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Letter

Au(I)/(*R*)-BINOL−Ti(IV) Concerted Catalyzed Asymmetric Cascade Cycloaddition Reaction of Arylalkynols

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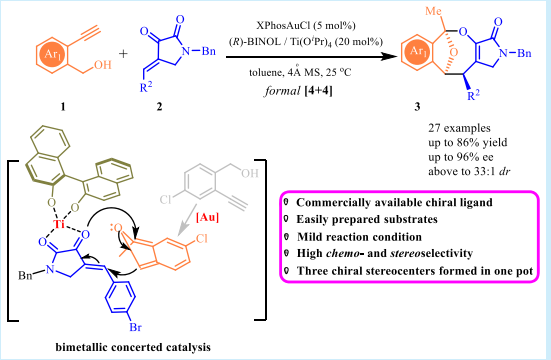
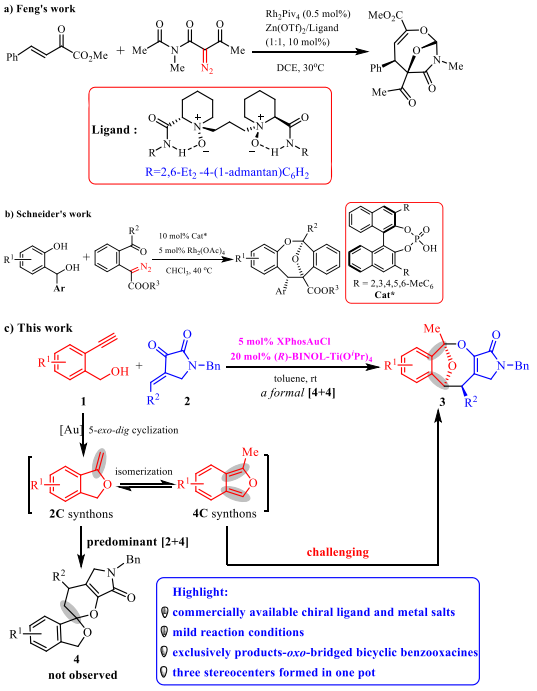
ABSTRACT: An efficient catalytic asymmetric cascade cycloaddition reaction of arylalkynols with dioxopyrrolidines was developed. This reaction was achieved using Au(I) and (*R*)-BINOL−Ti(IV) bimetallic catalysts and exclusively delivered a series of chiral oxo-bridged bicyclic benzooxacine compounds in up to 86% yield with 96% *ee* as well as >33:1 *dr*. Meanwhile, three new σ bonds and three new stereogenic centers were formed in a one-pot process.



Asymmetric synthesis has been widely used in many fields of chemistry. Among them, asymmetric catalysis is the most fashionable method, and it is devoted to the development of chiral catalysts to convert prochiral and racemic substrates into valuable chiral synthesis blocks. Thus, plenty of chiral catalysts have been exploited and synthesized to date. For example, chiral diols are among the most privileged scaffolds in asymmetric catalysis, especially for the derivatives of the chiral 1,1′-bi-2-naphthol (BINOL) skeleton.[1] Of course, it is highly desirable to directly use commercially available or easily synthesized chiral catalysts, as they will provide potential application in industry.

On the other hand, oxo-bridged heterocyclic skeletons are ubiquitous in natural products and bioactive molecules.[2] Therefore, the development of new and efficient methods for the construction of oxo-bridged heterocyclic compounds has attracted increasing attention, especially the development of intermolecular reactions, which are more appealing because of their flexible substrate candidates.[3] However, to the best of our knowledge, there are scarce reports on examples of the asymmetric synthesis of oxo-bridged bicyclic compounds. Recently, bimetallic relay catalysis has shown unique potential in modern asymmetric synthesis.[4] With the combination of a chiral catalytic system and a metal catalyst to activate two different substrates, highly efficient asymmetric chemical transformations can be achieved to afford complex chiral molecules in high yields with high enantio- and diastereoselectivities from simple starting materials. For example, Feng's research group developed an efficient asymmetric synthesis of oxo-bridged oxazocines through a Rh^{II}/Zn^{II} relay catalytic [4 + 3] cycloaddition reaction of diazoimides and β,γ-unsaturated α-keto esters (Scheme 1a).[5a] In their work, a relatively

Scheme 1. Synthesis of Chiral Oxo-Bridged Bicyclic Benzooxacines



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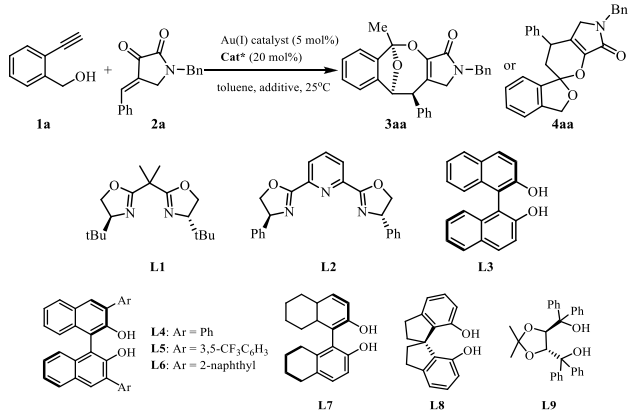
complicated chiral N−O ligand was used. Schneider and coworkers described a rhodium- and chiral phosphoric acid-cocatalyzed [4 + 3] cycloaddition of *o*-quinone methides and carbonyl ylides to furnish functionalized oxo-bridged dibenzooxacines in excellent yields and stereoselectivities in a single synthetic step (Scheme 1b).[5b] The authors employed a highly substituted chiral phosphoric acid as a chiral catalyst. These two reactions utilized diazoimides as substrates and proceeded through a [4 + 3] cycloaddition mode. In view of this and as a continuation of work by our research group,[6] here we developed a simple and highly efficient bimetallic relay catalytic asymmetric cascade cycloaddition reaction of arylalkynols **1**[7] and dioxopyrrolidines **2**[8] via a formal [4 + 4] cycloaddition reaction (Scheme 1c). The chiral oxo-bridged bicyclic compounds **3** were exclusively obtained with excellent diastereoselectivity and high enantioselectivity, and no dominant competitive spirocyclic compounds **4** were observed. More importantly, the commercially available chiral (*R*)-BINOL−Ti(O^iPr)$_4$ complex and XPhosAuCl are directly used as bimetallic catalysts, which provides a great potential application in future synthesis of natural products and pharmaceutical intermediates. To the best of our knowledge, the use of arylalkynols as **4C** synthons to carry out a formal asymmetric [4 + 4] cycloaddition reaction is unprecedented.

2-(Ethynylphenyl)methanol (**1a**) and (*E*)-1-benzyl-4-benzylidenepyrrolidine-2,3-dione (**2a**) were initially chosen as the model substrates (Table 1). In the presence of achiral Ph_3PAuCl, which aimed at catalyzing the intramolecular 5-*exo-dig* hydroalkoxylative cyclization−isomerization of **1a** to give the reactive **4C** synthon intermediate, various chiral catalytic systems were used to activate **2a** and thus enantioselectively induce the subsequent formal [4 + 4] cycloaddition. As shown in Table 1, the two combinations of Zn(OTf)$_2$/^{t}Bu-Box (**L1**) and Y(OTf)$_3$/Ph-PyBox (**L2**) gave only undesired cascade [2 + 4] product **4aa** in excellent yields with 60% *ee* (entry 1) and 23% *ee* (entry 2), respectively. Using the (*R*)-BINOL−Ti(O^iPr)$_4$ complex, the oxo-bridged bicyclic benzooxacine **3aa** could be obtained in 74% yield with 60% *ee* and >20:1 *dr*, and no **4aa** was observed by ^{1}H NMR analysis of the crude product (Table 1, entry 3). Intrigued by this result, we conducted further screening of complexes of chiral BINOL derivatives and Ti(O^iPr)$_4$. To our surprise, using 3,3′-disubstituted (*R*)-BINOLS, regardless of the substituent (Ph, 3,5-$(CF_3)_2C_6H_3$, or 2-naphthyl), only a trace amount of the desired product **3aa** was generated, with a great amount of the starting materials remaining untouched (entries 4−6). Next, we changed the ligand species from (*R*)-BINOL to (*R*)-octahydro-binaphthol (**L7**), (*R*)-SPINOL (**L8**), or diol ligand **L9** derived from L-tartaric acid, and no reaction occurred (entries 7−9). The (*R*)-phosphoric acid (CPA) catalyst was also investigated to activate dicarbonyl substrate **2a** through hydrogen-bonding interactions. Consequently, this reaction afforded a 75% yield of the corresponding product **3aa** as a racemate (entry 10). Therefore, (*R*)-BINOL−Ti(O^iPr)$_4$ was determined to be the best chiral metal complex candidate. A variety of Au(I) species were then examined in the presence of 20 mol % (*R*)-BINOL−Ti(O^iPr)$_4$ (entries 11−21). It was found that 5 mol % XPhosAuCl gave the best result, affording **3aa** in 83% yield with 81% ee (entry 20). Other additives, such as molecular sieve (MS) types, were also examined with the XPhosAuCl/(*R*)-BINOL−Ti(O^iPr)$_4$ bimetallic catalyst system, and a surprising phenomenon was observed (entries 22−25). In the absence of 4 Å MS, the reaction gave as the major product the opposite enantiomer as with 4 Å MS (entry 22). Also, racemic **3aa** was obtained with 5 Å MS or $MgSO_4$ (entries 24 and 25), and no reaction occurred in the presence of 3 Å MS (entry 23). More details were investigated about the

Table 1. Screening of Chiral Catalytic Systems in the Cascade Reaction[a]



entry	Cat*	additive	yield (%)[b]	*ee* (%)[c]
1[d]	Zn(OTf)$_2$−**L1**	4 Å MS	96	60
2[d]	Y(OTf)$_3$−**L2**	4 Å MS	98	23
3	**Ti(O^iPr)$_4$−L3**	4 Å MS	**78**	**65**
4	Ti(O^iPr)$_4$−**L4**	4 Å MS	trace	–
5	Ti(O^iPr)$_4$−**L5**	4 Å MS	trace	–
6	Ti(O^iPr)$_4$−**L6**	4 Å MS	trace	–
7	Ti(O^iPr)$_4$−**L7**	4 Å MS	–	–
8	Ti(O^iPr)$_4$−**L8**	4 Å MS	–	–
9	Ti(O^iPr)$_4$−**L9**	4 Å MS	–	–
10	(*R*)-CPA	4 Å MS	75	0
11	IPrAuCl	4 Å MS	64	81
12	(2,4-(*t*-Bu)$_2C_6H_3O)_3$PAuCl	4 Å MS	58	80
13	$(CF_3Ph)_3$PAuCl	4 Å MS	68	70
14	(2-MePh)$_3$PAuCl	4 Å MS	76	67
15	Bu_3PAuCl	4 Å MS	70	40
16	$(PhO)_3$AuCl	4 Å MS	75	42
17	IPrAuNTf$_2$	4 Å MS	18	−7
18	(Me_2S)AuCl	4 Å MS	67	18
19	JohnPhosAuCl	4 Å MS	78	33
20	**XPhosAuCl**	4 Å MS	**83**	**81**
21[e]	XPhosAuCl	4 Å MS	75	79
22	XPhosAuCl	–	48	−29
23	XPhosAuCl	3 Å MS	–	–
24	XPhosAuCl	5 Å MS	70	0
25	XPhosAuCl	$MgSO_4$	68	0
26[f]	**XPhosAuCl**	4 Å MS	**78**	**84**

[a]Unless otherwise noted, all of the reactions were carried out with **1a** (40 mg, 0.3 mmol), **2a** (55 mg, 0.2 mmol), 4 Å MS (20 mg), Au(I) catalyst (0.01 mmol, 5 mol %), and catalyst (20 mol %) in toluene (2 mL) under N_2. All of the reactions gave the product **3aa** except for entries 1 and 2. Abbreviations: (*R*)-CPA = (*R*)-(−)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate; JohnPhosAuCl = 2-(di-*tert*-butylphosphino)-1,1′-biphenyl gold chloride; IPrAuNTf$_2$ = [1,3-bis(2,6-diisopropylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene][bis(trifluoromethylsulfonyl)azanylidene]gold; XPhosAuCl = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl gold chloride. In entries 1−10, Ph_3PAuCl was used as a catalyst. In entries 11−26, (*R*)-BINOL−Ti(O^iPr)$_4$ was used as a chiral catalyst. [b]Yields of the isolated products. In all cases, the *dr* was >20:1. [c]Determined by HPLC analysis. [d]**4aa** was obtained. [e]2.5 mol % Au catalyst was used. [f](2-Ethynyl-4-methoxyphenyl)methanol (**1b**) was used.

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MS (Table S1). All of these results indicated that 4 Å MS may have the appropriate aperture size and water absorption as well as the proper interactions with the substrate and BINOL−Ti(IV). The detailed reason remains unclear at present. Notably, when (2-ethynyl-4-methoxyphenyl)methanol (**1b**) was used as the substrate, **3ab** was generated with slightly enhanced enantioselectivity under the standard reaction conditions (entry 26).

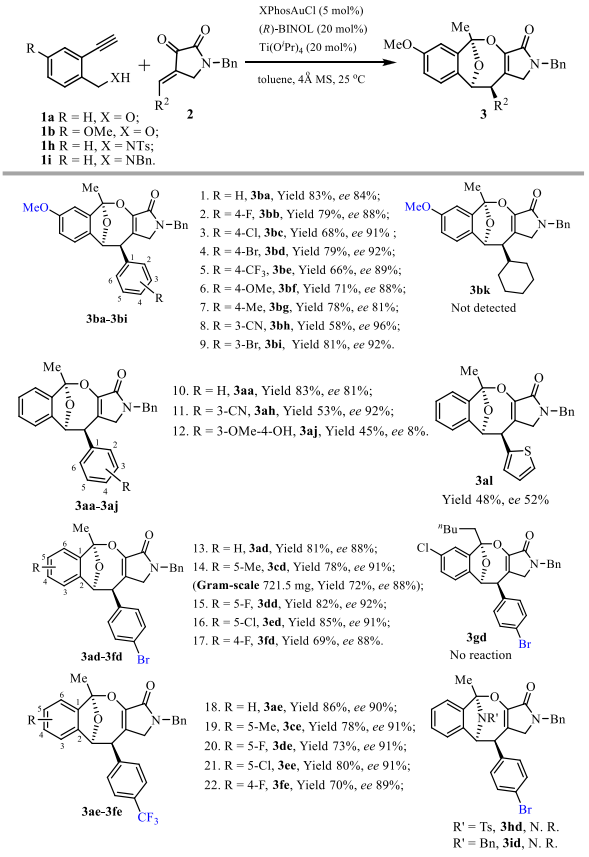
The reaction system concentration, the amount of (*R*)-BINOL−Ti(O^iPr)$_4$, the solvent, and temperature as well as the ratio of the two substrates were then examined in detail (Tables S2−S5). Overall, the optimized conditions were finally established as follows: arylalkynol **1** (0.3 mmol, 1.5 equiv) and dioxopyrrolidine **2** (0.2 mmol, 1.0 equiv) along with XPhosAuCl (5 mol %) and the (*R*)-BINOL−Ti(O^iPr)$_4$ complex (20 mol %) as dual catalysts in the presence of 4 Å MS in toluene (2 mL) at 25 °C under N_2.

With the optimal reaction conditions in hand, the substrate scope with respect to arylalkynols **1** and dioxopyrrolidines **2** was then investigated. As shown in Scheme 2, dioxopyrrolidines either with an electron-withdrawing substituent (F, Cl, Br, or CF_3; **2b**−**e**) or an electron-donating substituent (OMe or Me; **2f** and **2g**) at the *para* position of the aromatic ring delivered the corresponding chiral products **3ba**−**bg** in up to 79% yield with up to 92% *ee*. Interestingly, when R^2 on the dioxopyrrolidine was 3-cyanophenyl (**2h**), the reaction afforded the oxo-bridged benzooxacine **3bh** with the highest enantioselectivity (*ee* 96%), and 3-bromophenyl-substituted dioxopyrrolidine **2i** also gave the corresponding product **3bi** with high enantioselectivity (92% *ee*) and diastereoselectivity. Unfortunately, cyclohexyl-substituted dioxopyrrolidine **2k** failed to give the target compound **3bk**, which might be ascribed to the low reactivity of **2k**. In the case of **1a**, the reactions with **2a**, **2h**, and **2i** also afforded **3aa**, **3ah**, and **3ai**, respectively, in good yields (up to 83%, **3aa**) with high enantioselectivities (up to 92% *ee*, **3ah**). However, the reaction of **1a** and **2j** generated the product **3aj** in moderate yield with low *ee* with part of the starting material left over, even with a prolonged reaction time. Similarly, the 2-thienyl-substituted heteroaromatic **2l** also rendered a moderate yield and *ee* of the desired product **3al** with some starting material remaining. Also, it was observed that all of the arylalkynols **1**, regardless of whether they had an electron-withdrawing or electron-donating substituent at the *para* or *meta* position of the aromatic ring of the arylalkynol, reacted with **2d** and **2e** to deliver the corresponding products **3ad**−**fd** and **3ae**−**fe** in good yields (66−85%) with high enantioselectivities (up to 92% *ee*). The absolute configuration of the major enantiomer of **3ed** was unambiguously determined to be (5*S*,10*R*,11*S*) by single-crystal X-ray diffraction analysis (Figure S1).[9] However, no reaction occurred in the case of internal arylalkynol **1g**. When the nucleophilic O in substrate **1** (X = O) was changed to N (X = NTs (**1h**); X = NBn (**1i**)), no desired aza-bridged bicyclic compound (**3hd** or **3id**) was generated under the standard reaction conditions. These results implied that alkynyl alcohols have high reactivity in this formal [4 + 4] cycloaddition while alkynyl amides or alkynyl amines have low reactivity under the current reaction conditions. Notably, a scaled-up reaction of **1c** (3.0 mmol) and **2d** (2.0 mmol) was carried out and afforded 725.1 mg of **3cd** in 72% yield with 88% *ee*.

The corresponding oxo-bridged bicyclic benzooxacines **3** could be further transformed (Scheme S1). For example, an elegant Suzuki coupling reaction between **3cd** and *p*-tolylboronic acid was conducted and gave the desired product **5cd** in 76% yield with a nearly unchanged *ee* value (87% *ee*) with the oxo-bridged bicyclic benzooxacine structure unbroken (Scheme S1, eq 1). This result indicated that this structure was relatively stable and tolerant to the base, Pd catalyst, and high temperature. Interestingly, an unexpected ring-opened product **6cd** was obtained in 58% yield with 50:1 *dr* and 89% *ee*, in which the C−O bond was cleaved but the C═C double bond was unaffected when H_2/Pd/C reduction was used (Scheme S1, eq 2). Moreover, the Br atom on the aromatic ring was also reduced under these reaction conditions. This reaction demonstrated that the ketal structure of the oxo-bridged benzooxacine could be cleaved under certain reaction conditions. In addition, in the presence of the Lewis acid $BF_3{\cdot}OEt_2$ and the nucleophile TMSCN, a similar ring-opened product **7ae** was generated in 75% yield with retention of the *ee* (Scheme S1, eq 3).

Several control experiments were carried out to investigate the synergism of the Au(I) and (*R*)-BINOL−Ti(IV) bimetallic catalysts, and it was concluded that both Au(I) and BINOL/Ti(IV) were necessary to achieve this asymmetric cascade cycloaddition reaction—neither of them was dispensable (Scheme S2). Besides, a good linear relationship was observed between the *ee* of the chiral (*R*)-BINOL ligand and the *ee* of the product **3ad**, which indicated that one Ti(IV) center was coordinated by one BINOL (Scheme S3). On the basis of

Scheme 2. Substrate scope of Arylalkynols 1 and Dioxopyrrolidines 2[a]



[a]Yields refer to the isolated products, and *ee* values were determined by HPLC analysis. N. R. = no reaction.

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these results and the absolute configuration of **3ed**, we propose a possible transition state model (Figure 1). The dioxopyrro-

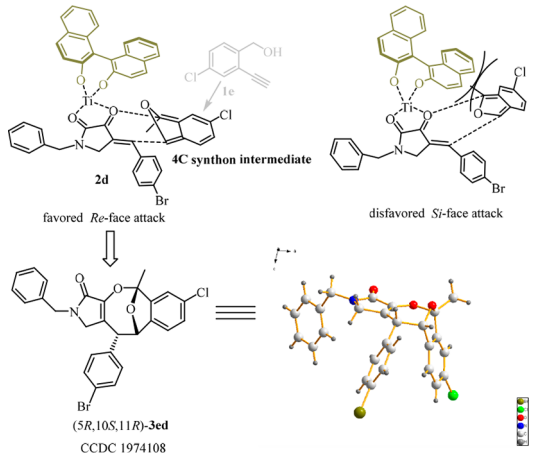

Figure 1. Proposed transition state model.

lidine is activated by coordination with the (*R*)-BINOL−Ti complex, and then the **4C** intermediate formed in situ prefers to approach the *Re* face of the dioxopyrrolidine but not the sterically hindered *Si* face. The final product is formed with the (5*R*,10*S*,11*R*) configuration.

In summary, a highly efficient asymmetric catalytic cascade reaction of arylalkynols and dioxopyrrolidines was developed. In this bimetallic cooperative catalysis, a simple and commercially available Au(I) catalyst and a chiral BINOL−Ti(IV) complex gave the corresponding fused oxo-bridged bicyclic benzooxacines in moderate to good yields with high enantioselectivities (up to 96% *ee*) under mild reaction conditions with the formation of three new σ bonds and three new chiral stereogenic centers in a one-pot process. Control experiments indicated that XPhosAuCl, (*R*)-BINOL, and $Ti(O^iPr)_4$ are all mutually reinforcing and indispensable. Furthermore, a plausible transition state model was proposed to explain the origin of the high stereoselectivity. Further applications of this catalytic strategy to other reactions are in progress in our group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00976.

Screenings of reaction conditions, reaction mechanism, product transformation, crystallographic data, synthesis of substrates, experimental procedures, characterization and analytical data of products, NMR spectra, and HPLC traces (PDF)

Accession Codes

CCDC 1974108 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This work is dedicated to the 100th anniversary of chemistry at Nankai University.

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(9) Crystal data for **3ed**: $C_{27}H_{21}BrClNO_3$, MW = 522.81; monoclinic, $P2_1$; final R indices $[I > 2\sigma(I)]$, $R_1 = 0.0481$, $wR_2 = 0.0858$; R indices (all data), $R_1 = 0.0842$, $wR_2 = 0.0774$; $a = 10.951(2)$ Å, $b = 6.5509(13)$ Å, $c = 15.865(3)$ Å, $V = 1128.6(4)$ Å^3, $Z = 2$; $T = 113$ K; 13739/5377 collected/unique reflections ($R_{int} = 0.079$); 3232 observations $[I > 2\sigma(I)]$; 299 parameters; goodness of fit on $F^2 = 0.97$. Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Center (CCDC 1974108).

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