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Cu/chiral phosphoric acid-catalyzed asymmetric (3 + 2) cycloaddition of donor–acceptor aziridines with aldehydes: synthesis of enantioenriched oxazolidines as potential antitumor agents†

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Chiral oxazolidines are pivotal structural motifs commonly found in natural products, medicinally important compounds, and chiral ligands. Among various synthetic strategies, the asymmetric formal (3 + 2) annulation of donor–acceptor (D–A) aziridines with dipolarophiles has emerged as a powerful method for constructing enantioenriched five-membered azaheterocycles with potential bioactivity. Herein, we present a Cu(II)/chiral phosphoric acid (CPA) cooperative catalytic system for the asymmetric intermolecular (3 + 2) cycloaddition of D–A aziridines with aldehydes *via* C–C bond cleavage. This approach enables the efficient and highly enantioselective synthesis of *cis*-(2*S*,5*S*)-1,3-oxazolidines with excellent atom economy, as well as exceptional chemo-, enantio-, and diastereoselectivities. This novel activation model, distinct from existing catalytic methodologies, serves as a complementary approach that significantly broadens the scope of asymmetric (3 + 2) cycloaddition of D–A aziridines. Moreover, the resulting chiral oxazolidines exhibited significant anti-proliferative activity against various human cancer cell lines, highlighting their potential for further advancement in medicinal chemistry.

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Introduction

Chiral oxazolidines represent a significant class of structural motifs found in diverse natural products and medicinally important compounds (Scheme 1A), including simplified caprazamycins, oxazolidine-containing uridine derivatives with antibacterial activity against drug-resistant bacteria,[1] mefloquine–oxazolidine derivatives as anticancer[2] and antitubercular[3] agents, oxidovoacangines demonstrating potent cannabinoid CB1 receptor antagonistic activity,[4] and COX-2 inhibitors.[5] Additionally, enantioenriched oxazolidines are highly regarded as versatile auxiliaries and chiral ligands,[6] extensively employed in asymmetric synthesis. Consequently, considerable efforts have been devoted to developing efficient methodologies for the synthesis of enantioenriched oxazolidines.[7] In this regard, enantioselective formal (3 + 2) cycloaddition has emerged as a pivotal strategy.[8]

Recently, the asymmetric formal (3 + 2) annulations of donor–acceptor (D–A)[9] aziridines with dipolarophiles[10] have garnered considerable attention as an efficient strategy for synthesizing enantioenriched five-membered azaheterocycles with potential bioactivity.[11] In 2016, Feng's group pioneered the enantioselective (3 + 2) cycloaddition of D–A aziridines with aldehydes enabled by a Nd(III)/*N*,*N*′-dioxide/$LiNTf_2$ catalyst system (Scheme 1B).[11a] Subsequently, Zhang's group disclosed an elegant asymmetric formal (3 + 2) cycloaddition of *N*-tosylaziridines and aldehydes catalyzed by a Ni(II)/Box complex (Scheme 1C).[11c] Despite these advancements, the asymmetric ring-opening cycloadditions of D–A aziridines predominantly depend on chiral metal complexes of *N*,*N*′-dioxides or Box.[12] Notably, the proposed reaction mechanism suggests the absence of direct interaction between the substrate and the chiral catalyst.[11a,c] Meanwhile, these reactions require 1.5–2.0 eq. of aldehydes to achieve satisfactory results. Thus, the pursuit of alternative, mechanistically distinct catalytic asymmetric strategies for the cycloadditions of D–A aziridines with aldehydes to access chiral oxazolidines in an atom-economical fashion

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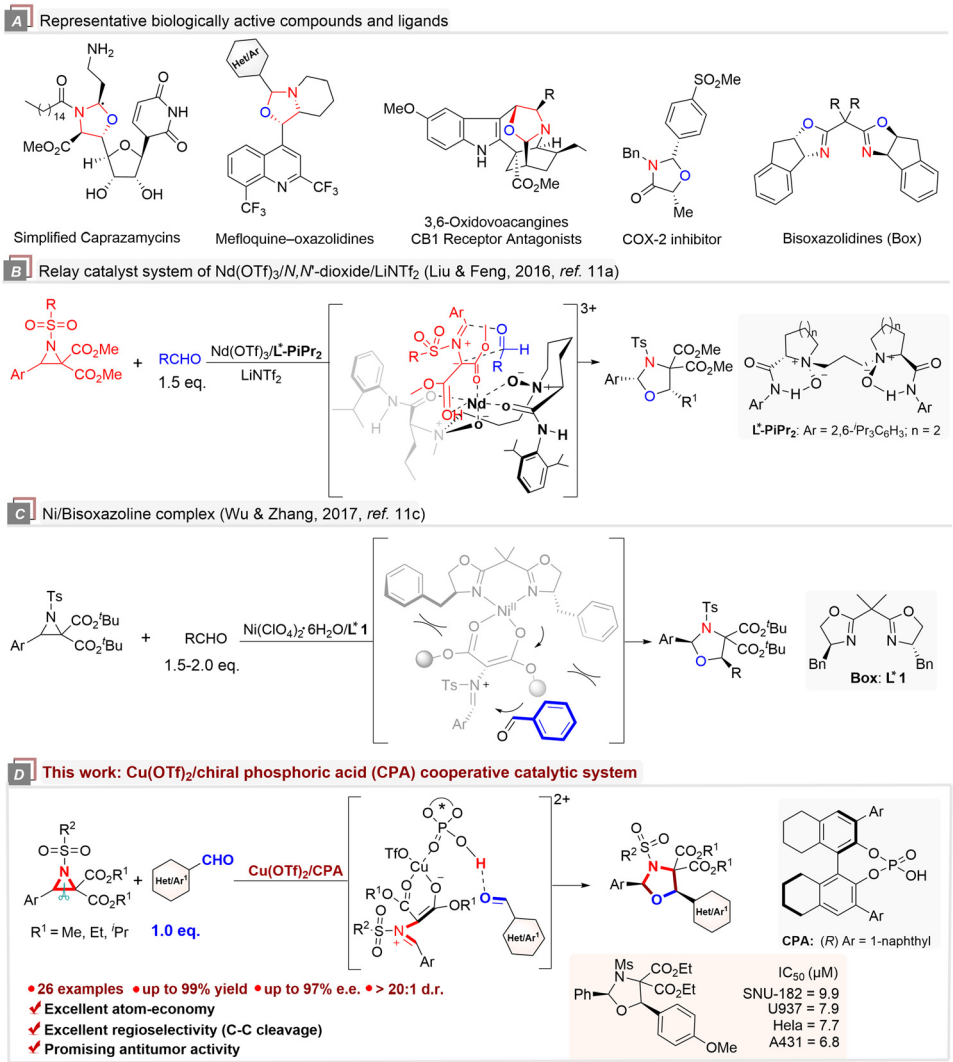


Scheme 1 Catalytic asymmetric intermolecular (3 + 2) cycloadditions of D–A aziridines with aldehydes to access a diverse range of enantio-enriched products.

remains highly desirable. Furthermore, the potential bioactivity of the resulting chiral oxazolidines has not yet been explored.

Considering the inherent instability and high reactivity of D–A aziridines due to their high-strain energy,[13] several challenges need to be addressed to fully realize this potential, including (1) chemoselectivity: achieving selective cleavage of either the C–C or the C–N bond in D–A aziridines while maintaining high enantioselectivity;[14] (2) competitive side reactions: the azomethine ylide formed *via* C–C bond cleavage may react with trace amounts of water to produce 2-amino-malonates and aldehydes;[11a,14a,15] and (3) steric hindrance: the sterically congested structure of D–A aziridines could impede interactions with bulky chiral catalysts, limiting the reaction efficiency.[11a,15] These challenges highlight the need for further innovation in catalytic design and methodology. Inspired by the remarkable success of our previous work on asymmetric ion-pair catalysis with a chiral phosphate counterion,[16] we envisioned that Cu(II)/CPA cooperative catalysis could address the challenges associated with the enantioselective (3 + 2) cycloaddition of donor–acceptor (D–A) aziridines with aldehydes. In this approach, it is proposed that the 1,3-dipole intermediate is generated *in situ via* the ring-opening of the D–A aziridine through C–C bond cleavage in the presence of $Cu(OTf)_2$/CPA, wherein Cu(II) is expected to coordinate simultaneously with both the exocyclic carbonyl group of the 1,3-dipole intermediate and the P═O moiety of the CPA, while the aldehyde is activated by the CPA through hydrogen bonding. This dual activation strategy is expected to suppress competing side reactions and minimize racemic background reactions, thereby significantly improving both reactivity and stereoselectivity. Furthermore, the activation modes employed are distinct from those of other existing catalytic systems.[11a,c] If successful, this strategy could open up new avenues for the applications of ion-pair catalysis in addressing challenging cycloadditions of D–A aziridines. Aligned with our ongoing efforts in Lewis acid-catalyzed asymmetric intermolecular

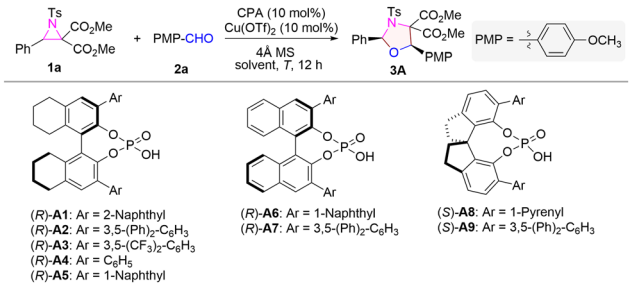
cycloadditions[17] and asymmetric ion-pair catalysis using a chiral phosphate counterion to catalyze asymmetric reactions for the construction of potentially bioactive azaheterocycles,[16] we herein disclose the $Cu(OTf)_2$/CPA-catalyzed asymmetric intermolecular (3 + 2) cycloadditions of racemic donor–acceptor aziridines with aldehydes *via* C–C bond cleavage to access a diverse range of enantioenriched *cis*-(2*S*,5*S*)-oxazolidines with excellent atom economy, as well as high chem-, enantio-, and diastereoselectivities, and the resulting chiral oxazolidines show promising anti-proliferative activity against several human cancer cell lines (Scheme 1D).

Results and discussion

To validate the feasibility of our proposed transformation, we initially investigated the asymmetric intermolecular (3 + 2) cycloaddition of racemic donor–acceptor aziridine **1a** with *p*-anisaldehyde **2a** in the presence of $Cu(OTf)_2$/**A1** in 4 Å M.S. and 1,2-dichloroethane (DCE) at room temperature under argon (Table 1). To our delight, the reaction proceeded smoothly to afford the desired oxazolidine **3A** in 66% ee. with excellent diastereoselectivity (Table 1, entry 1). Encouraged by the results, we then switched to further evaluate various CPAs, including $[H]_8$-BINOL-, BINOL- and SPINOL-derived CPAs (entries 2–9), and found that the enantioselectivities varied significantly from 4% to 81% ee. Remarkably, **A5** bearing a 1-naphthyl group at the 3,3′-position proved to be the most effective in promoting reactivity and enantioinduction in terms of both yield and ee. (83% yield, 81% ee, entry 5). Subsequent evaluation of various solvents revealed that $CHCl_3$ was identified as the best choice (entries 10–12). Additionally, reducing the reaction temperature to 0 °C could enhance the enantioselectivity of the reaction (entries 13 and 14). Furthermore, lowering the catalyst loading to 5 mol% affected the yield, but did not lead to a decrease in enantioselectivity (entries 15 and 16). Further investigation revealed that reducing the concentration of the reaction could enhance the stereoselectivity, affording the best result (entry 17). It was particularly noteworthy that the use of 1.0 eq. of aldehyde could also yield satisfactory results, featuring excellent atom economy compared with the previous reports (1.5 equiv.).[11a,c] A control experiment revealed that none of the desired product was observed in the absence of the copper catalyst (entry 18), unambiguously indicating that the acidity of CPAs was insufficient to activate the D–A aziridine for enantioselective (3 + 2) cycloaddition,[18] and the copper catalyst was essential for the transformation.

With the optimal reaction conditions being established, we next investigated the substrate scope of the $Cu(OTf)_2$/CPA-catalyzed asymmetric (3 + 2) cycloaddition of D–A aziridines and aldehydes (Table 2). Initially, several D–A aziridines with diverse ester groups were investigated, delivering the corresponding oxazolidine products **3A–3C** in 86–95% yields with 91–99% ee. Additionally, a range of diversely functionalized D–A aziridines, including those having phenyl groups with electron-donating (alkyne) or electron-withdrawing (F, Cl, Br, and CO_2Et) substituents, proved to be suitable to furnish the expected products **3D–3N** in 61–98% yields with 91–97% ee. Remarkably, alkynyl substituents **1m** and **1n** were well-tolerated to deliver alkynyl group-containing oxazolidines, synthetically useful building blocks for late-stage diversification to yield higher-value target compounds,[19] demonstrating the importance of this synthetic protocol for potential applications. It is particularly noteworthy that the alkynyl group was usually incompatible with Lewis acid-catalyzed (3 + 2) cycloadditions of D–A aziridines.[11f,20] Meanwhile, the resulting halo-substituted oxazolidine products could offer opportunities for further useful transformations. Furthermore, various sulfonyl motifs could also be well-tolerated, delivering the corresponding products **3O–3R** in 86–99% yields with 94–96% ee. Next, attention was then paid to aldehydes; thiophene/furan-substituted heteroaromatic aldehydes at different positions (*ortho* or *meta*) proceeded well to furnish the desired products **3S–3V** in 75–87% yields with 90–94% ee. The absolute configuration of **3S** was determined to be 2*S*,5*S* by X-ray crystallographic analysis (see ESI Fig. S1† for details). Remarkably, cin-

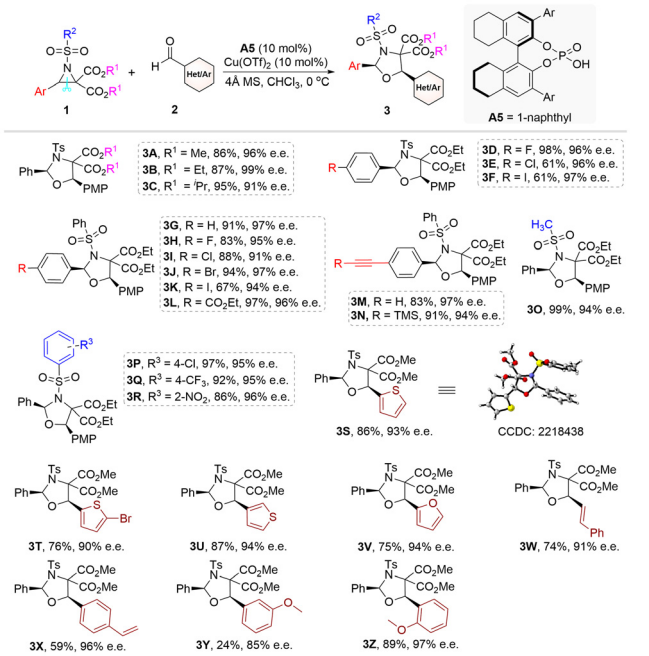
Table 1 Optimization of the reaction conditions[a]



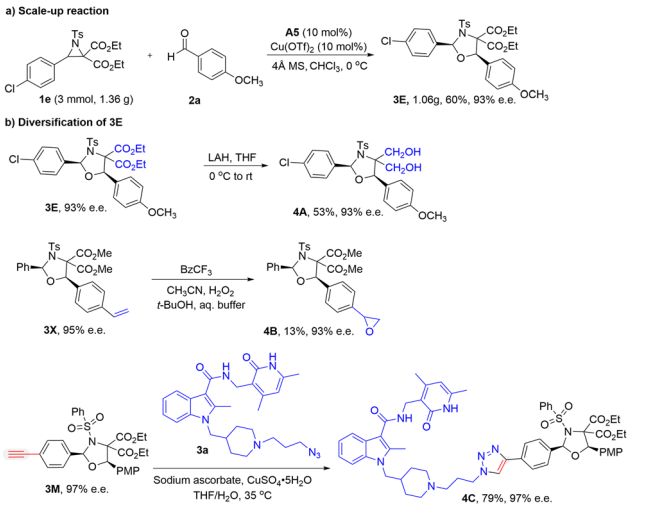
Entry	CPA	Solvent	Yield[b] (%)	ee[c] (%)
1	**A1**	DCE	82	66
2	**A2**	DCE	73	34
3	**A3**	DCE	75	15
4	**A4**	DCE	69	4
5	**A5**	DCE	83	81
6	**A6**	DCE	82	47
7	**A7**	DCE	80	18
8	**A8**	DCE	34	32
9	**A9**	DCE	40	27
10	**A5**	Toluene	72	47
11	**A5**	DCM	86	74
12	**A5**	$CHCl_3$	82	86
13[d]	**A5**	$CHCl_3$	80	93
14[e]	**A5**	$CHCl_3$	75	91
15[f]	**A5**	$CHCl_3$	82	90
16[g]	**A5**	$CHCl_3$	70	91
17[h]	**A5**	$CHCl_3$	85	96
18[i]	**A5**	$CHCl_3$	0	0

[a] Reactions were performed with **1a** (0.025 mmol), **2a** (0.025 mmol), $Cu(OTf)_2$ (10 mol%), CPAs (10 mol%) and 4 Å M.S. (12.5 mg) in 0.5 mL solvent at room temperature. [b] Yields were determined *via* ^1H NMR by using CH_2Br_2 as the internal standard. [c] Determined by HPLC analysis on a chiral stationary phase. [d] At 0 °C. [e] At −10 °C. [f] At 0 °C, CPA (5 mol%). [g] At 0 °C, $Cu(OTf)_2$ (5 mol%). [h] At 0 °C, 1.0 mL solvent. [i] In the absence of $Cu(OTf)_2$. DCE = 1,2-dichloroethane, DCM = dichloromethane, and M.S. = molecular sieves.

Table 2 Substrate scope of the $Cu(OTf)_2$/chiral phosphoric acid-catalyzed asymmetric (3 + 2) cycloaddition[a,b]



[a] Reactions were conducted on a 0.1 mmol scale. [b] Isolated yield based on **1** is given and ee. value was determined by HPLC analysis on a chiral stationary phase.



Scheme 2 (a) Scale-up reaction. (b) Diversification of enantioenriched products.

namaldehyde and 4-vinyl-benzaldehyde, simultaneously containing alkenyl and aldehyde groups, respectively, reacted smoothly to deliver the desired **3W** and **3X**, with the additional double bond intact, in 59–74% yields with 91–96% ee., and the alkenyl group was also incompatible with Lewis acid-catalyzed (3 + 2) cycloadditions of D–A aziridines,[11b,d,14a,21] thus indicating the high chemoselectivity of this catalytic asymmetric strategy. Moreover, *o*-anisaldehyde was also an effective substrate to afford product **3Z** in 89% yield with 97% ee. But compared to the smooth reactions with *ortho*- or *para*-OMe substituted aromatic aldehydes, the *meta*-OMe substituted benzaldehyde led to a decreased yield (24%) and ee. (85%). To validate the practicality of this newly developed method, a scale-up (3.0 mmol) synthesis of chiral oxazolidine **3E** was carried out (Scheme 2a), revealing no loss in reactivity or enantioselectivity (60%, 1.06 g, 93% ee). In addition, late-stage transformation of the chiral oxazolidines was studied to obtain functionalized scaffolds. The reduction of the diester furnished the diol **4A** in 52% yield with 93% ee. Additionally, the epoxidation of the product **3X** could smoothly generate the corresponding oxirane derivative **4B** (13%, 93% ee). Moreover, the chiral 1,3-oxazolidine **3M** could react with the fragment of EZH2 inhibitor[22] **3a** by copper(II)-catalyzed azide–alkyne cycloaddition to afford triazole derivative **4C** in 79% yields with 97% ee (Scheme 2b).

Considering the significance of enantioenriched 1,3-oxazolidines in medicinal chemistry and their favorable drug-like properties, we selected several chiral 1,3-oxazolidines from our collection to evaluate their anti-proliferative activity against six human cancer cell lines using Paclitaxel and Combretastatin A4 (CA-4) as positive controls,[23] including A431, MDA-MB-231, A549, HeLa, HT-29 and T47D (Table 3). The bromine-/chlorine-substituted products (**3J**, **3P**, and **3T**) demonstrated moderate but consistent antiproliferative activity across all tested cancer cell lines, exhibiting superior efficacy relative to other evaluated compounds. In addition, **3O** containing methylsulfonyl exhibited moderate antiproliferative activities against all cell lines (IC_{50} = 6–16 μM), suggesting that small steric hindrance of the substituent on the side of sulfonyl was beneficial for the anti-proliferation activity. Notably, among all the compounds, **3T** exhibited exceptional overall antitumor activity across all six tested tumor cell lines.

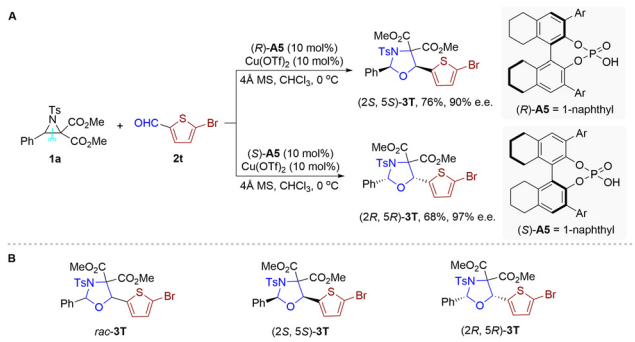
In the field of drug discovery, stereoisomers of a drug or biologically active compound often exhibit unique therapeutic effects or side effects.[24] Therefore, creating enantioselective approaches that allow for efficient construction of both enantiomers of chiral molecules is highly sought-after. Stereodivergent synthesis,[25] involving molecules with multiple stereogenic centers, has developed into a potent method for constructing various chemical entities in highly enantioenriched forms, leveraging both enantiomers of a chiral catalyst. Thus, we set out to establish stereodivergent access to (2*R*,5*R*)-**3T** using (*S*)-**A5**. Consequently, the enantiomer of (2*R*,5*R*)-**3T** was successfully obtained in high yield with excellent enantio- and diastereoselectivities (Scheme 3A). Subsequently, the antiproliferative activities of racemic **3T** and (2*R*,5*R*)-**3T** were evaluated. Compared with (2*S*,5*S*)-**3T**, these compounds exhibited no significant antitumor activities in A431 and HeLa cell lines, highlighting the critical role of chirality in the bioactive compounds for antitumor efficacy (Table 4).

Given that **3O** demonstrated the most potent activity against A431 cells, we subsequently evaluated its inhibitory effects on colony formation and migratory capacity in this cell line through colony formation and transwell migration assays.

Table 3 Antitumor activities of oxazolidines against human cancer cell lines

	IC_{50}[a] (μM)					
Compounds	A431	MDA-MB-231	A549	HeLa	HT-29	T47D
3B	21.2 ± 2.7	10.7 ± 1.1	12.2 ± 6.1	>25	>25	15.8 ± 7.2
3E	>25	13.6 ± 2.9	>25	>25	>25	>25
3G	>25	16.0 ± 4.2	>25	>25	>25	>25
3I	>25	12.0 ± 1.8	8.8 ± 3.7	3.8 ± 1.5	>25	>25
3J	10.0 ± 2.7	10.4 ± 0.8	7.2 ± 2.4	11.4 ± 3.8	20.3 ± 11.6	14.7 ± 7.6
3M	15.6 ± 4.5	13.8 ± 2.1	11.2 ± 3.6	5.9 ± 3.4	14.9 ± 4.4	10.2 ± 3.6
3O	6.8 ± 1.5	14.7 ± 0.9	12.1 ± 5.8	7.7 ± 2.8	10.6 ± 3.4	15.4 ± 5.2
3P	14.5 ± 4.7	6.4 ± 0.9	7.1 ± 2.5	5.5 ± 1.2	10.6 ± 5.4	9.3 ± 3.0
3Q	>25	3.6 ± 0.7	>25	>25	>25	>25
3T	9.7 ± 1.4	9.2 ± 1.4	7.7 ± 1.4	6.2 ± 0.2	14.0 ± 5.8	13.0 ± 8.1
3U	>25	10.8 ± 1.5	>25	>25	>25	>25
3V	7.4 ± 2.3	15.3 ± 2.0	9.7 ± 2.4	>25	11.5 ± 1.3	>25
3W	>25	8.4 ± 1.7	20.2 ± 3.2	>25	>25	>25
Paclitaxel[b]	4.1 ± 2.2[c]	26.6 ± 5.2[c]	9.5 ± 7.2[c]	5.9 ± 2.4[c]	3.9 ± 0.6[c]	99.9 ± 47.9[c]
CA-4[b]	463.6 ± 79.8[c]	NT[d]	NT[d]	2.1 ± 1.6[c]	NT[d]	32.8 ± 4.8[c]

[a] IC_{50} values were measured by the MTT assay upon 72 h of compound treatment. Data are expressed as the mean ± SD (standard error) from the dose response curves of three independent experiments. The IC_{50} value is the concentration of a compound that was able to cause 50% cell death with respect to the control culture. [b] Used as the positive control. [c] The unit of IC_{50} for Paclitaxel and CA-4 is nM. [d] NT = Not tested.

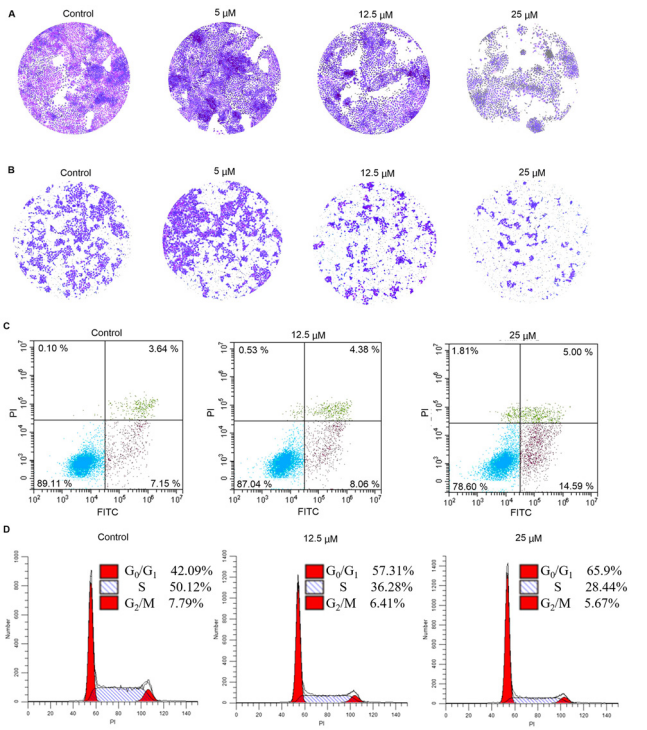


Scheme 3 Stereodivergent synthesis of **3T** and compounds for antitumor activity testing.

Table 4 Antitumor activity in human cancer cell lines

	IC_{50}[a] (μM)	
Compounds	A431	HeLa
Rac-**3T**	>25	>25
(*S*,*S*)-**3T**	9.7 ± 1.4	6.2 ± 0.2
(*R*,*R*)-**3T**	>25	>25
Paclitaxel[b]	2.4 ± 0.7[c]	4.6 ± 1.1[c]
CA-4[b]	145.5 ± 91.0[c]	1.4 ± 1.1[c]

[a] IC_{50} values were measured by the MTT assay upon 72 h of compound treatment. Data are expressed as the mean ± SD (standard error) from the dose response curves of three independent experiments. The IC_{50} value is the concentration of a compound that was able to cause 50% cell death with respect to the control culture. [b] Used as the positive control. [c] The unit of IC_{50} for Paclitaxel and CA-4 is nM.



Scheme 4 Comp.**3O** exerted cytotoxic activity in A431 cells. (A) Cell viability, as determined by colony formation assay. (B) Cell invasion, as determined by transwell assay. (C) Comp.**3O** induces the apoptosis of A431 cells. (D) Comp.**3O** induced G_0/G_1 cell cycle arrest in A431 cells after treatment for 48 h.

3O was found to inhibit colony formation and reduce the invasive capacity of A431 cells in a dose-dependent manner at micromolar concentrations (Scheme 4A and B). Additionally, the pro-apoptotic effect of **3O** in the A431 cell line was evaluated using an Annexin-V/FITC binding assay. Treatment with 25 μM of **3O** increased the percentage of early-stage apoptotic cells from 7.15% to 14.59% and late-stage apoptotic cells from 3.64% to 5.00% (Scheme 4C). Furthermore, we also examined the effect of **3O** on cell cycle arrest. Flow cytometry analysis

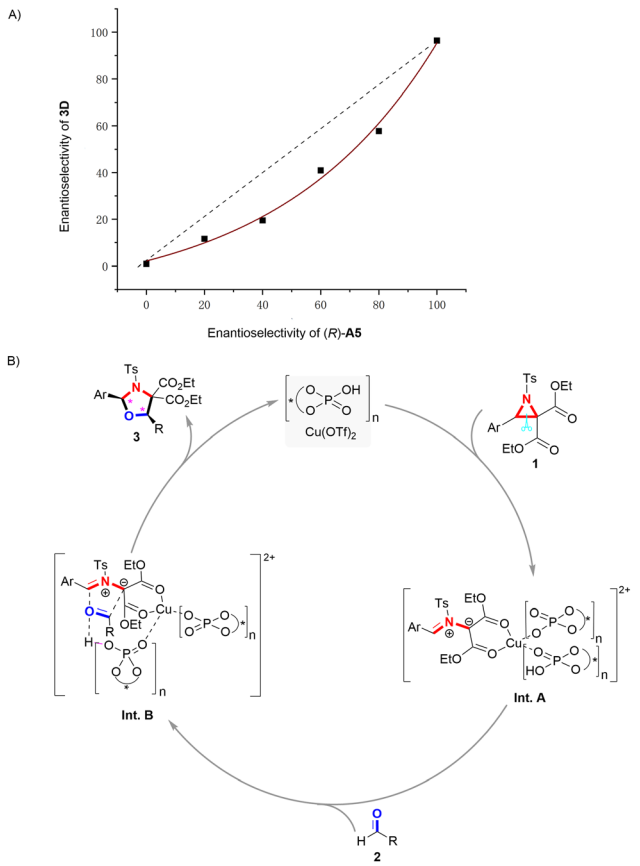
revealed that **3O** induced significant cell cycle arrest at the G_0/G_1 phase, increasing the percentage of cells in this phase from 42.09% in the DMSO to 65.9% at 25 μM (Scheme 4D). These findings suggest that **3O** holds promise as a potential candidate for further development as an antitumor drug.

In order to further investigate the pharmacokinetic profiles, the predicted results of **3O** and **3T** as calculated using ACD Percepta 14.0.0 were also prepared (Table 5).[26] According to Lipinski's rule of five, the results showed that **3O** and **3T** have predicted good oral bioavailability, and all predicted values were within a reasonable range for most drugs currently approved by the FDA. The solubility ($\log S$) is also within a reasonable range according to Jorgensen's "rule of three".

Table 5 Predicted pharmacokinetics properties of compounds **3O** and **3T**

	Lipinski's rule of five					
Comp.	MW [Da] (<500)	HBD[a] (≤5)	HBA[b] (≤10)	log *P* (<5)	*n*Rot[c] (≤10)	log *S* (>−5.7)
3O	477.15	0.0	9.0	2.47	10.0	−3.316
3T	579.0	0.0	8.0	3.55	8.0	−5.202
Range[d]	130–725	0–6	2–20	−2 to 6.5	—	−6.5 to 0.5

[a] Number of hydrogen bond donors. [b] Number of hydrogen bond acceptors. [c] Number of rotatable bonds. [d] Range for 95% of known drugs.



Scheme 5 (A) Nonlinear Effect Experiment. (B) Mechanistic proposal.

To gain further insight into the mode of catalyst activation, we found that the enantiopurity of the product shows a positive nonlinear effect with that of the catalyst (Scheme 5A). This result might suggest that more than one molecule of **A5** was likely to be involved in the transition state of the enantiodifferentiating step.[16d,27] These observations, together with the above-mentioned significant effects of different CPAs in the reaction condition optimization study, indicated that both Cu $(OTf)_2$ and CPA are essential for this transformation, and CPA might have played an important role in the activation of aldehyde (see ESI Fig. S2† for details). Therefore, a plausible reaction mechanism was proposed (Scheme 5B). The 1,3-dipole Int. **A** was generated *in situ* from the ring-opening reaction of the D–A aziridine **1** *via* C–C cleavage in the presence of $Cu(OTf)_2$ and **A5**, where Cu(II) could simultaneously coordinate with P═O and P–OH groups of **A5** for stereoinduction. Subsequently, the resulting Int. **A** reacts with aldehyde **2** to furnish the key Int. **B**, in which the aldehyde **2** is activated by **A5** *via* hydrogen bonding interactions for excellent stereocontrol. Finally, a concerted (3 + 2) cycloaddition occurs enantioselectively to yield the target oxazolidine, liberating the catalysts.[11a,28]

Conclusions

In summary, we have developed a Cu(II)/CPA cooperative catalytic system for the asymmetric intermolecular (3 + 2) cycloaddition of D–A aziridines with aldehydes *via* C–C bond cleavage, facilitating the efficient generation of a diverse range of enantioenriched *cis*-(2*S*,5*S*)-1,3-oxazolidines with excellent atom economy, as well as high chem-, enantio-, and diastereoselectivities under mild reaction conditions. This dual activation strategy is not only distinct from but also serves as a complementary approach to those employed by other existing catalytic systems, thereby creating new opportunities for the asymmetric (3 + 2) cycloaddition of D–A aziridines. Furthermore, the resulting chiral oxazolidines have exhibited promising anti-proliferative activity against several human cancer cell lines, highlighting their potential for further development in medicinal chemistry.

Author contributions

Z. Shi and J.-S. Lin designed this project. Z. Shi performed the chemical experiments and prepared the ESI.† T. Fan performed the biological activity test. J.-S. Lin and Y. Jiang supervised and directed the project. All authors analysed the results and provided insightful suggestions for analysing the data and editing the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article are included as part of the ESI.† Detailed experimental procedures, characterization data, and copies of the spectra of products (^{1}H, ^{13}C NMR and HRMS) are available in the ESI.† CCDC 2218438 ((2*S*,5*S*)-**3S**)† contains the supplementary crystallographic data for this paper.

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