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One-Pot Formation of Chiral Polysubstituted 3,4-Dihydropyrans via a Novel Organocatalytic Domino Sequence Involving Alkynal Self-Condensation

Li-Jin Dong,[†,‡] Tian-Tian Fan,[†,‡] Chao Wang,[†] and Jian Sun*[,†]

Natural Products Research Center, Chengdu Institute of Biology, Chinese Academy of Sciences, Chengdu 610041, China, and Graduate University of the Chinese Academy of Sciences, Beijing 100049, China

sunjian@cib.ac.cn.

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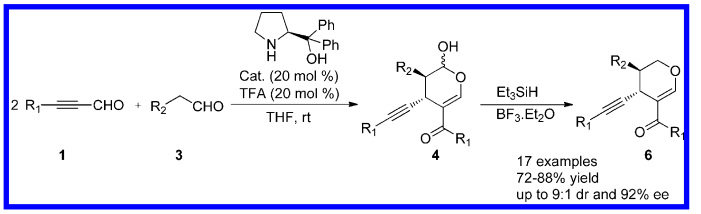
ABSTRACT



The self-condensation of alkynals was for the first time implemented under mild organocatalytic conditions and was successfully linked with a domino organocatalytic inverse-electron-demand oxa-Diels–Alder reaction, which led to the development of a facile one-pot method to produce a wide variety of polysubstituted chiral 3,4-dihydropyrans with good to high yields and diastereoselectivities and high enantioselectivities. The unprecedented alkynal self-condensation was revealed to pass through secondary amine-catalyzed C–C triple bond hydration and subsequent aldol condensation.

Organocatalytic asymmetric domino reactions have proven to be powerful tools for the efficient construction of complex chiral molecules under mild, environmentally benign conditions.[1,2] In recent years, various protocols have been developed, mainly based on the iminium/enamine activation strategy.[2] Many reactions have been incorporated into the domino sequences of these protocols,[3] for instance, the Michael addition, the Henry reaction, the Aldol reaction, the Mannich reaction, the Friedel–Crafts, etc. Nonetheless, it remains necessary to search for new organocatalytic reactions applicable in domino sequences, which could result in new domino protocols and thus useful new chiral products or new synthetic routes toward structurally complex molecules. Herein, we report our discovery that the self-condensation of alkynal could be activated by an organocatalyst and be incorporated into an organocatalytic domino protocol that leads to an easy access to polysubstituted chiral 3,4-dihydropyrans with good to high yields and diastereoselectivities and high enantioselectivities.

Activation of a carbonyl-conjugated C–C double bond through an iminium intermediate has proven to be a

[†] Chinese Academy of Sciences.
[‡] Graduate University of the Chinese Academy of Sciences.

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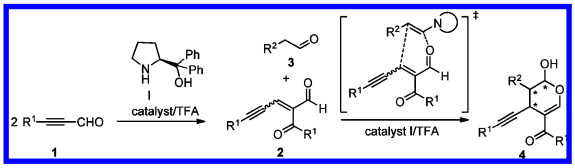
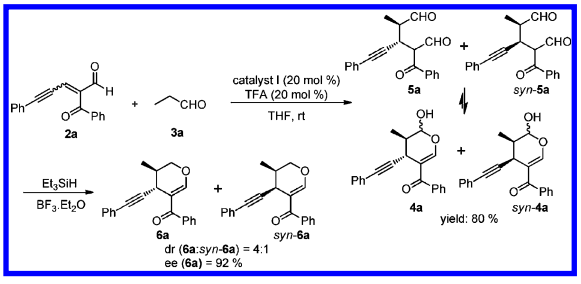
powerful strategy with frequent applications in asymmetric organocatalysis in the past years.[4] Recently, others and we have shown that the C−C triple bond could also be activated for asymmetric reactions through the same strategy.[5−8] In our continuing efforts to explore the reactivity and selectivity of carbonyl-conjugated C−C triple bonds under organocatalytic conditions, we observed the self-condensation of alkynals (**1**) under the catalysis of diphenyl L-prolinol (**I**) to generate an interesting type of alkynyl-bearing 1,3-dicarbonyl compounds **2** (Scheme 1). We envisioned that this novel reaction could be linked with another secondary amine-catalyzed inverse-electron-demand oxa-Diels−Alder reaction and furnish a novel one-pot domino protocol to deliver polyfunctionalized new chiral 3,4-dihyropyrans **4**.[9,10]

To implement this design, we first subjected the isolated intermediate **2a** (R^1 = Ph, *E*/*Z* = 4:1) to the inverse-electron-demand oxa-Diels−Alder[10] reaction with propanal **3a** (R^2 = Me) in the presence of catalyst **I**. As expected, the desired 3,4-dihydropyran hemiacetal **4a** and its diastereomer *syn*-**4a** were furnished as the major products in good yield (80%) with moderate diastereoselectivity (dr = 4:1) and excellent enantioselectivity (92% ee for **4a**) (Scheme 2). Due to the fast equilibrium of **4a** and *syn*-**4a** with **5a** and *syn*-**5a**, respectively, the analysis of stereoselectivity became complicated. Thus, the products **4a** and *syn*-**4a** were then reduced with $Et_3SiH/BF_3\cdot Et_2O$ to give products **6a** and *syn*-**6a**, which were stable and easy to analyze by HPLC.

Scheme 1. Design of an Organocatalytic Domino Sequence Incorporating Self-Condensation of Alkynal and Inverse-Electron-Demand Oxa-Diels−Alder Reaction



Scheme 2. Oxa-Diels−Alder Reaction between Isolated **2a** and Aldehyde **3a**



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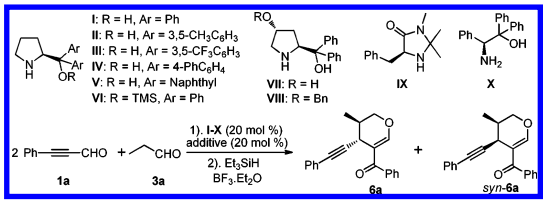
Next, we tried to combine the two separate reactions and operate them in a one-pot fashion. In the presence of 20 mol % catalyst **I**, 2.0 equiv of phenylacetylenyl aldehyde **1a** was mixed with propanal **3a** at rt. Delightfully, **4a** and *syn*-**4a** were still obtained as the major products with high yield (88%); the stereoselectivities were similar to those observed in the stepwise reactions (4:1 dr, 91% ee) (Table 1, entry 1). Interestingly, the possible intermediate **7** and products **8** stemming from the cross condensation of **1a** and **3a** were not observed (Figure S1, Supporting Information (SI)), suggesting that this reaction system has perfect chemical selectivity. Thus, we concentrated our efforts on the development of the one-pot domino protocol.

Some other catalysts were also tested for the domino reactions of **1a** and **3a**. Diarylprolinol analogues **II**−**V**, **VII**, and **VIII** all displayed good reactivities and stereoselectivities (Table 1, entries 2−5, 7, and 8), but none of them gave better results than **I**. The other typical catalysts diphenylprolinoltrimethylsilyl (TMS) ether **VI**, imidazolidine **IX**,

Table 1. Optimization of Reaction Conditions[a]



entry	cat.	additive	solvent	yield [%][b]	dr[c] (**6a**/*syn*-**6a**)	ee [%][c] (**6a**)
1	**I**	TFA	THF	88	4:1	91
2	**II**	TFA	THF	74	3:1	92
3	**III**	TFA	THF	59	4:1	80
4	**IV**	TFA	THF	50	3:1	88
5	**V**	TFA	THF	83	3:1	91
6	**VI**	TFA	THF	<5	–	–
7	**VII**	TFA	THF	43	3:1	73
8	**VIII**	TFA	THF	53	3:1	74
9	**IX**	TFA	THF	<20	–	–
10	**X**	TFA	THF	<5	–	–
11	**I**	-	THF	<5	–	–
12	**I**	AcOH	THF	<20	–	–
13	**I**	$PhCO_2H$	THF	<20	–	–
14	**I**	$MeSO_3H$	THF	<20	–	–
15	**I**	TfOH	THF	<20	–	–
16	**I**	HCl	THF	<20	–	–
17	**I**	TFA	$CHCl_3$	54	3:1	93
18	**I**	TFA	Toluene	55	3:1	88
19	**I**	TFA	MeCN	<5	–	–
20	**I**	TFA	DMF	<5	–	–
21[d]	**I**	TFA	THF	<5	–	–

[a] Unless otherwise noted, all reactions were performed with **1a** (0.2 mmol), **3a** (0.16 mmol), catalyst (0.04 mmol), and additive (0.04 mmol) in 1.0 mL of solvent at rt for 72 h. [b] Combined yield of **4a** and **5a**. [c] Determined by HPLC analysis. [d] The reaction was carried out at 0 °C. TMS = trimethylsilyl, Bn = benzyl, TFA = trifluoroacetic acid, TfOH = trifluoromethanesulfonic acid, THF = tetrahydrofuran, DMF = *N*,*N*-dimethylformamide.

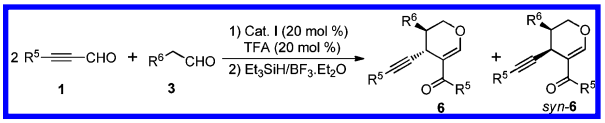
and primary amine **X** were all found to have little reactivity (Table 1, entries 6, 9, and 10).

To optimize the catalytic performance of **I**, different reaction conditions were examined. TFA proved to be a crucial additive; its absence or replacement with other Brønsted acids such as acetic acid, trifluoromethane/sulfonic acid (TfOH), and hydrochloride all led to a dramatic loss in reactivity (Table 1, entries 11−16). Solvents were also found to be an important factor. Switching THF to chloroform or toluene resulted in a significant decrease in yield, albeit only with marginal effects on the stereoselectivities (Table 1, entries 17 and 18). When acetonitrile or DMF was used as the solvent, the reactivity was completely suppressed (Table 1, entries 19 and 20). In addition, lowering the reaction temperature from rt to 0 °C caused a complete loss of reactivity (Table 1, entry 21).

Having established optimal conditions, we explored the generality of the present domino reaction system. As shown in Table 2, this reaction system exhibited a broad substrate spectrum. Various aryl alkynals underwent smooth reactions with either propional or butanal, affording the desired chiral 3,4-dihydropyran products (**6a**−**k**) with high yields (82−88%), moderate diastereoselectivities (4:1−2:1 dr), and excellent enantioselectivities (90−92% ee) (Table 2, entries 1−11). Relatively electron-rich aryl alkynals gave slightly lower enantioselectivities (Table 2, entries 12−14). Besides propional and butanal, benzyl acetaldehyde could also furnish the reaction to give product **6o** with high yield and enantioselectivity (Table 2, entry 15). In this case, high diastereoselectivity (9:1 dr) was achieved. Notably, a simple recrystallization of the obtained mixture products **6e** and its diastereomer and their enantiomers was demonstrated to improve the optical purity and give virtually pure product **6e** with >99:1 dr and >99% ee (entry 5).

To illustrate the utility of the present domino reaction, the chiral products were converted into several potentially useful new compounds in good to high yields with complete preservation of the stereo- and enantiopurity (Scheme 3). To determine the absolute stereochemistry of the products obtained in the present reaction system, a single crystal of **4e** was successfully achieved. X-ray crystallography analysis revealed that it has a (3*R*,4*S*)-configuration[11] (Figure S3, SI).

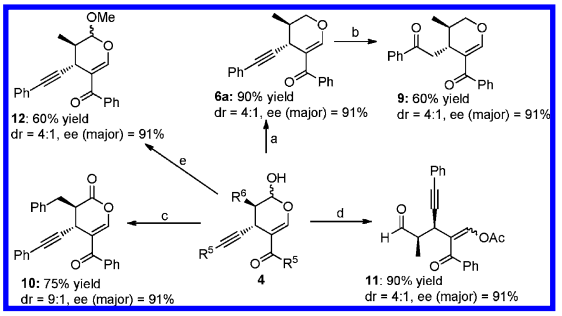
Table 2. Substrate Scope of the Domino Sequence[a]



entry	product	R^5/R^6	yield [%][b]	dr[c] (**6**/*syn*-**6**)	ee [%][c] (**6**)
1	C_6H_5/Me (**6a**)		88	4:1	91
2	C_6H_5/Et (**6b**)		80	2:1	91
3	4-$CF_3C_6H_4$/Me (**6c**)		80	3:1	91
4	4-$COOMeC_6H_4$/Me (**6d**)		82	4:1	91
5	4-CNC_6H_4/Me (**6e**)		83	4:1 (>99:1)[d]	92 (>99)[d]
6	4-FC_6H_4/Me (**6f**)		84	4:1	90
7	2,4-FC_6H_3/Me (**6g**)		82	3:1	90
8	4-ClC_6H_4/Me (**6h**)		81	3:1	91
9	4-BrC_6H_4/Et (**6i**)		80	2:1	92
10	2-naphthyl/Me (**6j**)		88	3:1	90
11	3-MeC_6H_4/Et (**6k**)		82	2:1	91
12	4-MeC_6H_4/Me (**6l**)		83	2:1	83
13	4-$^t BuC_6H_4$/Me (**6m**)		86	3:1	88
14	4-$MeOC_6H_4$/Me (**6n**)		72	3:1	82
15	C_6H_5/Bn (**6o**)		82	9:1	91
16	C_6H_5/$EtOOCCH_2$(**6p**)		81	4:1	85
17	C_6H_5/allyl (**6q**)		79	6:1	91

[a] Unless otherwise noted, all reactions were performed with **1** (0.2 mmol), **3** (0.16 mmol), catalyst **I** (0.04 mmol), and TFA (0.04 mmol) in 1.0 mL of THF at rt for 72 h. [b] Combined yield of **4** and **5**. [c] Determined by HPLC. [d] The data in parentheses were obtained by recrystallization of **4** in a mixture solvent of petroleum ether and ethyl acetate. Me = methyl, Et = ethyl, ^{t}Bu = *tert*-butyl, Bn = benzyl.

Scheme 3. Transformation of the Domino Products **4**[a]



[a] Reaction conditions: (a) Et_3SiH, $BF_3 \cdot Et_2O$, DCM, 0 °C, 12 h; (b) H_2O, Tf_2NH, DCM, rt, 2 h; (c) PCC, DCM, rt, 24 h; (d) Ac_2O, DIPEA, DCM, 0 °C, 1 h; (e) $Sn(OTf)_2$, MeOH, rt, 12 h.

As for the mechanistic aspects associated with the present domino reaction system, we initially suspected that the

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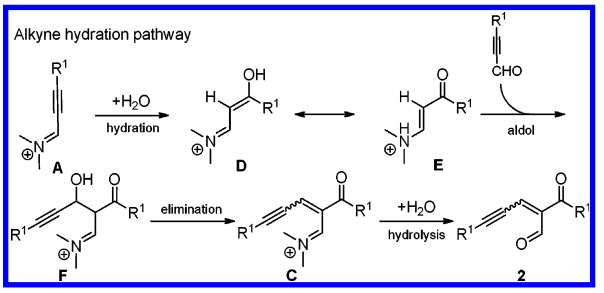
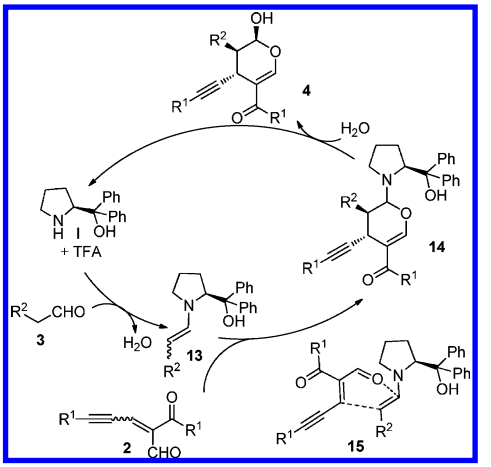
(11) CCDC 899100 contains the supplementary crystallographic data for **4e**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Scheme 4. Catalytic Pathway for the Formation of **2**



Scheme 5. Proposed Mechanism Model for the Formation of the Final Product **4**



self-condensation of alkynal **1** for the formation of **2** passes through an oxa [2 + 2] cycloaddition pathway (Figure S4, SI). But meanwhile, there also exists another possibility that the formation of **2** goes through an alkyne hydration pathway (Scheme 4). In the latter case, the hydration of the iminium-activated C−C triple bond gives rise to enol **D**, of which the resonance form **E** undergoes an aldol condensation to generate intermediate **F**. The elimination of a molecule of H_2O from **F** followed by hydrolysis furnishes **2**. These two unprecedented pathways both seem plausible.[12,13] To determine which pathway is truly adopted, we first monitored the reaction of **1a** by ^{1}H NMR spectroscopy (Figure S5, SI). Two distinct triplet peaks at 5.6 and 3.7 ppm, respectively, were observed soon after the initiation of the reaction, which became major peaks in the course of the reaction and disappeared at the end. This observation seems to suggest that the reaction should go through the hydration pathway because only the intermediate **F** can match with these two peaks. To find further evidence for this pathway, we used another compound, 3-oxo-3-phenylpropanal, to react with **1a** in the presence of catalyst **I**. Since this compound could easily react with the catalyst to generate the active enamine species **E**, the same sequence from **E** to **2** could be followed. As expected, the same product **2a** was formed as the major product, and the same peaks at 5.6 and 3.7 ppms were observed during the reaction and disappeared at the end. Thus, the hydration pathway is unequivocally proven for the formation of **2** and the oxa [2 + 2] cycloaddition pathway could be excluded. The observed excellent chemical selectivity of the self-condensation of alkynal **1** vs the cross condensation of **1** with **3** can also be well explained by the hydration pathway because alkynal is more active as an electrophile toward the aldol reaction than alkyl aldehyde.

For the mechanism of the reaction between **2** and aldehyde **3** to generate the final product **4**, a plausible reaction model is also depicted as in Scheme 5. The oxa-Diels−Alder reaction of **2** with the enamine **13** formed from aldehyde **3** and the catalyst gives the cyclized intermediate **14**, which releases the end product **4** upon hydrolysis. The observed stereochemistry is consistent with the plausible transition state model **15**,[10a] whereby the (*S*)-diphenylprolinol moiety shields the *Si* face of the enamine and makes the attack of the enal from the *Re* face much more energetically favorable.

In conclusion, we have developed a novel organocatalytic hydration/aldol/oxa-Diels−Alder domino reaction method to implement the facile one-pot formation of chiral polyfunctionalized 3,4-dihydropyrans under mild conditions. In the presence of (*S*)-diphenylprolinol as the catalyst, a broad range of alkynl aldehydes were reacted with several alkyl aldehydes to furnish the chiral 3,4-dihydropyrans products with good to high yields, moderate to good diastereoselectivities, and high enantioselectivities. This method not only for the first time implemented the organocatalytic alkynal self-condensation, which proved to be initiated by an unprecedented organocatalytic alkyne hydration followed by aldol condensation, but also provided a novel straightforward pathway for the construction of chiral polyfunctionalized 3,4-dihydropyrans.

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Supporting Information Available. Full experimental data. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.