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Desymmetrization of cyclohexadienones *via* D-camphor-derived triazolium salt catalyzed intramolecular Stetter reaction†

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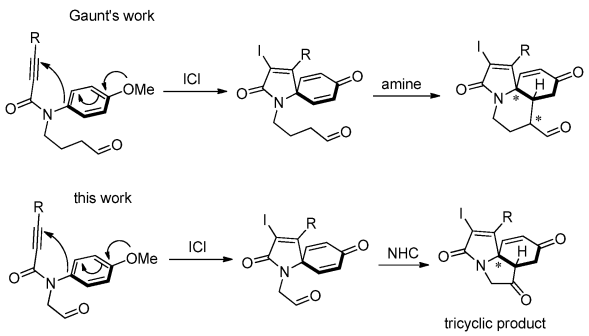
Enantioselective desymmetrization of cyclohexadienones *via* a D-camphor-derived triazolium salt catalyzed intramolecular Stetter reaction was realized. With 10 mol% of camphor-derived triazolium salt E and 10 mol% of DIEA, various substituted cyclohexadienones proceeded through an intramolecular Stetter reaction, affording tricyclic products in moderate to good yields and excellent ee.

N-Heterocyclic carbene (NHC) catalyzed umpolung reactions, by reversing the reactivity of an aldehyde functionality, have witnessed rapid development recently.[1] The Stetter reaction is undoubtedly one of the most important reactions in this class that take advantage of the umpolung reactivity of aldehydes.[2] Since the pioneering studies on the enantioselective intramolecular Stetter reaction reported by Enders and coworkers in 1996,[3] enormous efforts have been devoted to the development of efficient catalysts and protocols for asymmetric Stetter reactions.[4] Particularly elegant studies by Rovis and coworkers led to the discovery of the aminoindanol-derived triazolium salts as suitable catalysts and realized the highly enantioselective intramolecular Stetter reaction for the first time with broad range of substrates.[1h,5] Recently, Glorius and coworkers further demonstrated that unactivated alkenes are also suitable acceptors in the Stetter reaction,[1j,6] further highly broadening the reaction scope. On the other hand, dearomatization of phenols would provide cyclohexadienone derivatives, which are an excellent type of acceptor for the Stetter reaction. The dearomatization process together with desymmetrization reaction will provide a facile construction of optically active cyclic and polycyclic compounds from readily available starting materials.[7] In 2006, Rovis and Liu took advantage of this strategy to realize the highly enantioselective Stetter type desymmetrization of cyclohexadienones, prepared from the oxidative dearomatization of phenols.[8] Obviously, novel dearomatization reactions providing new cyclohexadienone derivatives would lead to diverse tricyclic structures and therefore be highly desirable. In this regard, recently, Gaunt and coworkers for the first time realized a secondary amine-catalyzed highly enantioselective desymmetrization process utilizing cyclohexadienone synthesized *via* an *ipso*-iodocyclization reaction (Scheme 1).[9] Intrigued by these elegant works, we envisaged that this interesting backbone might be suitable for a desymmetrization process *via* an NHC-catalyzed intramolecular Stetter reaction. In this communication, we report our preliminary results on this subject.



Scheme 1 *ipso*-Iodocyclization/desymmetrization protocols.

We began our studies with cyclohexadienone aldehyde **1a**, synthesized according to Larock's *ipso*-iodocyclization reaction,[10] as a model substrate for the NHC catalyzed desymmetrization reaction. With several readily available chiral NHCs (Fig. 1), the desymmetrization of cyclohexadienones *via* an intramolecular Stetter reaction was examined. The results are summarized in Table 1. Camphor-derived triazolium salts **A–D**,[11] were found to be almost ineffective for the intramolecular Stetter reaction (entries 1–4, Table 1). To our great delight, with 10 mol% of triazolium salt **E** bearing a C_6F_5 group and 10 mol% of DIEA in *o*-xylene, the desired intramolecular Stetter reaction proceeded smoothly affording desymmetrization product **2a** with excellent results (81% yield, 91% ee, entry 5, Table 1). Rather surprisingly, the reaction with 10 mol% of the

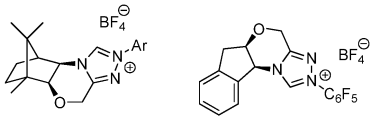


Fig. 1 Several readily available chiral NHC precursors.

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Table 1 Screening of the chiral NHC catalysts[a]

Entry	Catalyst	Yield (%)	ee[b] (%)
1	**A**	NR	—
2	**B**	NR	—
3	**C**	NR	—
4	**D**	<5	24
5	**E**	81	91
6	**F**	84	0

[a] Reaction conditions: **1a** (0.1 mmol), 10 mol% of catalyst, 10 mol% of DIEA in *o*-xylene (1.0 mL) at room temperature. [b] Determined by HPLC.

aminoindanol-derived triazolium salt **F**, under otherwise identical conditions gave the product in a racemic form, although a good yield (84%) was obtained (entry 6, Table 1). The high efficiency of triazolium salts **E** and **F** is likely due to acidic protons in the catalysts because of the electron-withdrawing aryl substituents.

In the presence of 10 mol% of triazolium salt **E**, different reaction parameters were further examined. The results are summarized in Table 2. All tested bases such as DIEA, KHMDS, DBU, Et_3N, and Cs_2CO_3 were well tolerated, affording the desired product with good yields and ees (entries 1–5, Table 2). DIEA gave the best enantioselectivity (91% ee), while Cs_2CO_3 resulted in the shortest reaction time. With DIEA as the base, several other solvents such as toluene, CH_2Cl_2, $CHCl_3$, and diethyl ether were tested (entries 6–10, Table 2). *o*-Xylene remained to be the optimal solvent.

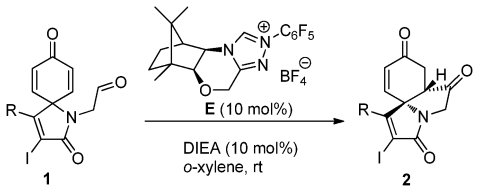
Under the optimized conditions (10 mol% of **E**, 10 mol% of DIEA, *o*-xylene, rt), various substrates were tested to investigate the generality of the reaction. The results are summarized in Table 3. When a tolyl group was introduced, the position of the methyl substituent had significant influence on the enantioselectivity (58% ee for 4-MeC_6H_4, 71% ee for 3-MeC_6H_4, 89% ee for 2-MeC_6H_4, entries 2, 4 and 6, Table 3). When Cs_2CO_3 was used as base, product **2b** (with 4-MeC_6H_4 substituent) could be obtained with 80% ee, while the ee value of 3-MeC_6H_4 product **2c** remained unchanged (entries 3, 5, Table 3). It is worth mentioning that product **2d** bearing a 2-MeC_6H_4 group seems to have two interconvertible atropisomers from NMR and HPLC analysis (two sets of peaks were observed), probably

Table 2 Optimization of the reaction conditions[a]

Entry	Base	Solvent	Time (h)	Yield (%)	ee[b] (%)
1	DIEA	*o*-Xylene	40	81	91
2	KHMDS	*o*-Xylene	40	84	83
3	DBU	*o*-Xylene	40	74	90
4	Et_3N	*o*-Xylene	40	67	80
5	Cs_2CO_3	*o*-Xylene	10	84	87
6	DIEA	Toluene	40	50	88
7	DIEA	THF	40	30	72
8	DIEA	CH_2Cl_2	40	64	50
9	DIEA	$CHCl_3$	40	60	28
10	DIEA	Et_2O	40	30	81

[a] Reaction conditions: **1a** (0.1 mmol), 10 mol% of **E**, 10 mol% of base in solvent (1.0 mL) at room temperature. [b] Determined by HPLC.

Table 3 NHC-catalyzed desymmetrization of cyclohexadienones *via* intramolecular Stetter reaction[a]



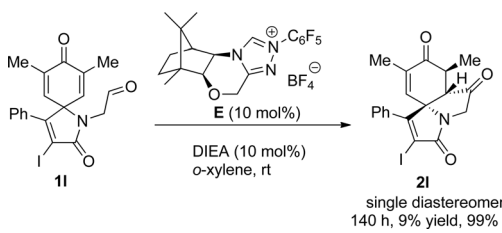
Entry	R	Product	Time (h)	Yield[b] (%)	ee[c] (%)
1	Ph	**2a**	40	81	91
2	4-MeC_6H_4	**2b**	50	65	58
3[d]	4-MeC_6H_4	**2b**	24	55	80
4	3-MeC_6H_4	**2c**	90	60	71
5[d]	3-MeC_6H_4	**2c**	72	60	71
6	2-MeC_6H_4	**2d**	50	52	89
7	4-FC_6H_4	**2e**	90	55	84
8[d]	4-ClC_6H_4	**2f**	48	54	86
9	2-Thienyl	**2g**	160	61	75
10	Me	**2h**	96	58	86
11	*n*-Pr	**2i**	60	60	85
12	Cyclopropyl	**2j**	72	85	88
13	*t*-Bu	**2k**	120	75	94

[a] Reaction conditions: **1** (0.2 mmol), 10 mol% of **E**, 10 mol% of DIEA in *o*-xylene (2.0 mL) at room temperature, unless noted otherwise. [b] Isolated yield. [c] Determined by HPLC. [d] With 10 mol% of Cs_2CO_3 as base.

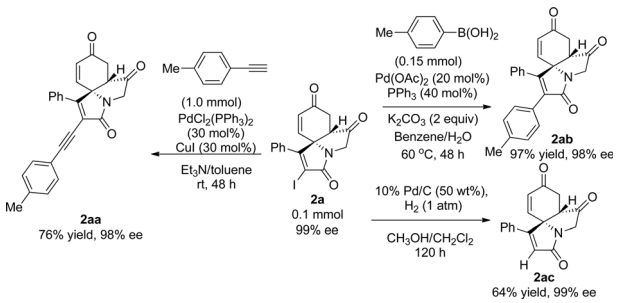
due to the fact that the 2-MeC_6H_4 group could not rotate freely in its surroundings. When R is an electron-deficient aryl group such as 4-FC_6H_4, the corresponding product **2e** was obtained in 55% yield and 84% ee (entry 7, Table 3). The substrate bearing a 4-ClC_6H_4 group led to product **2f** in 54% yield and 86% ee with Cs_2CO_3 as the base (entry 8, Table 3). Moreover, the 2-thienyl bearing substrate was also well tolerated under the optimized conditions, providing the desired tricyclic product with 75% ee (entry 9, Table 3). Various alkyl substituents were then evaluated as suitable substrates (entries 10–13, Table 3). The methyl, *n*-propyl, cyclopropyl and *tert*-butyl derived products were obtained in 58–85% yield and 85–94% ee. The absolute configuration of the product was determined by X-ray crystallographic analysis of the single crystal of enantiopure **2a** as (6*aS*,10*aR*).[12]

The dimethyl substituted cyclohexadienone substrate **1l** was also synthesized and tested in the intramolecular Stetter reaction. The desired product **2l** was obtained with excellent enantioselectivity (99% ee) but low yield (9%). The relative stereochemistry of the methyl substituent was determined by NOE experiment† (Scheme 2).

The highly functionalized tricyclic products generated here could be subjected to versatile chemoselective transformations. As shown in Scheme 3, enantiopure **2a**, obtained after one single recrystallization of **2a** (91% ee), was treated under Pd-catalyzed



Scheme 2 Reaction of the dimethyl substituted cyclohexadienone **1l**.



Scheme 3 Transformation of product **2a**.

Sonogashira and Suzuki cross-coupling reaction conditions respectively, their corresponding coupling products **2aa** and **2ab** were obtained in good to excellent yields without notable loss of enantiomeric purity. On treatment of **2a** with Pd/C under 1 atm H_2 at room temperature, deiodination product **2ac** was obtained in 64% yield and 99% ee.

In summary, desymmetrization of cyclohexadienones, derived from Larock's *ipso*-iodocyclization reaction, *via* an intramolecular Stetter reaction was realized. D-Camphor-derived triazolium salt was found to be the most efficient catalyst to furnish the intramolecular Stetter reaction in moderate to good yields and excellent ees. Highly functionalized tricyclic structures containing a quaternary stereogenic center and two contiguous stereocenters could be formed efficiently under mild reaction conditions, and the products were compatible for various chemical transformations.

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12 CCDC 870941 contains the supplementary crystallographic data for (6*aS*,10*aR*)-**2a**†.