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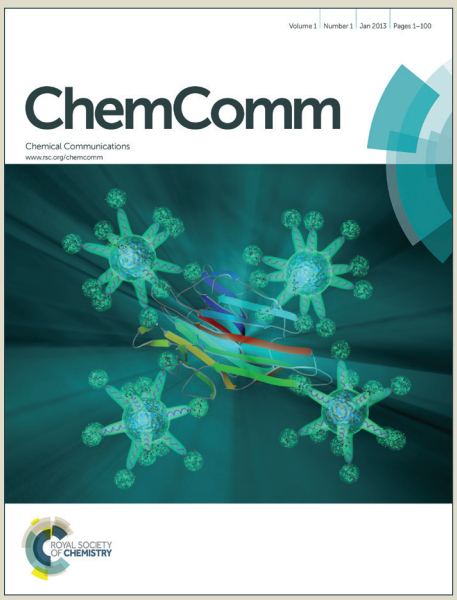

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ARTICLE TYPE

Catalytic Asymmetric Diels-Alder Reactions Involving Aryl Vinyl Ketones†

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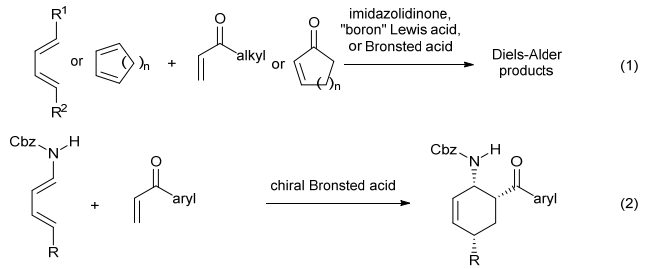
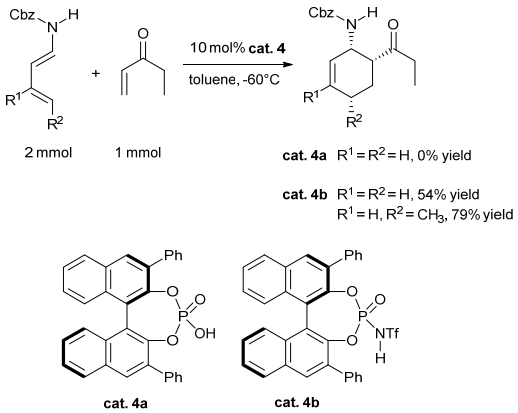
A catalytic asymmetric Diels-Alder reaction of aryl vinyl ketone with 1,3-dienylcarbamate has been developed. Cyclohexenes bearing vicinal amino and aroyl groups in a *cis*-configuration were prepared in excellent ee (>99%) and endo (single diastereomer) selectivity. The absolute configuration of one DA product was unambiguously confirmed by XRD analysis. The transition state structure was proposed on the basis of DFT calculations.

Diels-Alder (DA) reaction has a history of more than 80 years. Catalytic asymmetric Diels-Alder reactions have been realized mainly with Lewis acid catalysts.[1] In comparison with α,β-unsaturated aldehydes (enals), α,β-unsaturated ketones (enones) as dienophiles have been found much less applications in asymmetric reactions. Only few examples have been reported to date (**eq. 1**).[2-5] A clear fact is that aryl vinyl ketones have never been reported to give the DA products in good ee. In this communication, we report our efforts in pursuing new DA reactions involving aryl vinyl ketones as well as alkyl vinyl ketones (**eq. 2**).



In 2007, Yamamoto et al. reported asymmetric DA reactions of ethyl vinyl ketone with structurally varied 3-siloxy-1,3-dienes catalyzed by a chiral Brønsted acid, which is a phosphoramide derived from 3,3'-disubstituted BINOL.[5] This is the first example using chiral Brønsted acid to catalyze highly enantioselective DA reactions.[6] Several research groups have exploited applications of this kind of chiral Brønsted acid catalysts.[7-11] Encouraged by the promising results from Yamamoto and Terada's research groups,[5,6d] we hope to apply chiral Brønsted acids for the DA reactions of vinyl ketones with 1,3-dienylcarbamates,[2,6d,12,13] and to further broaden the substrate scope of chiral Brønsted acid catalyzed DA reactions.

At the outset, we selected benzyl (1*E*)-1,3-butadienylcarbamate (R^1 = R^2 = H) and commercially available ethyl vinyl ketone (EVK) as reactants (**Scheme 1**).[14] (2*E*)-2,4-Pentadienoic acid prepared from acrolein and malonic acid was converted to benzyl 1,3-butadienylcarbamate via intermediacy of the corresponding acyl azide and then the isocyanate.[15] When chiral phosphoric acid (**cat. 4a**, 10 mol%) was used as the catalyst, no reaction between benzyl 1,3-butadienylcarbamate and ethyl vinyl ketone was observed even after a prolonged reaction time (2 d). When chiral phosphoramide (**cat. 4b)** was used as the catalyst, the DA product was isolated in 54% yield and 73% *ee*. Even at -78°C, the dienylcarbamate decomposed gradually in several hours. When benzyl 3-methyl-1,3-butadienylcarbamate (R^1 = CH_3, R^2 = H) was used, decomposition of the carbamate was even serious. We then tested the reaction of benzyl (1*E*,3*E*)-1,3-pentadienylcarbamate (**1a**, R^1 = H, R^2 = CH_3), which was easily prepared from commercially available sorbic acid.[15] With **cat. 4b** as the catalyst, a one pot reaction between **1a** and ethyl vinyl ketone delivered the DA product in 79% yield and 75% *ee*. 4Å molecular sieve was found to be beneficiary to slow down decomposition of the carbamate. To the best of our knowledge, only two reports concerning 4-substituted 1,3-dienylcarbamate had appeared: a thermal DA reaction of 1,3-pentadienylcarbamate was reported by Overman et al. in 1981;[13c] an asymmetric DA reaction of 1,3-pentadienylcarbamate or 4-phenyl-1,3-butadienylcarbamate with methacrolein was reported by Rawal et al. in 2002.[16]

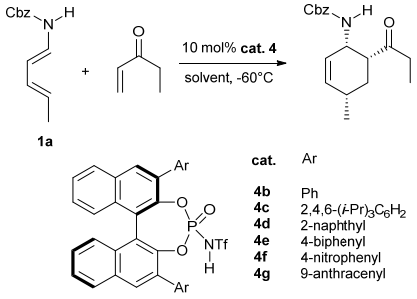


Scheme 1 Screening of suitable catalyst and substrate.

The effect of the chiral phosphoramide catalyst on the enantioselectivity was then evaluated (**Table 1**). Series of chiral phosphoramides possessing different aryl groups at 3,3'-positions were prepared according to published procedures.[15] With these

chiral phosphoramides in hand, the reaction between ethyl vinyl ketone and benzyl 1,3-pentadienylcarbamate (**1a**) was carefully studied. Catalyst bearing 9-anthracenyl group (**4g**) turned out to be the best one delivering the product with 97% *ee* (entry 9). Chloroform was found to be better than toluene with respect to the *ee* (Table 1, entry 2 *vs* 1, entry 9 *vs* 8). When the carbamate solution was added via a syringe pump over 5 hours, the yield was improved to 72% while the same *ee* (97%) was observed (entry 10). This fact confirmed that no background reaction was incorporated to the DA reaction under the reaction conditions.

Table 1 Screening of phosphoramides using 1,3-dienylcarbamate **1a**.[a]



Entry	Cat.	Solvent	Time(d)	Yield (%)[b]	ee (%)[c]
1	**4b**	toluene	4	79	75
2	**4b**	$CHCl_3$	3	78	85
3	**4c**	toluene	3	35	9
4	**4c**	$CHCl_3$	3	28	28
5	**4d**	toluene	2	35	85
6	**4e**	toluene	4	72	90
7	**4f**	toluene	1	53	74
8	**4g**	toluene	3	74	80
9	**4g**	$CHCl_3$	7 h	66	97
10	**4g**	$CHCl_3$	12 h	72[d]	97

a. 1 mmol of EVK and 2 mmol of carbamate was reacted in one pot. b. Only *endo* product isolated. c. *ee* determined by HPLC using an OD-H column. d. Carbamate in $CHCl_3$ was added via syringe pump over 5 h.

Catalyst **4g** was then used to investigate DA reactions of **1a** with different types of vinyl ketones (Table 2). Following ethyl vinyl ketone, methyl vinyl ketone was reacted with **1a** using **4g** as the catalyst. The product (**3b**) was isolated in 66% yield and 80% *ee*. Though the *ee* was not as high as that for ethyl vinyl ketone, it was a fairly good one for DA reactions involving methyl vinyl ketone. In both cases, only the *endo* DA products were observed. This unique *endo* selectivity for 1,3-dienylcarbamate were previously reported by Overman[13] in a thermal DA reaction and by Terada and Momiyama[6d] in a catalyzed asymmetric DA reaction. Encouraged by the unique *endo* selectivity and the excellent *ee* obtained for ethyl vinyl ketone, we further investigated the DA reactions of aryl vinyl ketones, which could be challenging dienophiles with respect to enantioselectivity, due to their high reactivity and significant uncatalyzed background reaction leading to racemic products. To our delight, the reaction of **1a** with phenyl vinyl ketone gave the product (**3c**) in 70% yield and 94% *ee* (**Table 2**). Influence of a methyl group *ortho*-, *meta*- or *para*- to the propenoyl group on the phenyl ring clearly indicated that the *ortho*-substituent was deleterious to the reactivity of aryl vinyl ketone under the reaction conditions. **3d** was isolated in a yield of less than 5%. With a *meta*-methyl group, the product (**3e**) was formed with lower yield (43%) and good *ee* (91%). With a *para*-methyl group, the product (**3f**) was obtained in higher yield (80%) and *ee* (97%). Then, series of *para*-substituted phenyl vinyl ketones were reacted with **1a**. It was obvious that an electron-donating group gave the DA product (**3g**) in higher yield while an electron-withdrawing group gave the DA product (**3h** and **3i**) in lower yield. In all cases, the reaction proceeded in a highly enantioselective manner. 2-Naphthyl vinyl ketone was also tested. The DA product (**3j**) was obtained in 85% *ee*, which was lower than that for phenyl vinyl ketones (**3c-3i**). When vinyl ketones bearing a heteroaromatic ring such as 2-furyl or 2-thiophenyl group, which is more electron rich than phenyl group, the product (**3k**, **3l**) regained extra high *ee*. In the case of 2-thiophenyl vinyl ketone, slow addition of 1,3-dienylcarbamate was not necessary. The product (**3l**) was obtained in 97% yield in a one-pot feeding way. This nice yield was the highest one obtained for the tested vinyl ketones. Single crystals of product **3l** were successfully obtained from a solution in CH_2Cl_2 and hexanes. One single crystal was used for X-ray diffraction experiment. The absolute configuration of **3l** was determined as (1*S*, 4*S*, 6*R*) (**Figure 1**).[17] This result accords with an *endo* selective cycloaddition, which is prevailing in most DA reactions.

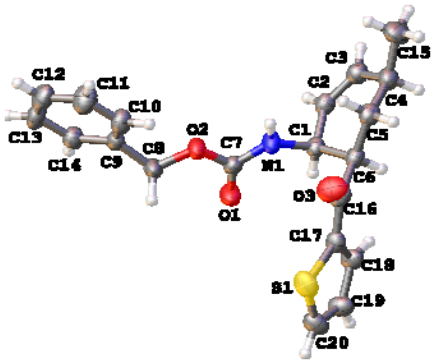
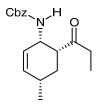
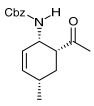
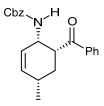
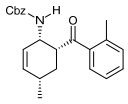
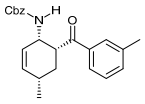
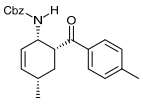
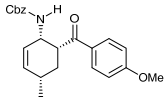
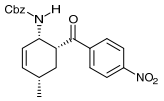
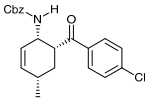
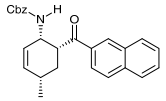
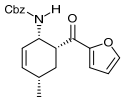
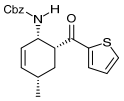
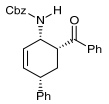
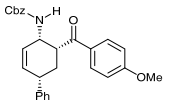
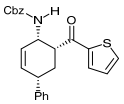
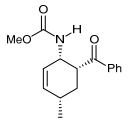
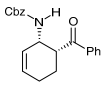
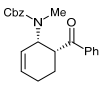


Figure 1 Crystal structure of enantiomerically pure **3l**.

Benzyl 4-phenyl-1,3-butadienylcarbamate (**1b**) was also reacted with three representative vinyl ketones. It was fairly stable in the reaction system and one equivalent of the carbamate was used for the DA reaction. Good to excellent yields as well as excellent *ee* were obtained for the products (**3m-3o**). Methyl carbamate **1c** and benzyl carbamate **1d** were reacted respectively with phenyl vinyl ketone. While **1c** gave the DA product (**3p**) in similar yield and *ee* as the corresponding benzyl carbamate, **1d** gave the product (**3q**) in much lower *ee* and yield. The decreased *ee* was definitely a result of the background uncatalyzed reaction of the highly reactive carbamate. Despite the high reactivity of **1d**, when the hydrogen of its NH group was replaced with a methyl group, reactivity of the corresponding carbamate completely disappeared under the reaction conditions. The expected product **3r** was not observed in the reaction mixture. This fact clearly indicates the presence of NH group in the carbamate molecule was essential for DA reaction to proceed.

Table 2 Asymmetric Diels-Alder reactions of 1,3-dienylcarbamates **1a-1d** with vinyl ketones.[a-e]

 **3a**, 72%, 97% ee	 **3b**, 66%, 80% ee	 **3c**, 70%, 94% ee
 **3d**, <5%, n.d.	 **3e**, 43 (75)%,[f] 91% ee	 **3f**, 80%, 97% ee
 **3g**, 80%, 99% ee	 **3h**, 37 (67)%,[f] 99% ee	 **3i**, 60 (71)%,[f] 96% ee
 **3j**, 69%, 85% ee	 **3k**, 60%, >99% ee	 **3l**, 97%,[g] 99% ee
 **3m**, 66%,[h] 97% ee	 **3n**, 77%,[h] >99% ee	 **3o**, 94%,[h] >99% ee
 **3p**, 66%, 94% ee	 **3q**, 40%, 76% ee	 **3r**, 0%, n.d.

a. 1 mmol of vinyl ketone and 2 mmol of carbamate were used for each reaction. b. Carbamate in $CHCl_3$ was added via syringe pump over 5 h and the reaction quenched after 24 h. c. Only *endo* product was isolated in each case. d. Yields were isolated ones for the *endo* products. e. *ee* was determinded by HPLC using OD-H, AD-H or OJ-H column. f. Vinyl keone was not completely converted. Number in parenthesis represents yield based on converted vinyl ketone. g. Carbamate was added in one pot. h. 1 mmol of vinyl ketone and 1 mmol of carbamate were reacted in one pot.

In the light of the above experimental results and two reported crystal structures of BINOL derived phosphoramides,[7a,18] we propose the following transition state structure for asymmetric DA reaction of dienylcarbamate **1a** and 2-thiophenyl vinyl ketone catalyzed by (*R*)-**4g** (**Figure 2**). *Ab initio* density functional theory (DFT) calculations at B3LYP/6-31G* level clearly indicate two possible hydrogen bonds (shown as dot lines) between the catalyst and each of the two DA reaction partners.[15] The vinyl ketone took an "s-*cis*" conformation and the dienylcarbamate approached the vinyl group from the *si*- face of C_α, delivering the cycloadduct **3l** with the observed (1*S*, 4*S*, 6*R*) configuration. According to the proposed reaction model, an electron rich aryl group (*p*-methoxyphenyl or thiophenyl) facilitated the hydrogen bonding between C=O (vinyl ketone) and NH (phosphoramide), thus the cycloadduct was obtained in excellent *ee* and yield. On the other hand, when hydrogen bonding between NH (carbamate) and P=O (phosphoramide) was missed, no DA reaction took place, which would account for the fruitlessness of product **3r**.

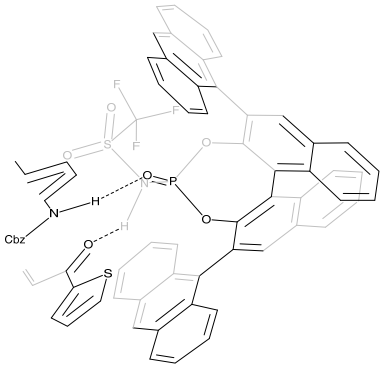


Figure 2 Proposed transition state structure of the DA reaction.

Conclusions

We disclosed a class of highly *endo* and enantioselective DA reactions involving aryl vinyl ketones and ethyl vinyl ketone. 1,3-Pentadienylcarbamate (**1a**) or 4-phenyl-1,3-butadienylcarbamate (**1b**) was reasonably selected as the diene reactant. For the first time, aryl vinyl ketones were used in catalytic DA reactions exhibiting extra high enantioselectivities. Enantiomerically pure cyclohexenes bearing *cis* amino and aroyl groups were obtained. The absolute configuration of one DA product was unambiguously confirmed by XRD analysis and rationalized by *ab initio* quantum chemistry calculations of possible "catalyst-reactants" complex. In addition, this catalyzed reaction adds to the richness of chiral phosphoramide catalysis and further expands the applications of chiral Brønsted acid catalyst in organic syntheses. Further derivatization and utilization of the DA products will be reported in due course.

Notes and references

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† Electronic Supplementary Information (ESI) available: experimental procedures, characterization data of new compounds as well as calculated minimum structure of the complex of catalyst **4g** with 1,3-dienylcarbamate **1a** and 2-thiophenyl vinyl ketone. See DOI: 10.1039/b000000x/

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14 1 mmol of EVK and 2 mmol of carbamate were reacted in one pot during a period of 5 h.

15 See Supplementary Information for details.

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17 CCDC 100789 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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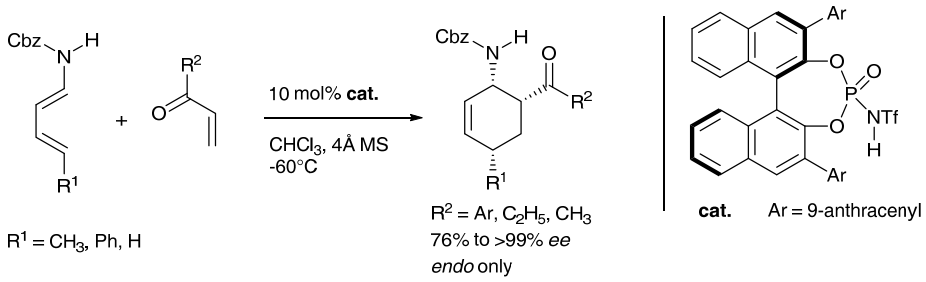
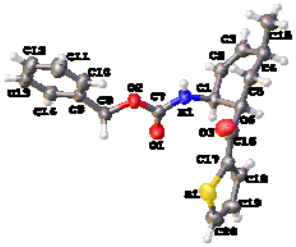
Graphic abstract



R^1 = CH_3, Ph, H

R^2 = Ar, C_2H_5, CH_3
76% to >99% *ee*
endo only

cat. Ar = 9-anthracenyl



(1*S*, 4*S*, 6*R*) R^1 = CH_3, R^2 = 2-thiophenyl