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Gold(I)-catalyzed enantioselective [3+2] and [3+3] cycloaddition reactions of propargyl acetals/ketals

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ABSTRACT

An asymmetric gold(I)-catalyzed [3+2] cycloaddition of propargyl acetals/ketals and aldehydes is reported, which proceeds via stepwise migration-fragmentation of acetals/ketals and cycloaddition of the in situ generated gold-carbenoid intermediate. Various functionalized 2,5-dihydrofurans were obtained in good yields and high enantioselectivities. Furthermore, an example of the first gold(I) catalyzed [3+3] cycloaddition of secondary propargyl ketals and nitrones is presented.

1. Introduction

There is an increasing demand for the development of methods and strategies that allow the transformation of readily available precursors into target-relevant products in a rapid, economical and efficient manner. Cycloaddition reactions are synthetic tools, which fit these criteria, because they can produce a rapid increase in skeletal complexity with controlled regio- and stereoselectivities.[1] In recent years, gold complexes have emerged as excellent catalysts for novel types of cycloaddition reactions, because of their unique ability to activate carbon–carbon π-systems.[2] Gold(I) or gold(III) complexes tend to activate alkynes, alkenes or allenes in a highly selective manner. This activation mode allows for interesting reaction pathways that usually involve carbocationic intermediates. The properties of the metal can be modulated through modification of its ancillary ligand (phosphines, *N*-heterocyclic carbenes …).[3] The rapid rise in interest in gold catalysis has been accompanied by efforts to develop enantioselective variants of gold-catalyzed reactions to further increase the synthetic utility of these processes.[4]

The gold-catalyzed 1,2-rearrangement of propargyl esters has provided the basis for the development of a wide range of transformations. These reactions are hypothesized to proceed through gold-stabilized cationic intermediates that show reactivity analogous to electrophilic transition metal vinyl carbenoids.[5] As expected these cationic species can demonstrate either carbene like 1,1-reactivity (cyclopropanation) or participate in vinylogous 1,3-functionalization reactions that have typically been associated with 1,3-dipoles.[6] In the context of the latter, Iwasawa[7] first invoked a gold-containing 1,3-dipole to prepare tricyclic indole derivatives in 2006. In 2008, we also proposed gold azomethine ylides as intermediates to understand the reaction of propargylic benzoates with α,β-unsaturated imines.[5h] We obtained azepine products, through a stepwise [4+3] annulation process between the imines and the gold vinylcarbenoids, generated upon 1,2-migration of the ester group. Similarly, Zhang et al.[8] reported that migration-fragmentation of propargyl acetals/ketals allowed for a [3+2]-cycloaddition with electron-rich aromatic aldehydes to form highly functionalized 2,5-dihydrofurans, useful building blocks in organic synthesis. However, an enantioselective version of this transformation has not been reported before. Finally, in 2009 we reported a gold(III)-catalyzed [3+3]-cycloaddition of tertiary propargyl esters and azomethine imines.[9] This example of a formal cycloaddition between metal vinylcarbenoids and 1,3-dipoles was followed by a reported by Zhang et al. employing nitrones as to be effective 1,3-dipoles for gold(I)-catalyzed [3+3] cycloaddition with 2-(1-alkynyl)-2-alken-1-ones.[10] With this information in hand, we envisioned that gold(I)-catalyzed [3+3] cycloaddition of propargyl ketals and nitrones could occur, and this transformation would give us new insights in the fast growing field of gold catalysis.

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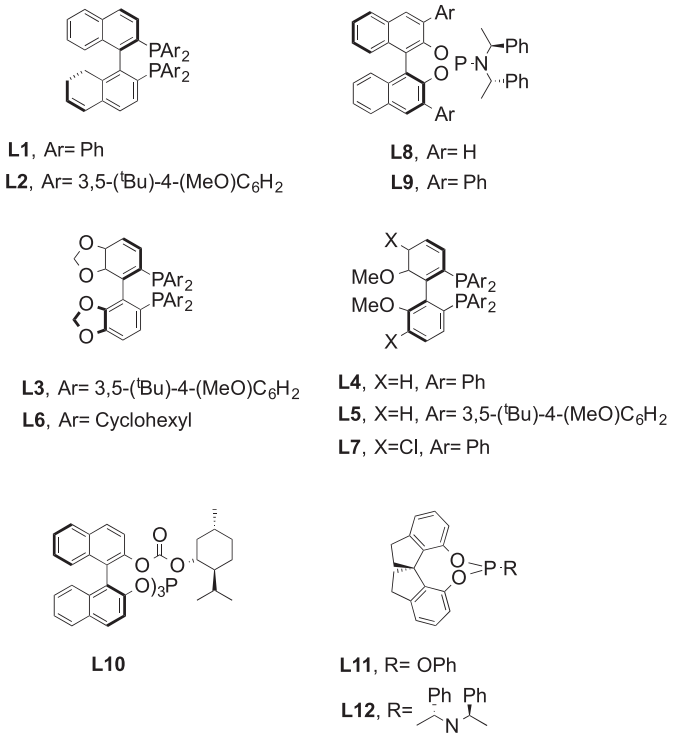


Fig. 1. Chiral ligands used for the cycloaddition reactions.

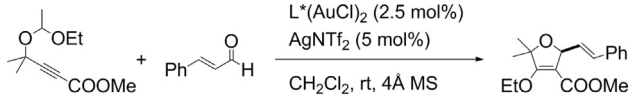
We report herein the first asymmetric gold(I)-catalyzed [3+2] cycloaddition of propargyl acetals and aldehydes, which proceeds via stepwise migration-fragmentation of the acetal and cycloaddition of the in situ generated gold-carbenoid intermediate. Furthermore, we present an example of the first gold(I)-catalyzed [3+3]-cycloaddition reaction of secondary propargyl ketals and nitrones and the corresponding enantioselective version. Fig. 1.

2. Gold(I)-catalyzed [3+2] cycloaddition reactions between propargyl acetals/ketals and aldehydes

2.1. Optimization of the reaction conditions

We began our investigation using propargyl ester **1a** and *trans*-cinnamaldehyde **2a** as suitable test substrates for this [3+2] cycloaddition. We examined different cationic gold(I) catalysts bearing chiral bisphosphine ligands (Table 1, entries 1–5). In all cases the gold complexes were activated by $AgNTf_2$ and afforded desired product **3aa** in good yields. The use of phosphine ligand **L1**=(*R*)-BINAP (Table 1, entry 1) induced moderated enantioselectivities in the formation of 2,5-dihydrofuran **3aa**. More bulky **L2**=(*R*)-DTBM-BINAP (Table 1, entry 2) afforded **3aa** almost as racemic mixture. **L3**=(*R*)-DTBM-SEGPHOS gave **3aa** in higher yields but similar enantioselectivity as **L1**=(*R*)-BINAP. (90% yield, 77% ee; Table 1, entry 3). **L4**=(*R*)-MeO-BIPHEP afforded **3aa** in 91% yield but almost as a racemic mixture. (3% ee; Table 1, entry 4) However, more bulky (*R*)-DTBM-MeO-BIPHEP provided 2,5-dihydrofuran **3aa** in good yields and very high levels of enantioinduction (80% yield, 95% ee; Table 1, entry 5).

Table 1
Optimization of the gold-catalyzed enantioselective [3+2] cycloaddition reaction[a]



1a **2a** **3aa**

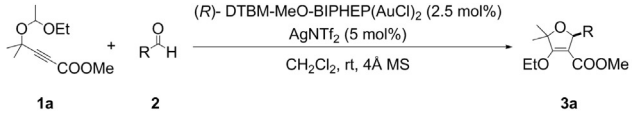
Entry	Ligand (L*)	Yield[b] (%)	ee[c] (%)
1	**L1**=(*R*)-BINAP	60	72
2	**L2**=(*R*)-DTBM-BINAP	77	2
3	**L3**=(*R*)-DTBM-SEGPHOS	89	77
4	**L4**=(*R*)-MeO-BIPHEP	91	3
5	**L5**=(*R*)-DTBM-MeO-BIPHEP	80	95

[a] Reaction conditions: 2.5 mol% gold catalyst, 5 mol% $AgNTf_2$, 0.15 mmol (1 equiv) of **1a**, 0.23 mmol (1.5 equiv) of *trans*-cinnamaldehyde **2a**, 10 mg of 4 Å molecular sieves (MS), 0.8 mL CH_2Cl_2, 1.5 h.
[b] Isolated yields.
[c] Enantiomeric excess values were determined by chiral HPLC analysis. Racemic trace obtained using *rac*-BINAP$(AuCl)_2$ as gold catalyst.

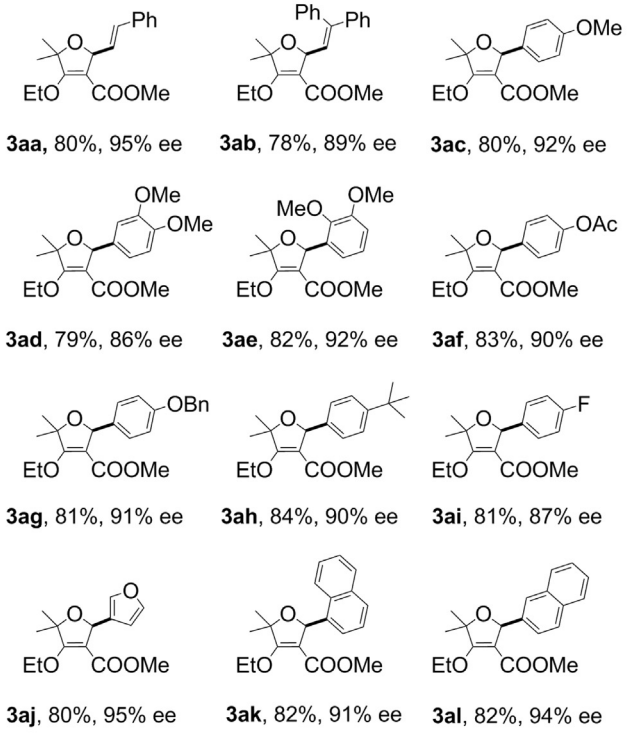
2.2. Aldehyde scope

With optimal conditions in hand (Table 1, entry 5), we explored the scope of the gold(I)-catalyzed enantioselective cycloaddition. The reaction is general for a wide range of aldehydes (**2a**–**2l**). (Table 2). More bulky enal **2b** afforded **3ab** in 78% yield and 89% ee. Electron rich aromatic aldehydes **2c**, **2d** and **2e** afforded **3ac**, **3ad**

Table 2
Asymmetric [3+2] cycloaddition reaction: aldehyde scope[a,b,c,d]



1a **2** **3a**



[a] Reaction conditions: 2.5 mol% gold catalyst, 5 mol% $AgNTf_2$, 0.15 mmol (1 equiv.) of **1a**, 0.23 mmol (1.5 equiv.) of aldehyde **2**, 10 mg of 4 Å molecular sieves (MS), 0.8 mL CH_2Cl_2, 1.5 h.[d] Reaction between substrate **1a** and 3-Phenylpropanal afforded the desired product **3a** with 30% conversion. This lack of reactivity of aliphatic aldehydes was also observed as well by Zhang *et.al.*[8]
[b] Isolated yields.
[c] Enantiomeric excess values were determined by chiral HPLC analysis. Racemic trace obtained using rac-BINAP$(AuCl)_2$ as gold catalyst.

and **3ae** in 80%, 79% and 82% yield, and 92%, 86%, and 92% ee, respectively. Aromatic aldehydes substituted in the *para*-position with acetyl **2f** or benzyl **2g** groups also behaved as expected giving products **3af** and **3ag** in 90% and 91% ee, respectively. *tert*-Butyl substituent in the *para*-position **2h** gave **3ah** in 84% yield and 90% ee. *para*-Substitution of the aromatic ring with a moderately electron-withdrawing group **2i** didn't affect the success of this transformation, so that **3ai** was isolated in 81% yield and 87% ee. 3-Furaldehyde **2j**, 1-naphthaldehyde **2k** and 2-naphthaldehyde **2l** afforded the corresponding 2,5-dihydrofurans **3aj**, **3ak** and **3al** in high yields and 95%, 91%, and 94% ee, respectively.

2.3. Secondary propargyl ketals

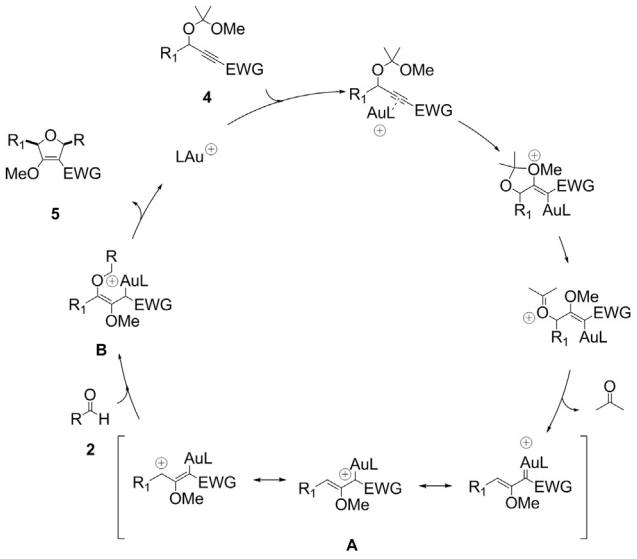
Propargyl ketal **4** reacted with *trans*-cinamaldehyde **2a** under different reaction conditions (Table 3). The desired product **5** was obtained in all cases with moderate yields and enantioselectivities. (*R*)-BINAP(AuNTf$_2$)$_2$ catalyzed the cycloaddition reaction with 79% yield and 50% enantiomeric excess (Table 3, entry 1). In order to optimize the enantioinduction, other chiral dinuclear gold(I) catalysts were examined. (Table 3, entries 2–5). Reaction with (*R*)-DTBM-MeO-BIPHEP(AuNTf$_2$)$_2$ in the same conditions previously optimized for substrate **1a** afforded **5aa** in 62% ee. (Table 3, entry 5) However, the yield of the reaction in this case dropped to 51%. Increasing the bulk of the propargyl substituent from methyl to isopropyl (Table 3, entry 6), resulted in a further decrease in yield with a very small increase in enantiomeric excess. The use of (*R*)-BINAP as chiral ligand for the bulky isopropyl substrates didn't give better yields this time. (Table 3, entry 7) In all this cases, excellent diastereoselectivities were observed as only the *cis*-isomers were isolated.

2.4. Mechanism

The mechanism proposed for the transformation of both kinds of propargyl acetals/ketals is in line with the one proposed by Zhang et al. in 2008. (Scheme 1) Gold(I) promoted a 1,2-migration-fragmentation sequence of the ketal substrate into a migrated alcoxy group and a ketone, which behaves as a good leaving group to generated intermediate **A**. Subsequent stepwise addition of aldehyde generates the desired product.

3. Gold(I)-catalyzed [3+3] cycloaddition reactions between secondary propargyl ketals and nitrones

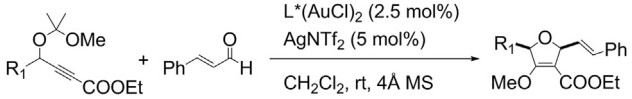
After this, we briefly explored 1,3-dipoles as nucleophilic components for this reaction. To our delight, secondary propargyl ketal



Scheme 1. Mechanistic hypothesis for the formation of functionalized 2,5-hydrofurans.

4c substituted with electron rich *p*-MeO-Ph substituent reacted with nitrones **6a** and **6b** under $Ph_3PAuOTf$ catalysis, affording compounds **7ca** and **7cb** in 90% yield in both cases. (Table 4, entries 1 and 2) This is a formal gold(I) catalyzed [3+3] cycloaddition reaction between both components. When nitrones **6c** and **6d** were used, both substrate **4c** without the ketal moiety and the corresponding nitrone were recovered. (Table 4, entries 3 and 4). Therefore both substituents must be aromatic to obtain the desired product. In order to check if this transformation could be rendered assymetric, we used **L3**=(*R*)-DTBM-SEGPHOS and **L5**=(*R*)-DTBM-MeO-BIPHEP as chiral ligand for the gold(I) catalyst, successful in our previous experiments. Surprisingly, the cycloaddition didn't occur at all this time. (Table 4, entries 5 and 6) Therefore, we decided to explore mononuclear chiral gold(I)-phosphite and phosphoramidite complexes. Chiral phosphite and phosphoramidite ligands had been previously used to induce high levels of enantioselectivity in different gold(I)-catalyzed processes.[11] In our case, using phosphite ligand **L10** almost no product was obtained. (Table 4, entry 7). **L11** afforded the desired product in 60% yield and 19% ee (Table 4, entry 8). When we tried phosphoramidite ligand **L12** with similar scaffold, **7ca** was obtained in 55% yield and 50% ee. (Table 4, entry 9) Gold(I)-catalyst with phosphoramidite ligand **L8** afforded

Table 3
Asymmetric [3+2] cycloaddition reaction: secondary propargyl ketals (scope and optimization)[a]

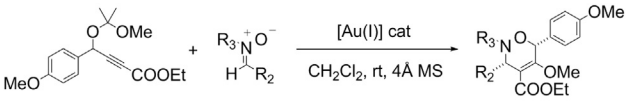


4 **2a** **5**

Entry	R_1	Ligand (L*)	Product[b] (% yield)	*cis*:*trans*	ee[c] (%)
1	**4a** (R_1=Me)	**L1**=(*R*)-BINAP	**5aa** (79)	>7:1	50
2	**4a** (R_1=Me)	**L6**=(*S*)-Cy-SEGPHOS	**5aa** (75)	>3:1	27
3	**4a** (R_1=Me)	**L4**=(*R*)-MeO-BIPHEP	**5aa** (58)	>5:1	10
4	**4a** (R_1=Me)	**L7**=(*R*)-Cl-MeO-BIPHEP	**5aa** (74)	>7:1	10
5	**4a** (R_1=Me)	**L5**=(*R*)-DTBM-MeO-BIPHEP	**5aa** (51)	>5:1	62
6	**4b** (R_1=^{i}Pr)	**L5**=(*R*)-DTBM-MeO-BIPHEP	**5ba** (40)	>10:1	66
7	**4b** (R_1=^{i}Pr)	**L1**=(*R*)-BINAP	**5ba** (40)	>10:1	53

[a] Reaction conditions: 2.5 mol % gold catalyst, 5 mol % $AgNTf_2$, 0.15 mmol (1 equiv) of **4**, 0.23 mmol (1.5 equiv) of aldehyde **2**, 10 mg of 4 Å molecular sieves (MS), 0.8 mL CH_2Cl_2, 1.5 h.
[b] Isolated yields for the major *cis* isomer.
[c] Enantiomeric excess values were determined by chiral HPLC analysis. Racemic trace obtained using *rac*-BINAP(AuCl)$_2$ as gold catalyst.

Table 4
Gold(I)- catalyzed [3+3] cycloaddition of secondary propargyl ketals and nitrones[a]



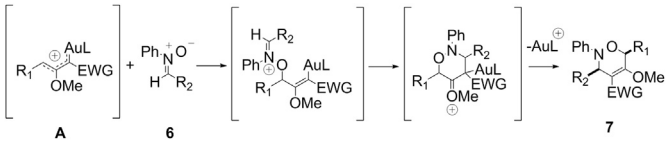
4c **6** **7**

Entry	Nitrone	Gold(I) catalyst	Product (yield %, ee %)[b,c]
1	**6a** (R_2=Ph, R_3=Ph)	Ph_3PAuCl	**7ca** (90, na)
2	**6b** (R_2=*p*-MeO-Ph, R_3=Ph)	Ph_3PAuCl	**7cb** (90, na)
3	**6c** (R_2=*p*-MeO-Ph, R_3=Me)	Ph_3PAuCl	**7cc** (No reaction)
4	**6d** (R_2=*p*-MeO-Ph, R_3=Bn)	Ph_3PAuCl	**7cd** (No reaction)
5[d]	**6a** (R_2=Ph, R_3=Ph)	(*R*)-**L3**$(AuCl)_2$	**7ca** (No reaction)
6[d]	**6a** (R_2=Ph, R_3=Ph)	(*R*)-**L5**$(AuCl)_2$	**7ca** (No reaction)
7	**6a** (R_2=Ph, R_3=Ph)	(*S*), (−)-**L10**AuCl	**7ca** (3, 70)
8	**6a** (R_2=Ph, R_3=Ph)	(*R*)-**L11**AuCl	**7ca** (60, 19)
9	**6a** (R_2=Ph, R_3=Ph)	(*R,R,R*)-**L12**AuCl	**7ca** (55, 50)
10	**6a** (R_2=Ph, R_3=Ph)	(*S,S,S*)-**L8**AuCl	**7ca** (70, 72)
11	**6a** (R_2=Ph, R_3=Ph)	(*S,S,S*)-**L9**AuCl	**7ca** (20, 45)
12	**6b** (R_2=*p*-MeO-Ph, R_3=Ph)	(*S,S,S*)-**L8**AuCl	**7cb** (60, 55)

[a] Reaction conditions: 5 mol % gold(I) catalyst, 5 mol % AgOTf, 0.17 mmol (1 equiv) of **4c**, 0.17 mmol (1 equiv) of nitrone **6**, 10 mg of 4 Å molecular sieves (MS), 1 mL CH_2Cl_2, 12 h.
[b] Isolated yields.
[c] Enantiomeric excess values were determined by chiral HPLC analysis. Racemic trace obtained using Ph_3PAuCl as gold(I)-catalyst.
[d] 2.5 mmol gold(I) catalyst.

compound **7ca** in 70% yield and 72% ee. (Table 4, entry 10) Using nitrone **6b**, desired product **7cb** was obtained in 60% yield and 55% ee. (Table 4, entry 12) When more bulky ligand phosphoramidite ligand **L9** was used, the desired product was obtain only in 20% yield and 45% ee (Table 4, entry 11).

We envisioned similar reactivity as above for this [3+3] cycloaddition transformation. Gold(I) promoted a 1,2-migration-fragmentation sequence of the ketal substrate **4c** into a migrated alcoxy group and a ketone as proposed in previous page, (see Scheme 1) generating intermediate **A** (as in all its resonance forms). This intermediate reacted with the 1,3-dipole (nitrones **6a** and **6b**) in a formal [3+3] cycloaddition. (Scheme 2). Nucleophilic attack by the nitrone on the gold carbene was followed by intramolecular iminium ion addition to the catalyst activated vinyl ether. Similar cycloadducts had been obtained when reacting the equivalent diazocompounds with the same nitrones under copper catalysis.[12]



A **6** **7**

Scheme 2. Mechanistic hypothesis for the cycloaddition of secondary propargyl ketals and nitrones.

4. Conclusion

In conclusion, we have developed a gold(I)-catalyzed enantioselective [3+2] cycloaddition of propargyl acetals/ketals and aldehydes, which allowed a variety of highly enantioenriched functionalized 2,5-dihydrofurans with good efficiencies. This proceeds via migration and fragmentation of the ketal substrate and cycloaddition of the in situ generated gold carbenoid intermediate. Furthermore, the development of a new gold(I)-catalyzed [3+3]-cycloaddition of secondary propargyl acetals and nitrones and its enantioselective version provides us more insight understanding of the powerful role of gold(I) in catalysis and foreshadows new cycloaddition reactions.

5. Experimental section

5.1. General

Unless otherwise noted, reagents were obtained from commercial sources and used without further purification. All reactions were carried out under air unless otherwise stated. Dry THF, dichloromethane, diethyl ether, and triethylamine were obtained by passage through activated alumina columns under argon. All other dried solvents were obtained by storage over 3 Å or 4 Å molecular sieves overnight. TLC analysis of reaction mixtures was performed on Merck silica gel 60 F254 TLC plates and visualized by UV, or potassium permanganate solution. Flash chromatography was carried out with ICN Sili Tech 32–63 D 60 Å silica gel. ^1H and ^{13}C NMR spectra were recorded with Bruker AV-300, AVQ-400, AVB-400 and DRX-500 spectrometers and were referenced to residual 1H and 13C signals of the deuterated solvent. Structures were confirmed using NOESY, COSY and HSQC experiments. Data are reported as follows: chemical shift (δ), multiplicity, integrated intensity, coupling constant (J) in hertz (Hz). Abbreviations to denote the multiplicity of a particular signal are s (singlet), d (doublet), t (triplet), dd (double doublet), q (quartet), m (multiplet). Mass spectral data were obtained via the Micro-Mass/Analytical Facility operated by the College of Chemistry, University of California, Berkeley. Enantioselectivity was determined by chiral HPLC using Daicel CHIRALPAK AD-H, WH and IC columns (0.46×25 cm). Substrates **1a**,[8] **4**,[8] and **6**[13] and gold catalyst (*S,S,S*)-**L8**AuCl, (*S,S,S*)-**L9**AuCl, (*S*), (−)-**L10**AuCl and (*R,R,R*)-**L12**AuCl[14] were prepared following literature procedures. All characterization data was in complete agreement with the reported values.

5.2. General procedure for gold(I)-catalyzed [3+2] cycloadditions

To a small vial was added $AgNTf_2$ (0.008 mmol, 0.05 equiv) and the appropriate dinuclear catalyst (0.004 mmol, 0.025 equiv) in dichloromethane (0.5 mL). The resulting mixture was sonicated for 3 min. The resulting suspension was filtered through glass fiber into a solution of the corresponding propargyl ketal/acetal **1** or **4** (0.15 mmol, 1 equiv) and aldehyde **2** (0.23 mmol, 1.5 equiv) in dichloromethane (0.3 mL) with 4 Å molecular sieves. The reaction mixture was stirred for 1.5 h at room temperature. After this period, the crude mixture was filtered through a short pad of silica gel, eluted with EtOAc and concentrated under reduced pressure to give crude **3** or **5**. Reaction crudes were purified via silica gel flash column chromatography with hexanes:ethyl acetate mixtures. All racemic material was synthesized utilizing *rac*-BINAP (0.025 equiv) and $AgNTf_2$ (0.05 equiv), following the above mentioned procedure. The enantiomeric excess was determined by chiral HPLC analysis using AD-H, WH and IC columns.

5.3. General procedure for gold(I)-catalyzed [3+3] cycloadditions

To a small vial was added AgOTf (0.009 mmol, 0.05 equiv) and the appropriate catalyst (0.009 mmol, 0.05 equiv) in dichloromethane (0.5 mL).The resulting mixture was sonicated for 3 min. The resulting suspension was filtered through glass fiber into a solution of propargyl ketal **4c** (0.17 mmol, 1 equiv) and the corresponding nitrone **6** (0.17 mmol, 1 equiv) in the same solvent (0.3 mL) with 4 Å molecular sieves. The reaction mixture was stirred for 12 h at room temperature. After this period, the crude mixture was filtered through a short pad of silica gel, eluted with EtOAc and concentrated under reduced pressure to give crude **7**. Reaction crudes were purified via silica gel flash column chromatography with hexanes:ethyl acetate mixtures. All racemic material

was synthesized using Ph_3PAuCl (0.009 mmol, 0.05 equiv) and AgOTf (0.009 mmol, 0.05 equiv), following the procedure mentioned above. The enantiomeric excess was determined by chiral HPLC analysis using AD-H columns.

5.4. Characterization of the reaction products

*5.4.1. Methyl (2S)-4-ethoxy-5,5-dimethyl-2-[(E)-2-phenylethenyl]-2,5-dihydrofuran-3-carboxylate (**3aa**).* Colorless oil. 80% Yield. ^{1}H NMR (500 MHz, CD_2Cl_2): δ 7.45–7.40 (m, 2H), 7.37–7.31 (m, 2H), 7.29–7.23 (m, 1H), 6.65 (d, 1H, J=16.0 Hz), 6.26 (dd, 1H, J=7.0 Hz, J=16.0 Hz), 5.45 (d, 1H, J=7.0 Hz), 4.56–4.47 (m,1H), 4.42–4.33 (m, 1H), 3.69 (s, 3H), 1.43 (s, 3H), 1.38 (s, 3H), 1.34 (t, 3H, J=7.0 Hz). ^{13}C NMR (125.73 MHz, CD_2Cl_2): δ 168.1, 163.6, 137.0, 131.0, 130.7, 128.5, 128.5, 127.5, 126.5, 126.5, 100.8, 85.0, 82.4, 70.4, 51.1, 27.0, 26.1, 15.1. HRMS (EI) calcd for $C_{18}H_{22}O_4$ $(M)^+$: 302.1518. Found: 302.1525. HPLC (Chiralpak AD-H column, 99:01 hexanes/isopropanol, 1 ml/min), tr=13.7 min (major), 19.5 min (minor); ee=95%.

*5.4.2. Methyl (2S)-(2,2-diphenylethenyl)-4-ethoxy-5,5-dimethyl-2,5-dihydrofuran-3-carboxylate (**3ab**).* Colorless oil. 78% Yield. ^{1}H NMR (500 MHz, CD_2Cl_2): δ 7.48–7.16 (m, 10H), 5.96 (d, 1H, J=9.9 Hz), 5.33 (d, 1H, J=9.9 Hz), 4.56–4.46 (m, 1H), 4.39–4.31 (m, 1H), 3.65 (s, 3H), 1.43 (s, 3H), 1.32 (t, 3H, J=7.0 Hz), 1.30 (s, 3H). ^{13}C NMR (125.73 MHz, CD_2Cl_2): δ 168.4, 163.6, 144.6, 142.5, 139.3, 130.2, 130.2, 129.8, 128.1, 128.1, 128.0, 128.0, 127.7, 127.7, 127.5, 127.3, 101.1, 84.8, 79.0, 70.3, 51.0, 27.3, 26.0, 15.1. HRMS (EI) calcd for $C_{24}H_{26}O_4$ $(M)^+$: 378.1831. Found: 378.1837. HPLC (Chiralpak AD-H column, 98:02 hexanes/isopropanol, 1 ml/min), tr=8.0 min (major), 8.6 min (minor); ee=89%.

*5.4.3. Methyl (2S)-4-ethoxy-2-(4-methoxyphenyl)-5,5-dimethyl-2,5-dihydrofuran-3-carboxylate (**3ac**).* Colorless oil. 80% Yield. ^{1}H NMR (500 MHz, CD_2Cl_2): δ 7.28 (d, 2H, J=8.4 Hz), 6.88 (d, 2H, J=8.1 Hz), 5.77 (s, 1H), 4.66–4.55 (m, 1H), 4.33–4.23 (m, 1H), 3.82 (s, 3H), 3.49 (s, 3H), 1.42 (s, 3H), 1.39 (s, 3H), 1.36 (t, 3H, J=7.1 Hz). ^{13}C NMR (125.73 MHz, CD_2Cl_2): δ 167.9, 163.9, 159.4, 134.3, 128.7, 128.7, 113.4, 113.4, 101.9, 84.65, 83.4, 70.1, 55.2, 50.9, 26.4, 25.7, 15.1. HRMS (EI) calcd for $C_{17}H_{22}O_5$ $(M)^+$: 306.1467. Found: 306.1462. HPLC (Chiralpak AD-H column, 98:02 hexanes/isopropanol, 1 ml/min), tr=9.8 min (major), 12.0 min (minor); ee=92%.

*5.4.4. Methyl (2S)-2-(3,4-dimethoxyphenyl)-4-ethoxy-5,5-dimethyl-2,5-dihydrofuran-3-carboxylate (**3ad**).* Colorless oil. 79% Yield. ^{1}H NMR (300 MHz, CD_2Cl_2): δ 6.95–6.76 (m, 3H), 5.74 (s, 1H), 4.67–4.50 (m, 1H), 4.32–4.15 (m, 1H), 3.82 (s, 6H), 3.47 (s, 3H), 1.40 (s, 3H), 1.37 (s, 3H), 1.33 (t, 3H, J=7.1 Hz). ^{13}C NMR (100.61 MHz, CD_2Cl_2): δ 167.6, 163.8, 148.8, 148.8, 134.8, 119.8, 110.8, 110.8, 101.7, 84.6, 83.7, 70.0, 55.7, 55.6, 50.8, 26.4, 25.6, 15.0. HRMS (EI) calcd for $C_{18}H_{24}O_6$ $(M)^+$: 336.1573. Found: 336.1579. HPLC (Chiralpak AD-H column, 98:02 hexanes/isopropanol, 1 ml/min), tr=22.2 min (major), 32.4 min (minor); ee=86%.

*5.4.5. Methyl (2S)-2-(2,3-dimethoxyphenyl)-4-ethoxy-5,5-dimethyl-2,5-dihydrofuran-3-carboxylate (**3ae**).* Colorless oil. 82% Yield. ^{1}H NMR (500 MHz, CD_2Cl_2): δ 7.05 (d, 1H, J=7.7 Hz), 6.91–6.85 (m, 2H), 6.26 (s, 1H), 4.68–4.57 (m, 1H), 4.43–4.33 (m, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.48 (s, 3H), 1.39 (s, 3H), 1.37 (t, 3H, J=7.0 Hz), 1.36 (s, 3H). ^{13}C NMR (125.73 MHz, CD_2Cl_2): δ 168.8, 163.7, 152.9, 147.7, 135.9, 123.9, 119.4, 111.8, 101.0, 84.9, 76.7, 70.4, 61.0, 55.7, 50.9, 26.4, 25.9, 15.1. HRMS (EI) calcd for $C_{18}H_{24}O_6$ $(M)^+$: 336.1573. Found: 336.1574. HPLC (Chiralpak AD-H column, 98:02 hexanes/isopropanol, 1 ml/min), tr=9.4 min (major), 12.9 min (minor); ee=92%.

*5.4.6. Methyl (2S)-2-[4-(acetyloxy)phenyl]-4-ethoxy-5,5-dimethyl-2,5-dihydrofuran-3-carboxylate (**3af**).* Colorless oil. 83% Yield. ^{1}H NMR (500 MHz, CD_2Cl_2): δ 7.39 (d, 2H, J=8.7 Hz), 7.07 (d, 2H, J=8.7 Hz), 5.83 (s, 1H), 4.67–4.54 (m, 1H), 4.39–4.29 (m, 1H), 3.51 (s, 3H), 2.30 (s, 3H), 1.43 (s, 3H), 1.41 (s, 3H), 1.36 (t, 3H, J=7.1 Hz). ^{13}C NMR (125.73 MHz, CD_2Cl_2): δ 169.5, 168.5, 163.6, 150.4, 140.0, 128.6, 128.6, 121.3, 121.3, 101.6, 85.0, 83.3, 70.3, 50.9, 26.4, 25.7, 20.9, 15.1. HRMS (EI) calcd for $C_{18}H_{22}O_6$ $(M)^+$: 334.1416. Found: 334.1410. HPLC (Chiralpak AD-H column, 98:02 hexanes/isopropanol, 1 ml/min), tr=11.7 min (major), 13.8 min (minor); ee=90%.

*5.4.7. (2S)-2-[4-(Benzyloxy)phenyl]-4-ethoxy-5,5-dimethyl-2,5-dihydrofuran-3-carboxylate (**3ag**).* White solid. 81% Yield. ^{1}H NMR (500 MHz, CD_2Cl_2): δ 7.49–7.33 (m, 5H), 7.29 (d, 2H, J=8.6 Hz), 6.96 (d, 2H, J=8.6 Hz), 5.78 (s, 1H), 5.09 (s, 2H), 4.65–4.55 (m, 1H), 4.35–4.24 (m, 1H), 3.49 (s, 3H), 1.43 (s, 3H), 1.40 (s, 3H), 1.36 (t, 3H, J=7.0 Hz). ^{13}C NMR (125.73 MHz, CD_2Cl_2): δ 167.9, 163.6, 158.5, 137.2, 134.8, 128.8, 128.8, 128.5, 128.5, 127.9, 127.6, 127.6, 114.3, 114.3, 101.8, 84.7, 83.4, 70.1, 69.9, 50.9, 26.4, 25.7, 15.1. HRMS (EI) calcd for $C_{23}H_{26}O_5$ $(M)^+$: 382.1780. Found: 382.1774. HPLC (Chiralpak AD-H column, 98:02 hexanes/isopropanol, 1 ml/min), tr=13.6 min (major), 16.8 min (minor); ee=91%.

*5.4.8. Methyl (2S)-2-(4-tert-butylphenyl)-4-ethoxy-5,5-dimethyl-2,5-dihydrofuran-3-carboxylate (**3ah**).* Colorless oil. 84% Yield. ^{1}H NMR (500 MHz, CD_2Cl_2): δ 7.38 (d, 2H, J=7.1 Hz), 7.28 (d, 2H, J=7.1 Hz), 5.80 (s, 1H), 4.64–4.55 (m, 1H), 4.35–4.26 (m, 1H), 3.51 (s, 3H), 1.42 (s, 3H), 1.40 (s, 3H), 1.39–1.32 (m, 12H). ^{13}C NMR (125.73 MHz, CD_2Cl_2): δ 167.9, 163.9, 150.9, 139.3, 127.2, 125.1, 101.7, 84.8, 83.7, 70.2, 50.9, 34.4, 31.1, 31.1, 31.1, 26.4, 25.8, 15.1. HRMS (EI) calcd for $C_{20}H_{28}O_4$ $(M)^+$: 332.1988. Found: 332.1991. HPLC (Chiralpak IC column, 95:05 hexanes/isopropanol, 1 ml/min), tr=7.4 min (major), 8.0 min (minor); ee=90%.

*5.4.9. Methyl (2S)-4-ethoxy-2-(4-fluorophenyl)-5,5-dimethyl-2,5-dihydrofuran-3-carboxylate (**3ai**).* Colorless oil. 81% Yield. ^{1}H NMR (500 MHz, CD_2Cl_2): δ 7.38–7.33 (m, 2H), 7.07–7.01 (m, 2H), 5.81 (s, 1H), 4.67–4.55 (m, 1H), 4.35–4.25 (m, 1H), 3.51 (s, 3H), 1.43 (s, 3H), 1.40 (s, 3H), 1.36 (t, 3H, J=7.1 Hz). ^{13}C NMR (125.73 MHz, CD_2Cl_2): δ 168.2, 164.6, 163.6, 161.4, 138.4, 129.3, 129.3, 114.9, 114.7, 101.6, 85.0, 83.2, 70.2, 50.9, 26.4, 25.6, 15.0. HRMS (EI) calcd for $C_{16}H_{19}O_4F$ $(M)^+$: 294.1267. Found: 294.1266. HPLC (Chiralpak AD-H column, 99:01 hexanes/isopropanol, 1 ml/min), tr=9.4 min (major), 10.1 min (minor); ee=87%.

*5.4.10. Methyl (2S)-4-ethoxy-2-(furan-3-yl)-5,5-dimethyl-2,5-dihydrofuran-3-carboxylate (**3aj**).* Colorless oil. 80% Yield. ^{1}H NMR (500 MHz, CD_2Cl_2): δ 7.43 (s, 1H), 7.34 (s, 1H), 6.41 (s,1H), 5.85 (s, 1H), 4.61–4.52 (m, 1H), 4.35–4.27 (m, 1H), 3.61 (s, 3H), 1.39 (s, 3H), 1.37 (s, 3H), 1.34 (t, 3H, J=7.1 Hz). ^{13}C NMR (125.73 MHz, CD_2Cl_2): δ 167.9, 163.6, 142.9, 140.3, 127.8, 109.2, 100.9, 84.8, 75.9, 70.2, 51.0, 26.5, 25.8, 15.1. HRMS (EI) calcd for $C_{14}H_{18}O_5$ $(M)^+$: 266.1154. Found: 266.1157. HPLC (Chiralpak AD-H column, 99:01 hexanes/isopropanol, 1 ml/min), tr=10.6 min (major), 11.9 min (minor); ee=95%.

*5.4.11. Methyl (2S)-4-ethoxy-5,5-dimethyl-2-(naphthalen-1-yl)-2,5-dihydrofuran-3-carboxylate (**3ak**).* Colorless oil. 82% Yield. ^{1}H NMR (500 MHz, CD_2Cl_2): δ 8.35 (d, 1H, J=8.5 Hz), 7.91 (d, 1H, J=7.6 Hz), 7.87–7.81 (m, 1H), 7.62–7.43 (m, 4H), 6.70 (s, 1H), 4.77–4.65 (m, 1H), 4.55–4.46 (m, 1H), 3.45 (s, 3H), 1.46 (s, 3H), 1.42 (t, 3H, J=7.0 Hz), 1.31 (s, 3H). ^{13}C NMR (125.73 MHz, CD_2Cl_2): δ 169.0, 163.9, 138.1, 133.9, 132.0, 128.5, 128.3, 125.9, 125.6, 125.3, 124.2, 123.9, 100.5, 85.2, 79.4, 70.6, 51.0, 26.3, 25.9, 15.2. HRMS (EI) calcd for $C_{20}H_{22}O_4$ $(M)^+$: 326.1518. Found: 326.1519. HPLC (Chiralpak AD-H column, 99:01 hexanes/isopropanol, 1 ml/min), tr=10.7 min (major), 12.2 min (minor); ee=91%.

*5.4.12. Methyl (2S)-4-ethoxy-5,5-dimethyl-2-(naphthalen-2-yl)-2,5-dihydrofuran-3-carboxylate (**3al**).* Colorless oil. 82% Yield. ^{1}H NMR

(500 MHz, CD_2Cl_2): δ 7.94–7.79 (m, 4H), 7.56–7.46 (m, 3H), 6.00 (s, 1H), 4.71–4.60 (m, 1H), 4.40–4.29 (m, 1H), 3.45 (s, 3H), 1.49 (s, 3H), 1.46 (s, 3H), 1.39 (t, 3H, *J*=7.0 Hz). ^{13}C NMR (125.73 MHz, CD_2Cl_2): δ 168.2, 163.9, 139.6, 133.3, 133.2, 128.0, 127.9, 127.6, 126.8, 125.9, 125.9, 125.3, 101.6, 85.1, 84.1, 70.3, 50.9, 26.4, 25.8, 15.1. HRMS (EI) calcd for $C_{20}H_{22}O_4$ $(M)^+$: 326.1518. Found: 326.1523. HPLC (Chiralpak AD-H column, 99:01 hexanes/isopropanol, 1 ml/min), tr=15.4 min (major), 24.8 min (minor); ee=94%.

*5.4.13. Ethyl (2S,5R)-4-methoxy-5-methyl-2-[(E)-2-phenylethenyl]-2,5-dihydrofuran-3-carboxylate (**5aa**).* Colorless oil. 51% Yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41–7.38 (m, 2H), 7.35–7.30 (m, 2H), 7.27–7.23 (m, 1H), 6.66 (d, 1H, *J*=15.5 Hz), 6.22 (dd, 1H, *J*=15.5 Hz, *J*=6.9 Hz), 5.51–5.47 (m, 1H), 4.85–4.79 (m, 1H), 4.26–4.01 (m, 2H), 4.05 (s, 3H), 1.46 (d, 3H, *J*=6.5 Hz), 1.24 (t, 3H, *J*=7.0 Hz). ^{13}C NMR (151 MHz, $CDCl_3$): δ 166.2, 163.1, 136.8, 131.9, 130.3, 128.5, 128.5, 127.6, 126.6, 126.6, 102.8, 84.6, 78.7, 60.5, 60.5, 21.1, 14.2. HRMS (EI) calcd for $C_{17}H_{20}O_4$ $(M)^+$: 288.1362. Found: 288.1360. HPLC (Chiralpak AD-H column, 98:02 hexanes/isopropanol, 1 ml/min), tr=10.4 min (minor), 11.0 min (major); ee=62%.

*5.4.14. Ethyl (2S,5R)-4-methoxy-2-[(E)-2-phenylethenyl]-5-(propan-2-yl)-2,5-dihydrofuran-3-carboxylate (**5ba**).* Colorless oil. 40% Yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 (m, 2H), 7.31 (m, 2H), 7.23 (m, 1H), 6.64 (d, 1H, *J*=15.8 Hz), 6.16 (dd, 1H, *J*=15.7 Hz, *J*=7.8 Hz), 5.48 (dd, 1H, *J*=7.9 Hz, *J*=3.1 Hz), 4.57 (t, 1H, *J*=3.0 Hz), 4.21–4.01 (m, 5H), 2.23–1.96 (m, 1H), 1.19 (t, 3H, *J*=7.1 Hz), 1.05 (d, 3H, *J*=7.0 Hz), 0.94 (t, 3H, *J*=7.0 Hz). ^{13}C NMR (125.73 MHz, $CDCl_3$): δ 164.6, 163.3, 136.85, 132.7, 129.4, 128.6, 128.6, 127.8, 126.8, 126.8, 103.7, 87.4, 84.8, 61.1, 60.3, 30.8, 19.1, 16.3, 14.3. HRMS (EI) calcd for $C_{19}H_{24}O_4$ $(M)^+$: 316.1675. Found: 316.1672. HPLC (Chiralpak WH column, 99:01 hexanes/isopropanol, 1 ml/min), tr=10.4 min (minor), 13.5 min (major); ee=66%.

*5.4.15. Ethyl (3R,6S)-5-methoxy-6-(4-methoxyphenyl)-2,3-diphenyl-3,6-dihydro-2H-1,2-oxazine-4-carboxylate (**7ca**).* White solid. ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.46 (d, 2H, *J*=8.7 Hz), 7.39–7.34 (m, 2H), 7.23–7.15 (m, 5H), 6.99 (d, 4H, *J*=8.7 Hz), 6.89 (t, 1H, *J*=7.5 Hz), 5.72 (s, 1H), 5.47 (s, 1H), 4.14–4.04 (m, 2H), 3.84 (s, 3H), 3.71 (s, 3H), 1.12 (t, 3H, *J*=7.1 Hz). ^{13}C NMR (125.73 MHz, CD_2Cl_2): δ 164.9, 160.4, 147.6, 137.8, 130.6, 130.6, 129.5, 129.5, 128.5, 128.5, 128.2, 128.1, 128.1, 127.7, 127.7, 127.6, 122.14, 116.9, 114.0, 114.0, 110.2, 79.7, 64.4, 61.0, 60.6, 55.3, 13.8. HRMS (ESI) calcd for $C_{27}H_{28}NO_5$ $(M+H)^+$: 446.1962. Found: 446.1963. HPLC (Chiralpak AD-H column, 95:05 hexanes/isopropanol, 1 ml/min), tr=12.9 min (major), 15.1 min (minor); ee=72%.

*5.4.16. Ethyl (3R,6S)-5-methoxy-3,6-bis(4-methoxyphenyl)-2-phenyl-3,6-dihydro-2H-1,2-oxazine-4-carboxylate (**7cb**).* White solid. ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.50 (d, 2H, *J*=8.6 Hz), 7.30 (d, 2H, *J*=8.1 Hz), 7.22 (t, 2H, *J*=7.6 Hz), 7.06–6.97 (m, 4H), 6.92 (t, 1H, *J*=7.6 Hz), 6.75 (d, 2H, *J*=8.1 Hz), 5.70 (s, 1H), 5.50 (s, 1H), 4.21–4.05 (m, 2H), 3.88 (s, 3H), 3.74 (s, 6H), 1.17 (t, 3H, *J*=7.1 Hz). ^{13}C NMR (125.73 MHz, CD_2Cl_2): δ 165.0, 160.3, 159.1, 147.8, 131.2, 130.6, 130.6, 130.6, 130.6, 129.6, 128.5, 128.5, 122.0, 116.9, 114.0, 114.0, 114.0, 114.0, 112.9, 112.9, 110.3, 79.8, 64.0, 61.0, 60.6, 55.3, 55.0, 13.9. HRMS (ESI) calcd for $C_{28}H_{30}NO_6$ $(M+H)^+$: 476.2068. Found: 476.2068. HPLC (Chiralpak AD-H column, 95:05 hexanes/isopropanol, 1 ml/min), tr=21.0 min (major), 24.5 min (minor); ee=55%.

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Supplementary data

Supplementary data (Experimental procedures, compound characterization data) related to this article can be found at http://dx.doi.org/10.1016/j.tet.2015.04.109.

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