Gold Catalysis

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Diastereo- and Enantioselective Gold(I)-Catalyzed Intermolecular Tandem Cyclization/[3+3]Cycloadditions of 2-(1-Alkynyl)-2-alken-1-ones with Nitrones**

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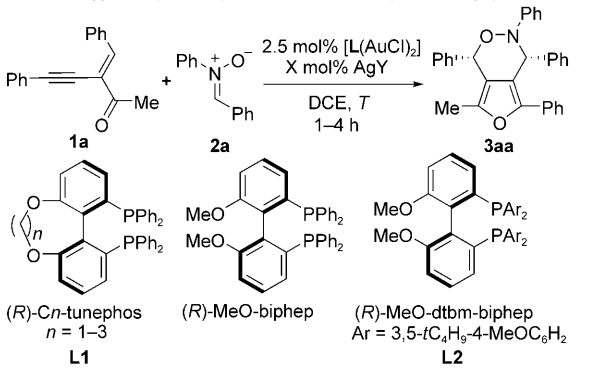
In memory of Xian Huang

Asymmetric cationic gold(I)-catalyzed intermolecular[1] and intramolecular[2] reactions have emerged as powerful tools for the enantioselective synthesis of versatile carbocycles and heterocycles over the past five years.[3] Aside from a few examples using a chiral counteranion strategy[4] and monodentate phosphoramidite ligands,[2a–c] most of these transformations have largely relied on the use of bis(phosphines) as ligands. In order to gain high enantioselectivity, these ligands are often further modified by introducing bulky substituents onto the phosphorous aryl moieties.[1b–e,2f–j] We have recently reported the gold(I)-catalyzed intermolecular regio- and diastereoselctive tandem cyclization/[3+3]-cycloaddition reactions[5] of 2-(1-alkynyl)-2-alken-1-ones[6] with nitrones, thus leading to fused heterobicyclic furo[3,4-d]-[1,2]oxazines.[7,8] The preliminary result showed that (*R*)-MeO-biphep can induce a moderate enantioselectivity. We envisaged that better enantioselectivity might be obtained by modification of this chiral MeO-biphep ligand. Herein, we report the gold(I)-catalyzed diastereo- and enantioselective intermolecular tandem cyclization/[3+3]-cycloaddition reactions of 2-(1-alkynyl)-2-alken-1-ones with nitrones using (*R*)-C_1-tunephos (which acts through modification the bite angle) and (*R*)-MeO-dtbm-biphep (which acts through introduction of bulky substituents on the phosphorous aryl moieties) as chiral ligands. To the best of our knowledge, this is the first report using C_n-tunephos/$(AuCl)_2$ as a chiral catalyst in asymmetric gold-catalyzed reactions.[9]

Ketone **1a** and nitrone **2a** were selected as the model substrates for screening the chiral ligand (Table 1). The (*R*)-MeO-biphep-derived gold complex catalyzed the reaction in dichloromethane at 10 °C, furnishing the desired product **3aa** in 95 % yield and in an encouraging 56 % *ee* (Table 1, entry 1). Inspired by the success of tunephos in asymmetric rhodium-catalyzed hydrogenation,[9a–c] we turned our attention to examining a series of tunephos ligands. We were pleased to find that C_1-tunephos-derived gold complex catalyzed this reaction in 1,2-dichloroethane at −10 °C, thus providing the product **3aa** as single diastereomer in 97 % yield with 95 % *ee* (Table 1, entry 4). Performing the reaction at −20 °C did not further increase the enantioselectivity. However, the ratio of gold(I)-complex/silver also affect the selectivity. Changing the

Table 1: Gold(I)-catalyzed asymmetric tandem cyclization/cycloaddition.



Entry	Ligand (L)	AgX (mol %)	*T* [°C]	Yield [%] (% *ee*)
1	(*R*)-MeO-biphep	AgOTf (2.5)	−10	95 (56)
2[a]	**L1**	AgOTf (5)	−10	94 (76)
3	**L1**	AgOTf (3.75)	−10	99 (89)
4	**L1**	AgOTf (2.5)	−10	97 (95)
5	**L1**	AgOTf (2.5)	−20	95 (94)
6[b]	**L1**	AgOTf (2.5)	−10	81 (96)
7	**L1**	$AgPF_6$ (2.5)	−10	92 (93)
8	**L1**	$AgBF_4$ (2.5)	−10	91 (93)
9	**L1**	$AgSbF_6$ (2.5)	−10	99 (94)
10	(*R*)-C_2-tunephos	AgOTf (2.5)	−10	91 (81)
11	(*R*)-C_3-tunephos	AgOTf (2.5)	−10	94 (88)
12[c]	**L2**	AgOTf (2.5)	0	94 (99)
13	(*S*)-binap	AgOTf (2.5)	−10	99 (29)
14	(*R*)-tolyl-binap	AgOTf (2.5)	−10	99 (−38)

[a] **L1** = (*R*)-C_1-tunephos. [b] $CHCl_3$ was used as solvent, ca. 10% diastereomer was isolated; in other cases, the d.r. was greater than 20:1. [c] **L2** = (*R*)-MeO-dtbm-biphep, Ar = 3,5-*t*C_4H_9-4-$MeOC_6H_2$. DCE = 1,2-dichloroethane. Tf = trifluoromethanesulfonyl.

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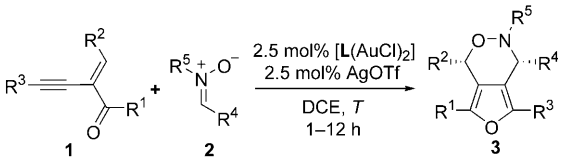
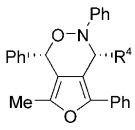
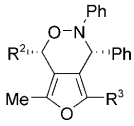
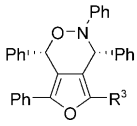
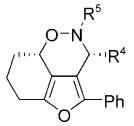
ratio from 1:1 to 1:2 caused the enantiomeric excess of the product to decrease from 95% to 76% (Table 1, entries 2–4). There is an obvious solvent effect on the reactivity and diastereoselectivity rather than enantioselectivity. No reaction occurred in toluene or ether, despite chloroform giving **3aa** in excellent enantiomeric excess but with a relatively lower diasteroselectivity (Table 1, entry 6). Moreover, the excellent enantioselectivity was maintained when $AgPF_6$ (Table 1, entry 7), $AgBF_4$ (Table 1, entry 8), or $AgSbF_6$ (Table 1, entry 9) were employed as silver additives. Replacement of C_1-tunephos with C_2- or C_3-tunephos led to lower enantioselectivities (Table 1, entries 10 and 11). To our delight, introduction bulky substituents onto the phosphine aryl rings (*R*)-MeO-dtbm-biphep also dramatically increased the enantioselectivity in comparison to (*R*)-MeO-biphep, thus providing **3aa** in 94% yield with 99% *ee* at 0°C. In contrast, the gold(I) complexes of (*S*)-binap (binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl) and (*R*)-tolyl-binap induced 29% and 38% *ee*, respectively, but with the enantiomer *ent*-**3aa** as the major isomer for the latter case (Table 1, entries 13 and 14).

Under the optimized reaction conditions, various (1-alkynyl)-2-alken-1-ones and nitrones were examined to study the scope and limitations of this enantioselective gold(I)-catalyzed tandem reaction (Table 2). In general, for those ketones with aromatic R^4 groups, both **L1** and **L2** ligands gave the desired products in high yields with excellent enantio- and diastereoselectivity (d.r. > 20:1) (Table 2, entries 1–7). However, placing aliphatic R^2 substituents on the olefin moiety or R^3 substituents on the alkyne moiety of the ketone resulted in dramatic decreases in enantio- and diastereoselectivity. For examples, the bicyclic products **3da** with $R^3 = n$Bu (**L1**; Table 2, entry 8) and **3ea** with $R^2 = n$Bu (Table 2, entry 9) were obtained under the catalysis of [**L1**$(AuCl)_2$]/AgOTf in 55% and 75% *ee*, respectively. These results indicate that there is a steric demand to obtain excellent enantioselectivity. Gratifyingly, a cyclohexenyl group was tolerated as R^3, and was bulky enough to afford excellent yield and enantioselectivity (Table 2, entry 11; see entry 12). The attempt to improve *ee* values of **3da** and **3ea** by using an [**L2**$(AuCl)_2$]/AgOTf complex as the catalyst failed, thus providing the desired products with even lower *ee* values (**L2**, Table 2, entries 8 and 9). The reactions of cyclic ketone **1h** with nitrones **2a–f** (Table 2, entries 13–18) proceed smoothly to give the corresponding bicyclic products in good yields and greater than 92% *ee* with the use of either **L1** or **L2** as ligand. The (*R*)-C_1-tunephos complex gave a higher enantioselectivity than (*R*)-MeO-dtmb-biphep for the reaction of **1h** with *N*-benzyl nitrone **2g** at room temperature (Table 2, entry 19). The absolute configuration of the products were confirmed by single-crystal X-ray diffraction analysis of representative compounds **3ae** and **3he** (Figure 1).[10]

Table 2: Reaction scope.[a]



1 2 3

Entry	Product		R	Yield [%] (% *ee*) L1	L2
1		**3ab**	R^4 = 1-furanyl	90 (96)	97 (96)
2		**3ac**	R^4 = 4-$NO_2C_6H_4$	93 (95)	93 (97)
3		**3ad**	R^4 = 4-$MeOC_6H_4$	98 (95)	95 (95)
4		**3ae**	R^4 = 4-BrC_6H_4	85 (94)	95 (95)
5		**3af**	R^4 = styryl	97 (97)	88 (97)
6		**3ba**	R^2/R^3 = Ph/4-MeC_6H_4	99 (92)	99 (95)
7		**3ca**	R^2/R^3 = Ph/4-$MeOC_6H_4$	72 (96)	99 (95)
8		**3da**	R^2/R^3 = Ph/*n*-C_4H_9	77 (55)	59 (32)
9		**3ea**	R^2/R^3 = *n*-C_4H_9/Ph	92 (75)	84 (64)
10		**3fa**	R^3 = Ph	92 (93)	94 (98)
11		**3ga**	R^3 = 1-cyclohexenyl	99 (92)	87 (94)
12		**3ia**	R^3 = 1-hexenyl	92 (28)	62 (4)
13		**3ha**	R^4/R^5 = Ph/Ph	90 (97)	75 (97)
14		**3hb**	R^4/R^5 = 1-furanyl/Ph	84 (98)	63 (97)
15		**3hc**	R^4/R^5 = 4-$NO_2C_6H_4$/Ph	84 (98)	82 (97)
16		**3hd**	R^4/R^5 = 4-$MeOC_6H_4$/Ph	74 (92)	55 (97)
17		**3he**	R^4/R^5 = 4-BrC_6H_4/Ph	94 (95)	78 (97)
18		**3hf**	R^4/R^5 = styryl/Ph	74 (96)	51 (94)
19[b]		**3hg**	R^4/R^5 = Ph/Bn	61 (84)	59 (57)

[a] **L1**: the reaction temperature is −10°C for entries 1-11, −30°C for entries 12–18; **L2**: 0°C for entries 1–18. [b] Room temperature.

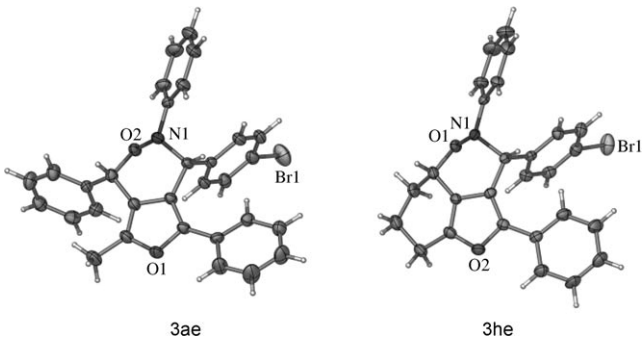


Figure 1. X-ray crystal structures of compounds **3ae** (left) and **3he**. Ellipsoids are drawn at the 30% probability level.[10]

The structure of gold complexes **4** (Figure 2) and **5** (Figure 3) were also determined by single-crystal X-ray diffraction analysis.[10] The dihedral angels of complexes **4** and **5** were 63.3 and 77.7°, respectively. Interestingly, the Au–Au bond lengths of complexes **4** and **5** were 2.994 and 5.316 Å, respectively, which indicates the presence of Au–Au interactions in complex **4** but not complex **5**.[11] This Au–Au interaction lends the structure of complex **4** a degree of rigidity. This difference may account for the observation that complex **4** gives better results than complex **5** for substrates with flexible alkyl groups (Table 2, entries 8 and 9).

Furthermore, catalyst loading could be reduced to 0.2 mol% with a larger reaction scale (5 mmol) without loss of any selectivity and efficiency, providing **3aa** in quantitative yield with 93% *ee* [Eq. (1)]. To our delight, enantioenriched

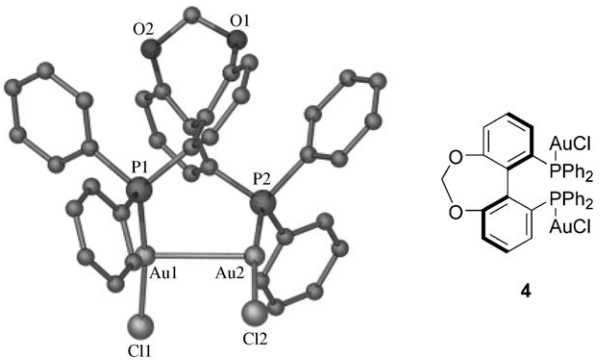


Figure 2. ORTEP view of complex **4** showing Au–Au bonding. Solvent and hydrogen atoms are omitted for clarity . Selected bond angles [°] and lengths [Å]: Dihedral angle is 63.3, Au1–Au2 2.994, P1-Au1-Cl1 171.3, P2-Au2-Cl2 173.6; P1–Au1 2.230(1) , Au1–Cl1 2.279(1), P2–Au2 2.232(1) , Au2–Cl2 2.292(1).

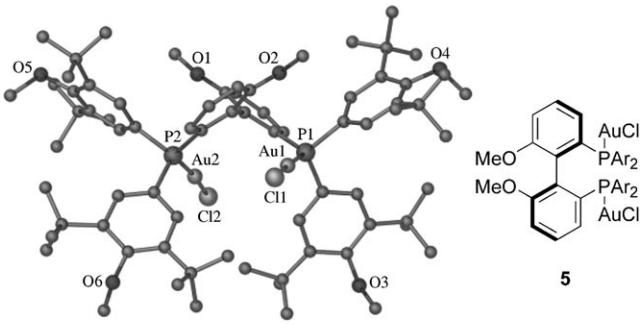
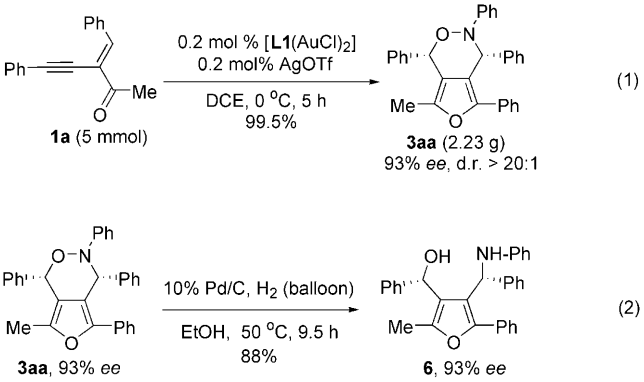


Figure 3. ORTEP view of complex **5.** Hydrogen atoms are omitted for clarity. Selected bond lengths [Å] and angles [°]: Dihedral angle is 77.7, P1-Au1-Cl 174.2, P2-Au2-Cl2 171.4, Au1-Au2 5.316, P2-Au2-Cl2 173.6, P1–Au1 2.224 (1), Au1–Cl1 2.275 (2), P2–Au2 2.228(1), Au2–Cl2 2.276(2).

3aa could undergo further chemoselective transformation to give the isolated optically active multi-functionalized furan **6** in 88% yield without loss of *ee* from the Pd/C-catalyzed hydrogenation [Eq. (2)].[12]



In summary, we have described the catalytic enantioselective intermolecular tandem reactions of (1-alkynyl)-2-alken-1-ones with nitrones for the synthesis of opitically active heterobicyclic furo[3,4-d][1,2]oxazines with excellent diastereoselectivities. Two chiral ligands, (*R*)-C_1-tunephos and (*R*)-MeO-dtmb-biphep are used, thus indicating that two strategies of modification of MeO-biphep are effective, with the former one being more efficient in some cases, owing to the Au–Au interaction which may make the structure more rigid. Furthermore, this reaction is also attractive by its easy scale up and the chemoselective functional group transformation in the product. The development of enantioselective reactions relying on the tunephos-derived gold(I)-complexes as catalyst is underway.

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Keywords: cyclization · cycloaddition · enantioselectivity · gold · regioselectivity

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[10] CCDC 777745 (**3ae**), 777746 (**3he**), 777747 (**4**), and 777748 (**5**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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