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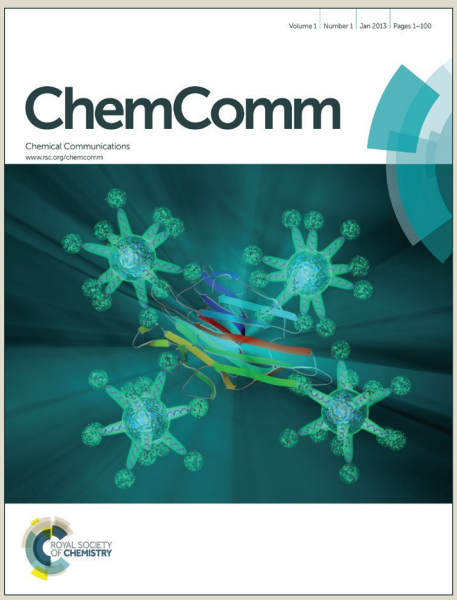

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N-Heterocyclic Carbene-Catalyzed Desymmetrization of Functionalized 1,4-Dienes via Stetter Reaction

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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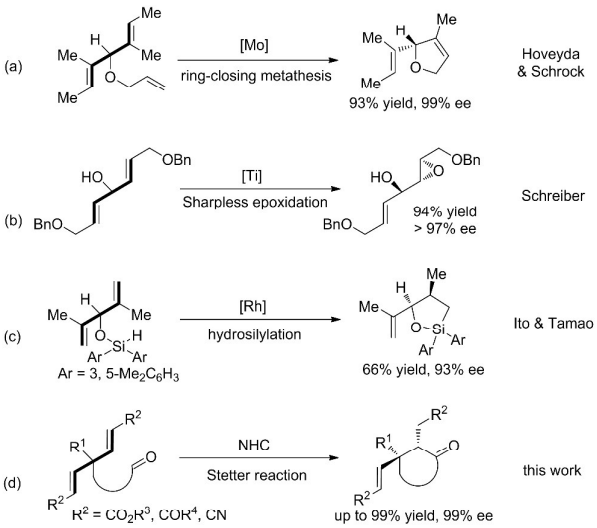
The asymmetric desymmetrization of 1,4-dienes via chiral N-heterocyclic carbene catalyzed Stetter-type umpolung reaction was demonstrated. A variety of differently substituted dienes were tolerated very well, affording cyclic ketones with two consecutive stereogenic centers (including one quaternary carbon) in moderate to high yields and with high to excellent enantioselectivities. This work expanded both reaction types of catalytic diene desymmetrizations and substrate diversity in NHC catalyzed desymmetric transformations.

The importance of alkenes in organic synthesis has been witnessed by numerous alkene-mediated transformations, including many well-known named reactions.[1] Enantioselective transformations of alkene substrates have been the research focus during the last several decades, and the construction of stereogenic centers is undoubtedly the key point in these investigations.[2] Comparing with traditional alkene reactions, asymmetric desymmetrization[3] of structurally symmetric dienes can result in one more stereocenter in most cases, and the remaining olefin moiety can be applied in further conversions (Scheme 1), therefore, alkene-mediated desymmetric reactions have drawn the attention of global research interests.[4] By employing approaches such as molybdenum catalyzed ring-closing-metathesis (Scheme 1a),[4h] Sharpless epoxidation (Scheme 1b),[4a,c] rhodium catalyzed hydrosilylation (Scheme 1c),[4d] etc, a series of synthetically useful chiral molecules were accessed and used in further studies such as natural products synthesis.[4b,e,f,g] However, to the best of our knowledge, most of these reactions were based on transition-metal catalysis; successful instances with organo-catalyzed desymmetrizing diene transformations were scarcely reported.



Scheme 1 Selected examples of desymmetric transformations of dienes

The umpolung strategy enabled by N-heterocyclic carbene (NHC) catalysis has been extremely successful during the last decade.[5] The desymmetrization reactions via NHC catalysis have also attracted considerable research interests recently.[6-8] In 2007, Scheidt group revealed an NHC catalyzed desymmetrization of 1,3-diketones through enolate mediated aldol reaction;[6] In 2009, Ema group developed a desymmetric benzoin reaction based on cyclic 1,3-diketones;[7] Rovis and You group achieved the synthesis of bi- or tricyclic compounds through desymmetrization of cyclohexadienones.[8] However, despite great progress being made, limitations and challenges remain. For example, only 1,3-diketones and cyclohexadienones have been successfully developed into their desymmetrization versions, leaving new substrate types to be further exploited. To address the issues of developing an organocatalyzed desymmetrization of dienes, and also to enhance the substrate diversity of NHC mediated desymmetric transformations, we disclose here the chiral carbene catalyzed enantioselective desymmetrizing annulation of 1,4-dienes

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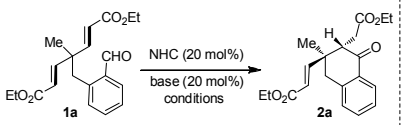
†Electronic Supplementary Information (ESI) available: Experimental procedures and spectroscopic data for all new compounds. CCDC 1438493. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/x0xx00000x

(Scheme 1d). This approach allows for the synthesis of tetralone and chromanone derivatives and other cyclic ketones bearing two stereogenic centers and diverse functional groups in moderate to good yields, and with high to excellent enantioselectivities, and it's noteworthy that these products are both useful building blocks in organic synthesis and widely existed key units in a large variety of natural products and pharmaceuticals.[9]

We started by selecting **1a** as the standard substrate and triazolium salts **C1**-**C5** initially developed by Rovis and Bode groups to validate our strategy. Although the phenyl or 4-bromophenyl catalysts[10a] **C1** and **C2** were ineffective (Table 1, entry 1), the catalyst **C3**[10b] showed exciting result with the desired annulation product obtained in 65% yield and with a promising 87% *ee*, albeit with 4.2:1 d.r. (Table 1, entry 2). Further study indicated that catalyst **C4**[10c] had a positive effect on the enantioselectivity (99% *ee*), but the yield of **2a** was moderate (49%) (Table 1, entry 3). To our delight, Rovis catalyst **C5**[10d], with a trichlorophenyl substituent, was proved to be an ideal choice considering both the yield and *ee* (93% yield, 4.3:1 d.r. and 99% *ee*, Table 1, entry 4). Efforts to increase the diastereoselectivity of **2a** revealed that the combination of KO^{t}Bu and toluene was optimal (Table 1, entry 5-9). A series of Lewis acids and Brønsted acids were also introduced into the reaction as additives, but did not lead to better d.r. (results not shown in Table 1, see supporting information for more details). At last, we found that lower temperature was able to increase the d.r. value to 7.2:1 (Table 1, entry 10). So the final reaction condition was set to be –25 °C, with **C5** as the catalyst, KO^{t}Bu as the base and toluene as the solvent; the corresponding desymmetric annulation product was librated in 99% yield, with 7.2:1 d.r. and 99% *ee* (Table 1, entry 10).[11]

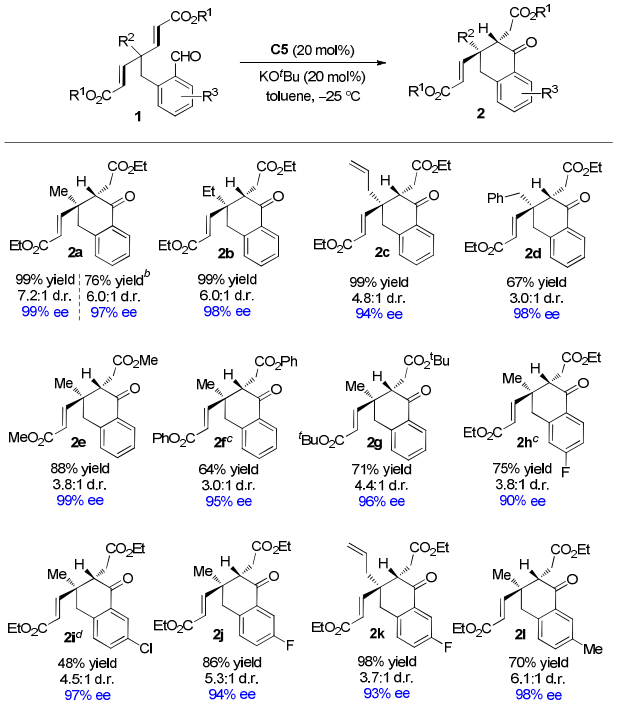
Table 1 Optimization of the reaction condition[a]



Entry	NHC	Base	Solvent	Yield (%)[b]	d.r.[c]	ee[d]
1	**C1-C2**	KHMDS[e]	toluene	trace	-	-
2	**C3**	KHMDS[e]	toluene	65	4.2:1	87
3	**C4**	KHMDS[e]	toluene	49	5.2:1	99
4	**C5**	KHMDS[e]	toluene	93	4.3:1	99
5	**C5**	K_2CO_3	toluene	87	4.3:1	97
6	**C5**	DBU	toluene	75	4.3:1	99
7	**C5**	KO^{t}Bu	toluene	99	4.3:1	99
8	**C5**	KO^{t}Bu	CH_2Cl_2	99	3.6:1	98
9	**C5**	KO^{t}Bu	THF	99	4.4:1	99
10[f]	**C5**	**KO^{t}Bu**	**toluene**	**99**	**7.2:1**	**99**

[a] Reaction condition: **1a** (0.1 mmol), NHC (0.02 mmol), base (0.02 mmol), solvent (2 mL), 23 °C, under argon protection. [b] Isolated yields based on **1a**. [c] Determined by ^{1}H NMR analysis of the reaction mixture. [d] Determined via chiral HPLC analysis on a chiral stationary phase; the absolute configuration was determined via X-ray single crystal analysis of **4e** (Table 3).[12] [e] 1.0 M in toluene. [f] –25 °C.

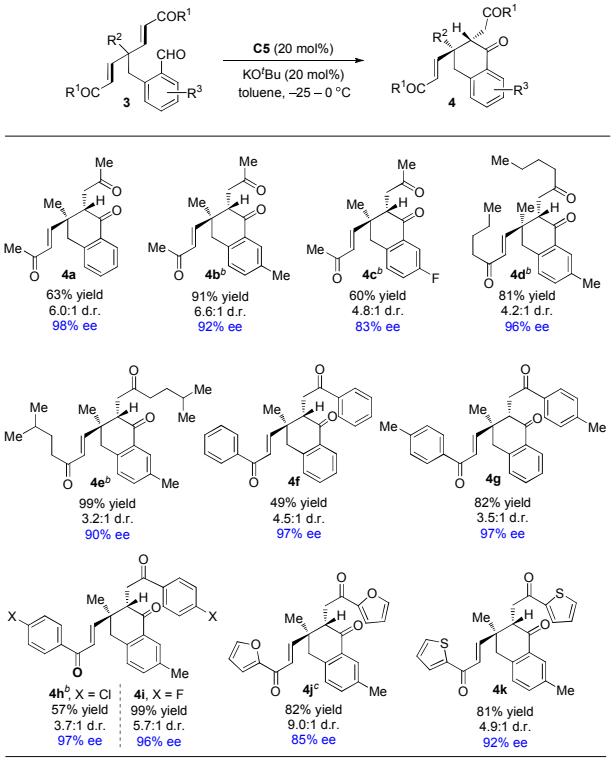
Table 2 Substrate scope of 1,4-dienes with ester substituents[a]



[a] Reaction condition: **1** (0.1 mmol), **C5** (0.02 mmol), KO^{t}Bu (0.02 mmol), toluene (2 mL), -25 °C, under argon protection. All isolated yields were based on substrate **1**; The diastereomeric ratios were determined by ^{1}H NMR analysis; *ee* values were determined via HPLC analysis on a chiral stationary phase. [b] 0.4 g scale. [c] –25 °C – 0 °C. [d] –25 °C – 23 °C .

Having established the optimized condition, we set on to evaluate the substrate scope and limitation of this methodology. Pleasingly, a variety of ester groups substituted 1,4-dienes can undergo the reaction smoothly, delivering products with excellent *ee* in all the cases (Table 2). For example, variation of R^2 substituent from methyl group to ethyl, allyl or benzyl groups furnished the corresponding products with excellent enantioselectivities (94-98% *ee*), although the diastereoselectivities decreased slightly (Table 2, **2b**-**2d**). To be noted, increase of the steric bulkiness of R^2 substituents was previously observed to encumber the enantioselectivity in NHC catalyzed 1,3-diketone desymmetrization.[6] But in this work, no significant impact was observed (Table 2, **2b**-**2d**). Subsequently, replacement of the ethyl ester group with methyl, phenyl or *tert*-butyl groups was insensitive to the reaction condition and enantiopure products were isolated (95-99% ee, Table 2, **2e**-**2g**). Variation on the substitution pattern of the formyl aryl units was also examined. Substrates equipped with electron-withdrawing fluoro or chloro groups on the phenyl ring were tolerable, affording desymmetric products with excellent enantioselectivities (90-97% ee, Table 2, **2h**-**2k**). Similarly,

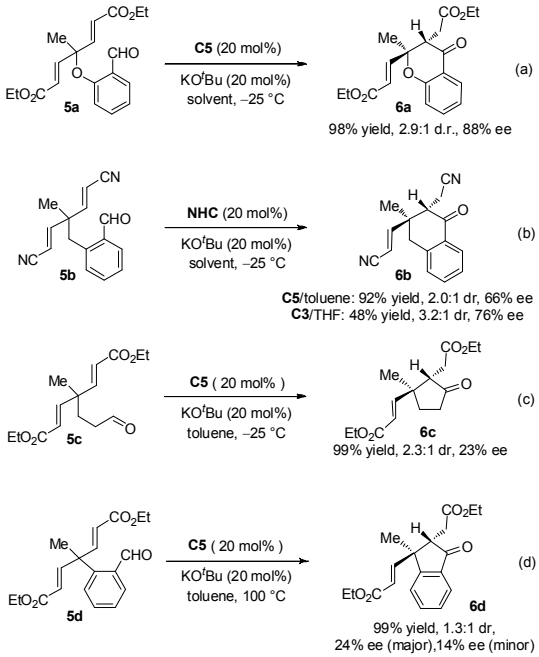
Table 3 Substrates scope of 1,4-dienes with ketone groups[a]



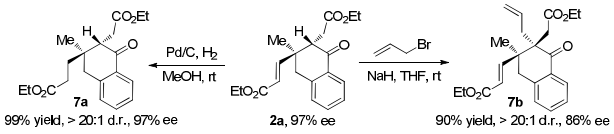
[a] Reaction condition: **3** (0.1 mmol), **C5** (0.02 mmol), KO^{t}Bu (0.02 mmol), toluene (2 mL), –25 °C – 0 °C, under argon protection. All isolated yields were based on substrate **3**; The diastereomeric ratios were determined by ^{1}H NMR analysis; *ee* values were determined via HPLC analysis on a chiral stationary phase. [b] 23 °C. [c] KHMDS instead of KO^{t}Bu, 23 °C.

electron-donating methyl group on the phenyl moiety had no significant impact on the outcome, leading to the product of **2l** with 98% ee (Table 2, **2l**). It is noteworthy that a large scale reaction with **1a** (0.4 g) was also conducted, and the product of **2a** was separated in 76% yield with 6:1 d.r. and 97% ee, which highlighted the synthetic potential of this methodology (Table 2, **2a**, condition b).

To further demonstrate the utility of this organocatalyzed desymmetrization reaction, a variety of 1,4-dienes with ketone substituents were also surveyed. Diene **3a** with an acetyl substitutent, was firstly evaluated. The reaction was relatively slow under the standard conditions employed in Table 2, but we were pleased to discover that increasing the temperature to 0 °C enabled full consumption of the starting material, with no apparent negative effect on the product (63% yield, 6:1 d.r. and 98% ee, Table 3, **4a**). More substrates were then examined under this slightly modified conditions. The introduction of electron-rich methyl group or electron-poor fluoro group on the aryl rings didn't encumber the reactions and good results were still perceived (Table 3, **4b**-**4c**). Replacement of acetyl with pentanoyl or 4-methylpentanoyl groups had little influence on the reaction in terms of both the ee values and the yields (Table 3, **4d**-**4e**). The substrate with phenyl ketone group was amenable, releasing the annulation product in moderate yield and with excellent 97% ee (Table 3, **4f**). The reaction was also not sensitive to the substitution patterns on the aromatic ketone moieties, with excellent 96-97% ee detected (Table 3, **4g**-**4i**). Similarly, replacement of the aryl ketone substitutents with furyl or thienyl ketone groups led to products **4j** and **4k** in good yields and with good to excellent ee (Table 3).



Scheme 2 Substrates diversity.



Scheme 3 Product derivatization

An oxygen tethered substrate **5a** was also tested. The corresponding chromanone derivative **6a** was furnished in high yield and with 88% ee (Scheme 2a). 1,4-Diene with other substituent such as cyano group was also examined. High yield and moderate 66% ee were obtained under the standard conditions in Table 2; and the enantioselectivity can be increased to 76% ee when catalyst **C3** and THF were introduced (Scheme 2b). We also checked substrate **5c** with an aliphatic aldehyde group, and the annulation product **6c** was isolated in almost quantitative yield, but unfortunately, low enantioselectivity was realized under all the conditions we screened (Scheme 2c, see supporting information for more details). Likewise, five-membered benzocyclic ketone **6d** didn't show high ee and a high temperature (100 °C) was necessary to ensure a good conversion (Scheme 2d). Moreover, our preliminary efforts to employ hexa-substituted 1,4-diene in this NHC catalyzed desymmetrization reaction were not successful[13] and further endeavours will be put to address this issue[14].

The synthetic application of this methodology can be demonstrated by the chemo- and stereoselective derivatizations of the products shown in Scheme 3. For example, catalytic hydrogenation of the olefin moiety of **2a** under balloon-pressure hydrogen atmosphere generated **7a** in quantitative yield and without loss of ee. The α-allylation of the ketone functional group was also operational, affording product **7b** with two contiguous quaternary stereocenters in high yield and with good enantioselectivity.[15]

In conclusion, the desymmetrization of 1,4-dienes via chiral NHC catalyzed intramolecular Stetter reaction was demonstrated. A series of tetralone derivatives and other types of cyclic ketone products bearing two consecutive stereocenters were obtained in good to excellent yields and with high to excellent enantioselectivities in most cases. And more importantly, this work enhanced the reaction diversity of catalytic asymmetric desymmetrization of 1,4-dienes, and represents a new substrate type in NHC catalyzed desymmetrization reactions.

This work was supported by National Science Foundation of China (21402199, 21502192), the Chinese Recruitment Program of Global Experts and Fujian Institute of Research on the Structure of Matter (FJIRSM). We are grateful to Professor Shu-Li You in SIOC for providing camphor-derived catalyst. We also thank Jihui Jia, Linrong Cai and Guangsai Yang in FJIRSM for the help of X-ray structure determination and data analysis.

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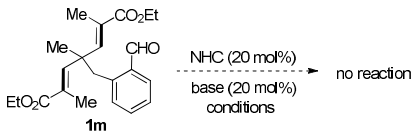
11 For the full list of the reaction condition optimization, see supporting information.

12 CCDC 1438493 contains the the supplementary crystallographic data for this paper. These data is free of charge from The Cambridge Crystallographic Centre via www.ccdc.cam.ac.uk/data_request/cif.

13 Substrate **1m** failed to undergo the desymmetrization reaction under all the conditions we screened.



1m

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