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Dynamic Kinetic Asymmetric Domino Oxa-Michael/Carbocyclization by Combination of Transition-Metal and Amine Catalysis: Catalytic Enantioselective Synthesis of Dihydrofurans

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Domino reactions can give access to multiple C–C and C–hetero atom bonds in one-pot and allow for the chemical synthesis of demanding organic structures.[1] This improves parameters such as atom economy[2] and allows for the development of green chemistry.[3] Transition-metal catalysis is an important research field of homogeneous catalysis.[4] In this context, metal-mediated C–H bond functionalization is a powerful tool in the development of methods for the assembly of complex organic molecules.[5] In particular, metal-catalyzed carbocyclizations give access to versatile and useful molecular structures.[6] On the other hand, organic catalysis involving enamine and iminium activation of aldehydes and ketones has grown tremendously during the last decade and significantly contributed to the research field of asymmetric catalysis.[7]

In 2006, we disclosed that C–C bond formation could be achieved by transition-metal catalysis combined with amine catalysis, involving enamine activation of an aldehyde or a ketone.[8] This gives access to chemical reactivity that is only possible by metal and amine co-catalysis.[9–11] For example, co-catalytic systems based on this concept to achieve carbocyclization have been reported.[9e,f] However, with respect to the development of domino reactions there are very few reports on the employment of amine and metal co-catalyzed transformations.[9e,12] In this context, we developed a catalytic dynamic kinetic asymmetric transformation (DYKAT) between enals and propargylated carbon acids involving a transition state in which both the metal and chiral amine are simultaneously present.[12] Furans are common heterocyclic substructures and can be found in several natural products (e.g., lignans, mycotoxines, polyether antibiotics, spiroketals, and amino acids) that have biological activities.[13] They are also versatile building blocks in organic synthesis.[14] Based on our previous research experience[15] and the importance of the furan structural motif,[13,14] we became intrigued in the challenge of developing a one-pot, catalytic, domino oxa-Michael/carbocyclization between α,β-unsaturated aldehydes **1** and propargyl alcohol (**2a**) by combination of transition-metal and amine catalysis (Scheme 1). However, there are only a few reports on the amine-catalyzed enantioselective conjugate addition (ECA) of oxygen-based nucleophiles to enals.[16] For example, the addition of aliphatic primary alcohols (e.g., ethanol) gives racemic oxa-Michael products in low yields.[16c] Thus, the equilibrium of the amine-catalyzed conjugate addition of **2a** to an enal **1** would not be towards formation of the oxa-Michael product **3** (Scheme 1). However, we envisioned that a DYKAT involving a metal and chiral amine co-catalyzed carbocyclization would push the equilibrium towards C–O bond formation by making the

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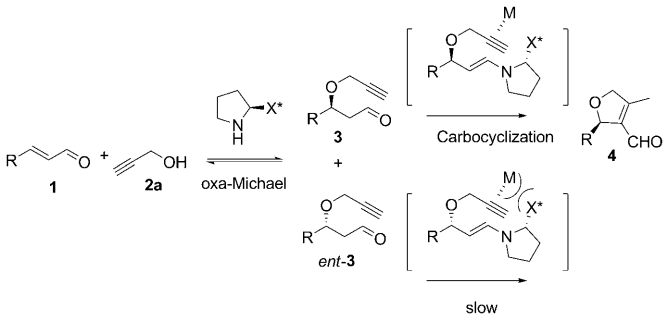


Scheme 1. Combined amine- and transition-metal-catalyzed oxa-Michael/carbocyclization between enals **1** and **2a**.

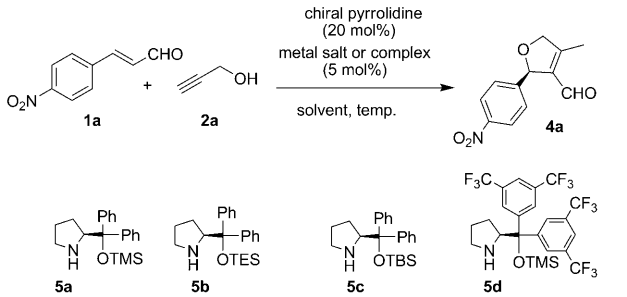
oxa-Michael reaction irreversible. The bulky group of the amine would also allow for a faster carbocyclization with oxa-Michael intermediate **3** over *ent*-**3** to form furan **4** due to less steric interactions in the transition state (Scheme 1).

Herein, we describe a highly enantioselective dynamic kinetic domino oxa-Michael/carbocyclization between α,β-unsaturated aldehydes **1** and propargylic alcohols **2** by the interconnected catalytic cycles of $PdCl_2$ and readily available chiral amines to afford dihydrofurans **4** (up to 99.5:0.5 e.r.).

We began to investigate the ability of Pd salts and complexes to catalyze the oxa-Michael/carbocyclization transformation between enal **1a** and **2a** (Table 1). The oxa-Michael product **3a** or dihydrofuran **4** were not formed in the absence of chiral amine (entry 2). The same reaction with only chiral amine **5a** did not afford **4** and only trace amount of **3a** (entry 1). The reaction with a Pd salt and a tertiary amine such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) did not render any product (entry 3). Thus, we began investigating the ability of a transition metal in combination with a chiral amine to catalyze the asymmetric domino reaction between **1a** and **2a**. The main results are shown in Table 1.

To our delight, we found that chiral amines and in particular protected diarylprolinol derivatives such as **5**[17] catalyzed the reaction with excellent chemoselectivity and high enantioselectivity to form the corresponding hydrofuran **4a** as the only product (Table 1). Several metal salts were investigated and we found that Au^{I}, Cu^{I}, Zn^{II}, Ag^{I}, Pd^{0}, and Pd^{II} were able to co-catalyze the reaction in combination with **5** with high chemo- and enantioselectivity (entries 4–10). However, the corresponding product **4a** was isolated in low yields. The influence of solvent and the employment of an acid additive were also investigated (entries 10–18).[18] For example, **4a** was isolated in 65% yield and 96.5:3.5 e.r. when $PdCl_2$ and **5a** were employed as the co-catalysts and benzoic acid was used as the additive in $CHCl_3$ (entry 12). The yield improved when the reaction temperature was decreased (entries 15–18). Increasing the bulk of the chiral pyrrolidine catalysts **5** as compared to **5a** in combination with $PdCl_2$ slightly improved the yield of **4a** (entries 16–18). For example, the combination of $PdCl_2$ and amine **5b** co-catalyzed the cascade reaction with the highest enantioselectivity and gave dihydrofuran **4a** in 77% yield and a 96.5:3.5 e.r.

Table 1. Initial investigation for the oxa-Michael/carbocyclization between **1a** and **2a**.[a]



	Amine	Metal salt	Solvent	T [°C]	t [h]	Yield [%][b]	e.r. [%][c]
1	**5a**	–	$CHCl_3$	RT	44	–	–
2	–	$PdCl_2$	$CHCl_3$	RT	44	–	–
3	DBU	$PdCl_2$	$CHCl_3$	RT	44	–	–
4	**5a**	$Pd(PPh_3)_4$	CH_3CN	RT	44	28	97:3
5	**5a**	$Au(PPh_3)NTf_2$	toluene	RT	65	10	96:4
6[d]	**5a**	$(CuOTf)+PPh_3$	toluene	RT	41	17	94:6
7	**5a**	$ZnCl_2$	toluene	RT	66	9	95:5
8	**5a**	$AgNTf_2$	toluene	RT	120	12	95.5:4.5
9[e]	**5a**	$PdCl_2$	CH_3CN	RT	140	12	94:6
10[d,e]	**5a**	$(CuOTf)+PPh_3$	toluene	RT	89	12	98:2
11[e]	**5a**	$PdCl_2$	CH_2Cl_2	RT	16	39	93:7
12[e]	**5a**	$PdCl_2$	$CHCl_3$	RT	18	65	96.5:3.5
13[e]	**5a**	$PdCl_2$	THF	RT	15	62	95:5
14[e]	**5a**	$Pd(OAc)_2$	THF	RT	15	21	94:6
15[e]	**5a**	$PdCl_2$	$CHCl_3$	4	15	72	96:4
16[e]	**5b**	$PdCl_2$	$CHCl_3$	4	20	77	96.5:3.5
17[e]	**5c**	$PdCl_2$	$CHCl_3$	4	96	77	95.5:4.5
18[e]	**5d**	$PdCl_2$	$CHCl_3$	4	19	75	95.5:4.5

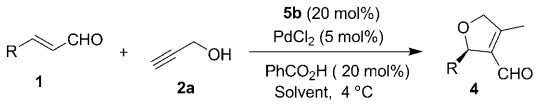
[a] Experimental conditions: A mixture of **2a** (0.375 mmol) and metal salt or complex (5 mol%) in solvent (0.5 mL) was stirred for 5 min. Next, aldehyde **2a** (0.25 mmol) and chiral amine **5** (20 mol%) were added and the reaction was stirred at RT or 4°C for the time shown in the table. [b] Isolated yield of aldehyde **4a** after silica gel column chromatography. [c] Determined by chiral-phase HPLC analysis. [d] 5 mol% CuOTf and 20 mol% PPh_3 were used. [e] 20 mol% benzoic acid was added.

(entry 16). With these results in hand, we decided to investigate the combined transition metal- and amine-catalyzed oxa-Michael/carbocyclization by using chiral pyrrolidine **5b** and $PdCl_2$ as the catalysts, benzoic acid as the additive and $CHCl_3$ as the solvent (Table 2).

Under the optimized reaction conditions, the α,β-unsaturated aldehydes bearing electron-withdrawing groups afforded the corresponding products **4a–e** and **4i** in high yields and 95.5:4.5–99.5:0.5 e.r. (entries 1–5 and 9). In some cases, changing the solvent to THF improved the efficiency and enantioselectivity (entries 4–9). The co-catalyzed cascade reactions with α,β-unsaturated aldehydes **1** without an electron-withdrawing group gave the corresponding nearly enantiopure dihydrofurans **4** (99.5:0.5 e.r., entries 6–8). The reaction was also highly enantioselective with aliphatic enals as acceptors (entry 10).

We also investigated the domino reaction using secondary and tertiary propargylic alcohols **2** (Scheme 2). In all cases, the chiral amine **5b** and $PdCl_2$ co-catalyzed the asymmetric formation of dihydrofurans **4** with high enantioselectivity.

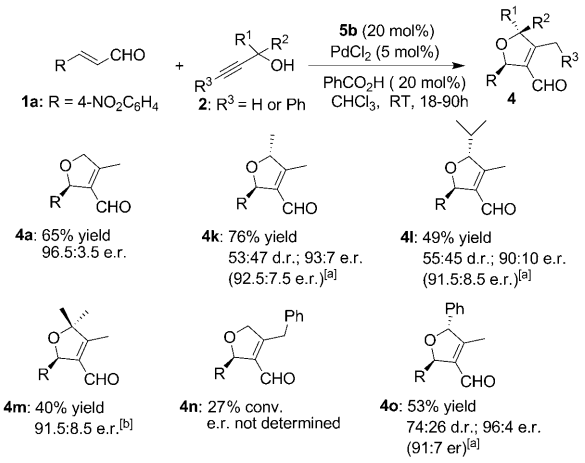
Table 2. The combined metal- and chiral amine-catalyzed domino oxa-Michael/carbocyclization between enals **1** and **2a**.[a]



1 2a 4

	R	Product	Solvent	*t* [h]	Yield [%][b]	e.r. [%][c]
1		**4a**	$CHCl_3$	20	77	96.5:3.5
2		**4b**	$CHCl_3$	18	75	95.5:4.5
3		**4c**	$CHCl_3$	18	75	96:4
4[d,f]		**4d**	THF	23	67	99.5:0.5
5[d]		**4e**	THF	50	63	97.5:2.5
6[d,e]		**4f**	THF	96	57	99.5:0.5
7[d–f]		**4g**	THF	144	51 (91)[g]	99.5:0.5
8[d]		**4h**	THF	40	72	99.5:0.5
9[d]		**4i**	THF	48	70	98:2
10[h,j]		**4j**	THF	70	40	95.5:4.5

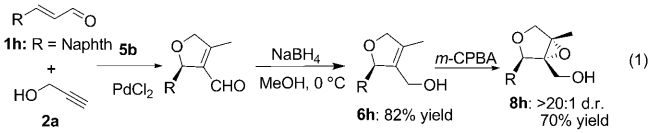
[a] Experimental conditions: A mixture of **2** (0.375 mmol) and $PdCl_2$ (5 mol%) in $CHCl_3$ or THF (0.5 mL) was stirred for 5 min. Next, aldehyde **2** (0.25 mmol), amine **6** (20 mol%) and benzoic acid (20 mol%) were added and the reaction was stirred at 4 °C for the time shown in the table. [b] Isolated yield of the corresponding product **4** after silica gel column chromatography. [c] Determined by chiral-phase HPLC analysis. [d] Reaction volume was 0.25 mL and 0.75 mmol propargyl alcohol **2a** was used. [e] Reaction was run at RT. [f] 10 mol% $PdCl_2$. [g] Yield based on recovered starting material. [h] 2.5 mmol of propargyl alcohol **2a** was used. [i] e.r. determined by chiral-phase GC analysis.



Scheme 2. Co-catalyzed asymmetric synthesis of dihydrofurans **4**. [a] E.r. of the minor diastereoisomer. [b] Reaction run in THF.

Secondary alcohol **2c** with a bulky *i*Pr group and tertiary alcohol **2d** reacted slower than the secondary alcohol **2b** and the primary alcohol **2a**. The relative stereochemistry of **4k** and **4l** was established by NOE experiments of **4l**, which confirmed the relative configuration of the *p*-nitrophenyl and *i*Pr groups to be *anti*. Initial experiments, with a propargylic alcohol with an internal alkyne as the substrate, formed the corresponding product **4n** in 27% conversion after 17 h.

The dihydrofurans **4** were readily converted to the corresponding alcohols **6** by reduction with $NaBH_4$ in MeOH and oxidation with $NaClO_2$ afforded the corresponding acids **7** in high yields (see Supporting Information). Highly diastereoselective epoxidaton of alcohols **6h** with *m*-CPBA provided the corresponding epoxide **8h** in high yield with >20:1 d.r. [Eq. (1)].



(1)

This type of epoxide scaffold is synthetically useful and is present in natural products such as verrucosidin. Moreover, epoxide opening gives the scaffold of the related mycotoxins (e.g., citreovindin).[13p,q] X-ray analysis of the crystalline product **6e**[19] established the absolute configuration at C2 to be (*R*) (Figure 1).

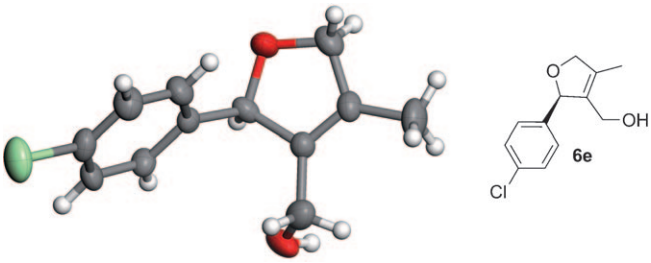
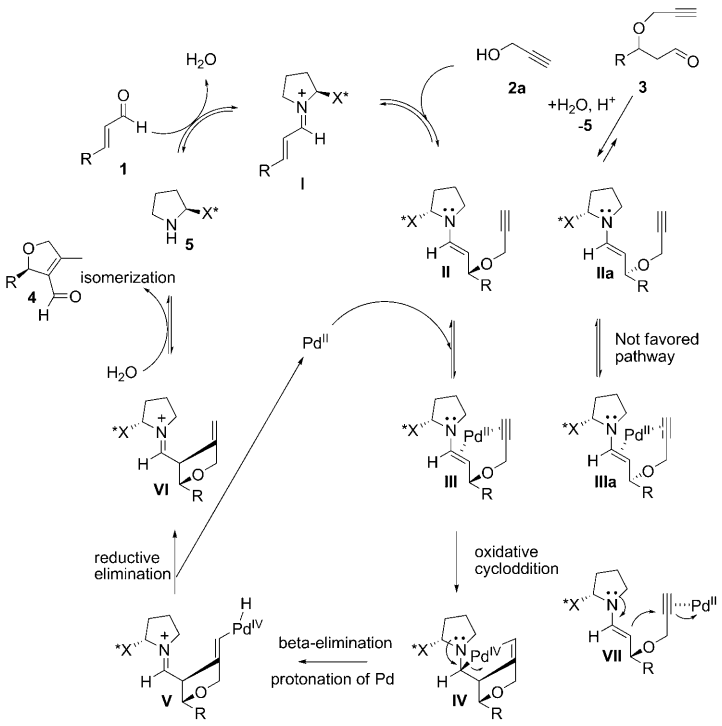


Figure 1. ORTEP picture of compound **6e**.

Based on the established absolute configuration and our experimental results, we propose the following mechanism for the reaction pathway (Scheme 3).

The proposed mechanism is a formal DYKAT and the reaction starts by formation of iminium intermediate **I**.[12a,20] Next, oxa-Michael addition of **2a** to **I** renders chiral enamine intermediates **II** and **IIa**. Hydrolysis of **II** and **IIa** can give **3**; however, retro-Michael reaction and racemization is favored and gives back the starting materials **1** and **2a**. Next, stereoselective *Re*-facial oxidative cycloaddition, according to the mechanism proposed by Trost for enyne cycloisomerization, of the less sterically hindered chiral enamine **III** as compared to **IIIa** affords bicyclic Pd^{IV} intermediate **IV**.[6c] However, the possible alternative Lewis acid activa-



Scheme 3. Proposed reaction mechanism.

tion of the alkyne by Pd^{II} and simultaneous intermolecular nucleophilic attack by the chiral enamine **VII** cannot be completely ruled out. β-Elimination and protonation of palladium gives iminium intermediate **V**. Subsequent reductive elimination releases Pd^{II}, which can now take part in its catalytic cycle again, and renders iminium intermediate **VI**. Hydrolysis of **VI** releases the chiral amine catalyst and affords the dihydrofuran product **4** after isomerization. Thus, the simultaneous co-operative catalysis of the chiral amine and metal is essential to achieve product formation.

In summary, we have developed an unprecedented highly enantioselective domino oxa-Michael/carbocyclization between propargyl alcohols and enals by combination of asymmetric amine and transition-metal catalysis. The DYKAT gives access to valuable dihydrofurans in good to high yields with e.r. of up to 99.5:0.5. The development and expansion of the concept of one-pot combinations of transition metal and amine catalysis to other metals and reactants is currently ongoing in our group. Further results will be communicated in due course.

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Keywords: asymmetric catalysis · co-catalysis · domino reactions · furans · palladium

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[19] CCDC-775870 contains 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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