JOC The Journal of Organic Chemistry

Article

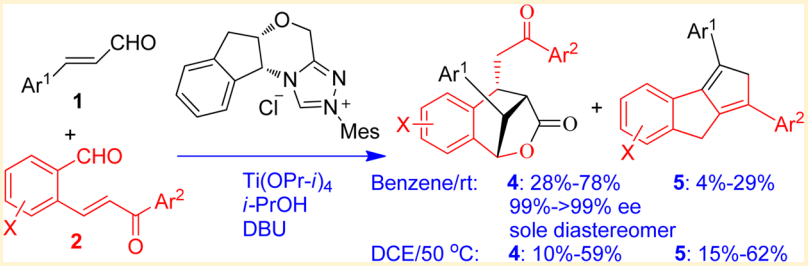
pubs.acs.org/joc

N-Heterocyclic Carbene/Lewis Acid Dual Catalysis for the Divergent Construction of Enantiopure Bridged Lactones and Fused Indenes

Zhan-Yong Wang, Ya-Li Ding, Shi-Ning Li, and Ying Cheng*

College of Chemistry, Beijing Normal University, Beijing 100875, China

Supporting Information



ABSTRACT: The chiral triazole carbene and Ti(OPr-*i*)$_4$ cocatalyzed reaction between α,β-unsaturated aldehydes and 2-(aroylvinyl)benzaldehydes was systematically studied. A divergence in reaction pathways was observed under different reaction conditions. In benzene solvent and at ambient temperature, the reaction produced 4,5-dihydro-1,4-methanobenzo[*c*]oxepin-3-ones, the bridged caprolactones, as the major products in moderate yields with excellent enantioselectivity. The same reaction in dichloroethane and at 50 °C, however, gave 2,8-dihydrocyclopenta[*a*]indenes as the major products in most cases. The application of the method developed was demonstrated by the transformation of the bridged lactone products into enantiopure 4-hydroxy-1,2,3,4-tetrahydronaphthalene-2-carboxylic acids.

INTRODUCTION

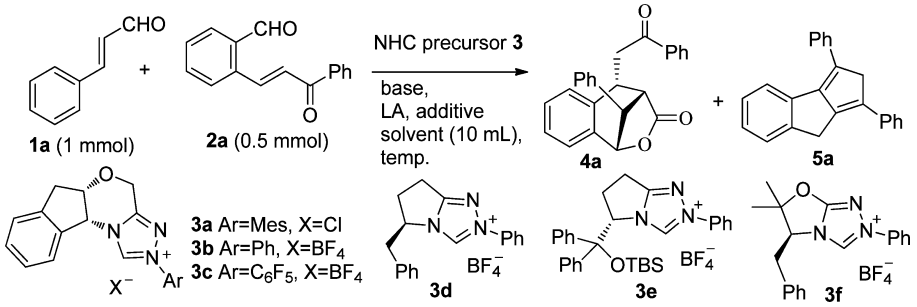
The development of new strategies for the stereoselective construction of multifunctional cyclic systems has been attracting increasing interest from organic chemists. In the past decades, the *N*-heterocyclic carbene catalysis has been developed into a powerful protocol for the synthesis of a wide range of carbocyclic and heterocyclic compounds.[1,2] Recently, the combination of NHC and acid catalysis emerges as a powerful strategy to expand the capabilities of NHC catalysis.[3] The cooperative catalysis of *N*-heterocyclic carbenes and acids is able to enhance the reactivity of substrates including those even previously inactive reaction partners, and to improve enantioselectivity or/and diastereoselectivity.[4,5] Under the cooperative catalysis of chiral NHC and Lewis or Brønsted acid catalysts, various α,β-unsaturated aldehydes undergo diverse reactions to afford five- and six-membered carbocyclic and heterocyclic compounds in enantioselective fashion.[4,5] For example, the chiral triazole carbene and Ti(OPr-*i*)$_4$ cocatalyzed dimerization of α,β-unsaturated aldehydes and the reactions between α,β-unsaturated aldehydes and α,β-unsaturated ketones permit efficient synthesis of substituted cyclopentanes or cyclopentenes with excellent enantioselectivity.[4a,b] On the other hand, under the dual catalysis of chiral triazole carbene and LiCl or chiral phosphoric acid, the alkenyl aldehydes or alkynyl aldehydes underwent formal [3+2] cycloaddition with the C═O bond of α-carbonyl ketones including α-ketoesters and isatins to produce γ-butyrolactones or γ-lactone-spiro-oxindoles in good yields with high stereoselectivities.[4c,5a] Similarly, the [3+2] cycloaddition of α,β-unsaturated aldehydes to the C═N bond of α,β-unsaturated imines or hydrazones catalyzed by the chiral triazole carbene and Lewis or Brønsted acid has been reported to generate enantiopure γ-butyrolactam derivatives.[4f,5b] Furthermore, both the reaction of α-bromoenals with isatins catalyzed by chiral NHC/Lewis acid and the reaction of enals with α-trifluoromethyl ketones catalyzed by a combination of NHC, Lewis acid, and oxidant underwent [4+2] cycloadditions, leading to the formation of δ-lactone-spiro-oxindoles or δ-lactone derivatives.[4e,g] Although many NHC-catalyzed reactions have been employed successfully in the synthesis of mono-, fused-, and spiro-heterocycles or carbocycles, to the best of our knowledge, the construction of bridged cyclic compounds by NHC catalysis is very rare.[6]

We have been interested for many years in the development of new NHC-catalyzed reactions for the divergent synthesis of complex molecules based on the same starting materials.[7] We were delighted to discover very recently that the NHC catalysts combined with Lewis acid are capable regulating reaction pathways under varied conditions, transforming therefore the same reactants into diverse products.[8] For instance, while the triazole carbene-catalyzed dimerization of 2-formylcinnamates underwent benzoin condensation followed by intramolecular oxa-Michael addition to afford isochromeno[4,3-*c*]isochromene products, the triazole carbene and Ti(OPr-*i*)$_4$ cocatalyzed dimerization of 2-formylcinnamates proceeded through a completely different route to furnish the formation of

Received: September 23, 2016
Published: November 4, 2016

DOI: 10.1021/acs.joc.6b02329
J. Org. Chem. 2016, 81, 11871−11881

Table 1. Optimization of Reaction Conditions



entry	3 (mol%)	base (mol%)	LA (mol%)	additive (mol%)	sol.	temp. (°C)	t (h)	yield of 4a (%)[a]	ee of 4a (%)[b]	yield of 5a (%)[a]
1	**3a** (10%)	DBU (20%)	no	no	DCM	rt	48			
2	**3a** (10%)	DBU (20%)	Ti(OPr-*i*)$_4$ (100%)	no	DCM	rt	48	21	> 99	8
3	**3b** (10%)	DBU (20%)	Ti(OPr-*i*)$_4$ (100%)	no	DCM	rt	48	13	99	10
4	**3c** (10%)	DBU (20%)	Ti(OPr-*i*)$_4$ (100%)	no	DCM	rt	48	trace		trace
5	**3d** (10%)	DBU (20%)	Ti(OPr-*i*)$_4$ (100%)	no	DCM	rt	48	11	−91	8
6	**3e** (10%)	DBU (20%)	Ti(OPr-*i*)$_4$ (100%)	no	DCM	rt	48	trace		trace
7	**3f** (10%)	DBU (20%)	Ti(OPr-*i*)$_4$ (100%)	no	DCM	rt	48	trace		trace
8	**3a** (10%)	DBU (20%)	Ti(OPr-*i*)$_4$ (100%)	*i*-PrOH (100%)	DCM	rt	48	29	97	13
9	**3a** (10%)	DBU (20%)	Ti(OPr-*i*)$_4$ (100%)	*i*-PrOH (100%)	DCM	reflux	12	41	96	38
10	**3a** (10%)	DBU (20%)	Ti(OPr-*i*)$_4$ (100%)	*i*-PrOH (200%)	DCM	reflux	12	37	87	33
11	**3a** (10%)	DBU (50%)	Ti(OPr-*i*)$_4$ (100%)	*i*-PrOH (100%)	DCM	reflux	12	32	98	22
12	**3a** (10%)	NaOAc (20%)	Ti(OPr-*i*)$_4$ (100%)	*i*-PrOH (100%)	DCM	reflux	24	30	97	3
13	**3a** (10%)	K_2CO_3 (20%)	Ti(OPr-*i*)$_4$ (100%)	*i*-PrOH (100%)	DCM	reflux	24	10	ND	trace
14	**3a** (10%)	NaH (20%)	Ti(OPr-*i*)$_4$ (100%)	*i*-PrOH (100%)	DCM	reflux	24	23	90	15
15	**3a** (10%)	Cs_2CO_3 (20%)	Ti(OPr-*i*)$_4$ (100%)	*i*-PrOH (100%)	DCM	reflux	24	mess		mess
16	**3a** (10%)	*i*-BuOK (20%)	Ti(OPr-*i*)$_4$ (100%)	*i*-PrOH (100%)	DCM	reflux	24	14	98	4
17	**3a** (10%)	DMAP (20%)	Ti(OPr-*i*)$_4$ (100%)	*i*-PrOH (100%)	DCM	reflux	48	5	ND	20
18	**3a** (10%)	DBU (20%)	Ti(OPr-*i*)$_4$ (100%)	*i*-PrOH (100%)	$CHCl_3$	50	24	29	99	12
19	**3a** (10%)	DBU (20%)	Ti(OPr-*i*)$_4$ (100%)	*i*-PrOH (100%)	THF	50	12	12	98	5
20	**3a** (10%)	DBU (20%)	Ti(OPr-*i*)$_4$ (100%)	*i*-PrOH (100%)	CH_3CN	50	12	22	82	9
21	**3a** (10%)	DBU (20%)	Ti(OPr-*i*)$_4$ (100%)	*i*-PrOH (100%)	acetone	50	12	trace		trace
22	**3a** (10%)	DBU (20%)	Ti(OPr-*i*)$_4$ (100%)	*i*-PrOH (100%)	toluene	50	12	50	98	18
23	**3a** (10%)	DBU (20%)	Ti(OPr-*i*)$_4$ (100%)	*i*-PrOH (100%)	benzene	50	12	57	99	15
24	**3a** (10%)	DBU (20%)	Ti(OPr-*i*)$_4$ (100%)	*i*-PrOH (100%)	DCE	50	12	33	99	41
25	**3a** (10%)	DBU (20%)	Ti(OPr-*i*)$_4$ (100%)	*i*-PrOH (100%)	benzene	reflux	12	56	98	18
26	**3a (10%)**	**DBU (20%)**	**Ti(OPr-*i*)$_4$(100%)**	***i*-PrOH (100%)**	**benzene**	**rt**	**12**	**60**	**99**	**5**
27	**3a** (20%)	DBU (20%)	Ti(OPr-*i*)$_4$ (100%)	*i*-PrOH (100%)	benzene	rt	12	57		12
28	**3a** (10%)	DBU (20%)	Ti(OPr-*i*)$_4$ (150%)	*i*-PrOH (100%)	benzene	rt	12	55		16
29	**3a (10%)**	**DBU (20%)**	**Ti(OPr-*i*)$_4$(150%)**	***i*-PrOH (100%)**	**DCE**	**50**	**12**	**33**	**99**	**50**
30	**3a** (10%)	DBU (20%)	Ti(OPr-*i*)$_4$ (200%)	*i*-PrOH (100%)	DCE	50	12	34	99	48
31	**3a (20%)**	**DBU (20%)**	**Ti(OPr-*i*)$_4$(150%)**	***i*-PrOH (100%)**	**DCE**	**50**	**12**	**30**	**99**	**52**
32	**3a** (20%)	DBU (20%)	Ti(OPr-*i*)$_4$ (150%)	*i*-PrOH (100%)	DCE	reflux	12	34	99	44

[a]Isolated yields. [b]Determined by HPLC analysis on a AD-H column.

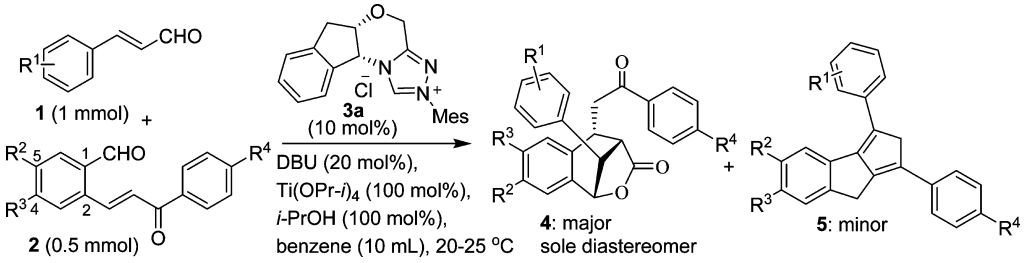
isochromenone derivatives.[8a] On the other hand, while chiral triazole carbenes catalyzed an intramolecular cyclization reaction of 2-aroylvinylcinnamaldehydes,[9] a combination of chiral triazole carbene and Ti(OPr-*i*)$_4$ catalyzed the intermolecular dimerization under the same reaction conditions.[8b] To generalize the concept and strategy of the cooperative NHC/Lewis acid catalyzed divergent synthesis, we undertook the current study of the reaction between *α,β*-unsaturated aldehydes and 2-(aroylvinyl)benzaldehydes, the formyl-bearing *α,β*-unsaturated ketones. Conceivably, various reactions would take place between these functionalized reactants. Herein we reported chiral triazole carbene/Ti(OPr-*i*)$_4$ cocatalyzed two distinct reactions, yielding 1,4-methanobenzo[*c*]oxepin-3-one and 2,8-dihydrocyclopenta[*a*]indene derivatives.

RESULTS AND DISCUSSION

We commenced our study by investigating the reaction between cinnamaldehyde **1a** and 2-(benzoylvinyl)benzaldehyde **2a**. In dry dichloromethane and at ambient temperature (about 20−25 °C), no reaction between **1a** and **2a** took place in the presence of a chiral triazolium precatalyst **3a** (10 mol%) and DBU (20 mol%). Addition of one equivalent of Ti(OPr-*i*)$_4$ as a cocatalyst, however, led to the formation of a bridged caprolactone, namely 5-(benzoylmethyl)-10-phenyl-4,5-dihydro-1,4-methanobenzo[*c*]oxepin-3-one **4a**, and 1,3-diphenyl-2,8-dihydrocyclopenta[*a*]indene **5a** in 21% and 8% yield, respectively (Table 1, entries 1 and 2). To improve the synthetic efficiency, other chiral carbenes were tested. Unfortunately, in the presence of Ti(OPr-*i*)$_4$, the variation of

DOI: 10.1021/acs.joc.6b02329
J. Org. Chem. 2016, 81, 11871−11881

Table 2. Chiral NHC/Ti(OPr-*i*)$_4$-Catalyzed Reaction of *α,β*-Unsaturated Aldehydes 1 with 2-(Aroylvinyl)benzaldehydes 2 in Benzene at Ambient Temperature



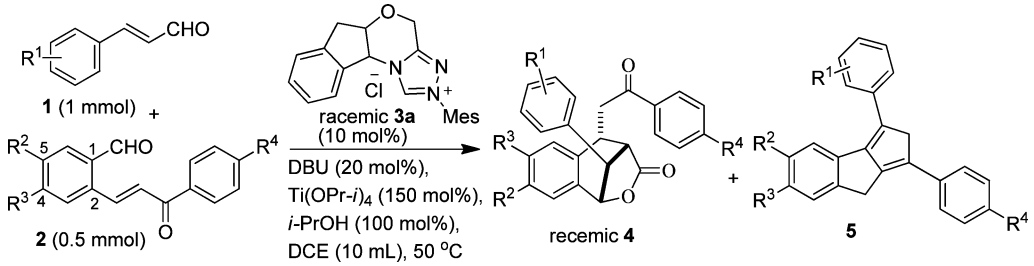
entry	1	R^1	2	R^2	R^3	R^4	time (h)	yield of 4 (%)[a]	ee of 4 (%)[b]	yield of 5 (%)[a]
1	**1a**	H	**2a**	H	H	H	12	**4a**: 60	99	**5a**: 5
2	**1b**	4-Br	**2a**	H	H	H	12	**4b**: 53	99	**5b**: 10
3	**1c**	4-Cl	**2a**	H	H	H	12	**4c**: 55	99	**5c**: 8
4	**1d**	2-Cl	**2a**	H	H	H	12	**4d**: 62	> 99	**5d**: 7
5	**1e**	3-Cl	**2a**	H	H	H	12	**4e**: 58	> 99	**5e**: 4
6	**1f**	4-Ac	**2a**	H	H	H	12	**4f**: 60	> 99	**5f**: 10
7	**1g**	4-Me	**2a**	H	H	H	12	**4g**: 49	> 99	**5g**: 15
8	**1h**	4-OMe	**2a**	H	H	H	12	**4h**: 28/34[c]/43[c,d]	> 99	**5h**: 11/19[c]/22[c,d]
9	**1i**	2-OMe	**2a**	H	H	H	12	**4i**: 47	99	**5i**: 14
10	**1a**	H	**2b**	F	H	H	12	**4j**: 41	> 99	trace
11	**1a**	H	**2c**	Me	H	H	12	**4k**: 64	99	**5k**: 6
12	**1a**	H	**2d**	OMe	H	H	12	**4l**: 70	> 99	**5l**: 8
13	**1a**	H	**2e**	H	F	H	24	**4m**: 22/25[c]	99	**5m**: 29/30[c]
14	**1a**	H	**2f**	H	Me	H	24	**4n**: 45/52[c]	> 99	**5n**: 22/26[c]
15	**1a**	H	**2g**	H	OMe	H	24	**4o**: 51/61[c]	> 99	**5o**: 24/28[c]
16	**1a**	H	**2h**	H	H	Br	12	**4p**: 48	> 99	**5p**: 6
17	**1a**	H	**2i**	H	H	Me	12	**4q**: 69	> 99	**5q**: 9
18	**1a**	H	**2j**	H	H	OMe	12	**4r**: 78	> 99	**5r**: 8

[a]Isolated yields. [b]Determined by HPLC analysis on a AD-H or AS-H column.The details of HPLC separation conditions for each product **4** have been listed in Supporting Information. [c]20 mol% of catalyst **3a** was used. [d]The reaction was carried out at 50 °C.

a serial of chiral triazoliumsalts **3b**−**3f** as NHC precatalysts did not result in the high yields of products **4** and **5** (Table 1, entries 3−7). On the other hand, however, the addition of one equivalent of isopropanol as an additive in the **3a**/Ti(OPr-*i*)$_4$-catalyzed reaction slightly increased the yields of **4a** and **5a** to 29% and 13%, respectively (Table 1, entry 8). To further promote the reaction of **1a** with **2a**, the reaction temperature was then elevated to the boiling point of dichloromethane. Pleasingly, the formation of the bridged lactone **4a** in 41% yield with 96% ee, along with the formation of 38% yield of fused indene **5a** (**4a**:**5a** ∼ 1:1) was observed (Table 1, entry 9). In refluxing DCM, the increase of the loading of *i*-PrOH to 200 mol% or of DBU to 50 mol% did not benefit to the formation of either **4a** or **5a** (Table 1, entries 10 and 11). The use of other Lewis acids, such as Mg(OBu-*t*)$_2$, Mg(OTf)$_2$, Sc(OTf)$_3$, and LiCl, did not facilitate the reaction. The replacement of DBU by other bases including AcONa, K_2CO_3, Cs_2CO_3, NaH, *t*-BuOK, and DMAP all led to diminished yields of both the major product **4a** and the total yields of **4a** and **5a** (Table 1, entries 12−17). Therefore, the combination of chiral triazolium salt **3a**, DBU, Ti(OPr-*i*)$_4$, and *i*-PrOH was chosen as a cooperative catalytic system for further optimization. The reaction of **1a** with **2a** was then examined in a number of solvents at 50 °C. It was found that the reactions in chloroform, THF, acetone, and acetonitrile gave even worse results than that in dichloromethane (Table 1, entries 18−21). Delightfully, both the chemical yield of product **4a** and the selectivity of **4a** over **5a** were improved when toluene and benzene were utilized as solvents. The bridged lactone **4a** was isolated in 50% and 57% yields, along with 18% and 15% yields of **5a**, respectively. Moreover, the enantiomeric excess values of 98% and 99% were obtained for product **4a** (Table 1, entries 22 and 23). Interestingly, the reaction in 1,2-dichloroethane reversed the selectivity between **4a** and **5a**, affording **4a** and **5a** in 33% and 41% yields at 50 °C (Table 1, entry 24).To further improve the chemical yield and the selectivity, other reaction parameters were further optimized in benzene and 1,2-dichloroethane, respectively. In benzene solvent, while an elevating reaction temperature as 80 °C marginally affected the formation of both **4a** and **5a**, the reaction at ambient temperature was found to significantly increase the selectivity, leading to the formation of **4a** in 60% (>99% ee) and **5a** only in 5% yields, respectively (Table 1, entries 25 and 26). The increase of the loading of carbene precatalyst **3a** to 20 mol% or Ti(OPr-*i*)$_4$ to 150 mol% in benzene has a negligible effect to the production of **4a** (55−57%), but led to a slightly increased yield of **5a** (12−18%) (Table 1, entries 27 and 28). In the case of reaction in 1,2-dichloroethane and at 50 °C, the reaction catalyzed by 10 mol% of carbene and 150 mol% of Ti(OPr-*i*)$_4$ produced 50% yield of **5a** and 33% yield of **4a** (99% ee) (Table 1, entry 29). When the carbene catalyst **3a** was loaded to 20 mol% or Ti(OPr-*i*)$_4$ to 200 mol%, or the reaction temperature was increased to the boiling point of 1,2-dichloroethane, no dramatic effect was observed in terms of efficiency and selectivity (Table 1, entries 30−32). In order to synthesize selectively the 2,8-dihydrocyclopenta[*a*]indene **5a**, some achiral triazolium, imidazolium, imidazolinium, and thiazolium salts were also employed as the carbene precatalysts. Disappointingly, none of

DOI: 10.1021/acs.joc.6b02329
J. Org. Chem. 2016, 81, 11871−11881

Table 3. NHC/Ti(OPr-$_i$)$_4$-Catalyzed Reaction of α,β-Unsaturated Aldehydes 1 with 2-(Aroylvinyl)benzaldehydes 2 in Dichloroethane at 50 °C



entry	1	R^1	2	R^2	R^3	R^4	time (h)	yield of 5 (%)[a]	yield of 4 (%)[a]
1	**1a**	H	**2a**	H	H	H	12	**5a**: 50	**4a**: 33
2	**1b**	4-Br	**2a**	H	H	H	12	**5b**: 38	**4b**: 18
3	**1c**	4-Cl	**2a**	H	H	H	12	**5c**: 42	**4c**: 15
4	**1g**	4-Me	**2a**	H	H	H	12	**5g**: 48	**4g**: 22
5	**1h**	4-OMe	**2a**	H	H	H	12	**5h**: 40	**4h**:11
6	**1i**	2-OMe	**2a**	H	H	H	12	**5i**: 40	**4i**: 29
7	**1a**	H	**2b**	F	H	H	12	**5j**: 15/20[b]	**4j**: 25/30[b]
8	**1a**	H	**2c**	Me	H	H	12	**5k**: 52	**4k**: 33
9	**1a**	H	**2d**	OMe	H	H	12	**5l**: 26/37[b]	**4l**: 41/34[b]
10	**1a**	H	**2e**	H	F	H	12	**5m**: 40	**4m**: 10
11	**1a**	H	**2f**	H	Me	H	12	**5n**: 62	**4n**: 20
12	**1a**	H	**2g**	H	OMe	H	12	**5o**: 62	**4o**: 18
13	**1a**	H	**2h**	H	H	Br	12	**5p**: 43	**4p**: 22
14	**1a**	H	**2i**	H	H	Me	12	**5q**: 36	**4q**:43
15	**1a**	H	**2j**	H	H	OMe	12	**5r**: 19/24[b]	**4r**: 59/49[b]

[a]Isolated yields. [b]The reaction was carried out under the catalysis of a combination of **3a** (20 mol%), DBU (50 mol%), Ti(OPr-*i*)$_4$ (200 mol%), and *i*-PrOH (200 mol%) in refluxing dichloroethane.

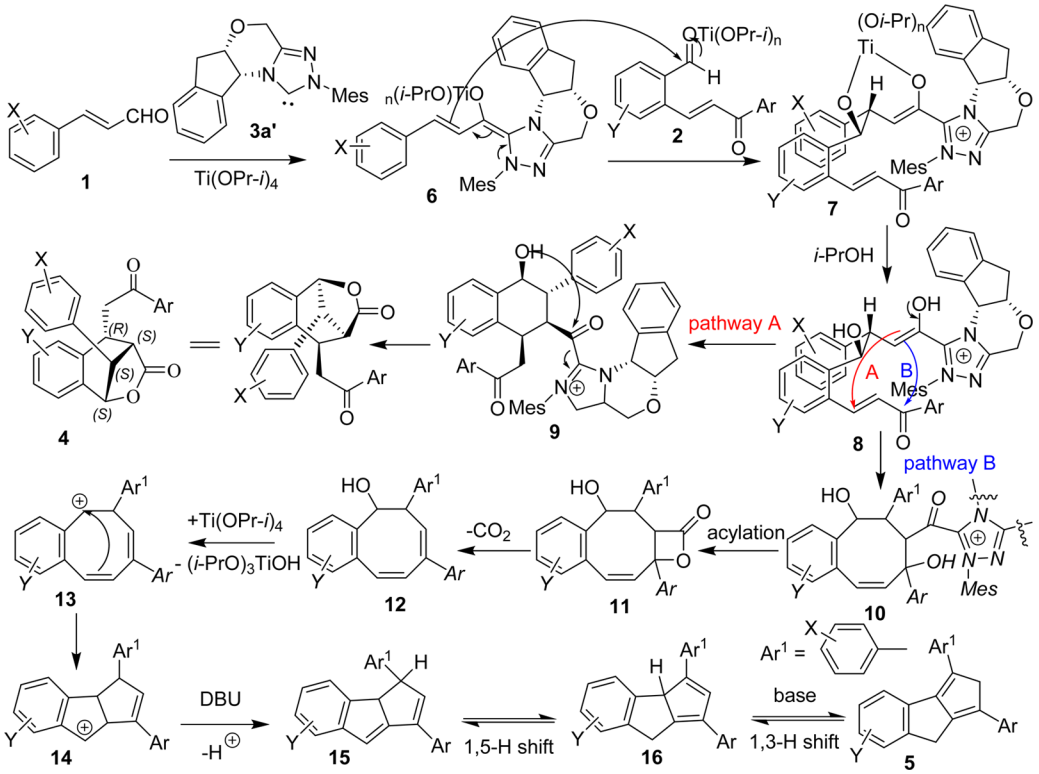
them acted as an efficient promoter for the reaction between **1a** and **2a**.

Under the optimized conditions for the selective formation of the bridged lactone **4a**, the substrate scopes were surveyed by employing different substituted cinnamaldehydes **1** and 2-(aroylvinyl)benzaldehydes **2**. The catalytic reaction was found to tolerate both electron-donating and electron-withdrawing groups of both reactants. The electronic nature and substitution pattern of substituents influenced, however, the reactivity and selective formation of two products. For example, under the catalysis of a combination of chiral triazoliumsalt **3a** (10 mol%), DBU (20 mol%), Ti(OPr-*i*)$_4$ (100 mol%), and *i*-PrOH (100 mol%) in benzene at room temperature (about 20−25 °C), the presence of an electron-withdrawn group (*p*-Br, *p*-Cl, *m*-Cl, *o*-Cl, or *p*-Ac) on the phenyl ring of cinnamaldehydes was beneficial to the reactions of **1b**−**1f** with **2a**, furnishing the formation of the corresponding lactones **4b**−**4f** in 53−62% yields with 99→99% ee. The byproducts **5b**−**5f** were found in very low yields (4−10%) (Table 2, entries 1−6). In contrast, when the cinnamaldehyde **1g** or **1h** was substituted by an electron-donating *p*-methyl or *p*-methoxy group, the reaction with **2a** became less efficient and led to the lower yield of product **4g** (49%) or **4h** (28%), although enantioselectivity remained excellent (Table 2, entries 7 and 8). An improved yield was achieved for **4h** (43% yield, > 99% ee) by increasing the loading of catalyst **3a** to 20 mol% and reaction temperature to 50 °C, albeit the yield of byproduct **5h** was also increased (Table 2, entry 8). The move of the methoxy group from *para*- to *ortho*-position of cinnamaldehyde resulted in the formation of product **4i** in a higher yield (47%) than that of **4h** under the same conditions (Table 2, entries 8 and 9). The substituent effect of 2-(aroylvinyl)benzaldehydes **2** on the reaction summarized in Table 2 indicated a favorable effect of an electron-donating group. This has been examplified by the reactions of 2-(benzoylvinyl)-5-methyl- (**2c**) and 2-(benzoylvinyl)-5-methoxybenzaldehyde **2d**, which reacted efficiently with cinnamaldehyde **1a** to give products **4k** and **4l** in 64% and 70% yields (99→99% ee) (Table 2, entries 11 and 12). The reaction of 2-(benzoylvinyl)-5-fluorobenzaldehyde **2b** with **1a** only produced 41% yield of **4j** (Table 2, entry 10). Similarly, the 2-(benzoylvinyl)-4-methylbenzaldehyde **2f** and 2-(benzoylvinyl)-4-methoxybenzaldehyde **2g** gave much better yields of the corresponding products **4** than the 2-(benzoylvinyl)-4-fluorobenzaldehyde **2e** in the reaction with **1a** (Table 2, entries 13−15). In comparison to 2-((*p*-bromobenzoyl)vinyl)-benzaldehyde **2h** that only formed 48% yield of product **4p**, 2-((*p*-methylbenzoyl)vinyl)benzaldehyde **2i** and 2-((*p*-methoxybenzoyl)vinyl)benzaldehyde **2j** also afforded higher yields of products **4q** (69%) and **4r** (78%) in the reaction with cinnamaldehyde **1a** (Table 2, entries 16−18). It was worth noting that, although the substituents of both substrates influenced the reactivity of reaction and the selectivity between product **4** and **5**, the stereoselectivity was not affected, as all products **4** being isolated as a sole diastereomer with 99→99% ee. In addition, the unconsumed cinnamaldehydes **1** that were excess to substrates **2** and the minor dimeric products of reactants **2** were also detected in the reactions.

In order to synthesize the cyclopenta[*a*]indene products **5**, the reactions between enals **1** and 2-(aroylvinyl)benzaldehydes **2** were then carried out in 1,2-dichloroethane at 50 °C under the catalysis of a combination of **3a** (10 mol%), DBU (20 mol %), Ti(OPr-*i*)$_4$ (150 mol%), and *i*-PrOH (100 mol%). Since cyclopenta[*a*]indane derivatives **5** are achiral compounds, the racemic catalyst **3a** was used in these reactions. It was found

DOI: 10.1021/acs.joc.6b02329
J. Org. Chem. 2016, 81, 11871−11881

Scheme 1. Proposed Mechanisms for the Formation of (1*S*,4*S*,5*R*,10*S*)-5-(Aroylmethyl)-10-aryl-4,5-dihydro-1,4-methanobenzo[*c*]oxepin-3-ones 4 and 1,3-Diaryl-2,8-dihydrocyclopenta[*a*]indenes 5



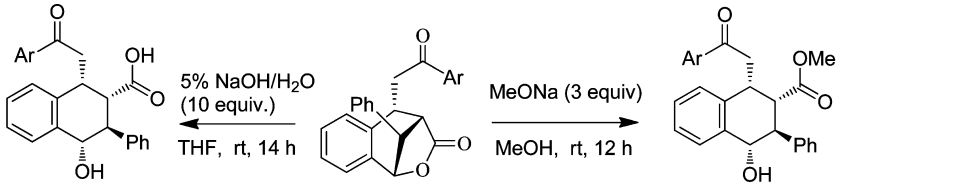
that, while reacting in 1,2-dichloroethane at 50 °C, the substituents of substrates strongly influenced the selectivity in the formation of products **4** and **5**. Although most of the reactions examined produced fused indenes **5** as the major products, the selectivity between **5** and **4** appeared in general less satisfactory. Even in a few cases, compounds **4** were isolated as the major products. For example, all reactions of 2-(benzoylvinyl)benzaldehyde **2a** with cinnamaldehydes **1** attached by different substituents including H, 4-Br, 4-Cl, 4-Me, 4-OMe, and 2-OMe groups produced the corresponding cyclopenta[*a*]indanes **5** as major products in 38−50% yields, along with the bridged cyclic lactones **4** in 11−33% yields (Table 3, entries 1−6). Compounds **5k** and **5m**−**5o** were also obtained as the major products in 40−62% yields from the reaction of cinnamaldehyde **1a** with 2-(benzoylvinyl)-benzaldehydes **2c** and **2e**−**2g**, which contained a 5-Me, 4-F, 4-Me, or 4-OMe group (Table 3, entries 8, 10−12). However, the 5-F and 5-OMe substituted 2-(benzoylvinyl)benzaldehydes **2b** and **2d** reacted with **1a** to give **5** in 15−26% yields and **4** in 25−41% yields (Table 3, entries 7 and 9). When 2-(aroylvinyl)benzaldehydes **2h**−**2j** were substituted by different aroyl groups, the electron-deficient 4-bromobenzoyl group was beneficial to the formation of product **5**, while the electron-rich 4-methylbenzoyl and 4-methoxybenzoyl groups favored to the formation of **4** (Table 3, entries 13−15). Although lots of efforts have been made to improve the yields of fused indenes **5** by varying the catalytic system, reaction conditions or sequence of mixing substrates and catalysts, no significant improvement were obtained. Finally, the reactions of **1a** with **2b**, **2d**, and **2j** that produced the corresponding indenes **5** in very low yields (15−26%) were repeated under the catalysis of a larger amount of catalysts [**3a** (20 mol%), DBU (50 mol%), Ti(OPr-*i*)$_4$ (200 mol%), and *i*-PrOH (200 mol%)] in refluxing dichloroethane. Under these conditions, the yields of products **5j**, **5l**, and **5r** were slightly increased to 20−37% (Table 3, entries 7, 9, 15).

The structures of products **4** and **5** were elucidated on the basis of spectroscopic data. The NMR spectra and mass data indicated that products **4** were 1+1 adducts of cinnamaldehydes **1** and 2-(aroylvinyl)benzaldehydes **2**. The products **5** were constructed from 1+1 addition of cinnamaldehydes **1** and 2-(aroylvinyl)benzaldehydes **2** with the loss of a CO_2 and a H_2O molecule. To determine the structures and especially the stereochemistry of products beyond doubt, single crystals were cultivated. X-ray diffraction studies confirmed unambiguously that the product **4b** was (1*S*,4*S*,5*R*,10*S*)-5-(benzoylmethyl)-10-(*p*-bromophenyl)-4,5-dihydro-1,4-methanobenzo[*c*]oxepin-3-one, and the product **5p** was 1-(*p*-bromophenyl)-3-phenyl-2,8-dihydrocyclopenta[*a*]indene (see single crystal structures of **4b** and **5p** in Supporting Information).

To account for the formations of (1*S*,4*S*,5*R*,10*S*)-5-(aroylmethyl)-10-aryl-4,5-dihydro-1,4-methanobenzo[*c*]oxepin-3-ones **4** and 1,3-diaryl-2,8-dihydrocyclopenta[*a*]indenes **5**, two distinct cascade pathways were proposed for the reaction of enals **1** and 2-(aroylvinyl)benzaldehydes **2**. As illustrated in Scheme 1, the nucleophilic addition of the homoenolates **6** derived from the enals **1** and NHC catalyst to the Ti-activated aldehyde group of 2-(aroylvinyl)benzaldehydes **2** yields an alcohol anion **7** that was coordinated with isopropoxytitanium. To avoid the steric hindrance of the indene ring, the NHC-substituted homoenolates **6** approach preferentially to the *si*-face of aldehyde, leading to the formation of two *S*-configured chiral carbon centers of **7**. The isopropanol additive might facilitate the disassociation of the coordination between hydroxyl groups and titanium(IV) to generate the free alcohol intermediates **8** from **7**. An intramolecular Michael addition of enolates to the enone species of **8**, which also occurs

DOI: 10.1021/acs.joc.6b02329
J. Org. Chem. 2016, 81, 11871−11881

Scheme 2. Hydrolysis and Alcoholysis of Products 4



18a: Ar = Ph, 75% yield, 99% ee
18r: Ar = *p*-MeOPh, 82% yield, 99% ee

4a, 4r

19a: Ar = Ph, 76% yield, 99% ee
19r: Ar = *p*-MeOPh, 70% yield, 98% ee

preferentially to the *si*-face of C=C bond, gives rise to the (1*R*,2*S*,3*S*,4*S*)-4-hydroxy-1-(aroylmethyl)-3-aryltetrahydronaphthalene-2-carbonylimidazolium intermediates **9** (Scheme 1, pathway A). Finally, the intramolecular lactonization reaction of **9** furnishes the formation of (1*S*,4*S*,5*R*,10*S*)-5-(aroylmethyl)-10-aryl-4,5-dihydro-1,4-methanobenzo[*c*]oxepin-3-ones **4**.

The formation of 2,8-dihydrocyclopenta[*a*]indenes **5** from enals **1** and 2-(aroylvinyl)benzaldehydes **2** is more intriguing than the formation of **4**. Since reaction intermediates could not been isolated, the reaction of **1a** with **2a** in DCE was monitored by HPLC-MS to detect the intermediates. During the process of the reaction, the HPLC-MS spectra indicated a compound having a molecule weight of $[M+H]^+$ = 325.1603 (ESI MS) in the reaction mixture, which was in agreement with the weight of (**1a** + **2a**-CO_2). Scheidt and co-workers have reported a NHC/Lewis acid-catalyzed reaction between enals and enones to form cyclopentenes via a decarboxylation of α-hydroxycarbonyl triazoium intermediates.[4a] Based on these messages, the mechanism for the formation of fused indenes **5** was proposed as indicated in Scheme 1. Plausibly, instead of the 1,4-addition of enolates to the enone species of intermediates **8** in the formation of lactones **4**, the enolates **8** undergo a 1,2-addition to the carbonyl groups of enone species to form the 5-(5,8-dihydroxy-5,6,7,8-tetrahydrobenzo[8]annulene-7-carbonyl)triazoium salts **10** (Scheme 1, pathway B). A intramolecular acylation and decarboxylation cascade affords the 5,6-dihydrobenzo[8]annulen-5-ols **12** (calculated MS for **12** (M+H) = 325.1592) via the β-lactone intermediates **11**. A Lewis acid-promoted dehydroxyl of **12** gives the transient tetrahydrobenzo[8]annulene carbocations **13**, which isomerizes into the fused indene carbocations **14**. A base-catalyzed deprotonation of **14** yields the dihydrocyclopenta[*a*]indenes **15**. Under the reaction conditions, the dihydrocyclopenta[*a*]-indenes **15** isomerize into products **5** via a [1,5]-H sigmatropic rearrangement[10] and a base-promoted [1,3]-hydrogen shift.[7b,d,11]

The 4,5-dihydro-1,4-methanobenzo[*c*]oxepin-3-one structure, a bridged lactone of 4-hydroxy-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid, occurs in some biological or pharmaceutical active molecules,[12,13] such as neopodophyllotoxin[12] that has been used in clinical antitumor agents.[14] The 4,5-dihydro-1,4-methanobenzo[*c*]oxepin-3-ones and 4-hydroxy-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid derivatives have also been used as the key intermediates in the total synthesis of various biological active natural and unnatural compounds.[15] Moreover, a large number of molecules of medicinal importance possess 1,2,3,4-tetrahydronaphthalene moiety.[16] We thought that the transformation of the resulting bridged lactones **4** would provide a direct approach to enantiomerically pure 1,2,3,4-tetrahydronaphthalene derivatives. To extend the application of the reaction between cinnamaldehydes **1** and 2-(aroylvinyl)benzaldehydes **2**, the hydrolysis or alcoholysis of compounds **4a** and **4r** was conducted with 5% aqueous NaOH in THF or MeONa in methanol at ambient temperature. These reactions produced 1-(aroylmethyl)-3-aryl-4-hydroxy-1,2,3,4-tetrahydronaphthalene-2-carboxylic acids **18a** and **18r** or the methyl carboxylates **19a** and **19r**, respectively, in 70–82% yields with 98–99% ee (Scheme 2).

CONCLUSION

In summary, we have studied the cooperative chiral NHC/Lewis acid catalyzed reaction between cinnamaldehydes and 2-(aroylvinyl)benzaldehydes. The (1*S*,4*S*,5*R*,10*S*)-5-(aroylmethyl)-10-aryl-4,5-dihydro-1,4-methanobenzo[*c*]oxepin-3-ones, a type of bridged caprolactones, were obtained in moderate yields with excellent enantioselectivity. Meanwhile, in most cases, the selective syntheses of 4,5-dihydro-1,4-methanobenzo-[*c*]oxepin-3-ones and 2,8-dihydrocyclopenta[*a*]indenes have been achieved by varying reaction conditions. The transformation of the bridged lactone products to the enantiopure 1,2,3,4-tetrahydronaphthalene derivatives extend the application of the reaction between cinnamaldehydes and 2-(aroylvinyl)benzaldehydes. Thus, this work developed novel and simple methods for highly enantioselective constructions of chiral 4,5-dihydro-1,4-methanobenzo[*c*]oxepin-3-ones and 1,2,3,4-tetrahydronaphthalene derivatives, both have potential application in the syntheses of pharmaceutically important molecules.

EXPERIMENTAL SECTION

General Procedure for the Enantioselective Synthesis of (1*S*,4*S*,5*R*,10*S*)-5-(Aroylmethyl)-10-aryl-4,5-dihydro-1,4-methanobenzo[*c*]oxepin-3-ones 4 from the Reaction of α,β-Unsaturated Aldehydes 1 with 2-(Aroylvinyl)benzaldehydes 2 in Benzene at Ambient Temperature. Under nitrogen atmosphere, cinnamaldehydes **1** (1 mmol), 2-(aroylvinyl)benzaldehydes **2** (0.5 mmol), (−)-*N*-mesityl-indeno[2,1-*b*]triazolo[4,3-*d*][1,4]-oxazinium salt **3a** (18.4 mg, 0.05 mmol), Ti(OPr-i)$_4$ (150 μL, 0.5 mmol), and *i*-PrOH (38.3 μL, 0.5 mmol) were mixed in dry benzene (10 mL). The resulting mixture was stirred for 5 min, and DBU (15 μL, 0.1 mmol) was added using a microsyringe. The reaction mixture was then stirred at room temperature (20–25 °C) for 12–24 h. After removal of the solvent, the residue was chromatographed on a silica gel column eluting with a mixture of petroleum ether and ethyl acetate (PE:EA from 20:1 to10:1) to give the products **4** in 28–78% and **5** in 4–29% yields.

(1S,4S,5R,10S)-5-(Benzoylmethyl)-10-phenyl-4,5-dihydro-1,4-methanobenzo[c]oxepin-3-one ***4a.*** White solid, 110 mg, 60%, ee 99%, $[\alpha]^{20}_D$ = −101.8 (c = 0.50, CH_2Cl_2), mp 216–217 °C; IR ν (KBr, cm^{-1}) 1771, 1683; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.01 (d, *J* = 7.3 Hz, 2H), 7.59 (t, *J* = 7.4 Hz,1H), 7.48 (t, *J* = 7.7 Hz, 2H),7.38 (dd, *J* = 7.2, 2.5 Hz, 1H), 7.21–7.26 (m, 4H), 7.16 (t, *J* = 7.1 Hz,1H),7.09 (d, *J* = 7.9 Hz, 2H), 7.04–7.07 (m, 1H), 5.67 (d, *J* = 4.7 Hz, 1H), 4.25 (t, *J* = 4.9 Hz,1H), 3.95–4.00 (m, 1H), 3.69 (dd, *J* = 18.7, 9.6 Hz, 1H), 3.58 (t, *J* = 4.6 Hz,1H), 3.37 (dd, *J* = 18.6, 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 198.4, 176.7, 136.8, 136.7, 134.2, 134.1, 133.4, 129.9, 128.8, 128.7, 128.5, 128.2, 127.8,

DOI: 10.1021/acs.joc.6b02329
J. Org. Chem. 2016, 81, 11871–11881

127.6, 127.0, 126.9, 80.9, 47.3, 44.6, 42.4, 30.7; HRMS (TOF-ESI): $[M+H]^+$ calcd for $C_{25}H_{21}O_3$: 369.1491; found: 369.1487.

(1S,4S,5R,10S)-5-(Benzoylmethyl)-10-(p-bromophenyl)-4,5-dihydro-1,4-methanobenzo[c]oxepin-3-one ***4b***. White solid, 119 mg, 53%, ee 99%, $[\alpha]^{20}_D$ = −52.5 (c = 0.50, CH_2Cl_2), mp 231−232 °C; IR ν (KBr, cm^{-1}) 1769, 1684; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.94 (d, J = 7.4 Hz, 2H), 7.52 (t, J = 7.3 Hz,1H), 7.41 (t, J = 7.8 Hz, 2H), 7.28−7.30 (m, 3H), 7.15−7.22 (m, 2H), 7.00 (d, J = 7.3 Hz, 1H), 6.90 (d, J = 8.1 Hz, 2H), 5.56 (d, J = 4.7 Hz, 1H), 4.10 (t, J = 4.8 Hz,1H), 3.82−3.86 (m, 1H), 3.62 (dd, J = 18.7, 9.8 Hz, 1H), 3.48 (t, J = 4.6 Hz,1H), 3.31 (dd, J = 18.7, 3.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 198.3, 176.3, 136.7, 136.5, 133.8, 133.5, 133.3, 131.7, 130.1, 129.5, 128.7, 128.2, 127.7, 127.2, 121.0, 80.5, 46.9, 44.4, 42.3, 30.7; HRMS (TOF-ESI): $[M+H]^+$ calcd for $C_{25}H_{20}O_3Br$: 447.0596; found: 447.0591.

(1S,4S,5R,10S)-5-(Benzoylmethyl)-10-(p-chlorophenyl)-4,5-dihydro-1,4-methanobenzo[c]oxepin-3-one ***4c***. White solid, 111 mg, 55%, ee 99%, $[\alpha]^{20}_D$ = −77.1 (c = 0.50, CH_2Cl_2), mp 214−215 °C; IR ν (KBr, cm^{-1}) 1768, 1685; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.01 (d, J = 7.6 Hz, 2H), 7.59 (t, J = 7.3 Hz,1H), 7.48 (t, J = 7.6 Hz, 2H), 7.37 (d, J = 6.6 Hz, 1H), 7.24−7.29(m, 2H), 7.21 (d, J = 8.4 Hz, 2H), 7.08 (d, J = 7.3 Hz, 1H), 7.03 (d, J = 8.2 Hz, 2H), 5.63 (d, J = 4.6 Hz, 1H), 4.19 (t, J = 4.7 Hz,1H),3.90−3.93 (m, 1H), 3.69 (dd, J = 18.6, 9.7 Hz, 1H), 3.55 (t, J = 4.6 Hz,1H), 3.38 (dd, J = 18.6, 3.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 198.2, 176.2, 136.7, 136.5, 133.8, 133.5, 132.9, 132.8, 130.1, 129.1, 128.8, 128.73, 128.70, 128.1, 127.7, 127.2, 80.6, 46.8, 44.5, 42.3, 30.7; HRMS (TOF-ESI): $[M+Na]^+$ calcd for $C_{25}H_{19}O_3ClNa$: 425.0914; found: 425.0913.

(1S,4S,5R,10S)-5-(Benzoylmethyl)-10-(o-chlorophenyl)-4,5-dihydro-1,4-methanobenzo[c]oxepin-3-one ***4d***. White solid, 125 mg, 62%, ee >99%, $[\alpha]^{20}_D$ = −189.2 (c = 0.50, CH_2Cl_2), mp 173−174 °C; IR ν (KBr, cm^{-1}) 1772, 1684; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.00 (d, J = 7.6 Hz, 2H), 7.57 (t, J = 7.3 Hz, 1H), 7.46 (t, J = 7.7 Hz, 2H), 7.38−7.44 (m, 2H), 7.28−7.33 (m, 2H), 7.14 (t, J = 7.6 Hz,1H), 7.11 (d, J = 8.0 Hz, 1H), 6.91 (t, J = 7.5 Hz,1H), 6.63 (d, J = 7.8 Hz, 1H), 5.62 (d, J = 4.3 Hz, 1H), 4.31 (t, J = 4.6 Hz,1H), 3.87 (t, J = 4.5 Hz,1H), 3.70−3.73 (m, 1H), 3.65 (dd, J = 17.8, 8.4 Hz, 1H), 3.35 (dd, J = 17.6, 3.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 197.9, 176.3, 137.1, 136.6, 134.5, 134.1, 133.3, 131.9, 130.2, 130.1, 129.1, 128.6, 128.5, 128.3, 128.1, 127.7, 127.3, 126.3, 80.4, 46.5, 44.6, 42.6, 30.9; HRMS (TOF-ESI): $[M+H]^+$ calcd for $C_{25}H_{20}O_3Cl$: 403.1101; found: 403.1096.

(1S,4S,5R,10S)-5-(Benzoylmethyl)-10-(m-chlorophenyl)-4,5-dihydro-1,4-methanobenzo[c]oxepin-3-one ***4e***. White solid, 117 mg, 58%, ee >99%, $[\alpha]^{20}_D$ = −75.6 (c = 0.50, CH_2Cl_2), mp 233−234 °C; IR ν (KBr, cm^{-1}) 1766, 1685; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.01 (d, J = 7.6 Hz, 2H), 7.59 (t, J = 7.3 Hz, 1H), 7.48 (t, J = 7.6 Hz, 2H), 7.39 (d, J = 7.7 Hz, 1H), 7.23−7.30 (m, 2H), 7.13−7.20 (m, 2H), 7.08 (d, J = 7.2 Hz, 1H), 7.04 (s, 1H), 7.01 (d, J = 7.1 Hz, 1H), 5.64 (d, J = 4.6 Hz, 1H), 4.20 (t, J = 4.6 Hz,1H), 3.94−3.97 (m, 1H), 3.68 (dd, J = 18.7, 9.6 Hz, 1H), 3.57 (t, J = 4.7 Hz,1H), 3.38 (dd, J = 18.7, 3.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 198.1, 176.0, 136.6, 136.4, 136.2, 134.3, 133.5, 133.3, 130.0, 129.7, 128.62, 128.57, 128.0, 127.9, 127.6, 127.2, 127.1, 125.8, 80.3, 46.9, 44.3, 42.2, 30.5; HRMS (TOF-ESI): $[M+H]^+$ calcd for $C_{25}H_{20}O_3Cl$: 403.1095; found: 403.1094.

(1S,4S,5R,10S)-10-(p-Acetylphenyl)-5-(benzoylmethyl)-4,5-dihydro-1,4-methanobenzo[c]oxepin-3-one ***4f***. White solid, 123 mg, 60%, ee >99%, $[\alpha]^{20}_D$ = −57.9 (c = 0.50, CH_2Cl_2), mp 225−226 °C; IR ν (KBr, cm^{-1}) 1774, 1682; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.01 (d, J = 7.4 Hz, 2H), 7.82 (d, J = 8.2 Hz, 2H), 7.60 (t, J = 7.3 Hz,1H), 7.49 (t, J = 7.6 Hz, 2H), 7.40 (dd, J = 8.7, 2.6 Hz, 1H), 7.25−7.28 (m, 2H), 7.21 (d, J = 8.0 Hz, 2H), 7.06 (d, J = 8.0 Hz, 1H), 5.70 (d, J = 4.6 Hz, 1H), 4.27 (t, J = 4.9 Hz,1H), 3.91−3.94 (m, 1H), 3.70 (dd, J = 18.7, 9.7 Hz, 1H), 3.62 (t, J = 4.6 Hz,1H), 3.37 (dd, J = 18.6, 3.4 Hz, 1H), 2.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 198.2, 197.4, 176.1, 139.7, 136.7, 136.5, 135.8, 133.8, 133.5, 130.2, 128.8, 128.7, 128.5, 128.1, 128.0, 127.7, 127.2, 80.5, 47.4, 44.4, 42.3, 30.8, 26.5; HRMS (TOF-ESI): $[M+Na]^+$ calcd for $C_{27}H_{22}O_4Na$: 433.1410; found: 433.1412.

(1S,4S,5R,10S)-5-(Benzoylmethyl)-10-(p-methylphenyl)-4,5-dihydro-1,4-methanobenzo[c]oxepin-3-one ***4g***. White solid, 94 mg, 49%, ee >99%, $[\alpha]^{20}_D$ = −80.1 (c = 0.50, CH_2Cl_2), mp 188−189 °C; IR ν (KBr, cm^{-1}) 1772, 1683; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.02 (d, J = 7.4 Hz, 2H), 7.59 (t, J = 7.4 Hz, 1H), 7.48 (t, J = 7.8 Hz, 2H), 7.38 (dd, J = 8.6, 2.1 Hz, 1H), 7.21−7.26 (m, 2H), 7.02−7.07 (m, 3H), 6.97 (d, J = 8.0 Hz, 2H), 5.65 (d, J = 4.7 Hz, 1H), 4.21 (t, J = 4.8 Hz,1H), 3.95−4.00 (m, 1H), 3.69 (dd, J = 18.7, 9.6 Hz, 1H), 3.55 (t, J = 4.6 Hz,1H), 3.37 (dd, J = 18.7, 3.6 Hz, 1H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 198.2, 176.7, 136.7, 136.4, 134.0, 133.3, 131.0, 129.7, 129.1, 128.58, 128.55, 128.0, 127.5, 127.4, 126.8, 80.8, 46.9, 44.6, 42.2, 30.5, 20.9; HRMS (TOF-ESI): $[M+H]^+$ calcd for $C_{26}H_{23}O_3$: 383.1647; found: 383.1644.

(1S,4S,5R,10S)-5-(Benzoylmethyl)-10-(p-methoxyphenyl)-4,5-dihydro-1,4-methanobenzo[c]oxepin-3-one ***4h***. White solid, 56 mg, 28% (43% from the reaction catalyzed by 20 mol% of **3a** at 50 °C), ee >99%, $[\alpha]^{20}_D$ = −79.3 (c = 0.50, CH_2Cl_2), mp 210−211 °C; IR ν (KBr, cm^{-1}) 1772, 1682; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.02 (d, J = 7.2 Hz, 2H), 7.59 (t, J = 7.4 Hz, 1H), 7.48 (t, J = 7.8 Hz, 2H), 7.37 (dd, J = 7.1, 2.0 Hz, 1H), 7.21−7.28(m, 2H), 7.07 (d, J = 7.3 Hz, 1H), 7.00 (d, J = 8.3 Hz, 2H), 6.76 (d, J = 8.7 Hz, 2H), 5.63 (d, J = 4.6 Hz, 1H), 4.19 (t, J = 4.9 Hz,1H), 3.94−3.98 (m, 1H), 3.73 (s, 3H), 3.69 (dd, J = 18.7, 9.6 Hz, 1H), 3.52 (t, J = 4.5 Hz,1H), 3.38 (dd, J = 18.7, 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 198.2, 176.7, 158.1, 136.67, 136.66, 134.0, 133.3, 129.8, 128.7, 128.6, 128.0, 127.4, 126.9, 126.0, 113.8, 80.9, 55.0, 46.6, 44.8, 42.2, 30.5; HRMS (TOF-ESI): $[M+H]^+$ calcd for $C_{26}H_{23}O_4$: 399.1596; found: 399.1591.

(1S,4S,5R,10S)-5-(Benzoylmethyl)-10-(o-methoxyphenyl)-4,5-dihydro-1,4-methanobenzo[c]oxepin-3-one ***4i***. White solid, 94 mg, 47%, ee 99%, $[\alpha]^{20}_D$ = −90.1 (c = 0.50, CH_2Cl_2), mp 134−135 °C; IR ν (KBr, cm^{-1}) 1770, 1684; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.01 (d, J = 7.1 Hz, 2H),7.58 (t, J = 7.4 Hz, 1H), 7.47 (t, J = 7.6 Hz, 2H), 7.36−7.38 (m, 1H), 7.23−7.27 (m, 2H), 7.16 (td, J = 7.7, 1.2 Hz, 1H), 7.06 (dd, J = 6.6, 2.2 Hz, 1H), 6.84 (d, J = 7.7 Hz, 1H), 6.75 (d, J = 7.2 Hz, 1H), 6.69 (t, J = 7.4 Hz, 1H), 5.71 (d, J = 4.4 Hz, 1H), 4.18 (t, J = 4.8 Hz,1H), 3.88 (s, 3H), 3.82−3.86 (m, 1H), 3.73 (td, J = 4.9, 0.9 Hz, 1H), 3.67 (dd, J = 18.5, 8.9 Hz, 1H), 3.33 (dd, J = 18.4, 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 198.2, 177.3, 157.8, 137.1, 136.8, 134.5, 133.2, 129.6, 128.7, 128.5, 128.33, 128.25, 128.0, 127.5, 126.7, 122.4, 120.0, 110.3, 81.2, 55.1, 44.73, 44.66, 42.6, 30.9; HRMS (TOF-ESI): $[M+H]^+$ calcd for $C_{26}H_{23}O_4$: 399.1590; found: 399.1592.

(1S,4S,5R,10S)-5-(Benzoylmethyl)-8-fluoro-10-phenyl-4,5-dihydro-1,4-methanobenzo[c]oxepin-3-one ***4j***. White solid, 79 mg, 41%, ee >99%, $[\alpha]^{20}_D$ = −65.8 (c = 0.50, CH_2Cl_2), mp 171−172 °C; IR ν (KBr, cm^{-1}) 1773, 1683; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.01 (d, J = 7.2 Hz, 2H), 7.60 (t, J = 7.4 Hz, 1H), 7.48 (t, J = 7.6 Hz, 2H), 7.24−7.27 (m, 2H), 7.18 (t, J = 7.3 Hz, 1H), 7.08−7.13 (m, 3H), 7.03 (dd, J = 8.5, 5.3 Hz, 1H), 6.94 (td, J = 8.5, 2.7 Hz, 1H), 5.62 (d, J = 4.4 Hz, 1H), 4.24 (t, J = 4.8 Hz,1H), 3.92−3.97 (m, 1H), 3.68 (dd, J = 18.7, 9.5 Hz, 1H), 3.58 (t, J = 4.5 Hz,1H), 3.33 (dd, J = 18.6, 3.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 198.0, 176.2, 160.9 (d, J_{C-F} = 246 Hz), 136.5, 135.9 (d, J_{C-F} = 6 Hz), 133.7, 133.4, 132.1 (d, J_{C-F} = 3 Hz), 129.4 (d, J_{C-F} = 8 Hz), 128.6, 128.5, 128.0, 127.5, 127.0, 116.7 (d, J_{C-F} = 21 Hz), 115.4 (d, J_{C-F} = 22 Hz), 80.0, 47.1, 44.3, 42.3, 30.1; HRMS (TOF-ESI): $[M+H]^+$ calcd for $C_{25}H_{20}O_3F$: 387.1390; found: 387.1389.

(1S,4S,5R,10S)-5-(Benzoylmethyl)-8-methyl-10-phenyl-4,5-dihydro-1,4-methanobenzo[c]oxepin-3-one ***4k***. White solid, 122 mg, 64%, ee 99%, $[\alpha]^{20}_D$ = −106.3 (c = 0.50, CH_2Cl_2), mp 215−216 °C; IR ν (KBr, cm^{-1}) 1772, 1683; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.01 (d, J = 7.2 Hz, 2H), 7.59 (t, J = 7.4 Hz, 1H), 7.48 (t, J = 7.6 Hz, 2H), 7.24 (t, J = 7.7 Hz, 2H), 7.19 (s, 1H), 7.17 (t, J = 7.7 Hz, 1H), 7.10 (d, J = 8.0 Hz, 2H), 7.05 (dd, J = 7.9, 1.1 Hz, 1H), 6.94 (d, J = 7.9 Hz, 1H), 5.62 (d, J = 4.6 Hz, 1H), 4.23 (t, J = 5.0 Hz,1H), 3.90−3.95 (m, 1H),3.66 (dd, J = 18.6, 9.7 Hz, 1H), 3.56 (t, J = 4.9 Hz,1H), 3.35 (dd, J = 18.6, 3.6 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 198.4, 176.7, 136.7, 136.6, 134.2, 133.8, 133.31,133.25, 130.5, 129.2, 128.5, 128.4, 128.0, 127.6, 127.3, 126.7, 80.9, 47.3, 44.6, 42.2, 30.3, 20.8; HRMS (TOF-ESI): $[M+H]^+$ calcd for $C_{26}H_{23}O_3$: 383.1641; found: 383.1641.

DOI: 10.1021/acs.joc.6b02329
J. Org. Chem. 2016, 81, 11871−11881

(1S,4S,5R,10S)-5-(Benzoylmethyl)-8-methoxy-10-phenyl-4,5-dihydro-1,4-methanobenzo[c]oxepin-3-one ***4l***. White solid, 139 mg, 70%, ee >99%, $[\alpha]^{20}_{D}$ = −142.4 (c = 0.50, CH_2Cl_2), mp 214−215 °C; IR ν (KBr, cm^{-1}) 1771, 1683; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.02 (d, J = 7.2 Hz, 2H), 7.59 (t, J = 7.4 Hz, 1H), 7.48 (t, J = 7.6 Hz, 2H), 7.24 (t, J = 7.6 Hz, 2H), 7.17 (t, J = 7.1 Hz, 1H), 7.10 (d, J = 7.9 Hz, 2H), 6.97 (d, J = 8.6 Hz, 1H), 6.92 (d, J = 2.7 Hz, 1H), 6.78 (dd, J = 8.6, 2.7 Hz, 1H), 5.60 (d, J = 4.5 Hz, 1H), 4.22 (t, J = 4.9 Hz,1H), 3.87−3.91 (m, 1H), 3.82 (s, 3H), 3.65 (dd, J = 18.6, 9.6 Hz, 1H), 3.56 (t, J = 4.5 Hz,1H), 3.33 (dd, J = 18.6, 3.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 198.4, 176.6, 158.1, 136.7, 135.1, 134.1, 133.3, 128.7, 128.6, 128.4, 128.1, 128.0, 127.6, 126.8, 115.1, 114.0, 80.8, 55.3, 47.3, 44.6, 42.2, 30.0; HRMS (TOF-ESI): $[M+H]^+$ calcd for $C_{26}H_{23}O_4$: 399.1596; found: 399.1592.

(1S,4S,5R,10S)-5-(Benzoylmethyl)-7-fluoro-10-phenyl-4,5-dihydro-1,4-methanobenzo[c]oxepin-3-one ***4m***. White solid, 42 mg, 22% (25% from the reaction catalyzed by 20 mol% of **3a**), ee 99%, $[\alpha]^{20}_{D}$ = −85.0 (c = 0.55, CH_2Cl_2), mp 194−195 °C; IR ν (KBr, cm^{-1}) 1770, 1683; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.01 (d, J = 7.7 Hz, 2H), 7.60 (t, J = 7.4 Hz, 1H), 7.49 (t, J = 7.6 Hz, 2H), 7.37 (dd, J = 8.3, 5.8 Hz, 1H), 7.23−7.27 (m, 2H), 7.18 (t, J = 7.2 Hz, 1H),7.08 (d, J = 7.3 Hz, 2H), 6.93 (td, J = 8.2, 1.9 Hz, 1H), 6.77 (d, J = 9.8 Hz, 1H), 5.68 (d, J = 4.7 Hz, 1H), 4.25 (t, J = 4.8 Hz,1H), 3.95−3.98 (m, 1H), 3.71 (dd, J = 18.7, 9.6 Hz, 1H), 3.58 (t, J = 4.8 Hz,1H), 3.30 (dd, J = 18.7, 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 197.8, 176.2, 163.3 (d, J_{C-F} = 247 Hz), 139.3 (d, J_{C-F} = 7 Hz), 136.4, 133.8, 133.4, 130.3 (d, J_{C-F} = 9 Hz), 130.0 (d, J_{C-F} = 4 Hz), 128.6, 128.5, 128.0, 127.6, 126.9, 114.8 (d, J_{C-F} = 23 Hz), 114.0 (d, J_{C-F} = 22 Hz), 79.9, 47.1, 44.1, 42.1, 30.7; HRMS (TOF-ESI): $[M+H]^+$ calcd for $C_{25}H_{20}O_3F$: 387.1396; found: 387.1393.

(1S,4S,5R,10S)-5-(Benzoylmethyl)-7-methyl-10-phenyl-4,5-dihydro-1,4-methanobenzo[c]oxepin-3-one ***4n***. White solid, 86 mg, 45% (52% from the reaction catalyzed by 20 mol% of **3a**), ee >99%, $[\alpha]^{20}_{D}$ = −109.6 (c = 0.50, CH_2Cl_2), mp 250−251 °C; IR ν (KBr, cm^{-1}) 1769, 1682; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.02 (d, J = 7.4 Hz, 2H), 7.59 (t, J = 7.3 Hz, 1H), 7.49 (t, J = 7.6 Hz, 2H), 7.22−7.27 (m, 3H), 7.16 (t, J = 7.1 Hz, 1H), 7.10 (d, J = 7.7 Hz, 2H), 7.03 (d, J = 7.6 Hz, 1H), 6.86 (s, 1H), 5.65 (d, J = 4.7 Hz, 1H), 4.22 (t, J = 4.9 Hz,1H), 3.91−3.96 (m, 1H), 3.70 (dd, J = 18.7, 9.8 Hz, 1H), 3.57 (t, J = 4.7 Hz,1H), 3.37 (dd, J = 18.7, 3.4 Hz, 1H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 198.3, 176.7, 139.6, 136.7, 136.3, 134.3, 133.3, 131.0, 128.6, 128.5, 128.4, 128.1, 128.0, 127.7, 127.6, 126.7, 80.6, 47.3, 44.5, 42.2, 30.5, 21.3; HRMS (TOF-ESI): $[M+H]^+$ calcd for $C_{26}H_{23}O_3$: 383.1647; found: 383.1644.

(1S,4S,5R,10S)-5-(Benzoylmethyl)-7-methoxy-10-phenyl-4,5-dihydro-1,4-methanobenzo[c]oxepin-3-one ***4o***. White solid, 101 mg, 51% (61% from the reaction catalyzed by 20 mol% of **3a**), ee >99%, $[\alpha]^{20}_{D}$ = −120.5 (c = 0.55, CH_2Cl_2), mp 189−190 °C; IR ν (KBr, cm^{-1}) 1768, 1683; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.02 (d, J = 8.0 Hz, 2H), 7.59 (t, J = 7.3 Hz, 1H), 7.48 (t, J = 7.7 Hz, 2H), 7.30 (d, J = 8.3 Hz, 1H), 7.23 (t, J = 7.6 Hz, 2H), 7.17 (t, J = 7.2 Hz, 1H), 7.09 (d, J = 7.6 Hz, 2H), 6.74 (dd, J = 8.3, 2.0 Hz, 1H), 6.57 (s, 1H), 5.65 (d, J = 4.8 Hz, 1H), 4.22 (t, J = 4.9 Hz,1H), 3.92−3.96 (m, 1H), 3.71 (dd, J = 18.6, 9.7 Hz, 1H), 3.70 (s, 3H), 3.55 (t, J = 4.9 Hz,1H), 3.34 (dd, J = 18.6, 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 198.2, 176.8, 160.5, 138.1, 136.6, 134.3, 133.3, 129.8, 128.6, 128.4, 128.0, 127.7, 126.7, 126.4, 113.5, 111.8, 80.5, 55.0, 47.3, 44.4, 42.3, 30.8; HRMS (TOF-ESI): $[M+H]^+$ calcd for $C_{26}H_{23}O_4$: 399.1590; found: 399.1590.

(1S,4S,5R,10S)-5-((p-Bromobenzoyl)methyl)-10-phenyl-4,5-dihydro-1,4-methanobenzo[c]oxepin-3-one ***4p***. White solid, 107 mg, 48%, ee >99%, $[\alpha]^{20}_{D}$ = −46.7 (c = 0.50, CH_2Cl_2), mp 195−196 °C; IR ν (KBr, cm^{-1}) 1771, 1684; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.86 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 8.4 Hz, 2H), 7.38 (dd, J = 8.6, 2.7 Hz, 1H), 7.20−7.25 (m, 4H), 7.15 (t, J = 7.3 Hz,1H), 7.07 (d, J = 7.4 Hz, 2H), 7.03 (dd, J = 8.3, 2.0 Hz, 1H), 5.66 (d, J = 4.8 Hz, 1H), 4.23 (t, J = 4.9 Hz,1H), 3.96−3.92 (m, 1H), 3.63 (dd, J = 18.6, 9.8 Hz, 1H), 3.55 (t, J = 5.0 Hz,1H), 3.30 (dd, J = 18.6, 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 197.2, 176.5, 136.3, 135.4, 134.0, 133.9, 131.9, 129.8, 129.5, 128.7, 128.5, 128.4, 127.6, 127.4, 127.0, 126.8, 80.7, 47.2, 44.4, 42.2, 30.5; HRMS (TOF-ESI): $[M+H]^+$ calcd for $C_{25}H_{20}O_3Br$: 447.0596; found: 447.0591.

(1S,4S,5R,10S)-5-((p-Methylbenzoyl)methyl)-10-phenyl-4,5-dihydro-1,4-methanobenzo[c]oxepin-3-one ***4q***. White solid, 132 mg, 69%, ee >99%, $[\alpha]^{20}_{D}$ = −73.6 (c = 0.50, CH_2Cl_2), mp 204−205 °C; IR ν (KBr, cm^{-1}) 1766, 1679; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.92 (d, J = 8.1 Hz, 2H), 7.38 (dd, J = 8.5, 2.3 Hz, 1H), 7.27 (d, J = 8.3 Hz, 2H), 7.21−7.24 (m, 4H), 7.15 (t, J = 7.1 Hz, 1H), 7.09 (d, J = 7.8 Hz, 2H), 7.05 (d, J = 7.7 Hz, 1H), 5.66 (d, J = 4.7 Hz, 1H), 4.23 (t, J = 4.9 Hz,1H), 3.95−4.00 (m, 1H), 3.66 (dd, J = 18.6, 9.6 Hz, 1H), 3.57 (t, J = 4.7 Hz,1H), 3.34 (dd, J = 18.5, 3.6 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 197.9, 176.7, 144.3, 136.9, 134.4, 134.3, 134.1, 129.9, 129.4, 128.7, 128.5, 128.3, 127.8, 127.6, 127.0, 126.9, 80.9, 47.4, 44.7, 42.2, 30.7, 21.7; HRMS (TOF-ESI): $[M+H]^+$ calcd for $C_{26}H_{23}O_3$: 383.1647; found: 383.1642.

(1S,4S,5R,10S)-5-((p-Methoxybenzoyl)methyl)-10-phenyl-4,5-dihydro-1,4-methanobenzo[c]oxepin-3-one ***4r***. White solid, 155 mg, 78%, ee >99%, $[\alpha]^{20}_{D}$ = −66.5 (c = 0.55, CH_2Cl_2), mp 154−155 °C; IR ν (KBr, cm^{-1})1772, 1673; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.00 (d, J = 8.9 Hz, 2H), 7.37 (dd, J = 7.2, 2.4 Hz, 1H), 7.20−7.24 (m, 4H), 7.15 (t, J = 7.1 Hz, 1H), 7.08 (d, J = 7.9 Hz, 2H), 7.06 (dd, J = 8.4, 2.1 Hz, 1H), 6.95 (d, J = 8.9 Hz, 2H), 5.66 (d, J = 4.6 Hz, 1H), 4.23 (t, J = 4.9 Hz,1H), 3.95−4.00 (m, 1H), 3.87 (s, 3H), 3.64 (dd, J = 18.4, 9.6 Hz, 1H), 3.56 (t, J = 4.6 Hz,1H), 3.31 (dd, J = 18.3, 3.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 196.8, 176.7, 163.8, 136.9, 134.3, 134.1, 130.5, 129.9, 128.7, 128.5, 127.8, 127.7, 127.0, 126.9, 113.9, 80.9, 55.5, 47.4, 44.7, 41.9, 30.8; HRMS (TOF-ESI): $[M+H]^+$ calcd for $C_{26}H_{23}O_4$: 399.1596; found: 399.1594.

General Procedure for the Preparation of 1,3-Daryl-2,8-dihydrocyclopenta[*a*]indenes 5 and Racemic 5-(Aroylmethyl)-10-aryl-4,5-dihydro-1,4-methanobenzo[*c*]oxepin-3-ones 4 from the Reaction of *α,β*-Unsaturated Aldehydes 1 with 2-(Aroylvinyl)benzaldehydes 2 in Dichloroethane at 50 °C. Under nitrogen atmosphere, cinnamaldehydes **1** (1 mmol), 2-(aroylvinyl)-benzaldehydes **2** (0.5 mmol), racemic *N*-mesityl-indeno[2,1-*b*]-triazolo[4,3-*d*][1,4]oxazinium salt **3a** (18.4 mg, 0.05 mmol), Ti-(OPr-i)$_4$ (225 μL, 0.75 mmol), and *i*-PrOH (38.3 μL, 0.5 mmol) were mixed in dry dichloroethane (10 mL). The resulting mixture was stirred for 5 min, and DBU (15 μL, 0.1 mmol) was added using a microsyringe. The reaction mixture was then stirred at 50 °C for 12 h. After removal of the solvent, the residue was chromatographed on a silica gel column eluting with a mixture of petroleum ether and ethyl acetate (PE:EA from 20:1 to 10:1) to give the 1,3-daryl-2,8-dihydrocyclopenta[*a*]indenes **5** in 15−62% and racemic **4** in 10−59% yields.

1,3-Diphenyl-2,8-dihydrocyclopenta[a]indene ***5a***. Yellow solid, 77 mg, 50%, mp 164−165 °C (174 °C[17]); IR ν (KBr, cm^{-1}) 1596, 1495; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.88 (d, J = 7.4 Hz, 1H), 7.62 (d, J = 7.2 Hz, 2H), 7.50 (d, J = 7.5 Hz, 2H), 7.35−7.39 (m, 3H), 7.33 (t, J = 8.0 Hz, 2H), 7.20−7.24 (m, 2H), 7.12−7.17 (m, 2H), 4.13 (s, 2H), 3.90 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 149.4, 147.7, 147.2, 137.2, 136.3, 136.2, 133.1, 132.8, 128.7, 128.6, 128.0, 127.4, 126.8, 126.7, 126.0, 125.97, 125.6, 122.7, 49.5, 32.7; HRMS [TOF-(-APCI)]: $[M-H]^-$ calcd for $C_{24}H_{17}$: 305.1335; found: 305.1335.

3-(p-Bromophenyl)-1-phenyl-2,8-dihydrocyclopenta[a]indene ***5b***. Yellow solid, 73 mg, 38%, mp 183−184 °C; IR ν (KBr, cm^{-1}) 1599, 1497, 1488; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.89 (d, J = 7.5 Hz, 1H), 7.57−7.53 (m, 6H), 7.47 (d, J = 7.4 Hz, 1H), 7.40 (t, J = 7.6 Hz, 2H), 7.31 (t, J = 7.2 Hz, 1H), 7.26−7.21 (m, 2H), 4.17 (s, 2H), 3.96 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 149.6, 148.4, 147.1, 136.2, 136.1, 135.9, 133.1, 131.7, 131.5, 128.9, 128.7, 128.3, 126.8, 126.2, 126.1, 125.7, 122.6, 120.3, 49.4, 32.6; HRMS [TOF-(-APCI)]: $[M-H]^-$ calcd for $C_{24}H_{16}Br$: 383.0440; found: 383.0443.

3-(p-Chlorophenyl)-1-phenyl-2,8-dihydrocyclopenta[a]indene ***5c***. Yellow solid, 71 mg, 42%, mp 190−191 °C; IR ν (KBr, cm^{-1}) 1599, 1494; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.88 (d, J = 7.5 Hz, 1H), 7.59 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 7.7 Hz, 2H), 7.45 (d, J = 7.3 Hz, 1H), 7.38−7.42 (m, 4H), 7.30 (t, J = 7.3 Hz, 1H), 7.21−7.26 (m, 2H),

DOI: 10.1021/acs.joc.6b02329
J. Org. Chem. 2016, 81, 11871−11881

4.14 (s, 2H), 3.93 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 149.5, 148.3, 147.1, 136.1, 135.9, 135.6, 133.1, 132.2, 131.5, 128.71, 128.69, 128.5, 128.2, 126.8, 126.12, 126.09, 125.6, 122.6, 49.4, 32.6; HRMS [TOF-(-APCI)]: $[M-H]^-$ calcd for $C_{24}H_{16}Cl$: 339.0946; found: 339.0943.

3-(p-Methylphenyl)-1-phenyl-2,8-dihydrocyclopenta[a]indene ***5g***. Yellow solid, 77 mg, 48%, mp 151−152 °C; IR ν (KBr, cm^{-1}) 1595, 1510, 1495; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.95 (d, J = 7.4 Hz, 1H), 7.59 (d, J = 8.6 Hz, 1H),7.56 (d, J = 10.2 Hz, 2H), 7.45 (d, J = 7.2 Hz, 1H), 7.40 (t, J = 7.4 Hz, 2H), 7.19−7.30 (m, 5H), 4.17 (s, 2H), 3.95 (s, 2H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 149.3, 147.24, 147.18, 136.6, 136.4, 136.3, 134.3, 133.3, 132.3, 129.3, 128.7, 127.9, 127.3, 126.7, 126.0, 125.9, 125.6, 122.7, 49.5, 32.7, 21.3; HRMS [TOF-(-APCI)]: $[M-H]^-$ calcd for $C_{25}H_{19}$: 319.1492; found: 319.1491.

3-(p-Methoxyphenyl)-1-phenyl-2,8-dihydrocyclopenta[a]indene ***5h***. Yellow solid, 68 mg, 40%, mp 170−171 °C; IR ν (KBr, cm^{-1}) 1601, 1510, 1495; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.88 (d, J = 7.2 Hz, 1H), 7.57 (d, J = 8.5 Hz, 2H), 7.49 (d, J = 7.7 Hz, 2H), 7.39 (d, J = 7.3 Hz, 1H), 7.25−7.15 (m, 3H), 6.95 (d, J = 8.5 Hz, 2H), 4.07 (s, 2H), 3.87 (s, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 158.6, 149.3, 147.3, 146.5, 136.5, 136.4, 133.0, 131.9, 129.9, 128.7, 128.6, 127.7, 126.7, 126.0, 125.8, 125.5, 122.5, 114.0, 55.4, 49.5, 32.7; HRMS [TOF-(-APCI)]: $[M-H]^-$ calcd for $C_{25}H_{19}O$: 335.1441; found: 335.1443.

3-(o-Methoxyphenyl)-1-phenyl-2,8-dihydrocyclopenta[a]indene ***5i***. Yellow solid, 67 mg, 40%, mp 139−140 °C; IR ν (KBr, cm^{-1}) 1595, 1572, 1491, 1462; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.53−7.56 (m, 3H), 7.49 (d, J = 7.6 Hz, 1H), 7.40 (d, J = 7.4 Hz, 1H), 7.36 (t, J = 7.4 Hz, 2H), 7.29 (t, J = 7.7 Hz, 1H), 7.13−7.23 (m, 3H), 6.96−7.02 (m, 2H), 4.27 (s, 2H), 3.93 (s, 2H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 156.7, 149.2, 149.1, 146.4, 136.6, 136.5, 133.2, 130.2, 129.7, 128.6, 128.4, 127.7, 126.5, 126.3, 125.8, 125.72, 125.65, 123.3, 120.5, 111.1, 55.3, 50.4, 32.7; HRMS [TOF-(-APCI)]: $[M-H]^-$ calcd for $C_{25}H_{19}O$: 335.1441; found: 335.1443.

5-Fluoro-1,3-diphenyl-2,8-dihydrocyclopenta[a]indene ***5j***. Yellow solid, 26 mg, 15% (20% from the reaction catalyzed by a combination of **3a** (20 mol%), DBU (50 mol%), Ti(OPr-*i*)$_4$ (200 mol%), and *i*-PrOH (200 mol%) in refluxing dichloroethane.), mp 168−169 °C; IR ν (KBr, cm^{-1}) 1595, 1493, 1468; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.89 (dd, J = 8.5, 5.4 Hz, 1H), 7.65 (d, J = 7.2 Hz, 2H), 7.54 (d, J = 7.6 Hz, 2H), 7.45 (t, J = 7.5 Hz, 2H), 7.40 (t, J = 7.6 Hz, 2H), 7.30 (t, J = 7.4 Hz, 1H), 7.22 (t, J = 7.4 Hz, 1H), 7.14 (dd, J = 8.8, 2.1 Hz, 1H), 6.94 (td, J = 8.8, 2.4 Hz, 1H), 4.19 (s, 2H), 3.95 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162.6 (d, J_{C-F} = 246 Hz), 151.8, 151.7, 146.8, 146.5, 137.0, 136.1, 133.0, 132.4 (d, J_{C-F} = 2 Hz), 132.2 (d, J_{C-F} = 2 Hz), 128.7, 128.6, 127.2, 126.8, 126.1, 125.6, 123.7 (d, J_{C-F} = 9 Hz), 113.9 (d, J_{C-F} = 23 Hz), 113.0 (d, J_{C-F} = 22 Hz), 49.4, 32.8; HRMS [TOF-(-APCI)]: $[M-H]^-$ calcd for $C_{24}H_{16}F$: 323.1241; found: 323.1241.

5-Methyl-1,3-diphenyl-2,8-dihydrocyclopenta[a]indene ***5k***. Yellow solid, 84 mg, 52%, mp 154−155 °C; IR ν (KBr, cm^{-1}) 1596, 1496; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.85 (d, J = 7.8 Hz, 1H), 7.68 (d, J = 7.5 Hz, 2H), 7.56 (d, J = 7.7 Hz, 2H), 7.45 (t, J = 7.6 Hz, 2H), 7.40 (t, J = 7.8 Hz, 2H), 7.29 (t, J = 7.4 Hz, 1H), 7.26 (s, 1H), 7.22 (t, J = 7.4 Hz, 1H), 7.06 (d, J = 7.8 Hz, 1H), 4.18 (s, 2H), 3.91 (s, 2H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 149.8, 147.7, 147.5, 138.1, 137.4, 136.4, 133.6, 132.6, 131.9, 128.6, 128.5, 127.6, 127.3, 126.64, 126.56, 125.9, 125.6, 122.5, 49.3, 32.6, 21.6; HRMS [TOF-(-APCI)]: $[M-H]^-$ calcd for $C_{25}H_{19}$: 319.1492; found: 319.1493.

5-Methoxy-1,3-diphenyl-2,8-dihydrocyclopenta[a]indene ***5l***. Yellow solid, 44 mg, 26% (37% from the reaction catalyzed by a combination of **3a** (20 mol%), DBU (50 mol%), Ti(OPr-*i*)$_4$ (200 mol %), and *i*-PrOH (200 mol%) in refluxing dichloroethane.), mp 144−145 °C; IR ν (KBr, cm^{-1}) 1614, 1596, 1493; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.86 (d, J = 8.5 Hz, 1H), 7.64 (d, J = 7.3 Hz, 2H), 7.52 (d, J = 7.6 Hz, 2H), 7.41 (t, J = 7.6 Hz, 2H), 7.40 (t, J = 7.9 Hz, 2H), 7.26 (t, J = 7.4 Hz, 1H), 7.19 (t, J = 7.4 Hz, 1H), 6.96 (d, J = 2.1 Hz, 1H), 6.78 (dd, J = 8.5, 2.4 Hz, 1H), 4.14 (s, 2H), 3.89 (s, 2H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 159.8, 151.6, 147.5, 147.2, 137.4, 136.4, 132.6, 130.4, 129.3, 128.7, 128.65, 127.1, 126.4, 125.9, 125.6, 123.6, 112.8, 111.1, 55.4, 49.1, 32.9; HRMS [TOF-(-APCI)]: $[M-H]^-$ calcd for $C_{25}H_{19}O$: 335.1441; found: 335.1443.

6-Fluoro-1,3-diphenyl-2,8-dihydrocyclopenta[a]indene ***5m***. Yellow solid, 65 mg, 40%, mp 147−148 °C; IR ν (KBr, cm^{-1}) 1597, 1493, 1470; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.64 (d, J = 7.6 Hz, 2H), 7.60 (d, J = 9.7 Hz, 1H), 7.55 (d, J = 7.6 Hz, 2H), 7.46 (t, J = 7.5 Hz, 2H), 7.36−7.42 (m, 3H), 7.32 (t, J = 7.4 Hz, 1H), 7.22 (t, J = 7.3 Hz, 1H), 6.99 (t, J = 8.4 Hz, 1H), 4.20 (s, 2H), 3.92 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162.0 (d, J_{C-F} = 241 Hz), 147.3, 147.0, 146.9, 144.7 (d, J_{C-F} = 2 Hz), 137.8, 137.7 (d, J_{C-F} = 5 Hz), 136.8, 136.1, 134.3, 133.0, 128.7, 127.3, 127.1, 126.7 (d, J_{C-F} = 9 Hz), 126.1, 125.6, 114.9 (d, J_{C-F} = 23 Hz), 109.5 (d, J_{C-F} = 24 Hz), 49.5, 32.0; HRMS [TOF-(-APCI)]: $[M-H]^-$ calcd for $C_{24}H_{16}F$: 323.1241; found: 323.1240.

6-Methyl-1,3-diphenyl-2,8-dihydrocyclopenta[a]indene ***5n***. Yellow solid, 100 mg, 62%, mp 200−201 °C; IR ν (KBr, cm^{-1}) 1595, 1493; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.74 (s, 1H), 7.67 (d, J = 7.5 Hz, 2H), 7.54 (d, J = 7.6 Hz, 2H), 7.44 (t, J = 7.5 Hz, 2H), 7.38 (t, J = 7.5 Hz, 2H), 7.27−7.33 (m, 2H), 7.19 (t, J = 7.2 Hz, 1H), 7.09 (d, J = 7.4 Hz, 1H), 4.16 (s, 2H), 3.88 (s, 2H), 2.34 (s, 3H);^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 147.7, 146.6, 137.3, 136.4, 136.29, 136.27, 132.8, 132.6, 129.0, 128.7, 128.6, 127.4, 126.7, 125.9, 125.63, 125.60, 123.2, 49.5, 32.3, 21.6; HRMS[TOF-(-APCI)]: $[M-H]^-$ calcd for $C_{25}H_{19}$: 319.1492; found: 319.1491.

6-Methoxy-1,3-diphenyl-2,8-dihydrocyclopenta[a]indene ***5o***. Yellow solid, 118 mg, 70%, mp 173−174 °C; IR ν (KBr, cm^{-1}) 1599, 1493, 1479; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.65 (d, J = 7.6 Hz, 2H), 7.53 (d, J = 7.7 Hz, 2H), 7.46 (d, J = 1.7 Hz, 1H), 7.42 (t, J = 7.6 Hz, 2H), 7.37 (t, J = 7.7 Hz, 2H), 7.32 (d, J = 8.4 Hz, 1H), 7.27 (t, J = 7.4 Hz, 1H), 7.19 (t, J = 7.3 Hz, 1H), 6.84 (dd, J = 8.3, 2.0 Hz, 1H), 4.15 (s, 2H), 3.85 (s, 2H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 158.5, 147.9, 147.6, 141.5, 137.1, 137.0, 136.2, 133.0, 132.5, 128.5, 128.4, 127.2, 126.7, 126.2, 125.8, 125.5, 114.2, 107.8, 55.3, 49.2, 31.8; HRMS[TOF-(-APCI)]: $[M-H]^-$ calcd for $C_{25}H_{19}O$: 335.1441; found: 335.1442.

1-(p-Bromophenyl)-3-phenyl-2,8-dihydrocyclopenta[a]indene ***5p***. Yellow solid, 82 mg, 43%, mp 148−149 °C; IR ν (KBr, cm^{-1}) 1597, 1490; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.94 (d, J = 7.4 Hz, 1H), 7.67 (d, J = 7.2 Hz, 2H), 7.50 (d, J = 8.6 Hz, 2H), 7.43−7.46 (m, 3H), 7.40 (d, J = 8.6 Hz, 2H), 7.27−7.33 (m, 2H), 7.24 (t, J = 7.2 Hz, 1H), 4.14 (s, 2H), 3.90 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 149.2, 148.0, 147.7, 137.0, 136.0, 135.2, 133.4, 131.7, 131.6, 128.6, 128.2, 127.3, 127.0, 126.9, 126.8, 126.0, 122.7, 119.5, 49.4, 32.6; HRMS [TOF-(-APCI)]: $[M-H]^-$ calcd for $C_{24}H_{16}Br$: 383.0440; found: 383.0441.

1-(p-Methylphenyl)-3-phenyl-2,8-dihydrocyclopenta[a]indene ***5q***. Yellow solid, 57 mg, 36%, mp 132−133 °C; IR ν (KBr, cm^{-1}) 1595, 1512; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.94 (d, J = 7.5 Hz, 1H), 7.66 (d, J = 7.8 Hz, 2H), 7.41−7.40 (m, 5H), 7.27 (t, J = 8.5 Hz, 2H), 7.23 (d, J = 7.2 Hz, 1H), 7.19 (d, J = 8.1 Hz, 2H), 4.15 (s, 2H), 3.91 (s, 2H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 149.6, 147.8, 146.2, 137.3, 136.3, 135.7, 133.6, 132.8, 132.6, 129.4, 128.5, 128.0, 127.3, 126.69, 126.65, 126.0, 125.6, 122.7, 49.5, 32.6, 21.2; HRMS [TOF-(-APCI)]: $[M-H]^-$ calcd for $C_{25}H_{19}$: 319.1492; found: 319.1493.

1-(p-Methoxyphenyl)-3-phenyl-2,8-dihydrocyclopenta[a]indene ***5r***. Yellow solid, 31 mg, 19% (24% from the reaction catalyzed by a combination of **3a** (20 mol%), DBU (50 mol%), Ti(OPr-*i*)$_4$ (200 mol %), and *i*-PrOH (200 mol%) in refluxing dichloroethane.), mp 166−167 °C; IR ν (KBr, cm^{-1}) 1601, 1510; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.93 (d, J = 7.4 Hz, 1H), 7.67 (d, J = 7.6 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 7.41−7.46 (m, 3H),7.22−7.30 (m, 3H), 6.95 (d, J = 8.3 Hz, 2H), 4.16 (s, 2H), 3.92 (s, 2H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 157.9, 149.6, 147.8, 145.0, 137.3, 136.3, 132.5, 132.1, 129.5, 128.5, 128.0, 127.3, 126.8, 126.7, 126.6, 126.0, 122.7, 114.2, 55.3, 49.5, 32.5; HRMS [TOF-(-APCI)]: $[M-H]^-$ calcd for $C_{25}H_{19}O$: 335.1441; found: 335.1440.

DOI: 10.1021/acs.joc.6b02329
J. Org. Chem. 2016, 81, 11871−11881

Hydrolysis of (1*S*,4*S*,5*R*,10*S*)-5-(Aroylmethyl)-10-aryl-4,5-dihydro-1,4-methanobenzo[*c*]oxepin-3-ones 4. The 5-(aroylmethyl)-10-aryl-4,5-dihydro-1,4-methanobenzo[*c*]oxepin-3-ones **4** (0.25 mmol) and the aqueous solution of NaOH (5% w/w, 1.9 mL, 10 equiv) were dissolved in THF (5 mL). The resulting mixture was stirred at room temperature for 14 h. The reaction mixture was neutralized with aqueous solution of HCl (1% w/w) to pH ∼ 5−6, and then dichloromethane (10 mL) was added. The organic phase was separated using a separating funnel, and the aqueous layer was extracted with dichloromethane (10 × 2 mL). The combined organic solution was dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was chromatographed on a silica gel column eluting with a mixture of petroleum ether, ethyl acetate, and dichloromethane from PE:EA = 5:1 to PE:EA:DCM = 1:1:1 to give the products **18** in 75−72% yields.

(1R,2S,3S,4S)-4-Hydroxy-1-(benzoylmethyl)-3-phenyl-1,2,3,4-tetrahydronaphthalene-2-carboxylate ***18a.*** White solid, 73 mg, 75%, ee 99%, $[\alpha]^{20}_D$ = +124.5 (c = 0.50, CH_2Cl_2), mp 98−99 °C; IR ν (KBr, cm^{-1}) 1708, 1686; ^1H NMR (400 MHz, CD_3COCD_3) δ (ppm) 7.99 (dd, *J* = 7.5, 1.3 Hz, 2H), 7.57−7.61 (m, 2H), 7.49 (t, *J* = 7.4 Hz, 2H), 7.40 (d, *J* = 7.3 Hz, 2H), 7.9 (t, *J* = 7.4 Hz, 2H), 7.17−7.22 (m, 4H), 4.84 (d, *J* = 8.8 Hz,1H), 4.21 (dd, *J* = 11.0, 5.7 Hz,1H), 3.95 (dd, *J* = 18.1, 6.4 Hz, 1H), 3.48 (dd, *J* = 11.4, 4.7 Hz,1H), 3.34−3.40 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 198.2, 176.4, 141.1, 138.9, 137.1, 136.9, 133.1, 128.8, 128.5, 128.12, 128.1, 128.0, 127.8, 127.3, 127.2,127.1, 74.3, 51.6, 48.0, 47.7, 43.6, 35.0; HRMS (FT-ESI): $[M+Na]^+$ calcd for $C_{25}H_{22}O_4Na$: 409.1410; found: 409.1403.

(1R,2S,3S,4S)-4-Hydroxy-1-((p-methoxybenzoyl)methyl)-3-phenyl-1,2,3,4-tetrahydronaphthalene-2-carboxylate ***18r.*** White solid, 85 mg, 82%, ee 99%, $[\alpha]^{20}_D$ = +144.8 (c = 0.50, CH_2Cl_2), mp 93−94 °C; IR ν (KBr, cm^{-1}) 1708, 1675, 1600; ^1H NMR (400 MHz, CD_3COCD_3) δ (ppm) 10.55 (br, 1H), 7.97 (d, *J* = 8.9 Hz, 2H), 7.58 (d, *J* = 7.6 Hz,1H), 7.39 (d, *J* = 7.3 Hz, 2H), 7.30 (t, *J* = 7.4 Hz, 2H), 7.18−7.25 (m, 3H), 6.99 (d, *J* = 8.9 Hz, 2H), 4.84 (d, *J* = 8.6 Hz,1H), 4.37 (brs, 1H), 4.19 (dd, *J* = 10.8, 5.7 Hz,1H), 3.87 (s, 3H), 3.84 (dd, *J* = 17.9, 6.0 Hz, 1H), 3.48 (dd, *J* = 11.4, 4.7 Hz,1H), 3.30−3.39 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 196.6, 175.7, 163.5,141.2, 138.9, 137.1, 130.4, 129.9, 128.9, 128.1, 127.9, 127.7, 127.4, 127.1, 126.9,113.7, 74.2, 55.4, 48.2, 47.8, 42.2, 35.0; HRMS (MALDI-TOF): $[M+K]^+$ calcd for $C_{26}H_{24}O_5K$: 455.1255; found: 455.1284.

Alcoholysis of (1*S*,4*S*,5*R*,10*S*)-5-(Aroylmethyl)-10-aryl-4,5-dihydro-1,4-methanobenzo[*c*]oxepin-3-ones 4. The 5-(aroylmethyl)-10-aryl-4,5-dihydro-1,4-methanobenzo[*c*]oxepin-3-ones **4** (0.25 mmol) and NaOMe (41 mg, 3 equiv) were dissolved in methanol (10 mL). The resulting mixture was stirred at room temperature for 12 h. The reaction was quenched by the addition of saturated aqueous solution of NH_4Cl (5 mL), and then dichloromethane (20 mL) was added. The organic phase was separated and the aqueous layer was extracted with dichloromethane (20 × 2 mL). The combined organic solution was dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was chromatographed on a silica gel column eluting with a mixture of petroleum ether and ethyl acetate (PE:EA from 10:1 to 5:1) to give the products **19** in 70−76% yields.

(1R,2S,3S,4S)-Methyl 4-hydroxy-1-(benzoylmethyl)-3-phenyl-1,2,3,4-tetrahydronaphthalene-2-carboxylate ***19a.*** White solid, 82 mg, 76%, ee 99%, $[\alpha]^{20}_D$ = +130.3 (c = 0.55, CH_2Cl_2), mp 136−137 °C; IR ν (KBr, cm^{-1}) 1732, 1682; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.93 (d, *J* = 7.5 Hz, 2H), 7.60 (d, *J* = 7.4 Hz,1H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.24−7.36 (m, 7H), 7.20 (t, *J* = 7.2 Hz, 1H), 4.87 (d, *J* = 9.1 Hz,1H), 4.29−4.33 (m, 1H), 3.98 (dd, *J* = 18.4, 7.9 Hz, 1H), 3.50 (dd, *J* = 11.9, 4.9 Hz,1H), 3.31 (dd, *J* = 11.9, 9.2 Hz, 1H), 3.29 (s, 3H), 3.18 (dd, *J* = 18.4, 3.8 Hz, 1H), 1.72 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 197.8, 172.8, 141.0, 139.2, 136.9, 133.0, 128.8, 128.6, 128.2, 128.1, 128.04, 128.0, 127.3, 127.2, 127.1,74.3, 51.6, 48.0, 47.7, 43.6, 35.0; HRMS (FT-ESI): $[M+Na]^+$ calcd for $C_{26}H_{24}O_4Na$: 423.1567; found: 423.1563.

(1R,2S,3S,4S)-Methyl 4-hydroxy-1-((p-methoxybenzoyl)methyl)-3-phenyl-1,2,3,4-tetrahydronaphthalene-2-carboxylate ***19r.*** White solid,75 mg, 70%, ee 98%, $[\alpha]^{20}_D$ = +146.8 (c = 0.50, CH_2Cl_2), mp 145−146 °C; IR ν (KBr, cm^{-1}) 1734, 1676, 1601; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.92 (d, *J* = 8.8 Hz, 2H), 7.59 (d, *J* = 7.4 Hz,1H), 7.24−7.36 (m, 7H), 7.21 (t, *J* = 7.4 Hz, 1H), 6.90 (d, *J* = 8.9 Hz, 2H), 4.86 (d, *J* = 9.1 Hz,1H), 4.28−4.32 (m, 1H), 3.99 (dd, *J* = 18.2, 7.8 Hz, 1H), 3.85 (s, 3H), 3.49 (dd, *J* = 11.9, 5.0 Hz,1H), 3.31 (dd, *J* = 11.8, 9.1 Hz, 1H), 3.29 (s, 3H), 3.13 (dd, *J* = 18.1, 4.0 Hz, 1H), 1.80 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 196.3, 172.7, 163.5, 141.1, 139.4, 137.2, 130.3, 130.0, 128.8, 128.2, 128.1, 128.0, 127.3, 127.1, 127.0,113.7, 74.3, 55.4, 51.5, 48.1, 47.8, 43.1, 35.1; HRMS (FT-ESI): $[M+Na]^+$ calcd for $C_{27}H_{26}O_5Na$: 453.1673; found: 453.1668.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02329.

Copies of ^1H NMR and ^{13}C NMR spectra of products **4**, **5**, **18**, and **19** and copies of HPLC chromatographs for product **4** (PDF)

X-ray crystallographic data of **4b** (CIF)

X-ray crystallographic data of **5p** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: ycheng2@bnu.edu.cn

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (No. 21372030).

■ REFERENCES

(1) Some reviews for NHCs organocatalysis: (a) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606−5655. (b) Marion, N.; Diez-Gonzalez, S.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2988−3000. (c) Grossmann, A.; Enders, D. *Angew. Chem., Int. Ed.* **2012**, *51*, 314−325.

(2) Examples for the constructions of cyclic compounds by NHC-catalyzed reactions of enals: (a) Lathrop, S. P.; Rovis, T. *J. Am. Chem. Soc.* **2009**, *131*, 13628−13630. (b) Gao, Z.-H.; Chen, X.-Y.; Zhang, H.-M.; Ye, S. *Chem. Commun.* **2015**, *51*, 12040−12043. (c) Chan, A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 5334−5335. (d) Rommel, M.; Fukuzumi, T.; Bode, J. W. *J. Am. Chem. Soc.* **2008**, *130*, 17266−17267. (e) Fang, X.; Jiang, K.; Xing, C.; Hao, L.; Chi, Y. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 1910−1913.

(3) A review for NHC/Lewis acid cooperative catalysis: Cohen, D. T.; Scheidt, K. A. *Chem. Sci.* **2012**, *3*, 53−57.

(4) Examples for the NHC/Lewis acid catalysis: (a) Cardinal-David, B.; Raup, D. E. A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2010**, *132*, 5345−5347. (b) Cohen, D. T.; Cardinal-David, B.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 1678−1682. (c) Dugal-Tessier, J.; O'Bryan, E. A.; Schroeder, T. B. H.; Cohen, D. T.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 4963−4967. (d) Bera, S.; Samanta, R. C.; Daniliuc, C. G.; Studer, A. *Angew. Chem., Int. Ed.* **2014**, *53*, 9622−9626. (e) Mo, J.; Chen, X.; Chi, Y. R. *J. Am. Chem. Soc.* **2012**, *134*, 8810−8813. (f) Raup, D. E. A.; Cardinal-David, B.; Holte, D.; Scheidt, K. A. *Nat. Chem.* **2010**, *2*, 766−771. (g) Xiao, Z.; Yu, C.; Li, T.; Wang, X.-S.; Yao, C. *Org. Lett.* **2014**, *16*, 3632−3635. (h) Patil, N. T. *Angew. Chem., Int. Ed.* **2011**, *50*, 1759−1761.

(5) The NHC/Brønsted acid catalysis: (a) Lee, A.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2014**, *53*, 7594−7598. (b) Zhao, X.; DiRocco, D. A.; Rovis, T. *J. Am. Chem. Soc.* **2011**, *133*, 12466−12469. (c) Li, J.-L.; Sahoo, B.; Daniliuc, C.-G.; Glorius, F. *Angew. Chem., Int. Ed.* **2014**,

53, 10515−10519. (d) Kato, T.; Matsuoka, S.; Suzuki, M. *J. Org. Chem.* **2014**, *79*, 4484−4491.
(6) (a) ElSohly, A. M.; Wespe, D. A.; Poore, T. J.; Snyder, S. A. *Angew. Chem., Int. Ed.* **2013**, *52*, 5789−5794. (b) Boddaert, T.; Coquerel, Y.; Rodriguez, J. *Chem. - Eur. J.* **2011**, *17*, 2266−2271.
(7) (a) Cheng, Y.; Peng, J.-H.; Li, Y.-J.; Shi, X.-Y.; Tang, M.-S.; Tan, T.-Y. *J. Org. Chem.* **2011**, *76*, 1844−1851. (b) Zhao, Y.; Wang, Z.-T.; Cheng, Y. *Adv. Synth. Catal.* **2014**, *356*, 2580−2590. (c) Wang, Z.-T.; Zhao, Y.; Wang, Z.-Y.; Cheng, Y. *J. Org. Chem.* **2015**, *80*, 1727−1734. (d) Mao, J.-H.; Wang, Z.-T.; Wang, Z.-Y.; Cheng, Y. *J. Org. Chem.* **2015**, *80*, 6350−6359.
(8) (a) Dang, H.-Y.; Wang, Z.-T.; Cheng, Y. *Org. Lett.* **2014**, *16*, 5520−5523. (b) Wang, Z.-Y.; Ding, Y.-L.; Wang, G.; Cheng, Y. *Chem. Commun.* **2016**, *52*, 788−791. (c) Wang, G.; Wang, Z.-Y.; Niu, S.-S.; Rao, Y.; Cheng, Y. *J. Org. Chem.* **2016**, *81*, 8276−8286.
(9) (a) Phillips, E. M.; Wadamoto, M.; Chan, A.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 3107−3110. (b) Li, Y.; Wang, X.-Q.; Zheng, C.; You, S.-L. *Chem. Commun.* **2009**, 5823−5825.
(10) Examples for 1,5-H sigmatropic rearrangements: (a) Flamini, A.; Fares, V.; Capobianchi, A.; Valentini, V. *J. Chem. Soc. Perkin Trans. 1* **2001**, 3069−3072. (b) Alajarin, M.; Sanchez-Andrada, P.; Lopez-Leonardo, C.; Alvarez, A. *J. Org. Chem.* **2005**, *70*, 7617−7623.
(11) Examples for 1,3-H shifts: (a) Wei, H.; Li, Y.; Xiao, K.; Cheng, B.; Wang, H.; Hu, L.; Zhai, H. *Org. Lett.* **2015**, *17*, 5974−5977. (b) Karmakar, R.; Mamidipalli, P.; Salzman, R. M.; Hong, S.; Yun, S. Y.; Guo, W.; Xia, Y.; Lee, D. *Org. Lett.* **2016**, *18*, 3530−3533.
(12) Examples for the synthesis of neopodophyllotoxin: (a) Charlton, J. L.; Koh, K. *J. Org. Chem.* **1992**, *57*, 1514−1516. (b) Renz, J.; Kuhn, M.; Wartburg, A. *Justus Liebigs Ann. Chem.* **1965**, *681*, 207−224. (c) Rajapaksa, D.; Rodrigo, R. *J. Am. Chem. Soc.* **1981**, *103*, 6208−6209.
(13) (a) Schwarz, J. S. P.; Weisenborn, F. L.; Neidleman, S. L.; Kinney, R. W. U.S. Patent US3438999A, 1969. (b) Kinney, R. W.; Neidleman, S. L.; Weisenborn, F. L.; Schwarz, J. S. P. U.S. Patent US3462487A, 1969.
(14) Some examples: (a) Sun, Z. CN Patent CN1887262A, 2007. (b) Gao, H.; Sun, Z. CN Patent CN1887262A, 2007. (c) Gao, H. CN Patent CN1846676A, 2006.
(15) Some examples: (a) Roulland, E.; Bertounesque, E.; Huel, C.; Monneret, C. *Tetrahedron Lett.* **2000**, *41*, 6769−6773. (b) Forsey, S. P.; Rajapaksa, D.; Taylor, N. J.; Rodrigo, R. *J. Org. Chem.* **1989**, *54*, 4280−4290. (c) Wu, Y.; Zhang, H.; Zhao, Y.; Zhao, J.; Chen, J.; Li, L. *Org. Lett.* **2007**, *9*, 1199−1202. (d) Kothari, P. J.; Hathaway, B. A.; Nichols, D. E.; Yim, G. K. W. *J. Med. Chem.* **1981**, *24*, 882−884. (e) Hathaway, B. A.; Nichols, D. E.; Nichols, M. B.; Yim, G. K. W. *J. Med. Chem.* **1982**, *25*, 535−538.
(16) Some examples: (a) Cimetiere, B.; Dubuffet, T.; Landras, C.; Descombes, J.-J.; Simonet, S.; Verbeuren, T. J.; Lavielle, G. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1381−1386. (b) Stutz, A.; Georgopoulos, A.; Granitzer, W.; Petranyi, G.; Berney, D. *J. Med. Chem.* **1986**, *29*, 112−125. (c) Dumas, M.; Dumas, J.-P.; Bardou, M.; Rochette, L.; Advenier, C.; Giudicelli, J.-F. *Eur. J. Pharmacol.* **1998**, *348*, 223−228. (d) Nichols, D. E.; Barfknecht, C. F.; Long, J. P.; Standridge, R. T.; Howell, H. G.; Partyka, R. A.; Dyer, D. C. *J. Med. Chem.* **1974**, *17*, 161−166.
(17) Ried, W.; Merkel, W.; Herrmann, H. J. *Liebigs Ann. Chem.* **1971**, *750*, 91−96.

DOI: 10.1021/acs.joc.6b02329
J. Org. Chem. 2016, 81, 11871−11881