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Acyl transfer-enabled catalytic asymmetric Michael addition of *α*-hydroxy-1-indanones to nitroolefins

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Abstract

We report herein an enantioselective acyl transfer protocol via electrophile activation. The reaction cascade sequence encompasses dinuclear zinc-catalyzed asymmetric Michael addition, intramolecular cyclization, and retro-Claisen reaction, which leads to a step- and atom-economic approach to a variety of protected cyclic tertiary *α*-hydroxyketones in good yields with excellent enantioselectivities (24 examples, 56%-82% yield, 1.5-13 dr and 79%-96% *ee*). Besides, the large-scale synthesis and further transformation of the products demonstrate the effectiveness of this method for organic synthesis.

Keywords: Acyl transfer, retro-Claisen reaction, zinc catalyst, nitroolefins, -hydroxy-1-indanones

INTRODUCTION

Acyl transfer presents an omnipresent and efficient chemoselective ligation process in biological systems[1], which has attracted extensive attention in the chemical community in recent years[2]. In order to circumvent

intrinsic reactivity or selectivity issues associated with mono-activated reactants, acyl transfer strategy utilizes the acyl group as a transient activating group to produce bis-activated reactants [Scheme 1A]. Such a chemical event involves a reaction cascade of X-Y bond formation, intramolecular cyclization, and the retro-Claisen reaction, where the challenging mono-activated function could be implemented formally. In this context, several catalytic asymmetric acyl transfer methods have been developed based on nucleophile activation [Scheme 1B]. For example, Mondal, Song *et al.* developed the asymmetric cascade Michael/acyl transfer reactions of α-nitroketones and 1,3-diketones using bifunctional organocatalysts[3-11]. Rodriguez and Luo reported the secondary or primary amine-catalyzed acyl transfer reactions[12-16]. Very recently, Yi *et al.* have established an elegant iridium-catalyzed asymmetric cascade allylation/acyl transfer reaction for the synthesis of enantiomerically enriched 3-hydroxymethyl pentenal units[17]. Besides, using acyl transfer, Zhou, Yang *et al.* prepared the medium-sized-ring lactams from cyclobutanone β-ketoamides[18-21]. Despite these achievements via nucleophile activation, acyl transfer via electrophile activation remains far less developed [Scheme 1C]. As far as we know, there was only one example from the Pan group, where nitroenone was used as an electrophilic acyl transfer reagent in catalytic asymmetric Friedel-Crafts and Michael reactions[22]. Therefore, the development of new catalytic asymmetric acyl transfer methods via electrophile activation is highly desired.

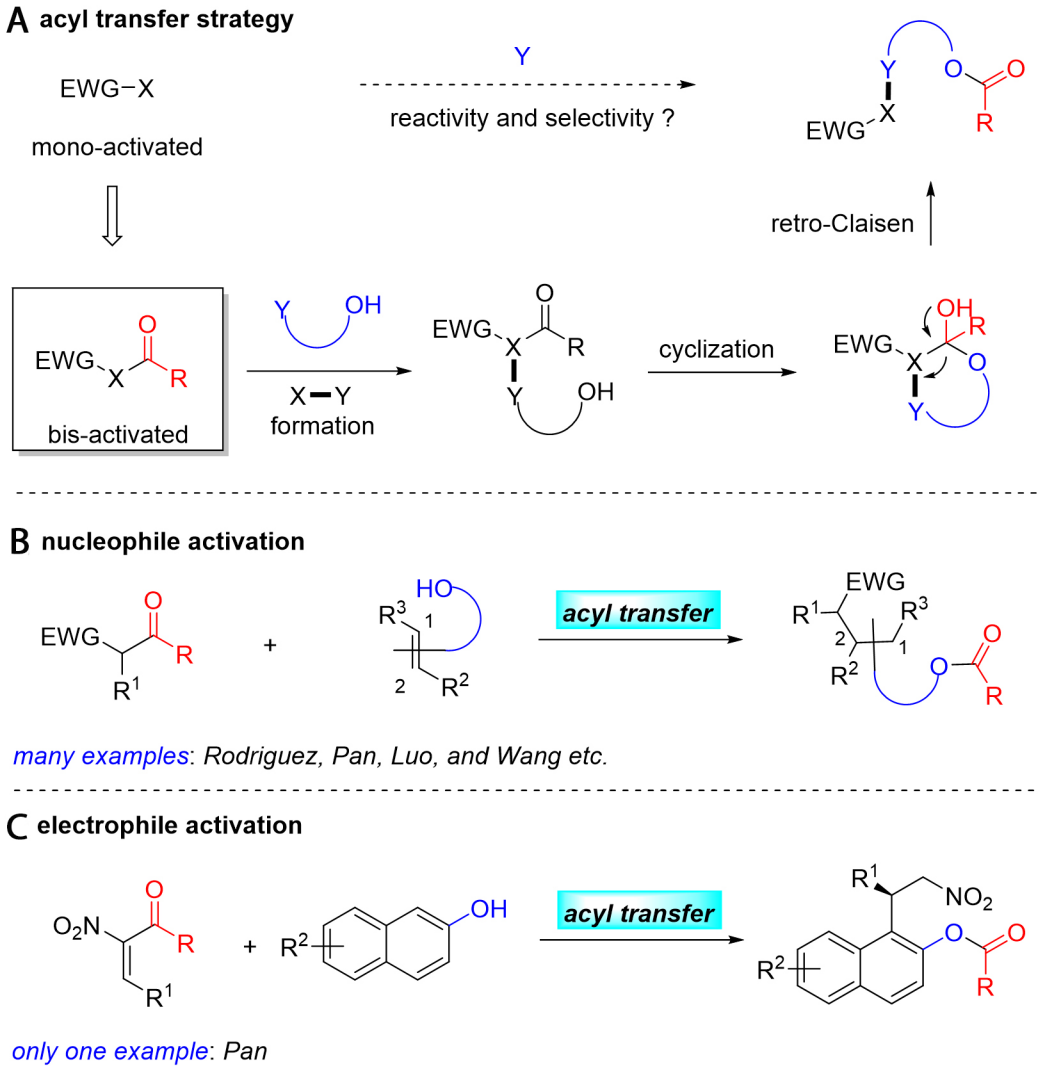
Our group has a long-standing interest in developing facile protocols for synthesizing biologically important molecules. Recently, we have discovered that α-hydroxy-1-indanones could serve as a valid synthon in cyclization reactions with activated Michael acceptors via chiral dinuclear zinc catalysis[23,24]. Along this line, we envisioned that dinuclear zinc-catalyzed asymmetric acyl transfer reaction between α-hydroxy-1-indanones **1** and nitroenones **2** was feasible via less-explored electrophile activation mechanism, generating thereby the protected cyclic tertiary α-hydroxyketones **3** in an enantioselective, step- and atom-economic manner. As illustrated in Scheme 2, the reaction cascade was triggered by dinuclear zinc-catalyzed Michael reaction[25,26], which led to the intermediate **Int-1**. The subsequent intramolecular cyclization/retro-Claisen reaction resulted in the acyl transfer product **3**. However, therein lie several synthetic organic chemistry challenges to this reaction proposal, which include: the enantioselective formation of the tetrasubstituted stereocenter, the side-formations of potential interruption product hemiketal **Int-2** and dehydration product dihydrofuran **4**. Herein, we introduce a highly enantioselective acyl transfer protocol via under-exploited electrophile activation by making use of dinuclear zinc-catalyzed Michael/cyclization/retro-Claisen reaction cascade, which led to a step- and atom-economic access to a variety of protected cyclic tertiary α-hydroxyketones in good yields with excellent enantioselectivities.

EXPERIMENTAL

Under a nitrogen atmosphere, a solution of diethylzinc (20 μL, 1.0 M in hexane, 0.02 mmol) was added dropwise to a solution of **L4** (0.01 mmol, 9.6 mg) in MeCN (2 mL). After the mixture was stirred for 30 min at 30 °C, **1a** (0.2 mmol, 29.6 mg) and **2a** (0.2 mmol, 50.6 mg) were added. The reaction mixture was stirred for 48 h at the same temperature. The reaction was quenched with HCl solution (1 M, 2 mL), and the organic layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure by using a rotary evaporator. The residue was purified by flash chromatography with petroleum ether/ethyl acetate (4:1) to afford the desired chiral product **3a**.

RESULTS AND DISCUSSION

The model reaction between α-hydroxy-1-indanone **1a** and 2-nitro-1,3-diphenylprop-2-en-1-one **2a** was initially performed in the presence of 10 mol % of dinuclear zinc catalyst *in situ* generated from 10 mol % of ligand **L1** and 20 mol % of $ZnEt_2$ in tetrahydrofuran (THF) at 30 °C oC Figure 1. The desired product **3a** was



Scheme 1. Acyl transfer strategies in asymmetric synthesis.

obtained in 56% yield with 1.5:1 diastereoselectivity and 39% *ee* value [Table 1, entry 1]. The screening of different chiral ligands including ProPhenol ligands (**L2**-**L5**) and AzePhenol ligands (**L6**-**L8**) indicated that **L4** bearing 4-$CF_3C_6H_4$ groups was the best ligand [Table 1, entries 2-8]. Subsequently, the examination of solvent effect demonstrated that MeCN could give a high *ee* value of 84% [Table 1, entries 9-13]. Unfortunately, raising or lowering the reaction temperature failed to optimize the efficiency and stereoselectivity. [Table 1, entries 14-17]. Finally, we turned our attention to investigating the catalyst loading, and found that by utilizing 5 mol % of ligand **L1** and 10 mol % of $ZnEt_2$, the yield and stereoselectivity could be improved to a high level (82% yield, 88% *ee*, 3:1 dr) [Table 1, entries 18-20].

With the best conditions in hand, the scope of both nitroenones and *α*-hydroxy-1-indanones for the projected reaction was examined [Scheme 3]. Firstly, the Ar^1 group of nitroenones was studied. A range of *ortho*-, *meta*-, *para*-substituted phenyl substrates **2** had been successfully employed to afford the corresponding products **3b**-**3f** in 56%-74% yields, 1.5:1-8.3:1 diastereoselectivities and 82%-94% enantioselectivities. In addition, 1-naphthyl group was also well tolerated, giving the desired product **3g** in

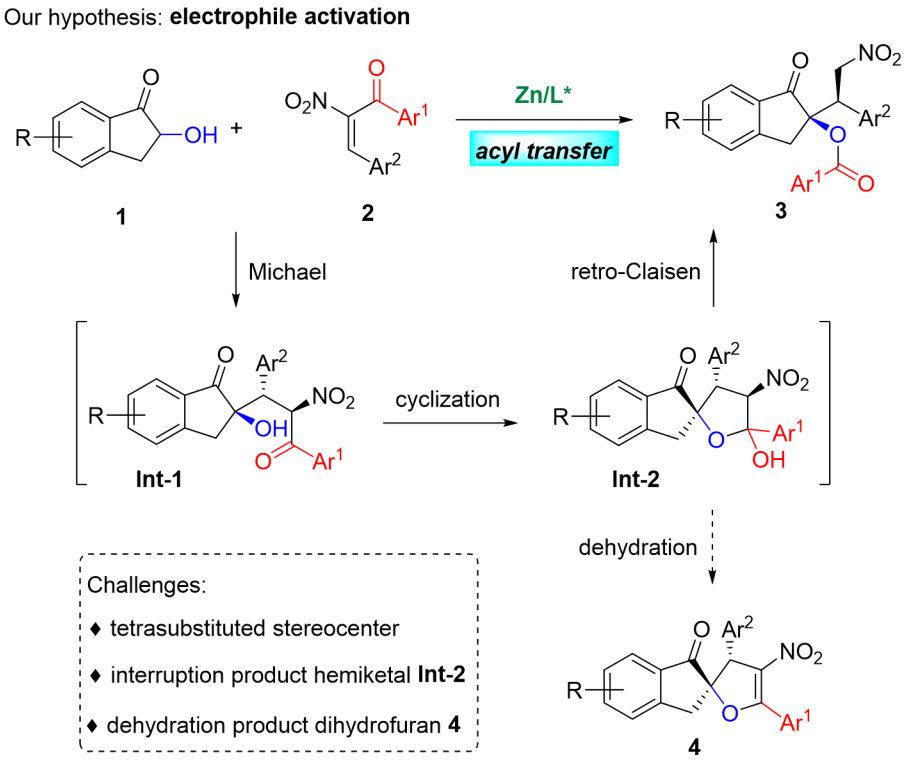
Table 1. Condition ptimization[a]

Entry	L	solvent	x	T (°C)	yield[b] (%)	dr[c]	ee [d] (%)
1	**L1**	THF	10	30	56	1.5:1	39
2	**L2**	THF	10	30	54	3.5:1	35
3	**L3**	THF	10	30	61	3.3:1	69
4	**L4**	THF	10	30	65	3.5:1	77
5	**L5**	THF	10	30	55	3.1:1	37
6	**L6**	THF	10	30	45	1.1:1	37
7	**L7**	THF	10	30	39	1.2:1	23
8	**L8**	THF	10	30	49	1:1	37
9	**L4**	PhMe	10	30	56	2.8:1	60
10	**L4**	MeCN	10	30	71	3:1	84
11	**L4**	CH_2Cl_2	10	30	65	2.7:1	75
12	**L4**	$CHCl_3$	10	30	70	1.7:1	59
13	**L4**	$PhCF_3$	10	30	60	2.1:1	63
14	**L4**	MeCN	10	0	46	1.5:1	40
15	**L4**	MeCN	10	10	69	3:1	80
16	**L4**	MeCN	10	40	71	3:1	84
17	**L4**	MeCN	10	50	69	3:1	82
18	**L4**	MeCN	3	30	54	3:1	85
19	**L4**	MeCN	5	30	82	3:1	88
20	**L4**	MeCN	15	30	74	3:1	80

[a]Reaction conditions: Unless otherwise noted, all reactions were conducted with x mol % of ligand, 2x mol % of $ZnEt_2$, 0.10 mmol **1a** and 0.10 mmol **2a** in 2 mL solvent. [b]Isolated yields. [c]The diastereomeric ratio parameter of **3a** was detected by ^{1}H NMR of the crude reaction mixture. [d]The enantiomeric excess (*ee*) value was determined by high-performance liquid chromatography (HPLC) analysis.

54% yield, 4.5:1 dr and 82% *ee* value. Next, the scope of Ar^2 group appended to the double bond of nitroenones was investigated. As illustrated in Scheme 3, both electron-rich and electron-deficient aryl groups could be tolerated, delivering the corresponding products **3h**-**3k** in 54%-79% yields, 2.8:1-9:1 diastereoselectivities and 79%-91% enantioselectivities. Furthermore, incorporating a heteroaromatic group (Ar^2 = 2-furyl) or a sterically bulky group (Ar^2 = 1-naphthyl) did not affect the efficiency of the reaction (**3l** and **3m**). Currently, only nitroenones bearing different aromatic substituents have been examined. Subsequently, we investigated the substrate generality of α-hydroxy-1-indanones by reacting them with 1-(2-methoxyphenyl)-2-nitro-3-phenylprop-2-en-1-one **2f**. Different substituents (from electron-donating to electron-withdrawing) at the C-4 to 6 positions of α-hydroxy-1-indanones **1** participated in the cascade reactions to give the desired products **3n**-**3x** in 62%-81% yields, 4.3:1-13:1 diastereoselectivities and 86%-96% enantioselectivities. Notably, the absolute configuration of the major isomer of product **3f** was determined by the X-ray crystallographic analysis and that of other products was assigned by analogy[27].

To showcase the synthetic utility of this protocol, a gram-scale synthesis of **3f** was carried out by using 5 mmol of **1a** and 5 mmol of **2f**. Under the standard condition, the reaction proceeded smoothly to give product **3f** in 69% yield (1.48 g) with 10:1 dr and 93% *ee* [Scheme 4A]. Further reduction of nitro group with the $NiCl_2/NaBH_4$ system and hydrolysis of the ester group took place in one-pot and afforded the indeno[1,2-*b*]pyrrol-(3*H*)-ol derivative **5** [Scheme 4B].



Scheme 2. Our designed catalytic asymmetric acyl transfer methods via electrophile activation.

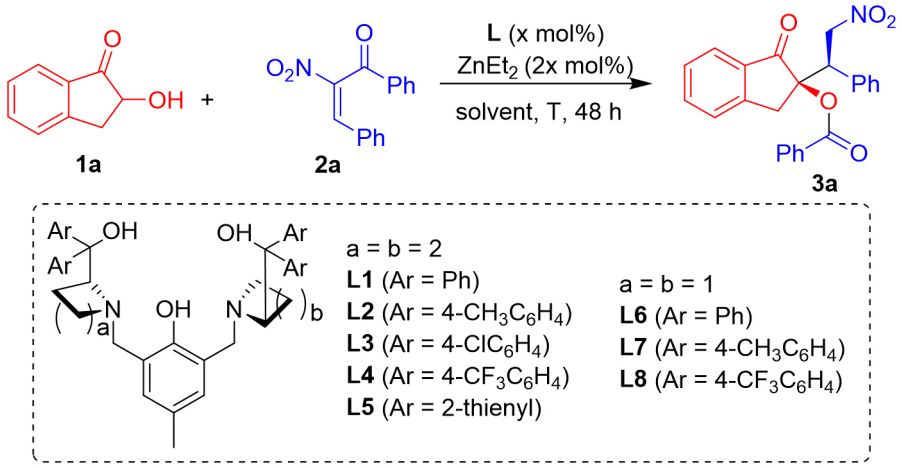
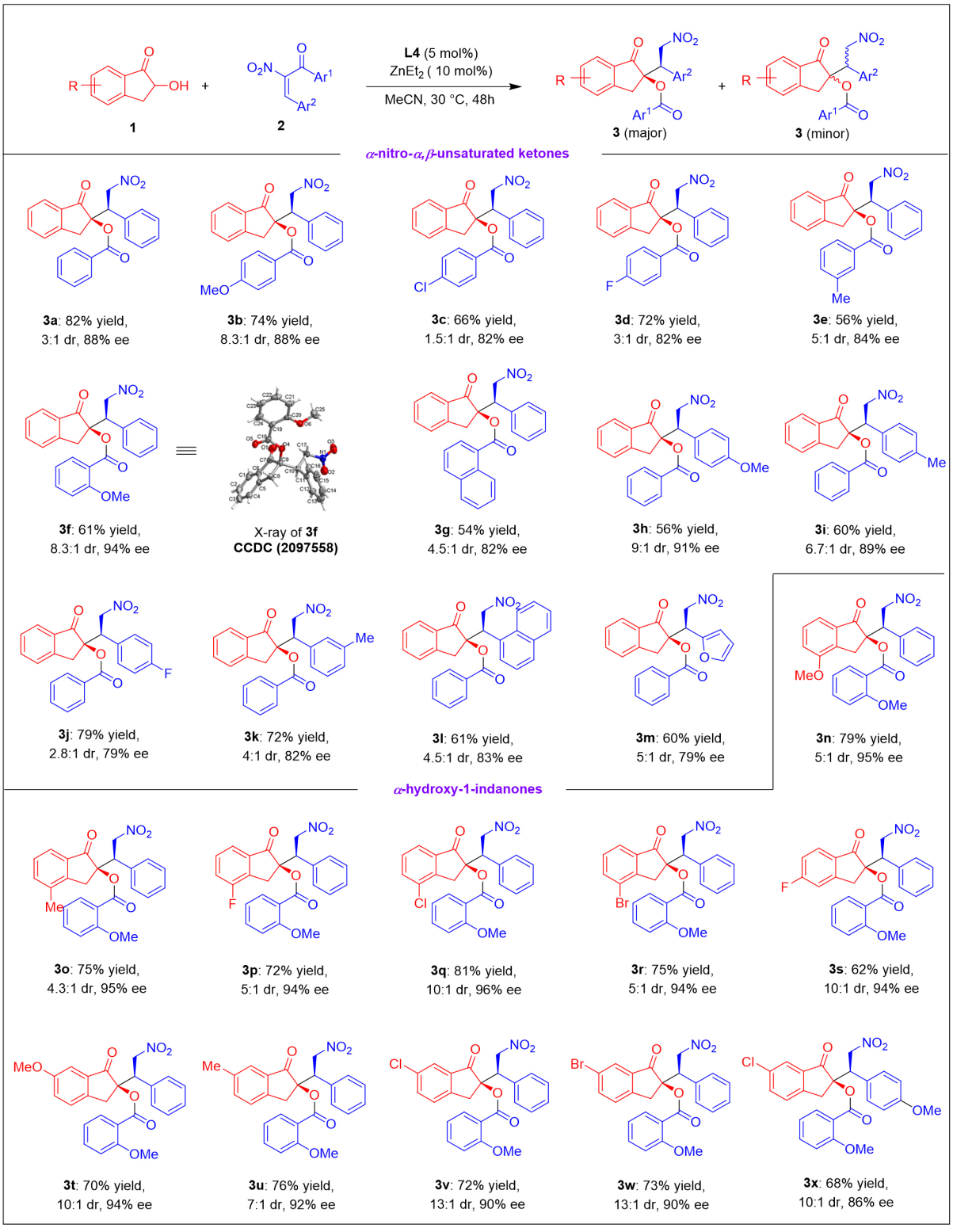
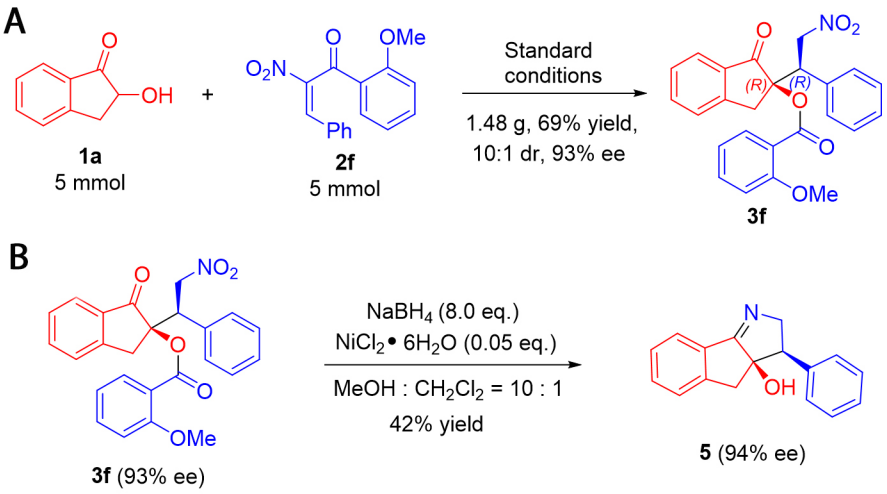


Figure 1. Reaction condition screening.

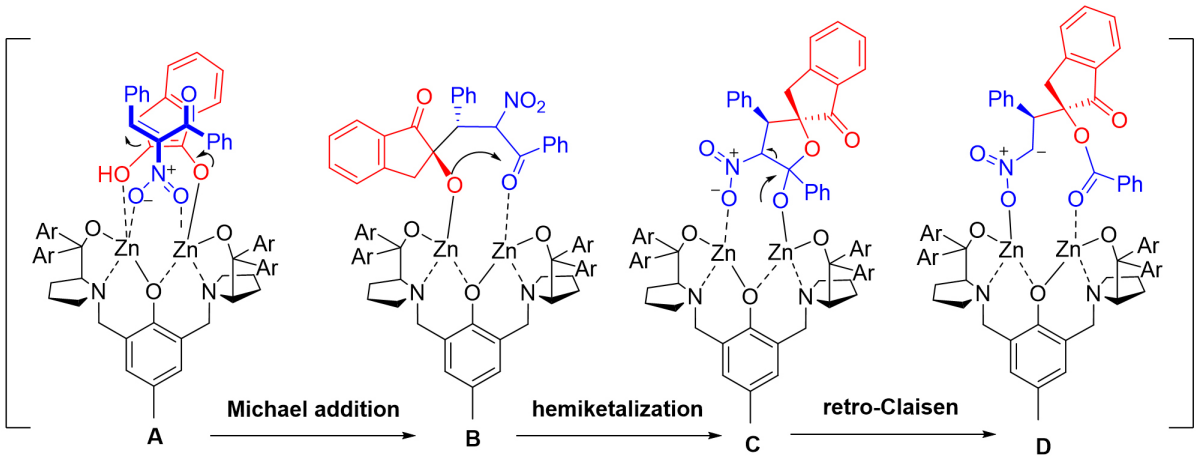
As previously described, a plausible reaction mechanism for this acyl transfer-enabled catalytic asymmetric Michael addition was illustrated in Scheme 5. Firstly, α-hydroxy-1-indanone **1a** and nitroenone **2a** were coordinated to the two zinc atoms in the chiral pocket of the dinuclear zinc complex in a less hindered manner. Then, the enantioselective Michael addition led to the intermediate **B**. Next, an intramolecular hemiketalization proceeded in the same chiral pocket to give intermediate **C**, which underwent the retro-Claisen reaction to afford the complex **D**. Finally, the catalytic cycle was restarted after a proton exchange of intermediate **D** with another α-hydroxy-1-indanone **1a**, followed by the release of product **3a**.



Scheme 3. Reaction scope. Reaction conditions: Unless otherwise noted, all reactions were conducted with 5 mol% of **L4**,10 mol % of $ZnEt_2$, 0.20 mmol **1** and 0.20 mmol **2** in 2 mL MeCN. Isolated yields. The diastereomeric ratio parameter of **3** was detected by ^{1}H NMR of the crude reaction mixture. The enantiomeric excess (*ee*) value was determined by HPLC analysis.



Scheme 4. Gram-scale reaction (A) and derivatization (B).



Scheme 5. Proposed reaction mechanism.

DFT calculations were performed on the enantioselectivity-determining step to elucidate the origins of selectivity. Model catalyst **IN1** [Figure 2] was used for the calculation. The ligand exchange of substrate **1a** and ethane leads to **IN2**, which is exergonic by 21.5 kcal/mol, followed by the Michael addition step. Our calculations show that the pathway leading to the major *RR*-enantiomer (via transition state **TS3-RR**) has a free energy barrier of 13.8 kcal/mol, which is 2.3 kcal/mol more favorable than that leading to the minor *SS*-enantiomer (via transition state **TS3-SS**) and agrees with experiment. Detailed analyses indicate that there is favorable C-H…π interactions between the C-H bond adjacent to C^1 in **1a** and the phenyl ring connecting to C^2 in **2a** (2.69 Å, Figure 2) in **TS3-RR**. On the other hand, however, unfavorable steric repulsion was found between hydrogen atoms of the two substrates in **TS3-SS** (the closest H-H distance is 2.04 Å, Figure 2). The steric repulsion between the two substrates in **TS3-SS** would retard the C^1-C^2 bond formation, as manifested by the much longer C^1-C^2 distance in **TS3-SS** (2.29 Å) than in **TS3-RR** (2.16 Å). Thus, our computations reveal that both the C-H…π interaction in **TS3-RR** and the steric effect in **TS3-SS** account for the observed enantioselectivity.

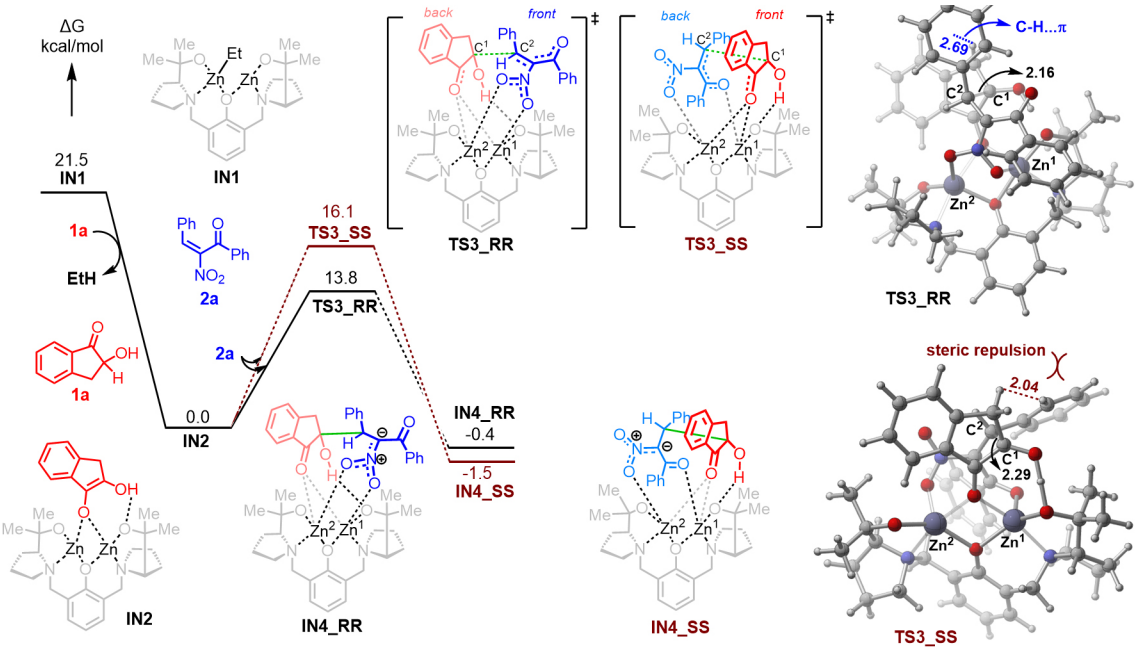


Figure 2. The calculated free energy profile and geometries of the key transition states for the enantioselectivity-determining Michael addition step (calculations were performed at the M06/6-311++G(d,p)/SDD//B3LYP-D3BJ/6-31G(d,p)/LANL2DZ//SMD(solvent=Acetonitrile) level of theory; bond distances are given in Å).

CONCLUSION

In conclusion, we have disclosed a novel acyl transfer-enabled catalytic asymmetric Michael reaction of α-hydroxy-1-indanones with nitroolefins via an underexplored electrophilic mode of activation. The chemical event underwent a reaction cascade of dinuclear zinc-catalyzed asymmetric Michael addition, intramolecular cyclization, and the retro-Claisen reaction. Good yields and stereoselectivities of the desired products were obtained with a wide substrate scope under mild conditions. In the activation mode, the dinuclear zinc complex acted as a bifunctional catalyst, wherein one zinc atom worked as a Lewis acid and the another functioned as a Brønsted base. Further applications of this catalytic asymmetric acyl transfer via electrophile activation for the synthesis of polyfunctional heterocycles are ongoing in our laboratory.

DECLARATIONS

Authors' contributions

Designing the experiments, writing the manuscript, and being responsible for the whole work: Jia SK, Wang MC, Mei GJ

Performing the experiments: Xu ZH, Hua YZ

Synthesizing the substrates: Chang ZR

DFT calculations: Li N, Xu LP

Availability of data and materials

Supplementary materials are available online for this paper.

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Conflicts of interest
All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

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