Diels–Alder Reactions

Deutsche Ausgabe: DOI: 10.1002/ange.201410957
Internationale Ausgabe: DOI: 10.1002/anie.201410957

Catalytic Asymmetric Diels–Alder Reaction of Quinone Imine Ketals: A Site-Divergent Approach**

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Abstract: *The catalytic asymmetric Diels–Alder reaction of quinone imine ketals with diene carbamates catalyzed by axially chiral dicarboxylic acids is reported herein. A variety of primary and secondary alkyl-substituted quinone derivatives which have not been applied in previous asymmetric quinone Diels–Alder reactions could be employed using this method. More importantly, we succeeded in developing a strategy to divert the reaction site in unsymmetrical 3-alkyl quinone imine ketals from the inherently favored unsubstituted C=C bond to the disfavored alkyl-substituted C=C bond.*

For decades, the quinone-based Diels–Alder reaction has been widely used in the synthesis of complex molecules, as it expediently generates functionalized *cis*-decalin structures from readily available materials.[1] Asymmetric catalysis has been recognized as an ideal way to promote this transformation enantioselectively. Chiral Lewis acid catalysis has played a central role in this regard,[2] while a couple of organocatalytic methods have also emerged in the last few years.[3] However, the uniqueness of quinones, having two carbonyl oxygen atoms as the coordination site of a catalyst and two C=C bonds as the reaction site, poses a critical challenge. Namely, the complex selectivity issue (*endo*/*exo*, site, enantio-, and regioselectivities) must be solved in face of a variety of possible transition states. To simplify the issue, this research field has been developed by using carefully selected quinones bearing substituents to mask or direct the coordination and reaction sites sterically and/or electronically. As a result, simple methyl-1,4-benzoquinone and other primary and secondary alkyl-substituted quinones have not been successfully utilized in this reaction (Figure 1a).[4] The only reported solution to this issue has employed 3-methyl quinone monoketal which has one carbonyl group and decreases the number of possible catalyst–substrate complexes (Figure 1b).[5] The reaction occurs at the inherently more-reactive unsubstituted C=C bond.

Cognizant of the above issue, we became interested in the development of catalytic asymmetric Diels–Alder reactions using quinone imine ketals as quinone surrogates.[6] It was anticipated that the presence of the singular lone pair for the coordination of the catalyst is advantageous compared with quinones. Although the use of quinone imine ketals as electrophiles in chiral Brønsted acid catalysis has been recently developed by us and others,[7] these studies utilize quinone imine ketals as aryl group equivalents and there has been no report wherein a stereogenic center is set in a quinone imine ketal. This study led us to establish a highly enantioselective Diels–Alder reaction between a variety of 3-alkyl quinone imine ketals and diene carbamates catalyzed by axially chiral dicarboxylic acids (*R*)-**1** (Figure 1c).[8] Moreover, we disclosed that the reaction site can be reversed to the more-hindered C=C bond (Figure 1c, left). This site-divergent strategy enabled the synthesis of cycloadducts having an all-carbon quaternary stereocenter while leaving the less-hindered C=C bond for later transformation.[9,10] This counter-intuitive selectivity will be explained by considering the *E*/*Z* isomerization of the imino functionality which acts as a fluxional directing group.

In the initial study, several conventional dienes were examined to understand the reactivity of simple, unfunctionalized quinone imine ketals **2** and **5** for Diels–Alder reaction by using axially chiral dicarboxylic acid catalyst (*R*)-**1**.[11] Diene carbamate **3a**[12] was found to be a good reaction partner from which the cycloadduct could be obtained in good yield [Eq. (1) and (2)]. We decided to focus our efforts on the

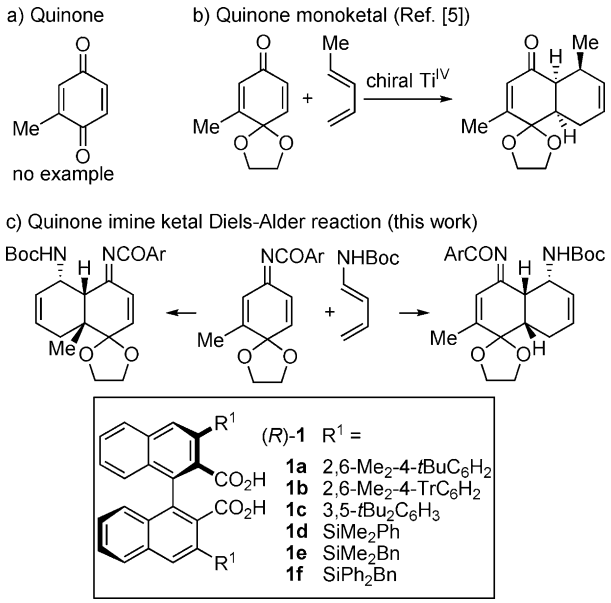

Figure 1. Use of methyl quinone and its derivatives in catalytic asymmetric Diels–Alder reactions. Boc = *tert*-butoxycarbonyl; Tr = trityl; Bn = benzyl.

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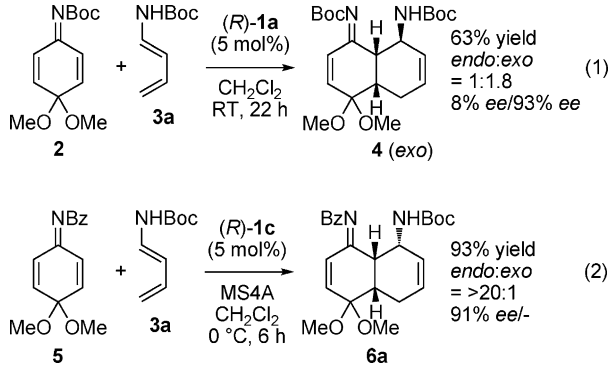
[**] This work was partially supported by a Grant-in-Aid for Scientific Research from the MEXT (Japan). H.N. thanks a Grant-in-Aid for the Research Fellowship of JSPS for Young Scientists.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201410957.

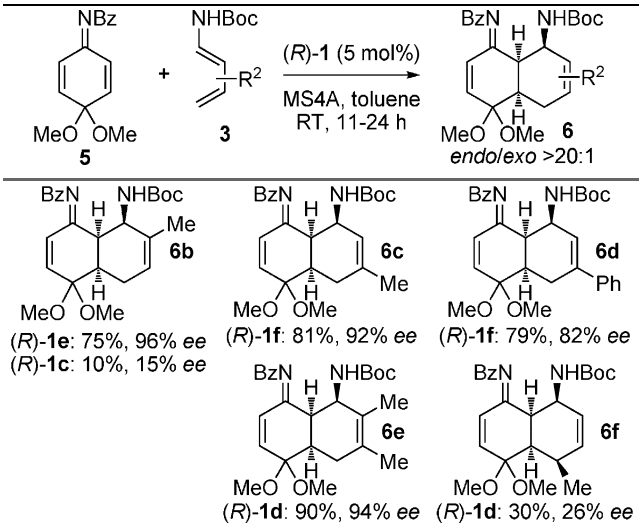
use of this diene in the reaction given the importance of nitrogen-functionalized *cis*-decalin systems as represented by antibiotic tetracycline and its analogues,[13] as well as the lack of precedent of using diene carbamate in catalytic asymmetric quinone-based Diels–Alder reactions.[14,15] Optimization of the reaction conditions resulted in the identification of two catalyst systems which gave either *exo* or *endo* cycloadducts with high enantioselectivities. (*R*)-**1a** catalyzed the reaction of *N*-Boc quinone imine ketal **2** with diene carbamate **3a** to give the *exo* cycloadduct **4** as the major product [Eq. (1)], whereas the reaction of *N*-Bz quinone imine ketal **5** (Bz = benzoyl) catalyzed by (*R*)-**1c** provided the *endo* cycloadduct **6a** with high stereoselectivities [Eq. (2)].



With these results in hand, we first looked into the applicability of other substituted diene carbamates[16] using *N*-Bz quinone imine ketal **5** (Table 1). For this purpose, it was necessary to re-evaluate the catalysts employed. For example, when (*R*)-**1c** was used as the catalyst in the reaction using 3-methyl diene carbamate, the product was obtained with only 15% *ee*. Catalysts 3,3′-disilyl-substituted (*R*)-**1d–f** were found to exhibit a general activity,[17] although the catalyst needed to be fine-tuned to attain high enantioselectivity for each diene carbamate. The reactions with dienes having a methyl group at the 2- and/or 3-positions gave *endo* cycloadducts **6b**, **6c**, and **6e**, respectively, with high enantioselectivities. A phenyl group could also be attached to the diene to afford **6d** in 79% yield with 82% *ee*. Use of *trans*-4-methyl diene resulted in the formation of **6f** in low yield and selectivity presumably as a result of the steric repulsion between the dimethyl ketal moiety and the 4-methyl group.

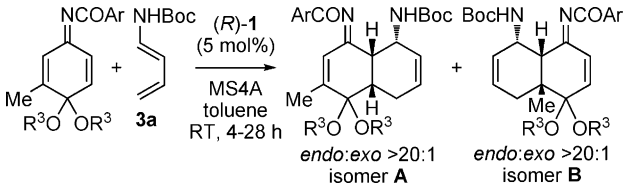
We next turned our focus to *N*-Bz 3-methyl quinone imine ketal **7** (Table 2), with the expectation that the less-hindered C=C bond would react exclusively. While the reaction with diene **3a** catalyzed by (*R*)-**1c** predominantly gave the expected site isomer **A**, albeit in low yield and low *ee*, we also identified a small portion of isomer **B** which formed from the reaction occurring at the methyl-substituted C=C bond (Table 2, entry 1). Both **A** and **B** were identified as *endo* cycloadducts. Surprisingly, the proportion of this sterically disfavored isomer **B** with an all-carbon quaternary center increased further by use of the disilyl catalyst (*R*)-**1d** (entry 2), even in consideration of the fact that some of isomer **A** further aromatized by the elimination of methanol.[6] This observation motivated us to establish procedures which provide each site isomer selectively with high enantioselectivity. The substrate was first replaced with more robust and less congested ethylene glycol ketal **8a**.[5] A substantial increase of the yield and enantioselectivity was achieved albeit with poor site selectivities (entries 3 and 4). With substrate **8a** in hand, we then carried out a catalyst screening. It was found that isomer **A** could be obtained selectively with good enantioselectivity by use of (*R*)-**1a** or **1b** (entries 5 and 6). Further modification of the reaction conditions led to the formation of the cycloadduct in good yield with a site selectivity of 85:15 (**A**:**B**) and 90% *ee* (entry 7). While the use

Table 1: Scope of diene carbamate substrates.[a]



[a] Reaction conditions: **5** (0.10 mmol), **3** (0.25 mmol), and (*R*)-**1** (0.005 mmol). The yield of the isolated product is given. The *ee* values were determined by HPLC analysis on a chiral stationary phase. MS4A = molecular sieves (4 Å).

Table 2: Optimization of the reaction conditions.[a]



Entry	**1**	R^3	Ar	**A**:**B**	% yield	% *ee*
1	**1c**	Me	Ph (**7**)	80:20	10	11/–
2	**1d**	Me	Ph (**7**)	52:48[b]	35	3/10
3	**1c**	$(CH_2)_2$	Ph (**8a**)	62:38	46	57/−77
4	**1d**	$(CH_2)_2$	Ph (**8a**)	48:52	34	53/27
5	**1a**	$(CH_2)_2$	Ph (**8a**)	80:20	52	80/−72
6	**1b**	$(CH_2)_2$	Ph (**8a**)	84:16	60	87/−82
7[c]	**1b**	$(CH_2)_2$	Ph (**8a**)	85:15	73	90/−83
8[c]	**1d**	$(CH_2)_2$	3,5-$Ph_2C_6H_3$ (**9a**)	33:67	62	49/88
9[c,d]	**1d**	$(CH_2)_2$	3,5-$Ph_2C_6H_3$ (**9a**)	18:82	70	44/92
10[c,d]	**1b**	$(CH_2)_2$	3,5-$Ph_2C_6H_3$ (**9a**)	84:16	54	68/−50

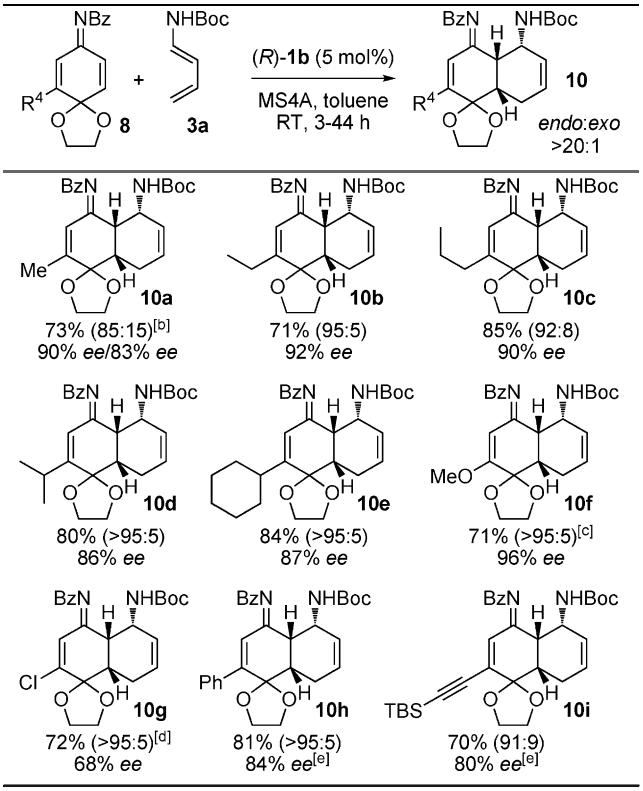
[a] Reaction conditions: Quinone imine ketal (0.10 mmol), **3a** (0.15 mmol), and (*R*)-**1** (0.005 mmol). The combined yield of **A** and **B** is given. The *ee* values were determined by HPLC analysis on a chiral stationary phase. [b] The ratio of (**A** and aromatized product of **A**):**B**. [c] Performed with **3a** (0.25 mmol). [d] Performed at 0°C.

of bulkier catalysts gave more of isomer **B** in general,[18] we were unable to further improve the site selectivity toward **B** by the catalyst screening. We therefore turned our attention to a substrate with a different *N*-aroyl group. We employed 3,5-diphenylbenzoyl quinone imine ketal **9a** in combination with (*R*)-**1d**, with which isomer **B** was obtained in a ratio of 33:67 (**A**:**B**) with high enantioselectivity (entry 8). The site selectivity and the enantioselectivity were further optimized at 0 °C (entry 9). At lower temperature, the reaction slowed down considerably while the site- and enantioselectivities remained unchanged (data not shown). It should be noted that the use of the isomer-**A**-selective catalyst (*R*)-**1b** for this quinone imine ketal reagent indeed led to the formation of isomer **A** (entry 10), underlying the critical role of the catalyst for controlling the site selectivity.

With the optimized conditions in hand, we examined the scope of the quinone imine ketal substrate for the reactions taking place at the unsubstituted C=C bond (Table 3). Primary and secondary alkyl chains were both tolerated as the substituent at the 3-position to give cycloadducts **10b–e** with high enantioselectivities. Attachment of an electron-donating methoxy group gave **10f** in good yield and with a good enantioselectivity. As for the use of 3-chloro quinone imine ketal to give **10g**, the reaction had to be carried out at a lower temperature with a higher catalyst loading to outcompete the uncatalyzed reaction. Quinone imine ketals bearing an aryl or alkynyl group were converted into the corresponding cycloadducts **10h** and **10i** with good enantioselectivities by use of (*R*)-**1a** as the optimal catalyst. The *endo* selectivity was retained irrespective of the electronic and steric differences of the substituent. Quinone imine ketals having a 2-substituent were far less reactive and required higher temperature to give the products with low enantioselectivities (data not shown).

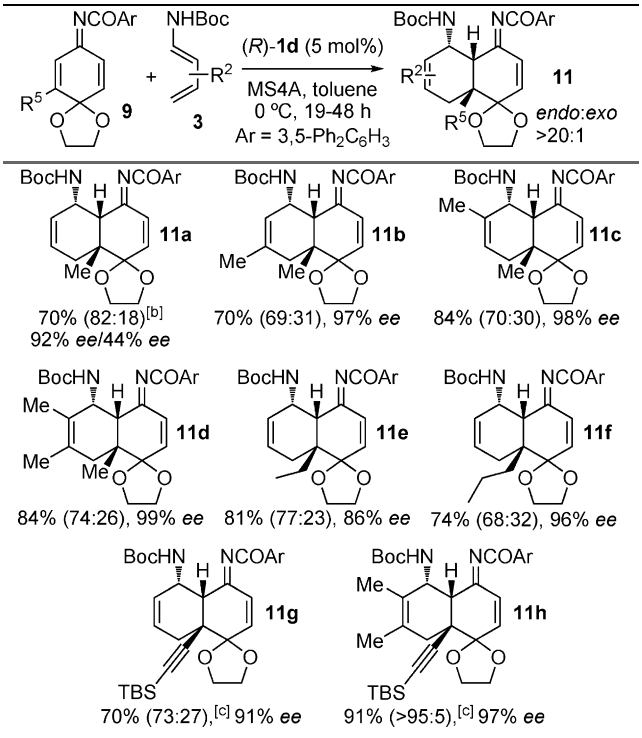
We then examined the substrate scope of the site-divergent Diels–Alder reaction, which gives cycloadducts **11** with an all-carbon quaternary center (Table 4). The reactions between several dienes and 3-methyl quinone imine ketal **9a** were investigated, which afforded compounds **11b–d** in uniformly high enantioselectivities. As for other quinone imine ketals, primary-alkyl-substituted derivatives generally gave cycloadducts **11e** and **11f** with high stereoselectivities. When bulkier alkyl-, aryl-, or heteroatom-substituted substrates were employed, the catalyst system could not overcome the innate reactivity at the less-hindered C=C bond (data not shown). One noteworthy substrate is 3-alkynyl quinone imine ketal from which cycloadducts **11g** and **11h** were obtained with fairly good site selectivities and enantioselectivities.

Table 3: Scope of quinone imine ketal substrates.[a]



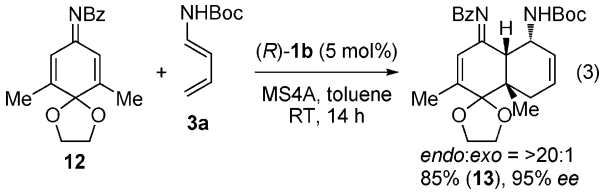
[a] Reaction conditions: **8** (0.10 mmol), **3a** (0.25 mmol), and (*R*)-**1b** (0.005 mmol). Combined yield of the site isomers is given. The *ee* values were determined by HPLC analysis on a chiral stationary phase. [b] The ratio of **10** and its site isomer was determined by ^{1}H NMR spectroscopic analysis of the crude material. [c] *endo*/*exo* = 9.4:1. [d] Performed with **3a** (0.50 mmol) and (*R*)-**1b** (10 mol%) at −20 °C. [e] Reaction carried out using (*R*)-**1a**. TBS = *tert*-butyldimethylsilyl.

Table 4: Site-divergent Diels–Alder reaction.[a]



[a] Reaction conditions: **9** (0.10 mmol), **3** (0.25 mmol), and (*R*)-**1d** (0.005 mmol). The combined yield of the site isomers is given. The *ee* values were determined by HPLC analysis on a chiral stationary phase. [b] The ratio of **11** and its site isomer determined by ^{1}H NMR spectroscopic analysis of the crude material. [c] Performed with (*R*)-**1d** (15 mol%).

As expected from the above experiments, 3,5-dimethyl quinone imine ketal also reacted smoothly with diene **3a** to give *endo* cycloadduct **13** in good yield and enantioselectivity [Eq. (3)].



This site divergence can be explained by taking the *E*/*Z* isomerization of quinone imine ketals into consideration. Rapid interconversion of the *E* and *Z* isomers at the reaction temperature was confirmed by NMR spectroscopy experiments (see the Supporting Information). The estimated energy barrier for the isomerization was around 10 kcal mol^{-1} in the absence of the catalyst. Although additional experimental and theoretical support is required to be conclusive, we hypothesized that each *E* and *Z* isomers was converted into different site isomers **A** and **B** via transition states **TS1** and **TS2**, respectively (Figure 2).[19] The use of the bulky 3,3′-disilyl catalyst (*R*)-**1d** in combination with 3,5-diphenylbenzoyl quinone imine ketal would destabilize **TS1** sterically, thereby diverting the pathway via **TS2** to give compound **B**. Accordingly, the geometry of the imine is considered to be acting as a fluxional directing group to promote the reaction at the more congested reaction site.

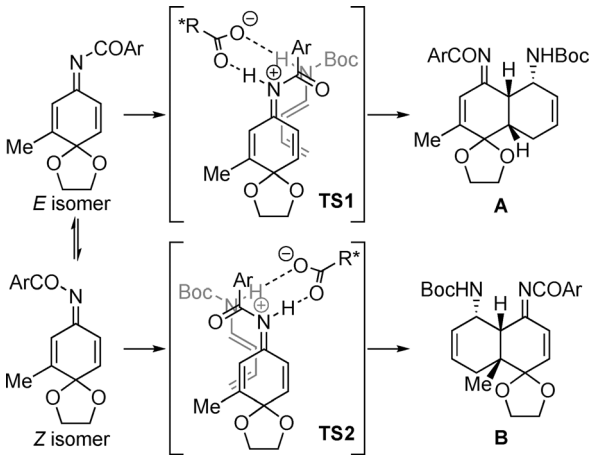


Figure 2. The origin of the site selectivity for the products obtained from the Diels–Alder reaction of quinone imine ketals.

As the capability of asymmetric catalysis expands, the control of enantioselectivity is no longer the only avenue to showcase catalyst performance. Additionally, site selectivity is also considered as a parameter to be optimized.[9,10] However, using catalyst control to overturn the inherent site selectivity of a substrate is still a challenging task. Our study on the quinone imine ketal Diels–Alder reaction serves as an example of using fluxional geometric isomers to govern the site selectivity of chemical reactions.

Keywords: asymmetric catalysis · Brønsted acids · carboxylic acids · Diels–Alder reactions · quinones

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 4617–4621
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[18] Use of benzoic acid as a simple carboxylic acid led to site selectivity of 9:1 in favor of the isomer **A**.

[19] We assumed that the carboxylic acid moiety of the catalyst simultaneously undergoes hydrogen bonding with both substrates in the transition state, according to previous studies (Refs. [7] and [14]).

Received: November 11, 2014
Revised: January 20, 2015
Published online: February 16, 2015

