–17902. (c) Spicer, J. A.; et al. *J. Med. Chem.* **2007**, *50*, 5090–5102. (d) Kim, K. S.; et al. *J. Med. Chem.* **2008**, *51*, 5330–5341.

(25) Ley, S. V.; Baxendale, I. R. *Nat. Rev. Drug Discov.* **2002**, *1*, 573–586.