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Asymmetric synthesis of functionalized tetrahydrofluorenones via an NHC-catalyzed homoenolate Michael addition

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The first example of an N-heterocyclic carbene-catalyzed asymmetric desymmetrization of enal-tethered cyclohexadienones via an intramolecular homoenolate Michael addition/esterification reaction is described. This new protocol offers a direct entry to various functionalized tetrahydrofluorenones with three contiguous stereocenters in high yields, good diastereoselectivities and excellent enantioselectivities.

The organocatalytic asymmetric desymmetrization of prochiral cyclohexadienones has been applied extensively in a wide range of transformations such as conjugate additions, Stetter reactions, Rauhut-Currier reactions and cycloadditions.[1-4] Functionalized chiral cyclohexenones are highly versatile synthetic building blocks in organic synthesis and the partially reduced tricyclic fluorene skeleton is a common structural unit found in many bioactive compounds such as asterogynin B, the estrogen receptor β-selective agonist, taiwaniaquinol B and the anti-inflammatory propanoic acid (Fig. 1).[5] Among various approaches towards the construction of enantioenriched cyclohexenones, the catalytic asymmetric desymmetrization of cyclohexadienones is one of the most straightforward and efficient protocols.

NHC catalysis has emerged as a powerful strategy for the construction of complex molecules over the past decades.[6] Important intermediates in NHC organocatalysis are the homoenolate equivalents, first reported independently by Bode and Glorius in 2004.[7] Since then, this unique reactive intermediate has received considerable attention in organic synthesis.[8] Later, Nair and coworkers investigated the NHC-catalyzed domino reaction of enals and chalcones to afford 1,3,4-trisubstituted cyclopentenes.[9]

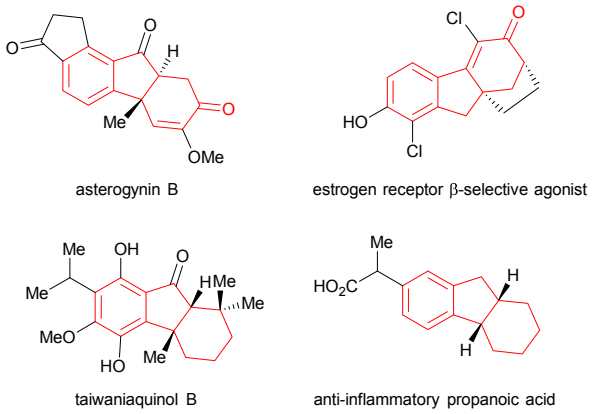

Fig. 1 Representative bioactive compounds containing a tricyclic partially reduced fluorene skeleton.

Most importantly, they found that the acylazolium intermediate in the domino process could be intercepted by an external alcohol to regenerate the NHC catalyst.[10] This finding opens the possibility for diverse carbocycles or acyclic compound synthesis. In previous reports, an internal nucleophile was indispensable in the starting material for the regeneration of the NHC catalyst, thus hindering the efficiency for the application of homoenolate intermediates.

In 2006, Rovis and coworkers reported the first NHC-catalyzed intramolecular Stetter reaction for the desymmetrization of prochiral cyclohexadienones to afford chiral hydrobenzofuranones.[11a, b] Later, You and coworkers further extended this process to other variants of cyclohexadienones.[11c-e] However, to the best of our knowledge, other NHC-catalyzed desymmetrizations of cyclohexadienones, especially via homoenolate intermediates have not been reported. We envisioned that the homoenolate or enolate intermediate generated *in situ* from α,β-unsaturated aldehydes might serve as a Michael donor and the enone motif of the cyclohexadienones as a Michael acceptor. This approach would be an extension to existing strategies for the NHC-catalyzed desymmetrization via Stetter reaction.

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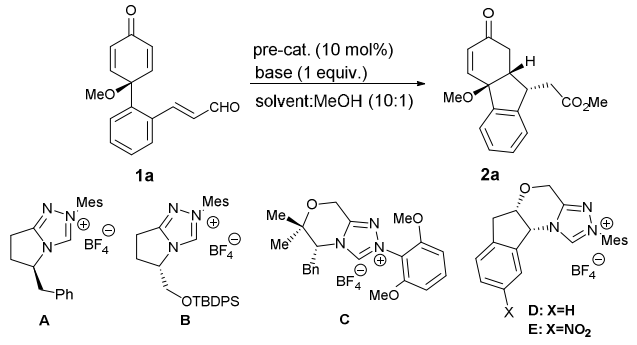
Our attempts with *p*-quinol and cinnamaldehyde under different conditions using an NHC catalyst were unsuccessful, probably owing to the relatively low reactivity of the dienone as compared to the enone system, which undergoes annulation smoothly according to previous literature. Despite the failure of this intermolecular version, we turned our attention to the investigation of the intramolecular homoenolate Michael addition for the desymmetrization of prochiral cyclohexadienones. Complementary to the previously reported Stetter reaction for the desymmetrization of cyclohexadienones, here we wish to report a homoenolate desymmetric Michael addition/ esterification sequence for the asymmetric synthesis of functionalized tetrahydrofluorenones.

Table 1 Optimization of the reaction conditions[a]

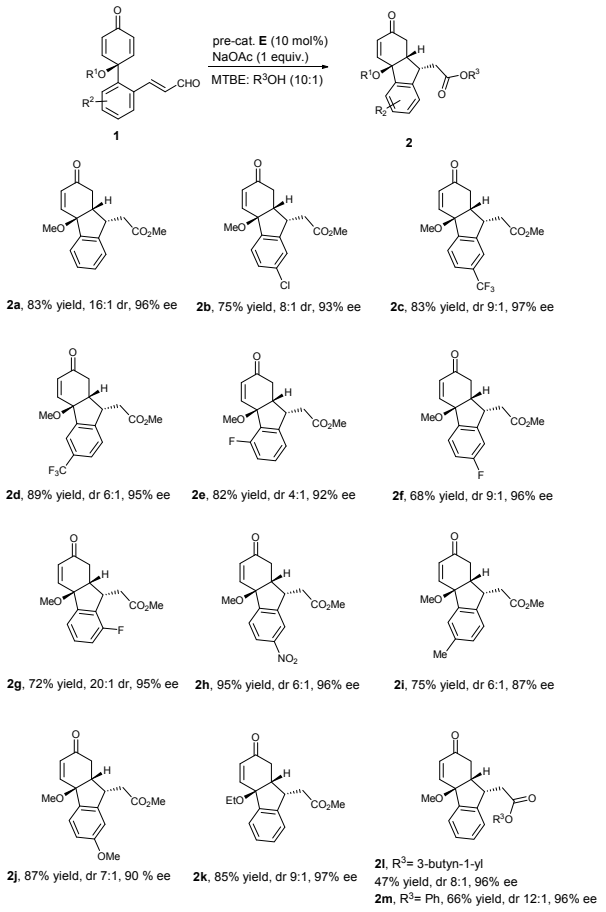


Entry	Pre-cat.	Solvent	Base	Yield (%)[b]	d.r[c]	ee[d]
1	**A**	Toluene	NEt_3	90	1.3:1	46
2	**B**	Toluene	NEt_3	61	3.7:1	77[e]
3	**C**	Toluene	NEt_3	64	4.6:1	59
4	**D**	Toluene	NEt_3	94	1.6:1	81
5	**E**	Toluene	NEt_3	82	3:1	95
6	**E**	Toluene	DBU	80	3.4:1	95
7	**E**	Toluene	DIPEA	76	4:1	94
8	**E**	Toluene	Na_2CO_3	49	3.5:1	99
9	**E**	Toluene	NaOAc	73	3:1	99
10	**E**	MTBE	NaOAc	73	5:1	97
11	**E**	$PhCF_3$	NaOAc	84	1.2:1	95
12	**E**	$CHCl_3$	NaOAc	77	4.8:1	97
13	**E**	Mesitylene	NaOAc	70	5:1	97
14[f]	**E**	MTBE	NaOAc	83	16:1	96

[a] Unless otherwise specified, all reactions were carried out with **1a** (0.1 mmol), pre-catalyst (10 mol%), base (1.0 equiv.) at rt. [b] Yield of isolated product **2a**. [c] d.r. was determined by ^{1}H NMR. [d] ee was determined by HPLC on a chiral stationary phase. [e] ee of *ent*-**2a**. [f] The reaction was carried out at 0 °C, 24 h.

With the enal-tethered cyclohexadienone **1a** in hand, chiral triazolium salts **A-E** were examined using triethylamine as base in toluene: MeOH (10:1 v/v, 1 mL) at room temperature (Table 1, entries 1-5). All the screened NHC catalysts afforded the cyclization product **2a** exclusively as five-membered ring via a homoenolate Michael addition pathway rather than a six-membered ring via an enolate Michael addition route. We were delighted to find that the nitro-substituted-aminoindanol-derived chiral triazolium catalyst **E** gave the best result with 82% yield and an enantiomeric excess of 95% as a 3:1 mixture of diastereomers (Table 1, entry 5). Several bases were screened using toluene as solvent, affording excellent enantioselectivities (entries 6-9), albeit with roughly 3:1 dr. The results indicated that bases show little impact on the diastereoselectivity. To further improve the diastereoselectivity, we turned our attention to a solvent screening and found that MTBE and mesitylene afforded **2a** in 5:1 dr (Table 1, entries 10 and 13). Using MTBE as solvent, the reaction was finished in only 4 h. Subsequently, we tried to lower the reaction temperature to 0 °C using MTBE as solvent. The enantioselectivity remained excellent and the dr increased to 16:1 with extended reaction time (24 h). The reaction was slugglish with further lowering the reaction temperature. We finally identified NHC **E** (10 mol%), NaOAc (100 mol%), MTBE: MeOH (10: 1) at 0 °C as the optimal conditions.

Table 2 Substrate scope of the asymmetric tetrahydrofluorenone synthesis.[a]



[a] All reactions were performed on a 0.2 mmol scale. The yields of the isolated products are those after column chromatography. The diastereomeric ratios were determined by ^{1}H NMR spectroscopy and the ee values were determined by HPLC on a chiral stationary phase.

With the optimal reaction conditions in hand, the substrate scope was examined. To assess the impact of the substituents on the aryl ring, we tested a variety of substituted enal-tethered cyclohexadienones and summarized the results in Table 2. All the reactions worked well and delivered the desired tricyclic frameworks in high yields and excellent enantioselectivities. A diverse set of electron-donating groups (OMe, OCH_2O, Me) and

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electron-withdrawing groups (NO_2, CF_3) on the aryl ring were well tolerated. Halogen-substituted aryl rings (3F, 5F, 6F, 5Cl) also worked well and afforded the corresponding cyclization products in high yields and excellent enantioselectivities. To further explore the substrate scope, alternative alcohols serving as nucleophiles to regenerate the NHC catalyst for the synthesis of different esters were also examined. The reactions proceeded well to afford the corresponding esters with excellent enantioselectivities employing different alcohols (**2l**: 3-butyn-1-ol, **2m**: PhOH).[12] The absolute configuration was unambiguously determined by X-ray crystal structure analysis of compound **2a** and all other configurations of the products **2b-m** were assigned by analogy (Fig. 2).[13]

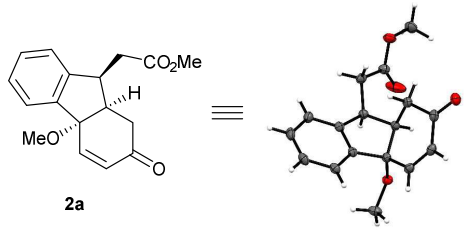
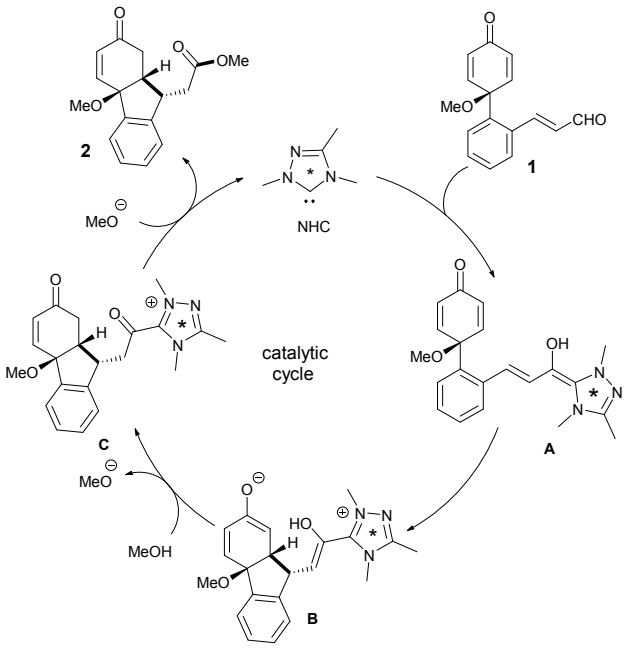


Fig. 2 Determination of the absolute configuration by X-ray crystal structure analysis of compound **2a**.

A proposed catalytic cycle for the NHC-catalyzed desymmetrization process is depicted in Scheme 1. The enal-tethered cyclohexadienone **1** undergoes an initial 1,2-addition of the NHC catalyst and proton transfer to generate the homoenolate equivalent **A**, which in turn leads to a desymmetric Michael addition to the prochiral cyclohexadienone moiety to form the intermediate **B**. Protonation and tautomerization to the acylazolium intermediate **C** allows for a subsequent esterification by the external alcohol to afford the desired product **2** and returns the NHC catalyst.



Scheme 1 Proposed catalytic cycle (NHC simplified for clarity).

In conclusion, we have developed an efficient method for the desymmetrization of prochiral cyclohexadienones via an NHC-catalyzed asymmetric homoenolate Michael addition/esterification reaction. By using a nitro-substituted aminoindanol-derived chiral triazolium salt **E** as pre-catalyst under mild conditions, a variety of functionalized tetrahydrofluorenones with three contiguous stereocenters including a tetrasubstituted one were obtained in good yields and high stereoselectivities.

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12. Because the starting materials bearing the OR^1 group were prepared through $PhI(OAc)_2$ mediated oxidative dearomatization in the corresponding alcohol solvents, so far this substituent could not be changed to alkyl and aryl groups to generate a quaternary stereocenter.
13. CCDC 1844760 (**2a**).

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