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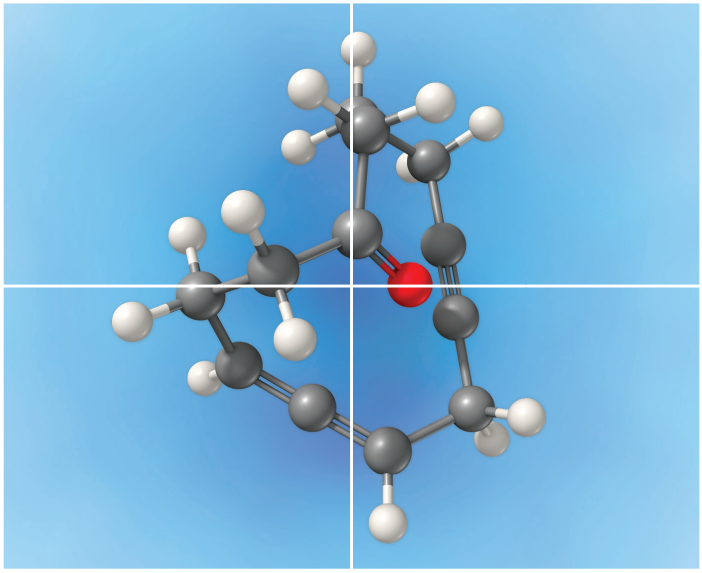

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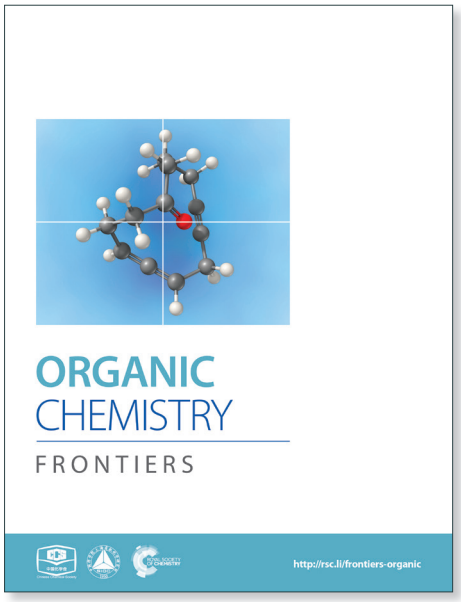

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Gold(I)-Catalyzed Asymmetric [3+2]-Cycloadditons of γ-1-Ethoxyethoxy-propiolates and Aldehydes

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A gold-catalyzed asymmetric intermolecular [3+2]-cycloadditon of γ-1-ethoxyethoxy-propiolate and aldehydes by the use of chiral phosphoramidite (*S*,*R*,*R*)-5a was developed, which provided a facile access to highly substituted 2,5-dihydrofurans in up to 84% yield with up to 97% ee. Control experiments support that this transformation indeed proceeds via an all-carbon gold 1,3-dipole with an open carbocation rather than a S_N2 type reaction.

The development of homogeneous gold catalyzed cycloadditions has been remarkably rapid in past years, [1] due to their good tolerance of air and moisture and high capability to activate C-C π-bonds. The inherent linear binding mode renders the chiral ligand of the gold complex away from the generated sterogenic center, which results in the development of enantioselective gold catalysis[2] still poses considerable difficulty, especially for those intermolecular cases,[3] despite some strategies have been developed to address this challenging issue.

Substituted 2,5-dihydrofurans represent a class of important structural scaffolds, which are not only frequently found in natural products and biologically active molecules but also as useful building blocks.[4] In 2008, The group of L. Zhang developed an elegant method for synthesis of substituted 2,5-dihydrofurans from readily available γ-1-ethoxyethoxy-propiolates and aldehydes or ketones via a gold-catalyzed intermolecular [3+2]-cycloaddition.[5] However, the enantioselective variant of this intermolecular cycloaddition and the mechanism (1,3-dipolar cycloaddition vs tandem S_N2/cyclization) of this reaction have not been well addressed so far. As the continual interest of developing asymmetric gold-catalysis,[6] we developed herein an enantioselective gold(I)-catalyzed intermolecular [3+2]-cycloaddition by the application of chiral Binol-derived phosphoramidite as the ligand. The control experiments support the reaction pathway of this reaction is through a 1,3-dipole rather than tandem S_N2/cyclization.[7]

γ-1-Ethoxyethoxy-propiolate **1a** and 4-methoxybenz-aldehyde **2a** were chosen as model substrates to test a series of chiral ligands. Given the success of chiral bisphosphines in gold-catalyzed enantioselective reactions, our initial efforts focused on the use of chiral bisphosphines such as chiral Bipheps as ligands (see supporting information), only privileged ligand (*R*)-MeO-dtbm-biphep **6** was found to the most efficient in enantioinduction to give 65% ee. We next turned to examine chiral phosphoramidties as ligand (Figure 1), which can be easily tuned in many positions.[8] We were pleased to find that a moderate degree of enantioinduction (68% ee) could be obtained with Binol-derived phosphoramidtie (*R*,*R*,*R*)-**4a** as ligand(Table 1, entry 1). With this encouraging result, other modified chiral phosphoramidties by introduction of various substituents at 3 and 3′-positions of the BINOL moieties were then prepared and investigated (Table 1, entries 3-6). 85% ee was observed by the use of (*R*,*R*,*R*)-**4c** with 3,3'-phenyl group as ligand albeit with only 33% yield (Table 1, **ent-ry** 4), while the corresponding (*S*)-BINOL derived (*S*,*R*,*R*)-**4c** induced a slightly lower enantioselectivity (77% ee, Table 1, entry 7). Attempts to improve the enantioselectivity failed by introducing other substituents such as methyl (**4b**), bulky Ph_3Si (**4d**) and 3,5-bis(3,5-bis-(trifluoro-methyl)phenyl (**4e**) at 3 and 3'-position of the chiral ligand. Spirobiindane derived phosphoramidtie (*S*)-SIPHOS-PE could not give high ee either (73% ee, Table 1, entry 8) and its diastereomer (*R*)-SIPHOS-PE even give lower ee (43% ee, Table 1, entry 9), which indicated that not only the chirality of the axial backbone but also the stereogenic center affect the enantioselectivity. The knowledge learned from our previous work[6a] that the bite angle also plays a crucial role in gold-catalyzed asymmetrical reaction encouraged us to test the octahydrobinol-derived phosphramidites **5a** and **5b** with different bite angle (Table 1, entries 10-12). After some attempts, the methyl substituted (*R*,*R*,*R*)-**5b** resulted in substantially higher enantioselectivity than the corresponding **4b** (82% ee vs 59% ee, Table 1, entries 11 vs 3). To our delight,

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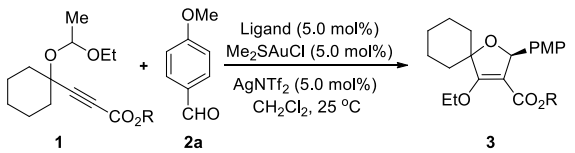
(*S*,*R*,*R*)-**5a** delivered excellent enantioselectivity (90% ee, Table 1, entry 12). Notably, (*S*,*R*,*R*)-**5a** and (*R*,*R*,*R*)-**5a** derived gold complexes result in different enantiomers of 2,5-dihydrofurans, indicating that the axial chirality dictates the absolute stereochemistry of the [3+2] cycloadduct. With the use of (*S*,*R*,*R*)-**5a** as chiral ligand, a series of silver salts such as AgOTf, $AgSbF_6$, $AgBF_4$, $AgO_2C_4F_7$ and $NaBAr_4$(Ar = 3,5-$CF_3C_6H_3$) were then examined, among which $AgNTf_2$ afforded the best result. There is a slight improvement in the enantioselectivity when the reaction was run at 0 °C. The addition of 3Å MS led to a remarkable improvement in yield. When 4 equivs of anisaldehyde **2a** were used, the desired product **3aa** could be isolated in 78 % yield with 92% ee (entry 18). These results clearly validated the strategy and suggested that further improvement might be feasible not only by introducing substituents at 3 and 3'-positions but also through modification the bite angle. Other γ-1-ethoxyethoxy-propiolate esters such as methyl (**1b**), ethyl (**1c**) and *tert*-butyl (**1d**) are applicable to the reaction conditions except the benzyl ester (**1e**), leading to similar level of enantioslectivity (Table 1, entries 19-22).

Table 1. Screening reaction conditions.[a]



1 2a 3

Entry	**1** R	Ligand	Solvent	product **3** (yield %)	ee%
1	^{i}**Pr**(**1a**)	(*R*,*R*,*R*)-**4a**	CH_2Cl_2	**3aa** (46)	-66
2	**1a**	(*S*,*R*,*R*)-**4a**	CH_2Cl_2	**3aa** (48)	68
3	**1a**	(*S*,*R*,*R*)-**4b**	CH_2Cl_2	**3aa** (30)	59
4	**1a**	(*S*,*R*,*R*)-**4c**	CH_2Cl_2	**3aa** (33)	85
5	**1a**	(*R*,*R*,*R*)-**4d**	CH_2Cl_2	**3aa** (35)	-66
6	**1a**	(*R*,*R*,*R*)-**4e**	CH_2Cl_2	**3aa** (23)	-77
7	**1a**	(*R*,*R*,*R*)-**4c**	CH_2Cl_2	**3aa** (56)	-77
8	**1a**	(*S*)-SIPHOS-PE	CH_2Cl_2	**3aa** (54)	73
9	**1a**	(*R*)-SIPHOS-PE	CH_2Cl_2	**3aa** (55)	-43
10	**1a**	(*R*,*R*,*R*)-**5a**	CH_2Cl_2	**3aa** (46)	-69
11	**1a**	(*R*,*R*,*R*)-**5b**	CH_2Cl_2	**3aa** (60)	-82
12	**1a**	(*S*,*R*,*R*)-**5a**	CH_2Cl_2	**3aa** (51)	90
13	**1a**	(*S*,*R*,*R*)-**5a**	DCE	**3aa** (48)	87
14	**1a**	(*S*,*R*,*R*)-**5a**	Toluene	**3aa** (24)	84
15	**1a**	(*S*,*R*,*R*)-**5a**	$CHCl_3$	**3aa** (45)	90
16[b]	**1a**	(*S*,*R*,*R*)-**5a**	CH_2Cl_2	**3aa** (50)	92
17[b,c]	**1a**	(*S*,*R*,*R*)-**5a**	CH_2Cl_2	**3aa** (73)	93
18[b,c,d]	**1a**	(*S*,*R*,*R*)-**5a**	CH_2Cl_2	**3aa** (78)	92
19	Me (**1b**)	(*S*,*R*,*R*)-**5a**	CH_2Cl_2	**3ba** (53)	87
20	Et (**1c**)	(*S*,*R*,*R*)-**5a**	CH_2Cl_2	**3ca** (61)	89
21	^{t}Bu (**1d**)	(*S*,*R*,*R*)-**5a**	CH_2Cl_2	**3da** (64)	83
22	Bn (**1e**)	(*S*,*R*,*R*)-**5a**	CH_2Cl_2	**3ea** (47)	77

[a] Unless otherwise noted, substrate **1** (0.4 mmol), 4-methoxybenzaldehyde **2a** (2 equiv) and $LAuNTf_2$ (5 mol%, LAuCl/AgX=1:1) in 8 mL of solvent at 25 °C for 1 h. Isolated yields are shown and enantiomeric excess determined by chiral HPLC. [b] Reaction performed at 0 °C. [c] 3Å MS (150 mg) was added. [d] 4 equiv of **2a** were used.

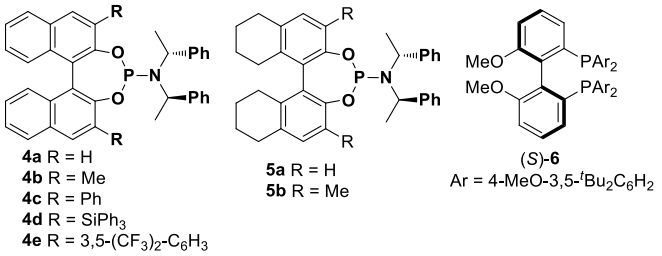
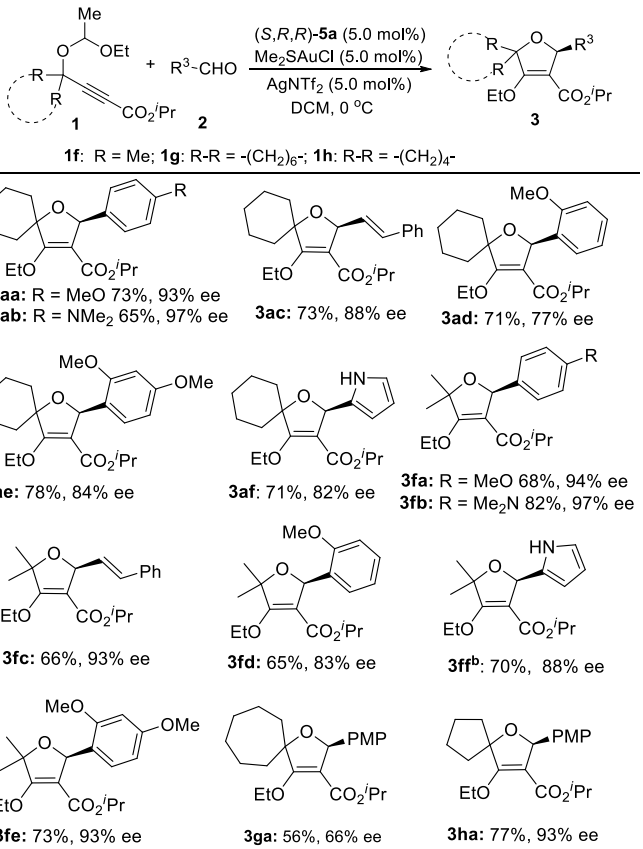


Figure 1. Screened chiral ligands

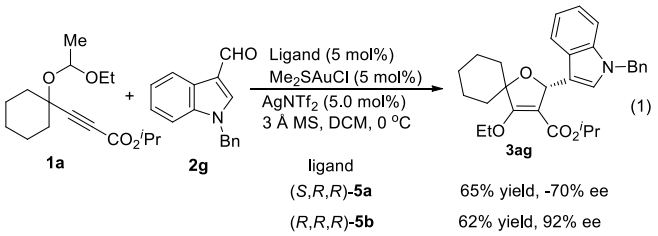
Table 2. Study the reaction scope by the use of (*S*,*R*,*R*)-**5a** as ligand.[a]



[a] Standard Reaction condtitons, PMP = *para*-methoxyphenyl. [b]Reaction was conducted at -20 °C.

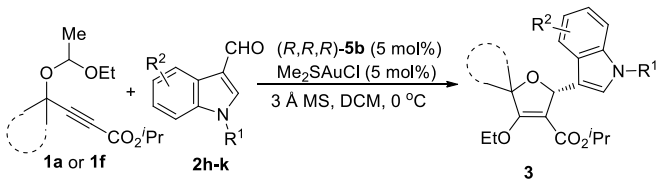
With the optimized conditions in hand, we explored the substrate scope of the reaction by variation of two reaction components (Table 2). In general, *para*-substituted aryl aldehyde gave better ees than those *ortho*-substituted ones. For example, the reaction of *para*-methoxybenzaldehyde **2a** with **1a** gave the product **3aa** with 93% ee, while only 77% ee of **3ad** was obtained from the corresponding *ortho*-methoxy benzaldehyde **2d**. **3ae** with 84% ee could be obtained in 78% yield from the corresponding 2,4-bismethoxybenzaldehyde **2e** and **1a**. The highest selectivity was observed in the case of the *p*-Me_2N-C_6H_4CHO as the substrate, where **3ab** and **3fb** were isolated in 97% ee. Gratifyingly, cinnamaldehyde is also compatible to this transformation to produce the corresponding products **3ac** and **3fc** in good yields with reasonable enantioselectivities. Heterocyclic 1-*H*-

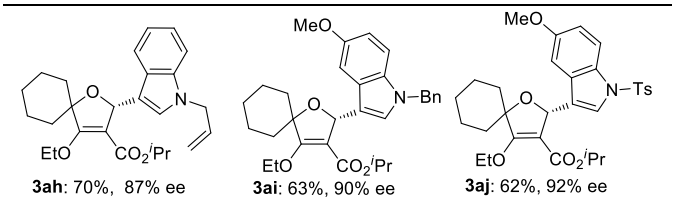
pyrrole-2-carbaldehyde also enables the highly enantioselective synthesis of pyrrol-2-ylsubstituted dihydrofurans **3af** and **3ff**. Acyclic **1f** and cyclic **1h** with a five-membered cyclopentane ring are applicable to this transformation very well. However, substrate **1g** with seven-membered cycle only afford the product **3ga** in moderate yield and enantioselectivity, indicating the ring size also affects the enantioselectivity.



When we tried to extend the scope of aldehyde to the indole-3-carbaldehyde, it was found that the present reaction conditions using (S,R,R)-5a as the chiral ligand were not applicable any more (Eq. 1). Significant erosion in the enantiomeric excess was observed (70% ee). This result indicated that the enantioselctivity of this reaction is a kind of substrate dependent. After further investigation, we were pleased to find that this issue can be well addressed by the use of (*R*,*R*,*R*)-**5b** as the chiral ligand, leading the product **3ag** as the opposite enantioisomer in 62% yield with 92% ee. Inspired by this result, the reactions of various indole-3-carbaldehydes with **1a** and **1f** were then examined under the catalysis of (*R*,*R*,*R*)-**5b**/gold complex (Table 3). The reaction of **1a** with *N*-allyl indole-3-carbaldehyde **2h** afforded the cycloadduct **3ah** in 70% yield with 87% ee. Similarly, the reaction of **1a** with 5-methoxy indole-3-carbaldehydes **2i** and **2j** also worked well to provide products **3ai** and **3aj** in reasonable yields with 90% and 92% ee, respectively.

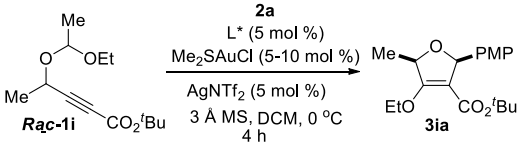
Table 3. (*R*,*R*,*R*)-**5b**/Au(I)-catalyzed [3+2] Reactions of **1** with various indole-3-carbaldehydes





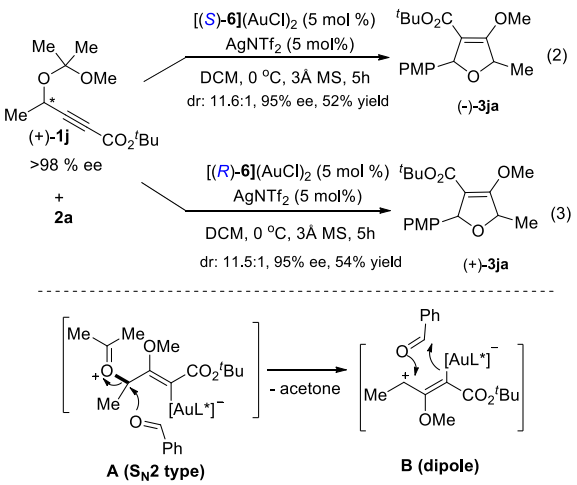
This catalyst system could be also well applied to the reactions of acyclic **1f** and indole-3-carbaldehydes, delivering the desired products **3fg**, **3fj** and **3fk** in high yields with 88-95% ees. The absolute configuration of the products was confirmed by single-crystal X-ray differaction analysis of compound **3fk**.[9] The absolute chemistry of other compounds was rationalized from the compound **3fk**. The X-ray crystal structure of (*R*, *R*, *R*)-5bAuCl was aslo obtained and shown in Supporting Information.

In order to gain insight of the reaction mechanism, racemic and enantioenriched secondary alcohol derived substrates were subjected to the reaction conditions. Notably, the reaction of racemic **1i** with **2a** gave the desired -2,5-dihydrofuran **3ia** with two stereocenters in 44% yield with only 16% ee and 6.0:1 dr under the catalysis of (*S*,*R*,*R*)-**5a** derived gold(I) complex, however, the diastero- and enantioselectivity could be dramatically improved when (*S*)-MeO-dtbm-biphep ((*S*)-**6**) was employed as the chiral ligand. The yield would be improved to 64% with 5 equivalents of aldehyde (Scheme 1).



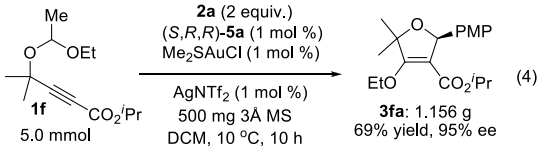
L*	2a	yield (%)	dr	ee (%)
(*S*,*R*,*R*)-**5a**	2 eq.	44	6.0:1	16
(*S*)-**6**	2 eq.	55	11.4:1	96
(*S*)-**6**	3 eq.	62	11.9:1	96
(*S*)-**6**	5 eq.	64	11.1:1	96

Scheme 1. Asymmetric cycloaddition of (±)-**1i** with **2a**.



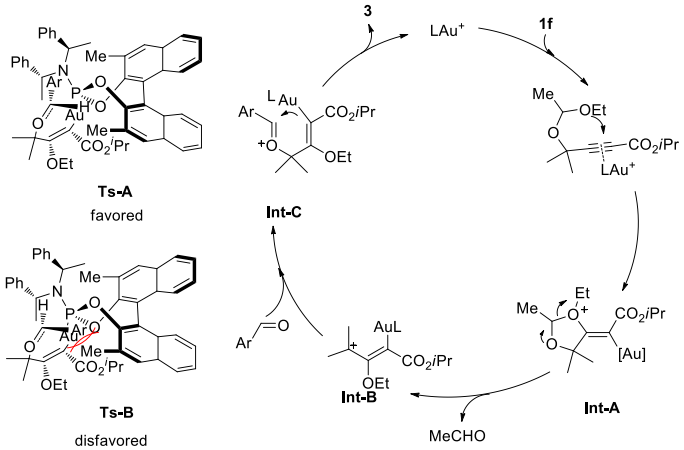
Two control reactions of (+)-**1j** (>98% ee) and **2a** were further carried out under the catalysis of two opposite absolute configuration ligand (*S* or *R*) derived gold complexes, affording (-)-**3ja** and its enantiomer (+)-**3ja**, respectively in almost same yield and selectivity (Eqs 2 and 3). These results support that this transformation proceeds via the all-carbon 1,3-dipole **B** bearing an open carbocation rather than the direct S_N2 attack[8c] of the intermediate **A** by aldehyde,

otherwise, the match and mismatch of the substrate with chiral ligand will lead to the same enantiomer with different ee.



Furthermore, this asymmetric gold(I)-catalyzed reaction is scalable up to a gram-scale without loss of any selectivity and efficiency. The catalyst loading could be reduced to only 1 mol % with a 5 mmol scale to furnish 1.156 g of **3fa** in 69% yield with 95% ee at 10 °C for 10 h (eq. 4), indicating this transformation has a potential practical use in organic synthesis.

A catalytic cycle is proposed as depicted in **Scheme 2**. The reaction is believed to be initiated by the *anti*-attack on a gold-activated C-C multiple bond (a π-complex) by intramolecular oxygen atom of acetal moiety, furnishing intermediate **Int-A**. Then a 1,3-dipole intermediate **Int-B** would be produced through elimination of one molecule acetaldehyde. Next, the aryl aldehyde attacks the open carbocation to form the intermediate **Int-C**. Finally, the product is delivered through cyclization and elimination of the catalytic gold species. The observed absolute stereochemistry can be explained by the proposed induction models shown. The transition state **Ts-A** is more favorably formed than **Ts-B** to preferentially give the desired product with observed stereochemistry, because of the steric repulsion between the Ar group and methyl group of the chiral catalyst.



Scheme 2. Possible mechanistic pathway and induction model.

Conclusions

In summary, we described a highly enantioselective gold-catalyzed [3+2] cycloaddition of in situ generated all-carbon gold-1,3-dipoles with aldehydes under mild conditions. The method has enabled the enantioselective synthesis of a wide variety of functionalized tri- and tertrasubstituted 2,5-dihydrofurans in moderate to high yields with good diastereoselectivities and enantioselectivities. A broad array of substrates are applied to this transformation by careful choice of octahydrobinol-derived phosphramidite or MeO-dtbm-biphep derived gold(I) complexes as catalyst. The control experiments support that this transformation indeed proceeds via an all-carbon gold 1,3-dipole with an open carbocation rather than a S_N2 type reaction. The easy scale-up character also adds value to this transformation to make it as potential practical useful method. Further studies including synthetic applications and extension the scope of dipolarophile are currently underway and will be reported in due course.

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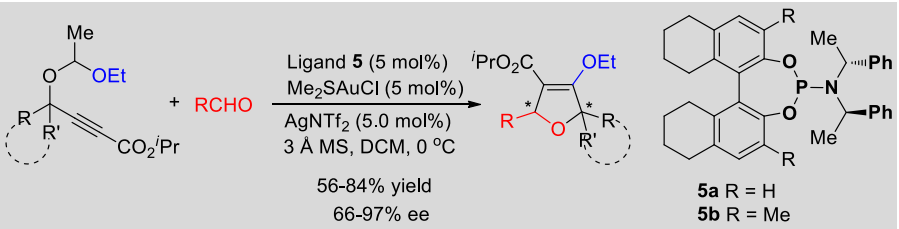
8. J. F. Teichert and B. L. Feringa, *Angew. Chem. Int. Ed.* 2010, **49**, 2486.

9 CCDC 926425 (**3fk**) and 926426 ((*R*,*R*,*R*)-**5b**AuCl).

Graphic abstract



A gold-catalyzed asymmetric intermolecular [3+2]-cycloadditon of γ-1-ethoxyethoxy-propiolate and aldehydes by the use of chiral phosphoramidite (*S*,*R*,*R*)-**5a** or **5b** was developed, which provided a facile access to highly substituted 2,5-dihydrofurans in up to 84% yield with up to 97% ee.