

This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

To be cited as: Chem. Asian J. 10.1002/asia.201900995

Link to VoR: http://dx.doi.org/10.1002/asia.201900995

A Journal of

ACES Asian Chemical Editorial Society A sister journal of Angewandte Chemie and Chemistry – A European Journal



WILEY-VCH

Water, an Essential Element for a Zn(II)-Catalyzed Asymmetric Quinone Diels-Alder Reaction: Multi-selective Construction of Highly Functionalized *cis*-Decalins

Kyosuke Morimoto[†], Thien Phuc Le[†], Sudipta Kumar Manna, I. N. Chaithanya Kiran, Shinji Tanaka, and Masato Kitamura*

Abstract: A Zn(II) complex of a C2-chiral bisamidine-type sp2N bidentate ligand (L_R) possessing two dioxolane rings at both ends catalyzes a highly efficient quinone asymmetric Diels-Alder reaction (qADA) between o-alkoxy-p-benzoquinones and 1-alkoxy-1,3butadienes to constructs highly functionalized chiral cis-decalins, proceeding in up to a >99:1 enantiomer ratio with a high generality in the presence of H_2O ($H_2O:Zn(II) = 4-6:1$). In the absence of water, little reaction occurs. The loading amount of the chiral ligand can be minimized to 0.02 mol% with a higher Zn/L_R ratio. This first success is ascribed to a supramolecular 3-D arrangement of substrates, in which two protons of an "H₂O-Zn(II)" reactive species make a linear hydrogen bond network with a dioxolane oxygen atom and onepoint-binding diene; the Zn(II) atom captures the electron-accepting two-points-binding quinone fixed on the other dioxolane oxygen atom via an n- π^* attractive interaction. The mechanisms has been supported by ¹H-NMR study, kinetics, X-ray crystallographic analyses of the related ZnL_R complexes, and ligand and substrate structure-reactivity-selectivity relationship.

Intermolecular Diels-Alder (DA) reactions of unsymmetrical pbenzoquinones and 1,3-dienes have been recognized as one of the most powerful methods for synthesizing many complex natural products^[1] ever since Woodward reported the first historic syntheses of cortisone and cholesterol using 2-methoxy-5-methyl-1,4benzoquinone (1a ($\mathbf{p} = \mathbf{r} = H$; $\mathbf{q} = CH_3$ in 1, Figure 1)) in 1952.^[2] As shown in Figure 1, combination of achiral dienophile 1 with CH₃O, **p**, **q**, and **r** substituents at $C_1(2)$, $C_1(3)$, $C_1(5)$, and $C_1(6)$ and achiral diene 2 with w, x, y, and z substituents at $C_2(4)$, $C_2(3)$, $C_2(2)$, and $C_2(1)$ lead to 16 possible stereoisomers of DA adducts, 3, 4, 5, and 6 by varying site-, diastereo- (endo/exo-), regio-, and enantio-selectivities. Although the multiple requirements for these selectivities have been mitigated through an understanding of the endo rule,^[3] calculated transition-state structures,^[4] and by using an appropriate Lewis acid catalyst, the catalytic asymmetric Diels-Alder reaction of p-benzoquinone (qADA) has still remained at an early stage in comparison to the well-studied DA of simple acrylate derivatives. The catalysts for qADA are limited to binolate-Ti(IV),^[5] tridentate pyridyl-bisoxazoline-Sm(III) and -Gd(III),^[6] cationic oxazaborolidines,^[7,8] and tridentate Schiff base-Cr(III).^[9] These chiral Lewis acids yield a high stereoselectivity in the dienophile/diene combination specific to each qADA but require a

K. Morimoto, T. P. Le, Dr. S. K. Mannna, Dr. I. N. C. Kiran, Dr. S. Tanaka, and Dr. M. Kitamura* Graduate School of Pharmaceutical Sciences Nagoya University Nagoya, Japan E-mail: kitamura@ps.nagoya-u.ac.jp These authors contributed equally to this work.

[[†]]

Supporting information for this article is given via a link at the end of the document.

high catalyst loading (4-20 mol%) at low temperature under strictly anhydrous conditions using molecular sieves (MS) or a glove box. In particular, qADA of 1a-type 2-alkoxybenzoquinone and 1-alkoxy-1,3-butadiene **2** ($\mathbf{z} = OR$) is the most attractive to construct highly functionalized chiral cis-decalins toward the natural product synthesis. $^{[10]}\,$ The best result was reported by Smith in $2017^{[11]}\,$ using chiral dialkoxide-Ti(IV) complex^[12,13] (20 mol%; MS 4A; -78 °C to -40 °C) to construct a key chiral intermediate with a 93:7 enantiomer ratio (er) for the total synthesis of (-)-nahuoic acid. A highly reactive, multi-selective, and productive catalyst functioning under ambient conditions has not yet been realized in qADA. In this paper, we report a breakthrough in this challenging qADA field through the development of a Zn(II) complex of our original chiral bisamidine-type sp²N bidentate ligand, (R,R)-Naph-diPIM-dioxo*i*Pr (L_R) (Figure 2a), that operates in the presence of "H₂O" at ambient temperature.



Figure 1. Asymmetric Diels–Alder reaction of quinone (qADA) requiring multiple selectivities. $C_1(6)_{S^i}$ indicates the S^i face of C(6) of dienophile **1**. Absolute configurations of the three carbon stereogenic centers at C(4a), C(8a), and **z**-substituted C(8) or C(5) of qADA adducts are shown.

The bisamidine ligand $\mathbf{L}_{\mathbf{R}}$ looks similar to a privileged sp²N ligand, R-BOX (R = t-Bu or Ph)^[14] (Figure 2b), but totally different. $\mathbf{L}_{\mathbf{R}}$ possesses the following unique electronic and steric properties: i) high planarity and rigidity with two sp²N atoms fixed to the same side; ii) ca. 90° bite angle; iii) an extended π -conjugated system showing pyridine-level π -accepting ability; iv) high σ -donating ability derived from the two amidine units; v) a wider C_2 chiral reaction site constructed by a 5,5,6,6,5,5 ring system that fuses two dioxolane rings up and down at the both ends; vi) sterically congested di-*i*-Pr-substituted dioxolane rings; and vii) existence of

the dioxolane oxygen lone pair n orbital at the reaction site. A series of properties i)–vi) of L_R enhance its metal-capturing ability and stabilize the corresponding metal complexes with various geometrical structures; L_R has been successfully used to catalyze efficient asymmetric reactions.^[15–18] We assume that the electron accepting and two-points bindindg benzoquinone dienophile in the qADA would be chirally fixed by the characteristics v)–vii) in the 2nd or 4th quadrant through coordination to an appropriate MX_n–L_R

reactions of acrylate,^[20-23] but not effective for qADA.^[24]

(Figure 2a), facilitating stereocontrol.^[19] Various MX_n-R-BOX complexes have been well studied in highly enantioselective DA



Figure 2. sp²N-Based bidentate ligands. Characteristics of Naph-diPIM-dioxo*i*Pr (L_{R} , **a**) and the related representative chiral bidentate ligand R-BOX (**b**) and the corresponding M– L_{R} and M–*t*-Bu-BOX complexes. Circle distinguished by white and black quadrants with 1–4 numbers represents the coordination regions made by horizontal and vertical lines crossing the central M atom. Black regions are sterically crowded.

The standard quinone dienophile and diene were set to $C_1(2)OCH_3/C_1(5)CH_3-1,4$ -benzoquinone (1a) and one-pointbinding $C_2(1)OCH_3$ -1,3-butadiene (2a), respectively (Table 1, reaction scheme), and MXn was screened under the standard conditions of $[MX_n] = [L_R] = 5 \text{ mM} (1 \text{ mol}\%), [1a] = 0.50 \text{ M}, [2a]$ = 1.0 M, 1,4-dioxane (589 ppm H₂O, Grubbs solvent purification system), 27 °C, and 4 h. Mg(OTf)₂, Fe(OTf)₃, Al(OTf)₃, Cu(OTf)₂, AgOTf, and Sn(OTf)₂ showed little reactivity, ^[25] whereas Zn(OTf)₂ afforded (4aR,8aR,8S)-3a in 91% yield with a >99:1 er without generation of any other stereoisomers, 4a, 5a, and 6a (Table 1, entry 1). Little reaction occurred under the standard conditions using Zn(II) complexes of achiral Naph-diPIM, which lacks the dioxolane rings of Naph-diPIM-dioxo-*i*Pr (L_R) as well as those of (S,S)-R-BOX (R = t-Bu or Ph) or Phen (entries 2–5). The water content exerted a significant effect on the reactivity. Contrary to previous reports,^{[5-} ^{7,9,11]} little reaction occurred in 1,4-dioxane dried over MS 4A or 5A (entries 6 and 7). By increasing the concentration of H_2O in 1,4dioxane, the reactivity was gradually enhanced and maximized at 360–500 ppm of H_2O (4–6 mol amounts for Zn(II)) (entries 8– 11).^[25] A further increase in the water content lowered the reactivity without deteriorating the selectivity. A wide range of solvents was usable, although the enantioselectivity was slightly reduced and the

Table 1. Catalytic qADA of dienophile 1a and diene 2a using a 1:1 mixture of $Zn(OTf)_2$ and sp^2N -based bidentate ligands.

CH ₃ O ³ ⁴ 0 +	⁴ ² ¹ ² ¹ ² ¹ ¹ ¹ ¹ ¹ ¹ ¹ ¹ ¹ ¹	ioxoane	CH ₃ O ² H = ⁸ / ₈ O OCH ₃	+ CH ₃ O ² ¹ H ^{4a} H ⁵ ₆ H ⁵ ₆ H ⁸ ⁷	+ •	••	
1a	2a		(4a <i>R</i> ,8a <i>R</i> ,8 <i>S</i>) -3a	(4a <i>S</i> ,8a <i>S</i> ,5 <i>R</i>)- 4a			

entry	ligand	H₂O (ppm)	% yield of 3a	3a/4a ^[a]	er of 3a ^[b]
1	L _R	589	91	>99:1	>99:1
2	Naph- diPIM ^[c]	589	<5	_	_
3	(S,S)- <i>t</i> - Bu-BOX	589	<5 (<5) ^[d]	—	() ^[d]
	Bubon			(—) ^[d]	()
4	(S,S)- Ph-BOX	589	<5 (85) ^[d]	— (90:10) ^[d]	— (77:23) ^[d]
5	Phen ^[e]	589	0	_	_
6	L _R	9 ^[f]	<5	_	_
7	L _R	17 ^[g]	<5	_	_
8	L _R	60	<5	_	_
9	L _R	360	>99	>99:1	>99:1
10	L _R	475	>99	>99:1	>99:1
11	L _R	880	65	>99:1	>99:1

Conditions: [1a] = 0.50 M; [2a] = 1.0 M, $[Zn(OTf)_2] = [L_R] = 5.0$ mM (1 mol%), 1,4-dioxane (Grubbs purification system; 589 ppm H₂O), 27 °C, 4 h. Content of H₂O was measured by Karl Fischer titration. [a] Determined by ¹H-NMR analysis. [b] Determined by HPLC analysis. [c] 1,2,11,12-Tetrahydronaphtho[1,2-b:7,8-b']dipyrroloimidazole.^[18] See below. [d] Value in parenthesis is the result obtained by using 5 mol% of $Zn(OTf)_2$ and chiral ligand at 27 °C for 24 h. [e] 1,10-Phenanthroline. See below. [f] 1,4-Dioxane (589 ppm H₂O) containing MS 4A (100 mg) for 1.0 mmol **1a** was used after 24-h stirring at 27 °C.



reaction time was increased with other solvents than 1,4-dioxane. The optimal H₂O amount, reaction time, and enantioselectivity for other solvents was as follows: THF (347 ppm, 48 h, 98:2 er); CPME (351 ppm, 24 h, 97:3 er); toluene (106 ppm, 24 h, 97:3 er); acetone (119 ppm, 4 h, 95:5 er), CH₃CN (800 ppm, 24 h, 98:2 er), CHCl₃ (351 ppm, 24 h, 96:4 er); and *t*-BuOH (370 ppm, 24 h, 97:3 er).^[25] In all cases, a decrease in the H₂O content to 4–11 ppm significantly lowered the reactivity. Little reaction occurred in DMA irrespective of H₂O content. *The presence of the two oxygen atoms at the reaction site with a spatially accessible environment and "H₂O" in the reaction system are essential for achieving high reactivity and selectivity.*

WILEY-VCH

The effect of the Zn/L_R ratio on the reactivity was also significant (Table 2). In the absence of Zn(OTf)₂ and L_R, no reaction occurred (entry 1). Zn(OTf)₂ itself was at least two orders less reactive than the catalyst prepared in a 1:1 ratio of Zn(OTf)₂ and L_R (entries 2 and 3). With a 1:2 ratio of Zn(OTf)₂ and L_R, the reactivity was nearly lost (entry 4). On the other hand, an increase in the Zn/L_R ratio from 1:1 enhanced the reactivity (entries 4–6 and 8–11): With Zn(OTf)₂:L_R = 10:1, the reaction completed in 1 h with little deterioration of the er (entry 8). Even in the presence of 0.02 mol% of L_R, the reaction was completed to give quantitatively (4aR,8aR,8S)-**3a** with a 98:2 er (entry 10). Further decrease in the catalyst loading to 0.01 mol% deteriorated the enantioselectivity to 94:6 (entry 11).

Figure 3 shows the molecular structures of $[Zn(H_2O)(\mathbf{L}_R)_2](OTf)_2$ (7) and $[Zn\mathbf{L}_R(Phen)_2](OTf)_2$ (8) in the crystals.^[25] In the complex 7, one H₂O coordinates to the central Zn(II) atom to make a trigonal bipyramidal geometry with sp²N(1), sp²N(2), sp²N(1') and sp²N(2') (N(1)–Zn–N(2) bite angle, 93°; N(2')–Zn–N(1'), 93°). The trigonal plane is made by the H₂O oxygen atom, sp²N(2) of \mathbf{L}_R , and sp²N(1') of another \mathbf{L}_R . The sp²N(1) and sp²N(2') occupy the apical positions. Two hydrogen atoms of H₂O–Zn(II), H_a and H_b, make a liner hydrogen bond

Table 2. Effect of $\text{Zn}/\text{L}_{\text{R}}$ ratio and catalyst loading on the reactivity and enantioselectivity.

entry	[Zn(OTf) ₂] (mM)	[L_R] (mM)	L_R (mol%)	Zn/ L _R	yield (%) ^[a]	er ^[b]
1	0	0	0	_	0	_
2	5	0	0	_	<5	_
3 ^[c]	5	5	1	1:1	>99	>99:1
4	5	10	2	1:2	6	94:6
5	10	5	1	2:1	>99 ^[d]	>99:1
6	25	5	1	5:1	>99 ^[e]	99:1
7 ^[f]	25	5	1	5:1	<5	_
8	50	5	1	10:1	>99 ^[g]	99:1
9	2.5	0.5	0.1	5:1	99 ^[h,i]	99:1
10 ^[]]	2.5	0.5	0.02	5:1	94 ^[i,k]	98:2
11 ⁰⁰	2.5	0.25	0.01	10:1	99 ^[i,k]	94:6

Conditions: [1a] = 0.50 M; [2a] = 1.0 M, 1,4-dioxane (360 ppm H₂O), 27 °C, 4 h unless otherwise specified. Dienophile 1a was not fully dissolved. In all cases only 3a was obtained. [a] Determined by ¹H-NMR analysis. [b] Determined by HPLC analysis. [c] Enough conditions for the $Zn(L_k)_2$ generation: 27 °C for 1 h and then 100 °C for 1 h. [d] 3 h. [e] 1 h. [f] 1,4-Dioxane (589 ppm H₂O) was dried over MS 4A (10 %w/w, 12 h, 27 °C) prior to use. [g] 1 h. [h] 48 h. [i] Isolated yield. [j] [1a] = 2500 mM, [2a] = 5000 mM. [k] 168 h.

network with the dioxolane O(1) (1.24 Å) in the 2nd quadrant and the other dioxolane O(1') (1.81 Å) in the 1st quadrant. Ligand L_R at the front side is located in the sterically disfavored 4th quadrant, indicating that there is an attractive donor-acceptor-type interaction between the dioxolane O(3) n orbital and naphthalene π^* orbital (O-sp²C = 3.09 Å).^[26] Complex **8** takes a Λ stereochemistry, in which the two Phen ligands occupy the spatially crowded 2nd and 4th quadrants to make an octahedral geometry with the L_R bite angle of 91° (N(1)–Zn–N(2)). Short distances of O(1)–sp²C = 3.12 Å, O(1)–sp²N(1') = 3.04 Å, O(3)–sp²C = 3.18 Å, and O(3)–sp²N(2') = 3.08 Å show that the π -extended two Phen ligands are induced by no(1) and no(3) orbitals into the sterically disfavored quadrants in the same way as the case of 7. These two molecular structures implicate the involvement of such a hydrogen bond and n/ π^* attractive interaction in the transition state of the present qADA.^[27]



Figure 3. Molecular structures of $[Zn(H_2O)(L_R)_2](OTf)_2$ (7) and Λ - $[Zn(L_R)(Phen)_2](OTf)_2$ (8) in the crystals. $\neg OTf$: omitted for clarity. In complex 7, a linear hydrogen bond network, O(1)--- H_a --O-- H_b ---O(1'), is constructed. In both complexes 7 and 8, another L_R or two Phen ligands are stabilized by n- π^* interactions in the sterically crowded quadrants.

Figure 4 illustrates the supposed mechanism for attaining high reactivity and multi-selectivity in the ZnL_R-catalyzed **1a/2a** qADA using 1,4-dioxane containing H₂O. Taking into consideration the structural characteristics of 7 and **8**, we propose the dicationic aqua complex $[Zn(H_2O)L_RS_n](OTf)_2$ (S: solvent, H₂O, **1a**, **2a**, etc.; n = 0, 1, or 2) (ZnL_R, \mathbf{A}) as the catalytically reactive species. **A** disproportionates to the less reactive $[Zn(L_R)_2S_n](OTf)_2$ ($Zn(L_R)_2$) and $Zn(OTf)_2$, but excess $Zn(OTf)_2$ retards this process to enhance the rate:^[25] A 1:1 mixture of $Zn(OTf)_2$ and L_R afforded a 91:9 mixture of ZnL_R and $Zn(L_R)_2$ after 3 h at 27 °C, whereas the ratio was increased to 99:1 with a 2:1 ratio and use of 5 mol amounts of

 $Zn(OTf)_2$ toward L_R completely suppressed the disproportionation. Little reaction occurred in a 5:1 $Zn(OTf)_2/L_R$ system using 1,4dioxane dried over MS 4A (Table 2, entry 7), supporting the importance of H₂O for generating the reactive species and excluding the mechanism that ZnL_R and $Zn(OTf)_2$ independently activate the dienophile and diene.



Figure 4. Supposed mechanism for catalysis and enantioface selection in the ZnL_{R} -catalyzed qADA of dienophile **1a** and diene **2a**. \Box OTf: omitted. S: solvent, H₂O, **1a**, **2a**, etc.; n = 0, 1, or 2. Coordination timing of **1a** and **2a** to **A** may be reversed.

First, A captures 1a and 2a as two-points- and one-point-binding substrates, respectively, to generate C via B. Then, a ratedetermining bond recombination occurs in C to give the qADA adduct by regenerating A, completing the catalytic cycle. Consistent with this view, the reaction followed 1st order kinetics for $[ZnL_R]_0$, $[1a]_{0}$, and $[2a]_{0}$.^[25] The enantioface of 1a is determined at the stage of generation of **B**_{65i}, in which the $C_1(5)_{Re}=C_1(6)_{Si}$ of **1a** faces the front side in the 4th quadrant. The region is sterically disfavored by the di-i-Pr-substituted dioxolane ring, but the lone pair n orbital induces the quinone dienophile 1a into the 4th quadrant in a similar manner observed with 7 and 8. The n- π^* interaction for the highly electron-acceptive p-benzoquinone 1a should be much stronger than that for L_R and Phen. The $C_1(5)=C_1(6)$ double bond possesses a lower LUMO coefficient and is more reactive than the electrondonative CH₃O-substituted $C_1(2)=C_1(3)$, which determines the site-selectivity. Furthermore, the two-points-binding of 1a to the Lewis acidic Zn(II) decreases the LUMO level and enhances the reactivity.[19]

One-point-binding **2a** interacts with **B**_{65i} via a hydrogen bond between the $C_2(1)OCH_3$ oxygen atom and H_R of $H_SH_RO-Zn(II)$, H_S of which is fixed by another hydrogen bond with the dioxolane oxygen atom in the 2^{nd} quadrant as observed in 7. In the resulting $C_{65i,1Re}$ with a linear hydrogen bond network, the $C_1(6)_{Si}$ of **1a** faces the $C_2(1)_{Re}$ of **2a**. The $C_{65i,1Re}$ intermediate is electronically matched for a ${}^{a-}C_1(6)={}^{s+}C_1(5)/{}^{s+}C_2(1)-{}^{s-}C_2(4)$ combination and geometrically well arranged for making secondary orbital interactions, determining the diastereoselectivity and leading to a smooth qADA to furnish the endo-adduct (4aR,8aR,8S)-**3a** as the sole product.^[28] The $C_2(1)OCH_3/H_R$ hydrogen bond changes the reaction mode from intermolecular to intramolecular to accelerate the rate-determining step but also controls the regioselectivity for the unsymmetrical diene.

Proton H_R of B_{6Re} , in which the $C_1(5)_{Si}=C_1(6)_{Re}$ of 1a is faced to the front side in the 4th quadrant, also captures the $C_2(1)OCH_3$ of 2ato give $C_{6Re,1Si}$ and $C_{2Si,1Re}$, from which enantiomers (4aS,8aS,8R)-3a and (4aS,8aR,5S)-5a are generated, respectively. However, the contribution of both $C_{6Re,1Si}$ and $C_{2Si,1Re}$ is thought to be negligible for the B_{6Si} -derived $C_{6Si,1Re}$ and $C_{2Re,1Si}$ because B_{6Re} -derived Cintermediates are geometrically disfavored for the endo-transition state with a maximized orbital interaction in either a $C_1(6)=C_1(5)/C_2(1)-C_2(4)$ or $C_1(2)=C_1(3)/C_2(1)-C_2(4)$ combination. Predominant contribution of $C_{6Si,1Re}$ in the 1a/2aqADA realizes high reactivity and multi-selectivity.

Table 4 summarizes the relationship between 1 and 2, reactivity, and selectivity, which was investigated using $2:1 \operatorname{Zn}(\operatorname{OTf})_2/\mathbf{L}_R$ with a ligand loading of 0.5 mol%. Generality was high with the following three requirements satisfied: i) no substituent at $C_1(3)$ of quinone dienophile 1; ii) existence of an alkoxy oxygen atom at $C_1(2)$ of 1; and iii) existence of an alkoxy oxygen atom at $C_2(1)$ of diene 2. These requirements can be well explained by the $H_2O-Zn(II)\mathbf{L}_R$ involved mechanism in Figure 4 as described below.

The methyl group at $C_1(5)$ of **1a** could be replaced with H, allyl, and *i*-Pr (entries 1-5). Use of the enantiomeric ZnL_s catalyst furnished the enantiomeric 3a (entry 3). Introduction of a t-Bu group decreased the reactivity, although the high selectivity was maintained (entry 6). All of $C_1(5)H/C_1(6)H$ -, $C_1(5)CH_3/C_1(6)H$ -, $C_1(5)H/C_1(6)CH_3$ -, and $C_1(5)CH_3/C_1(6)CH_3$ -substituted $C_1(2)OCH_3$ -quinones were usable (entries 1, 2, 7 and 8). With the $C_1(5)CH_3/C_1(6)CH_3$ -quinone, two consecutive quaternary stereogenic centers were installed into $C_3(4a)$ and $C_3(8a)$ of the *cis*decalin product 3 (entry 8). The enantioselectivity was lost by introduction of a CH₃ group at $C_1(3)$ (entry 9); this is explained by the inability to make the two-points-binding of $C_1(1)=O$ and $C_1(2)OCH_3$ to Zn(II) because the lone pair of $C_1(2)OCH_3$ is forced to be anti to the $C_1(1)=O$ lone pair to avoid a steric repulsion from the $C_1(3)CH_3$ group. The lowered reactivity and selectivity of pxyloquinone (entry 10) also supports the importance of a twopoints-binding of dienophile to forming the C intermediate. The methyl of $C_2(1)OCH_3$ of **2a** could be replaced with an easily removable p-methoxybenzyl (PMB) group (entry 11), increasing the synthetic utility. In this reaction, the reliability of the present qADA was confirmed on a 15-g scale.^[25] When the $C_2(1)OCH_3$ of 2a was replaced with t-butyl dimethyl silyloxy (TBSO), AcO, tertbutoxycarbonyl amino (BocNH), CH₃S, or a CH₃ group, the reactivity and selectivity were both significantly decreased (entries 12–16). The $C_2(1)$ OTBS-substituted diene (entry 12) would not be able to efficiently interact with $H_2O-Zn(II)L_R$ because of the

WILEY-VCH

Table 4. Scope and Limitation of the ZnL_R-Catalyzed qADA



Reactions were carried out at 27 °C in 1,4-dioxane (360 ppm H₂O) under the conditions of [dienophile] = 0.5 M; [diene] = 1.0 M; [Zn(OTf)₂] = 5 mM (1.0 mol%); [L_R] = 2.5 mM (0.5 mol%) on a ca. 100-mg scale unless otherwise specified. [a] Isolated yield. Value in parenthesis is ¹H-NMR yield. [b] Determined by HPLC analysis. [c] L_s was used instead of L_R. [d] 40 °C. [e] [Zn(OTf)₂] = [L_R] = 5 mM (1 mol%). [f] The relative and absolute configurations of the C(8a)H/C(8)OCH₃ regioisomer were not determined. [g] 15-g scale. [h] The absolute configuration was not determined. [i] 60 °C. [j] After treatment by silica gel (100 mg for 1 mmol of **1a**; 1.5 h).

large size and lowered donating ability of the TBSO oxygen atom. In the case of the $C_2(1)OAc$ - or NHBoc-substituted diene (entries 13 and 14), the most electron donative and coordinative C=O oxygen atom is located at the two-atoms elongated position from the case of $C_2(1)OCH_3$ that can directly interact with H₂O–Zn(II), intervening to take the desired C structure. Replacement of the $C_2(1)OCH_3$ of **1a** with $C_2(1)SCH_3$ (entry 15) would also destruct the C-type structure by a direct coordination of the high affinity sulfur atom to Zn(II). The reactivity was significantly decreased with either the $C_2(1)CH_3$ -substituted diene or 3-TBSO-1,3-

butadiene (entries 16 and 17), which has no alkoxy group at $C_2(1)$, because the C intermediate cannot be formed via an interaction with В. The Danishefsky-Kitahara diene possessing C₂(1)OCH₃ smoothly reacted with 1a to give the qADA adduct with a 96:4 er (entry 18). Introduction of a CH_3 substituent at $C_2(4)$ of **2a** simultaneously constructed four stereogenic centers with high selectivity in combination with various la-type dienophiles (entries 19-24). The $C_2(1)OCH_3$ group could be replaced with C₂(1)OCH₂OCH₃ (OMOM) (entries 20, 22, and 24).^[11] qADA adducts obtained in the reaction of **1a** with a $C_2(1)OCH_3/C_2(4)CH_3$ - or $C_2(1)OMOM/C_2(4)CH_3$ -substituted diene easily underwent elimination; therefore, the reaction mixture was treated with silica gel to convert the adducts to the corresponding hexadiene product with a >99:1 er in 85-88% yields (entries 21 and 22). A diene bridged between $C_2(1)$ and $C_2(4)$ was used to quantitatively furnish the tricyclic qADA adduct with a 99:1 er (entry 25). When a $C_1(5)CH_3/C_1(6)CH_3$ -substituted dienophile was used in combination with a $C_2(1)OCH_3/C_2(4)CH_3$ -substituted diene, the site selectivity for the $C_1(5)=C_1(6)/C_1(2)=C_1(3)$ double bond was lost to provide two enantiomerically pure qADA adducts 3 and 5 (entry 26). In the corresponding $C_1(6)CH_3/C_2(4)CH_3$ substituted C_{6Si,1Re}-type intermediate, two tri-substituted $sp^{2}C_{1}(5)CH_{3}$ and $sp^{2}C_{1}(6)CH_{3}$ must react with two di-substituted $sp^{2}C_{2}(1)OCH_{3}$ and $sp^{2}C_{2}(4)CH_{3}$, requiring a higher energy than the simple $C_{6Si,1Re}$ case. As a result, the contribution of an electronically disfavored but geometrically favored C2Re,1Si-type intermediate would be relatively increased to give the $C_1(2)_{Re} = C_1(3)_{Si}$ -site-selected product **5**. Reasonable justification for the substrate-reactivity-selectivity relationship in Table 4 strongly supports the mechanism in Figure 4.

In summary, we have discovered that a Zn(II) complex of a bisamidine-type sp²N-based bidentate ligand, (R,R)-Naph-diPIMdioxo-*i*Pr (L_R), efficiently catalyzes the challenging qADA in the presence of H₂O under ambient conditions. A catalyst loading of 0.5 mol% is generally acceptable and can be reduced to 0.02 mol% by increasing the Zn/L_R ratio. One "H₂O" molecule is captured by the Lewis acidic Zn(II) and one dioxolane oxygen lone pair of L_R to furnish a chiral reaction site possessing another dioxolane oxygen lone pair. In the spatially accessible environment that facilitates $n-\pi^*$ interactions and hydrogen bonding, o-alkoxy-p-benzoquinones 1 and 1-alkoxy-1,3-butadienes 2 (z = OR) are supramolecularly arranged to realize a highly efficient qADA. The $H_2O-Zn(II)L_R$ catalyzed qADA furnishes highly functionalized cis-decalins with high site-, diastereo- (endo/exo-), regio-, and enantio-selectivities. Four consecutive carbon stereogenic centers and two consecutive quaternary carbon centers can be installed. This first high performance qADA should provide chemists in the fields of total synthesis, medicinal chemistry, and process chemistry with a powerful tool for asymmetric syntheses of pharmaceutically products.^[1] important complex natural and unnatural Understanding the mechanism underlying the present qADA should provide important guidelines for the design of various chiral key intermediates and future chiral catalysts.

Acknowledgements

This work was aided by JSPS KAKENHI Grant Number JP16H02274, JP18H04250, and JP17H17415, the Platform Project for Supporting Drug Discovery and Life Science Research funded by Japan Agency for Medical Research and Development (AMED; Grant Number JP18am0101099), an Advanced Catalytic Transformation program for Carbon utilization (ACT-C; Grant Number JPMJCR12YC) from Japan Science and Technology Agency (JST), and The Sumitomo Foundation.

Keywords: Asymmetric catalysis • Diels-Alder reaction • Homogeneous catalyst • sp²N bidentate ligand • Zinc

- K. C. Nicolaou, S. A. Snyder, T. Montagnon, G. Vassilikogiannakis, Angew. Chem. Int. Ed. 2002, 41, 1668–1698.
- R. B. Woodward, F. Sondheimer, D. Taub, Heusler, K.; McLamore, W. M. The total synthesis of steroids. J. Am. Chem. Soc. 1952, 74, 4223–4251.
- [3] R. Hoffmann, R. B. Woodward, J. Am. Chem. Soc. 1965, 87, 4388– 4389.
- [4] I. Fernández, F. M. Bickelhaupt, J. Comput. Chem. 2014, 35, 371–376.
- [5] K. Mikami, M. Terada, Y. Motoyama, T. Nakai, *Tetrahedron: Asymmetry* 1991, 2, 643–646.
- [6] D. A. Evans, J. Wu, J. Am. Chem. Soc. 2003, 125, 10162–10163.
- [7] D. H. Ryu, G. Zhou, E. J. Corey, J. Am. Chem. Soc. 2004, 126, 4800– 4802.
- [8] K. Futatsugi, H. Yamamoto, Angew. Chem. Int. Ed. 2005, 44, 1484– 1487.
- [9] E. R. Jarvo, B. M. Lawrence, E. N. Jacobsen, Angew. Chem. Int. Ed. 2005, 44, 6043–6046.
- a) C. W. Bird, A. L. Brown, C. C. Chan, A. Lewis, *Tetrahedron Lett.* **1989**, 30, 6223–6226; b) A. I. Kim, S. D. Rychnovsky, *Angew. Chem. Int. Ed.* **2003**, 42, 1267–1270; c) M. Ohkubo, G. Hirai, M. Sodeoka,
 Angew. Chem. Int. Ed. **2009**, 48, 3862–3866.
- [11] a) Q. Liu, Y. Deng, A. B. Smith III, *J. Am. Chem. Soc.* 2017, *139*, 13668
 -13671. Other reports: b) S. M. Moharram, G. Hirai, K. Koyama, H. Oguri, M. Hirama, Tetrahedron Lett. 2000, 41, 6669–6673; c) Z. Yu, W. Penghui, C. Yong, L. Mingming, C. Guangyi, L. Yinping, Y. Deyong, *Chin. J. Org. Chem.* 2012, *32*, 1340–1343.
- [12] K. Narasaka, M. Inoue, N. Okada, Chem. Lett. 1986, 15, 1109–1112.
- [13] D. Seebach, A. K. Beck, R. Imwinkelzied, S. Roggo, A. Wonnacott, *Helv. Chim. Acta* **1987**, *70*, 954–974.
- [14] D. A. Evans, K. A. Woerpel, M. M. Hinman, M. M. Faul, J. Am. Chem. Soc. 1991, 113, 726–728.
- [15] M. Kitamura, K. Miyata, T. Seki, N. Vatmurge, S. Tanaka, Pure Appl. Chem. 2013, 85, 1121–1132.
- [16] T. P. Le, K. Higashita, S. Tanaka, M. Yoshimura, M. Kitamura, Org. Lett. 2018, 20, 7149–7153.
- [17] Y. Shuto, T. Yamamura, S. Tanaka, M. Yoshimura, M. Kitamura, *ChemCatChem* **2015**, 7, 1547–1550.
- [18] S. Tanaka, G. Ramachandran, Y. Hori, M. Kitamura, *Chem. Lett.* 2018, 47, 1486–1489.
- [19] J. S. Tou, W. Reusch, J. Org. Chem. 1980, 45, 5012–5014.
- [20] G. Desimoni, G. Faita, P. P. Righetti, *Tetrahedron Lett.* **1996**, 37, 3027– 3030.
- [21] E. J. Corey, K. Ishihara, Tetrahedron Lett. 1992, 33, 6807–6810.
- [22] J. S. Johnson, D. A. Evans, Acc. Chem. Res. 2000, 33, 325–335.
- [23] D. A. Evans, M. C. Kozlowski, J. S. Tedrow, *Tetrahedron Lett.* 1996, 37, 7481–7484.
- [24] M. A. Brimble, J. F. McEwan, *Tetrahedron: Asymmetry* **1997**, *8*, 4069–4078.
- [25] For details, see supporting information.

- [26] Reviews for n/π* interaction: a) R. W. Newberry, R. T. Raines, Acc. Chem. Res. 2017, 50, 1838–1846; b) J. Echeverría, Chem. Commun. 2018, 54, 3061–3064.
- [27] Reports implying the existence of n/π^* interaction in transition state: a) V. C. M. Duarte, H. Faustino, M. J. Alves, A. G. Fortes, N. Micaelo,

Tetrahedron: Asymmetry 2013, 24, 1063–1068; b) Y. Reddi, R. B. Sunoj, ACS Catal. 2015, 5, 1596–1603; c) A. J. Neel, A. Milo, M. S. Sigman, F. D. Toste, J. Am. Chem. Soc. 2016, 138, 3863–3875.
[28] R. G. F. Giles, G. H. P. Roos, Tetrahedron Lett. 1975, 4159–4960.

WILEY-VCH

Entry for the Table of Contents

COMMUNICATION

A new $[Zn(H_2O)L_R]^{2^+}$ complex has been developed to realize a highly efficient asymmetric quinone-Diels-Alder reaction. The presence of the two oxygen atoms of L_R at the reaction site with a spatially accessible environment and "H₂O" in the reaction system are essential. *o*-Alkoxy-*p*-benzoquinone and 1-alkoxy-1,3-butadiene are fixed by a linear hydrogen bond network and n- π^* attractive interaction to realize the high reactivity and multi-selectivity.



Kyosuke Morimoto, Thien Phuc Le, Sudipta Kumar Manna, I. N. Chaithanya Kiran, Shinji Tanaka, Masato Kitamura*

Page No. – Page No.

Water, an Essential Element for a Zn(II)-Catalyzed Asymmetric Quinone Diels-Alder Reaction: Multi-selective Construction of Highly Functionalized *cis*-Decalins