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Enantioselective Synthesis of Cyclopentene Carbaldehydes by a Direct Multicatalytic Cascade Sequence: Carbocyclization of Aldehydes with Alkynes

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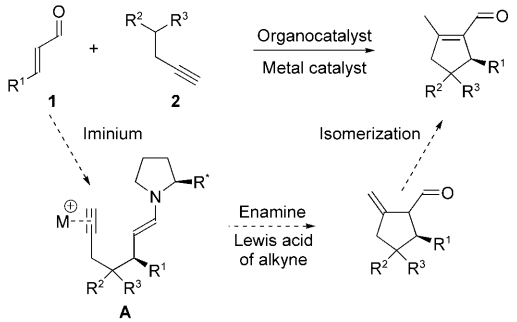
A major driving force for the many new developments in cascade, domino, and tandem reactions is the proficiency with which biological systems transform simple compounds into complex molecular frameworks.[1] Recently, asymmetric organocatalytic processes have become a powerful tool in the formation of multiple new bonds and stereogenic centers in a one-pot system without isolation of intermediates.[2] Secondary amine organocatalysts are capable of controlling the sequential introduction of a nucleophile and an electrophile by an iminium–enamine activation sequence.[3] This strategy is currently the most employed approach in developing new organocatalytic, asymmetric cascade reactions. Many catalytic cascade reactions rely on only one catalyst; however, an increased focus has recently been placed on the dual-activation concept, in which two separate catalysts are combined in one catalytic system.[4]

Over the past few years, a significant number of cascade reactions, often involving soft transition metals, such as gold and copper, have been reported. Activation of alkene, alkyne, and allene functionalities happens under mild conditions and low catalyst loading.[5] More specifically, cyclization reactions involving Lewis acids have emerged as a powerful strategy to construct complex carbocycles.[6] In recent years, the idea of combining transition-metal catalysis with organocatalysis has emerged as a promising strategy for developing and enabling unprecedented transformations.[7]

It has been shown by the group of Kirsch that gold and aminocatalysis can be combined in a direct carbocyclization of aldehydes with alkynes.[6e] Recently, Dixon and co-workers reported a cascade reaction of α,β-unsaturated ketones with propargylated malonates leading to racemic cyclopentene products by a combination of amino and copper catalysis.[8] This seminal work inspired us to develop this concept further by the application of other classes of electrophiles and nucleophiles in an asymmetric fashion.[9]

Herein, we present the reaction of α,β-unsaturated aldehydes **1** with alkyne-tethered nucleophiles, such as malononitriles and cyanoacetates **2**, in a highly enantio- and diastereoselective iminium–enamine-Lewis acid catalyzed cascade sequence to produce cyclopentene carbaldehydes of broad scope (Scheme 1). The present work demonstrates the dual-activation concept in which an organocatalyst is combined with a Lewis acid to activate an alkyne towards nucleophilic attack. Activation of an α,β-unsaturated aldehyde **1** through iminium-ion formation by using a secondary amine organocatalyst induces the Michael addition of the propargylated nucleophile **2**. The intermediate **A** undergoes a 5-*exo*-*dig* cyclization, forming a C–C bond in which both the organocatalyst and Lewis acid are involved, followed by double-bond isomerization (Scheme 1). The optically active products formed are key motifs in the synthesis of, for example,



Scheme 1. Organo- and Lewis acid catalytic approach to cyclopentene carbaldehydes.

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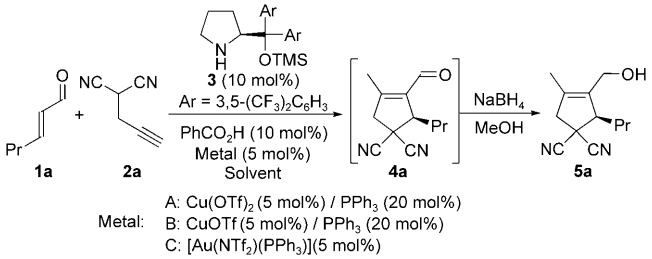
the biologically important iridoids and fusicoccane diterpenoids.[10]

At the outset of our studies, we examined different alkyne-tethered nucleophiles derived from malonate (R^2, $R^3 = CO_2Me$) and a 1,3-diketone (R^2, $R^3 = COMe$). Screening of different solvents, catalysts, and additives, such as Brønsted acids and bases, showed no reactivity after several days. We then modified the nucleophile to the more reactive propargylated malononitrile **2a** and examined the cascade reaction by treating it with hexenal **1a**, in the presence of (*S*)-2-{bis[3,5-bis(trifluoromethyl)phenyl]trimethylsilanyloxymethyl}pyrrolidine **3** as the organocatalyst and $Cu(OTf)_2$ (OTf = trifluoromethanesulfonate) as the Lewis acid (Table 1).

Table 1. Optimization of the cascade reaction.[a]



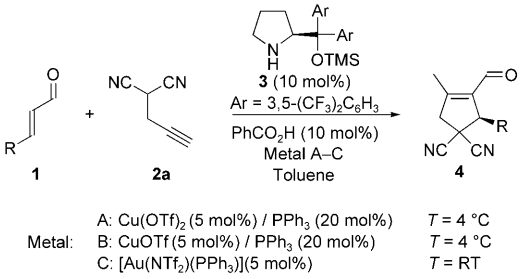
Entry	Solvent	Metal	*T* [°C]	Conversion to **4a** [%][b]	*ee* [%][c]
1	toluene	A	RT	100	96
2	CH_2Cl_2	A	RT	61	n.d.
3	$CHCl_3$	A	RT	100	80
4	MeOH	A	RT	57	n.d.
5	toluene	B	RT	100	94
6	toluene	B	4	100	99
7	toluene	C	RT	100	95

[a] See the Supporting Information. TMS = trimethylsilyl. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by chiral stationary phase HPLC; n.d. = not determined.

As revealed in the Table, full conversion and excellent enantioselectivity of the product **5a** was obtained in non-dried toluene (Table 1, entry 1). Screening of other solvents gave relatively lower conversions and selectivities (Table 1, entries 2–4). It is believed that Cu^{II} is reduced to Cu^{I} in the presence of excess Ph_3P.[11] We then examined a Cu^{I} species and **5a** was obtained with excellent enantiomeric excess (*ee*) (Table 1, entries 5 and 6). Lowering the temperature increased the enantioselectivity from 94 to 99% *ee*. Finally, the reaction also worked with a Au^{I} source (Table 1, entry 7). The reaction with gold is generally slower, but the advantage of gold compared with copper is that no additional phosphine is needed and the reaction can be performed in air. It should be pointed out that benzoic acid is important to achieve full conversion in the addition step.

The generality of the reaction was studied for a series of α,β-unsaturated aldehydes **1** in the presence of three different Lewis acids. The reaction with Au^{I} as Lewis acid proceeded well for both aliphatic and aromatic aldehydes (Table 2, entries 1–10). For aldehydes with linear, branched,

Table 2. Scope of the multicatalytic cascade reaction.[a]

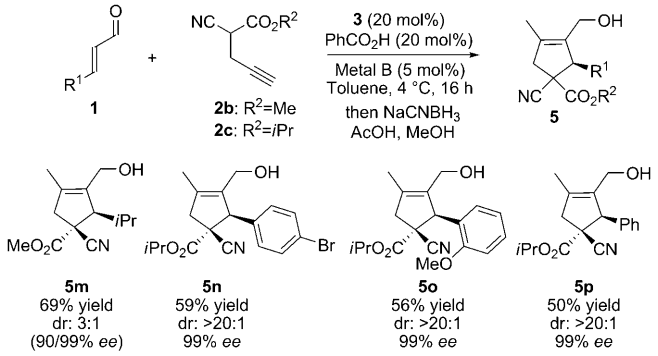


Entry	R	Metal	Product	Yield [%][b]	*ee* [%][c]
1	Pr (**1a**)	C	**4a**	88	95[d]
2	Et (**1b**)	C	**4b**	89	90[d]
3	hexyl (**1c**)	C	**4c**	66	95[d]
4	*i*Pr (**1d**)	C	**4d**	96	96[d]
5	(*Z*)-3-hexenyl (**1e**)	C	**4e**	62	89[d]
6	Bn[e] (**1f**)	C	**4f**	50	95
7	Ph (**1g**)	C	**4g**	80	93
8	*p*-CF_3-C_6H_4 (**1h**)	C	**4h**	69	95
9	*p*-OMe-C_6H_4 (**1i**)	C	**4i**	61	93
10	*o*-OMe-C_6H_4 (**1j**)	C	**4j**	72	85
11	Pr (**1a**)	A	**4a**	97	99[d]
12	*i*Pr (**1d**)	A	**4d**	92	96[d]
13	Ph (**1g**)	A	**4g**	61	92
14	Pr (**1a**)	B	**4a**	80	99[d]
15	hexyl (**1c**)	B	**4c**	72	99[d]
16	*i*Pr (**1d**)	B	**4d**	91	99[d]
17	(*Z*)-3-hexenyl (**1e**)	B	**4e**	66	90[d]
18	*p*-CF_3-C_6H_4 (**1h**)	B	**4h**	53	97
19	*o*-OMe-C_6H_4 (**1j**)	B	**4j**	55	99
20	*p*-Br-C_6H_4 (**1k**)	B	**4k**	64	99
21	naphthyl (**1l**)	B	**4l**	49	97

[a] See the Supporting Information. [b] Isolated by flash chromatography. [c] Determined by chiral stationary phase HPLC. [d] Determined from the corresponding alcohol **5**. [e] Bn = benzyl.

and nonconjugated unsaturated substituents, **1a**–**1f**, the products were obtained in good to excellent yields (50–96%) and with excellent enantioselectivities (89–96% *ee*). Aromatic aldehydes **1g**–**1j** also provided the products in good yields (61–80%) and excellent enantioselectivities (85–95% *ee*), although, the aromatic α,β-unsaturated aldehydes reacted more slowly. The reaction was also investigated with copper salts as the Lewis acid catalyst. By applying Cu^{II} salts, the products were obtained in good yields and excellent selectivities (Table 2, entries 11–13); however, the reactions with Cu^{I} as the Lewis acid were generally faster and provided almost enantiopure products (Table 2, entries 14–21).

We then investigated cyanoacetates with a terminal alkyne group as these would provide products with an additional stereogenic center; one of them being quaternary (Scheme 2). Methyl and isopropyl esters, **2b** and **2c**, respectively, provided the desired products **5m**–**5p** in good yields and excellent enantioselectivities. Notably, when aromatic α,β-unsaturated aldehydes were treated with **2c**, highly diastereo- (diastereomeric ratio (dr) > 20:1) and enantioenriched (99% *ee*) products **5n**–**5p** were formed. Propargylated β-ketoesters were also examined, but unfortunately no reaction was observed. This suggests that at least one cyano

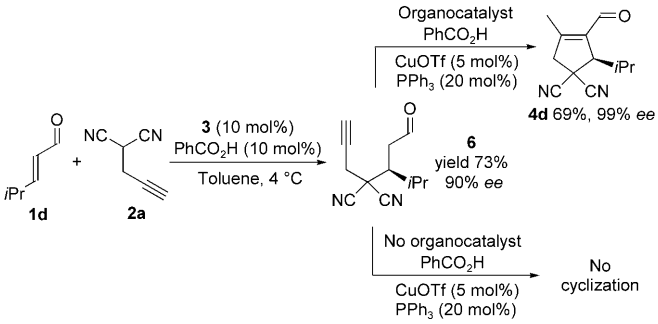


Scheme 2. Reaction of α,β-unsaturated aldehydes with cyanoacetates.

group is required in the nucleophile for this cascade sequence under the present reaction conditions.

The surprisingly high diastereocontrol in the reactions involving aromatic aldehydes led us to investigate this further. We, therefore, performed the reaction of cinnamaldehyde **1g** with nucleophile **2c** without the copper catalyst to determine the diastereoselectivity in the addition step. This led to a 1:1 mixture of diastereoisomers indicating no diastereocontrol in the addition step.[12] Since highly diastereoenriched products are formed in the cascade reaction this suggests a dual activation of organocatalyst and copper in the addition step.

An additional control experiment, leaving out the Lewis acid catalyst in the cyclization, was conducted to shed light on the mechanism (Scheme 3).



Scheme 3. Mechanistic study on the effects of the organocatalyst and Lewis acid in the cyclization reaction.

Acyclic aldehyde **6** was formed in 73% yield and with 90% *ee* in the absence of the Lewis acid. Subjecting **6** to normal reaction conditions gave the product **4d** in 69% yield and 99% *ee*. However, no cyclization took place in the absence of organocatalyst **3**, indicating a dual-activation mode in the cyclization step; that is, enamine and Lewis acid activation. Furthermore, the lower overall yield obtained for **4d** from the stepwise approach (50 versus 91%) suggests that both catalysts function more efficiently when combined, compared with the separate catalytic approach. A similar mechanistic study for Au^I was not performed, since it was shown that an amine catalyst is required for cyclization.[6e]

The absolute configuration of the product was assigned by single-crystal analysis of **5k** as shown in Figure 1.[13] The stereochemistry formed indicates that addition takes place, from below, to the *Re* face of the iminium ion.

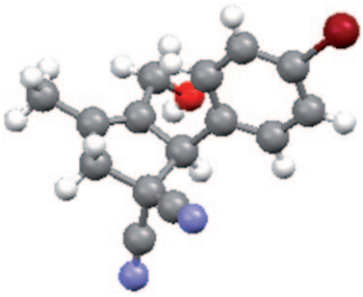
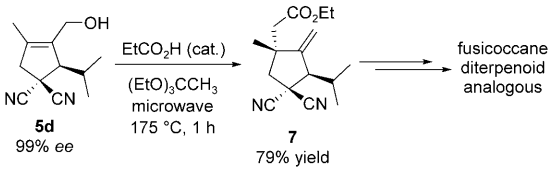


Figure 1. X-ray crystal structure of compound **5k**; C = gray, H = white, O = red, N = blue, Br = burgundy.

The cyclopentenyl alcohol motif is important in the total synthesis of, for example, fusicoccane diterpenoids.[10e] Optically active allylic alcohol **5d** was set up for a Claisen rearrangement by the Johnson orthoester protocol as outlined in Scheme 4. The sigmatropic process gave the product **7**, containing a newly formed quaternary stereogenic center, in high yield and stereoselectivity under unoptimized conditions. The transformation nicely demonstrates how cascade catalysis has emerged as a powerful tool for forming complex molecular structures.



Scheme 4. Claisen rearrangement of cyclopentenyl alcohol **5d**.

In conclusion, we have developed an enantioselective iminium–enamine-Lewis acid catalyzed cascade sequence for the synthesis of cyclopentene carbaldehydes.[14] The products are obtained in good yields and excellent enantio- and diastereoselectivities. A sigmatropic rearrangement was performed, leading to a highly versatile building block for the total synthesis of a fusicoccane diterpenoid analogue.

Experimental Section

In an ordinary vial under an inert atmosphere, aldehyde **1** (0.26 mmol) was added to a stirred mixture of nucleophile **2** (0.20 mmol), catalyst **3** (0.02 mmol), $PhCO_2H$ (0.02 mmol), $(CuOTf)_2{\cdot}PhCH_3$ (0.005 mmol), and PPh_3 (0.04 mmol) in toluene (0.4 mL for aliphatic aldehyde, 0.2 mL for aromatic aldehyde) at 4 °C. The mixture was stirred for 16 h at 4 °C. The

crude mixture was subjected to flash chromatography on silica affording the pure products (see the Supporting Information for more details).

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Keywords: aldehydes · cascade reactions · cyclopentenes · Lewis acids · organocatalysis

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[12] The diastereomeric ratio was determined by ^{1}H NMR spectroscopy on the crude reaction mixture.

[13] CCDC-749346 contains the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[14] Note added in proof: After the acceptance of this manuscript, a related paper based on kinetic asymmetric transformation (DYKAT) for the same reaction was published in this journal, see: G.-L. Zhao, F. Ullah, L. Deiana, S. Lin, Q. Zhang, J. Sun, I. Ibrahem, P. Dziedzic, A. Cordova, *Chem. Eur. J.* **2010**, *16*, 1585.

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