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Formation of Dihydronaphthalenes via Organocatalytic Enatioselective Michael–Aldol Cascade Reactions with Arylalkanes

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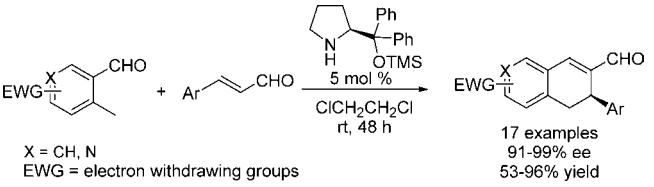
ABSTRACT



An organocatalytic highly enantioselective Michael–aldol cascade access to valuable chiral dihydronaphthalenes has been realized. Notably, the strategy via activation of nucleophilic alkyl chains by introducing nitro, chloro, or CF_3 group(s) at the *ortho*- and/or *para*-position(s) on an aromatic ring renders them readily deprotonated to produce highly reactive nulecophilic species in the cascade process under mild conditions.

The dihydronaphthalene framework is featured in a number of natural products with a broad spectrum of interesting biological activities,[1] such as lipoxygenase enzyme inhibition[1a] and anti-HIV[2] and -cancer properties.[3] They also serve as versatile building blocks in the construction of biologically important compounds.[4] Given their significance in medicinal and organic chemistry, several synthetic methods have been developed. Organometallic nucleophilic addition to electrophilic double bonds is a valuable approach to the scaffold.[5] Photoinitiated cyclizations to form dihydronaphthalene have been significantly expanded by Nicolaou and colleagues in the synthesis of biologically relevant tetralins.[6,7] Suzuki[8] presented a Pd(II)-catalyzed cross-coupling reaction via benzylic boronates, and Yamamoto[9] reported the $Cu(OTf)_2$-catalyzed [4 + 2] cycloaddition reaction of alkynylbenzenes with alkenes. However, the asymmetric versions for the synthesis

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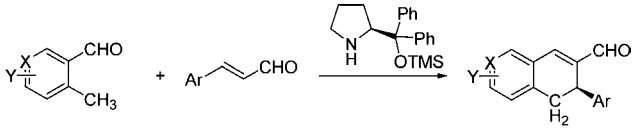
of enantioselective dihydronaphthalenes are very scarce. Tomioka disclosed a C_2-symmetric chiral diether catalyzed enantioselective conjugate addition of an organolithium to an α,β-unsaturated aldimine process to assemble the chiral molecular architecture.[5c] An elegant photochemical enantioselective process between *o*-alkyl-substituted benzaldehyde and dienophiles in the presence of a chiral complexing agent has been realized by Bach.[10] Enders and co-workers reported a nice organocatalytic enantioselective Michael–aldol approach to the chiral framework.[11] Nevertheless, in this study, one of the substrates is limited to 2-(nitromethyl)-benzaldehydes. To overcome the limitation, herein we disclose a new strategy without relying on the highly active preenolized or readily enolizable nucleophilic "C" species for the synthesis of the chiral dihydronaphthalenes (Scheme 1). Activation of the alkyl moiety by introducing electron-withdrawing groups on an aromatic ring enables the methyl and ethyl groups to serve as effective nucleophiles for the Michael–aldol cascade reaction.[12] Notably, for the first time, aryl methyl/ethyl nucleophiles are explored under mild reaction conditions in a cascade manner with excellent enantioselectivity while these activating groups can be conveniently transformed into new functionalities (Scheme 2).

Scheme 1. Organocatalytic Enantioselective Michael–Aldol Cascade Reactions



The very weak nucelophilicity of the benzene-tethered methyl group renders it impossible to perform a conjugate addition under mild conditions, where an organocatalyzed reaction is generally conducted. Recently, we have developed a novel masking strategy to activate the methyl group by introducing nitro group(s) at the *ortho*- and/or *para*-position(s) on an aromatic ring, thereby rendering the methyl group hydrogen acidic, and thus, it is readily deprotonated to produce highly reactive nulecophilic species.[13,14] Driven by the broad synthetic utility of this chemistry in the facile construction of ubiquitous chiral benzylic and related structures, we envision that incorporation of the functionality into a substrate bearing an electrophilic group such as an aldehyde at the *ortho*-position may create a new Michael–aldol cascade process for facile assembly of chiral dihydronaphthalenes.

To test the feasibility of the proposed Michael–aldol process, we carried out a model reaction between 2-methyl-3,5-dinitrobenzaldehyde (**1a**) with *trans*-cinnamaldehyde (**2a**, 1.0 equiv) in the presence of organocatalyst **I** in CH_2Cl_2 at rt for 48 h (Table 1).[15] Despite the low yield (36%) for the formed product **3a**, excellent enantioselectivity (95%) was obtained (entry 1). Encouraged by the outcome, we attempted to optimize reaction conditions to improve reaction yields. Under the same reaction conditions, solvent screening showed that the use of $Cl(CH_2)_2Cl$ as a solvent provided the highest yield (48%, entry 2), and THF gave a similar result (entry 3), while toluene and CH_3CN were not the choice (entries 4–5). No reaction took place with polar DMF and DMSO (entries 6–7). When an excess amount of 2-methyl-3,5-dinitrobenzaldehyde (1.2 equiv) was used, the reaction yield was raised to 54% (entry 8). Further increase of the ratio of **1a/2a** to 1.5 led to better yield (61%, entry 9). Interestingly, decreasing of the catalyst loading gave rise to higher efficiency (entries 10 and 11). Moreover, the reaction yield was increased to 79% when the reaction concentration was diluted to half with 5 mol % catalyst loading (entry 12). The optimal reaction was established with 2.0 equiv of **1a** and 1.0 equiv of **2a** in $Cl(CH_2)_2Cl$ catalyzed by 5 mol % of catalyst **I** (83% yield and 99% ee, entry 13).

With the optimal reaction conditions in hand, we next probed the scope of the tandem carbon-initiated Michael–aldol process by using 2-methyl-3,5-dinitrobenzaldehyde **1a** and in variation with α,β-unsaturated aldehydes **2**. As shown in Table 2, the reactions proceeded smoothly in high yields (70–96%) and excellent levels of enantioselectivities (91–99% ee) (Table 2). The electronic nature of the α,β-unsaturated aldehydes **2** has an influence on the reaction yields. Generally, α,β-unsaturated aldehydes **2** bearing electron-donating groups afforded higher yields (80–96%, entries 2–5) than those with electron-withdrawing moieties (70–81%, entries 6–10). Furthermore, a combination of withdrawing and donating groups on α,β-unsaturated aldehydes (entry 11) and heteroaromatic (entry 12) groups also could efficiently participate to afford chiral dihydronaphthalenes (entries 11 and 12). Finally, it appears that the steric effect of the α,β-unsaturated aldehydes is trivial (entries 2–7). Interestingly, more hindered substrates gave even higher yields (entries 2, 4, and 6). The limitation of this process is also recognized that enals bearing aliphatic chains could not work under these reaction conditions. The absolute configuration of the products is determined by single-crystal X-ray diffraction analysis based on compound **3g** (Figure S1, Supporting Information).[16]

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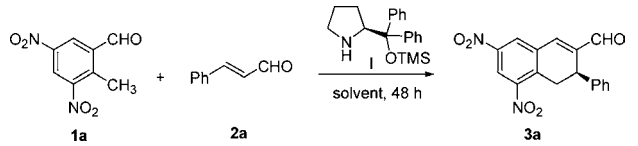
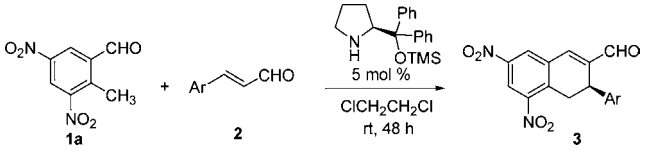
Table 1. Optimization of Reaction Conditions[a]



entry	solvent	ratio **1a/2a**	cat. loading (mol %)	yield[b] (%)	ee[c] (%)
1	CH_2Cl_2	1	20	36	95
2	$ClCH_2CH_2Cl$	1	20	48	99
3	THF	1	20	45	99
4	toluene	1	20	12	99
5	CH_3CN	1	20	23	99
6	DMF	1	20	0	[d]
7	DMSO	1	20	0	[d]
8	$ClCH_2CH_2Cl$	1.2	20	54	99
9	$ClCH_2CH_2Cl$	1.5	20	61	99
10	$ClCH_2CH_2Cl$	1.5	10	68	99
11	$ClCH_2CH_2Cl$	1.5	5	72	99
12[e]	$ClCH_2CH_2Cl$	1.5	5	79	99
13[e]	$ClCH_2CH_2Cl$	2.0	5	83	99

[a] Unless specified, a solution of **1a** (0.1 mmol) and **2a** with the catalyst (0.02 mmol) in a solvent (0.5 mL) was stirred at rt for 48 h. [b] Isolated yield. [c] The ee was determined by chiral HPLC analysis. [d] Not determined. [e] The reaction was run in 1.0 mL of solvent.

Table 2. Scope of Organocatalytic Enantioselective Michael–Aldol Cascade Reaction of 2-Methyl-3,5-dinitrobenzaldehyde (**1a**) with Enals (**2**)[a]

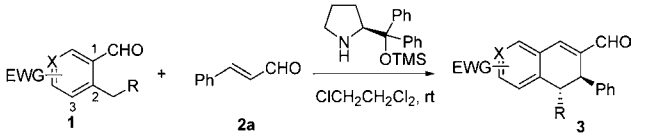


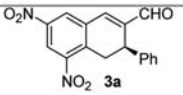
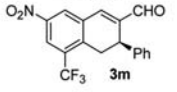
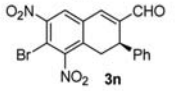
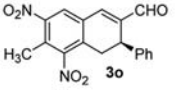
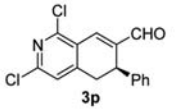
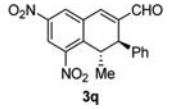
entry	Ar	yield[b] (%)	ee[c] (%)
1	C_6H_5 (**3a**)	83	99
2	2-$MeOC_6H_4$ (**3b**)	96	97
3	4-$MeOC_6H_4$ (**3c**)	93	97
4	2-MeC_6H_4 (**3d**)	86	99
5	4-MeC_6H_4 (**3e**)	80	97
6	2-ClC_6H_4 (**3f**)	81	98
7	4-ClC_6H_4 (**3g**)	78	99
8	3-FC_6H_4 (**3h**)	70	91
9	3-$CF_3C_6H_4$ (**3i**)	77	97
10	3-BrC_6H_4 (**3j**)	72	92
11	3-MeO-4-$AcOC_6H_3$ (**3k**)	72	96
12[d]	2-furanyl (**3l**)	73	92

[a] Unless specified, for reactions conditions see footnote [a] in Table 1 and the Supporting Information. [b] Isolated yield. [c] The ee was determined by chiral HPLC analysis. [d] 10 mol % of catalyst of TES instead of TMS of catalyst **I** was used.

Next, we examined the structural alternation of the substrates **1** (Table 3). It was found that significant variation of the electron-withdrawing groups on the aryl substrates could be tolerated. Moreover, as a result of weaker electron-withdrawing capacity of these groups, high catalyst loadings are necessary to ensure efficient transformations. For example, switch of the 3-nitro group to CF_3 functionality gave the desired product **3m** in high yield (84%) and with excellent ee value (98%, entry 2) when 20 mol % of catalyst **I** was used. It seems that the effect by the replacement of the proton by the groups, such as Br and methyl moieties at the 4-position of 2-methyl-3,5-dinitrobenzaldehyde, is limited (entries 3 and 4). In both cases, impressive results are achieved. The use of 2,6-dichloro-4-methylnicotinaldehyde without assistance from nitro group(s) can also make the cascade process possible (entry 5). The corresponding chiral dihydroisoquinoline **3p** was obtained with high yield and excellent enantioselectivity. Finally, we also probed the more sterically hindered 2-ethyl-3,5-dinitrobenzaldehyde in the cascade reaction (entry 6). To our delight, the process proceeded in good reaction yield and with high enantioselectivity. It is noteworthy that two stereogenic centers are created highly diastereoselectively (10:1 dr).

Table 3. Organocatalytic Enantioselective Michael–Aldol Cascade Reaction of **1** with *trans*-Cinnamaldehyde (**2**)[a]

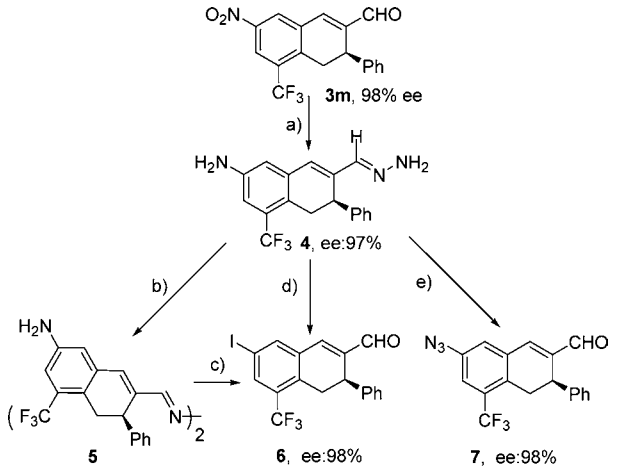


entry	product	cat. loading	t (h)	yield (%)[b]	ee[c]
1	 **3a**	5 mol %	48	83%	99%
2	 **3m**	20 mol %	48	84%	98%
3	 **3n**	20 mol %	48	79%	99%
4	 **3o**	30 mol %	48	53%	98%
5[d]	 **3p**	30 mol %	24	76%	98%
6	 **3q**	30 mol %	72	68%	96%[e]

[a] Unless specified, for reactions conditions see footnote [a] in Table 1 and the Supporting Information. [b] Isolated yield. [c] The ee was determined by chiral column. [d] DMSO was used as solvent in the reaction. [e] 10:1 dr; the diastereomeric ratio (dr) was calculated on the basis of crude ^1H NMR.

(16) The structure of compound **3g** was determined by X-ray crystal analysis. CCDC-953104 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk and see the Supporting Information.

Scheme 2. Transformations of the Nitro Group of **3m** to New Functionalities



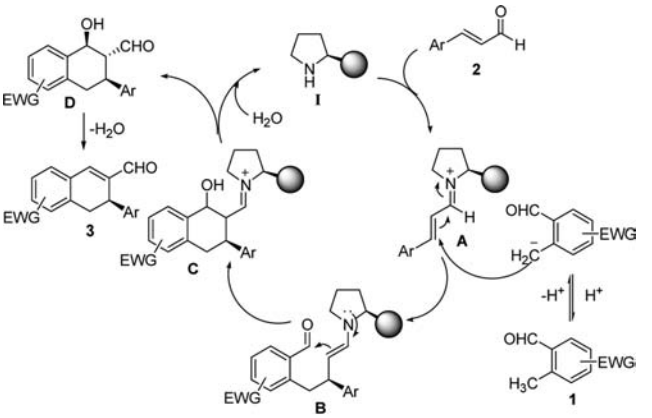
a): Pd/C, $N_2H_4{\cdot}H_2O$, EtOH, reflux, 100% yield
b): HCl, THF:H_2O=1:1, NaOH, 98% yield
c): $NaNO_2$, HCl, KI, H_2O, 0 °C to 90 °C, 83% yield
d): $NaNO_2$, HCl, KI, H_2O, 0 °C to 90 °C, 50% yield
e): $NaNO_2$, HCl, H_2O, 50 °C, 85% yield

We have demonstrated that introducing electron-withdrawing groups such as nitro group(s) at the *ortho*- and/or *para*-position(s) on an aromatic ring enables the methyl and ethyl groups to serve as effective nucleophiles for the Michael–aldol cascade reaction. Although they are necessary to activate the methyl and ethyl groups, it is desired that they can be transformed into other functionalities. Accordingly, we have carried out the studies using dihydronaphthalene **3m** as example (Scheme 2). It is found that the conversion of the aldehyde to hydrazone is necessary to achieve higher efficiency in these transformations. Hydrogenation of the nitro group gives rise to amine **4** in quantitative yield. The amine can be conveniently transferred to iodide **6** directly or via dimer **5** with higher yield in two steps. Furthermore, the amine **4** also can be transferred to azide product **7** in 85% yield. It is noteworthy that in these reactions no ee erosion is observed.

The proposed mechanism is described in Scheme 3. Activation of α,β-unsaturated aldehyde **2** by a chiral organocatalyst **I** produces iminium ion **A**. Then conjugate addition of a nucleophilic anion derived from **1** to **A** affords enamine **B**, followed by a subsequent intramolecular aldol process to give adduct **C**. Finally, the catalyst is recycled and meanwhile the formed intermediate **D** undergoes a spontaneous dehydration to give the product **3**.

In summary, we have developed a new organocatalytic highly enantioselective nucleophilic carbon initiated

Scheme 3. Proposed Mechanism for the Michael–Aldol Cascade Reaction



EWG = Electron-withdrawing group

Michael–aldol cascade reaction for "one-pot" construction of valuable chiral dihydronaphthalenes. Notably, for the first time, aryl methyl nucleophiles are explored under mild reaction conditions in a cascade manner. As demonstrated, activation of the alkyl group by the strong electron-withdrawing groups in aryl aldehydes enables the cascade process while they can be conveniently transformed into new functionalities. Further exploration of the strategy in new cascade reactions and the application of the methodology in the synthesis of biologically relevant molecules are being pursued in our laboratory.

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Supporting Information Available. Experimental procedures and ^1H and ^{13}C NMR and HRMS data for experimental procedures and characterization of the products **3** and **4**–**7** and X-ray information **3g** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.