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COMMUNICATION

Enantio- and diastereoselective hetero-Diels–Alder reactions between 2-aza-3-silyloxy-1,3-butadienes and aldehydes catalyzed by chiral dirhodium(II) carboxamidates†‡

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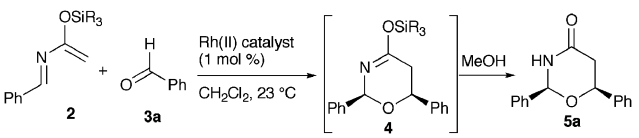
The first catalytic asymmetric hetero-Diels–Alder reaction between 2-aza-3-silyloxy-1,3-butadienes and aldehydes is described. With dirhodium(II) tetrakis[*N*-benzene-fused-phthaloyl-(*S*)-piperidinonate], Rh_2(*S*-BPTPI)$_4$, the cycloaddition reaction proceeded exclusively in an *endo* mode to give all-*cis*-substituted 1,3-oxazinan-4-ones in high yields with up to 98% ee.

The hetero-Diels–Alder (HDA) reaction of 2-aza-3-silyloxy-1,3-butadienes, originally introduced by Ghosez *et al.*,[1,2] with carbonyl compounds provides a convergent and practical route to substituted 1,3-oxazinan-4-ones, which have been demonstrated to serve as valuable precursors for the synthesis of 1,3-amino alcohols and β-hydroxy amide derivatives.[3–5] In this context, asymmetric HDA reaction of the corresponding chiral 2-azadienes with a wide array of aldehydes in the presence of a stoichiometric amount of BF_3·OEt_2 has been developed and extensively advanced by Panunzio *et al.*[3,6] However, despite the great synthetic importance, a catalytic asymmetric version of this cycloaddition reaction has not been addressed to date, probably because an achiral catalyst suitable for such a reaction has not been identified.[7]

Since the pioneering work by Doyle *et al.* on enantioselective HDA reactions of 1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (Danishefsky's diene) with aldehydes, chiral dirhodium(II) carboxamidates have been widely recognized as a new class of effective Lewis acid catalysts.[8–10] In this area, we reported that Rh_2(*S*-BPTPI)$_4$ (**1**), a dirhodium(II) carboxamidate complex that incorporates (*S*)-3-(benzene-fused-phthalimido)-2-piperidinonate as chiral bridging ligands, is a highly efficient Lewis acid catalyst for *endo*- and enantioselective HDA reactions of a diverse range of aldehydes with Danishefsky-type dienes and monooxygenated dienes as well as with Rawal's diene.[11] As part of our interest in further extension of the scope and utility of **1**, we herein report that Rh_2(*S*-BPTPI)$_4$ (**1**) catalyzes the HDA reaction between 2-aza-3-silyloxy-1,3-butadienes and aldehydes to provide 1,3-oxazinan-4-ones in high yields and with high levels of enantioselectivity (up to 98% ee).

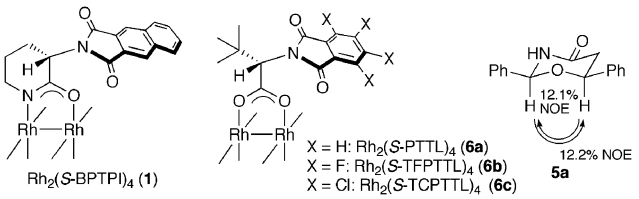
At the outset, we explored the HDA reaction between 2-aza-3-silyloxy-1,3-butadiene **2a** and benzaldehyde (**3a**) (1.5 equiv.) using 1 mol% of Rh_2(*S*-BPTPI)$_4$ (**1**). The reaction in dichloromethane at room temperature proceeded to completion in 24 h and gave, after desilylation with methanol according to Ghosez's procedure,[6] *cis*-2,6-disubstituted 1,3-oxazinan-4-one **5a** as the sole product in 95% yield with no signs of isomerization (Table 1, entry 1).[3h,4a,b] The *cis*-stereochemistry of **5a** was established by the ^{1}H NOE between C2–H and C6–H. The enantioselectivity of this reaction was determined to be 98% ee by HPLC analysis with a Daicel Chiralpak AD-H column. The preferred absolute stereochemistry of **5a** $[[\alpha]_D^{24}$ −39.8

Table 1 Enantioselective HDA reaction between 2-aza-3-siloxy-1,3-butadines and benzaldehyde (**3a**) catalyzed by Rh(II) complexes[a]



Entry	Diene	SiR_3	Catalyst	*t*/h	Yield[b] (%)	ee[c] (%)
1	**2a**	TBS	**1**	24	95	98
2	**2a**	TBS	**6a**	96	63	−34
3	**2a**	TBS	**6b**	96	50	−77
4	**2a**	TBS	**6c**	96	40	−70
5	**2b**	Me_3Si	**1**	24	68	90
6	**2c**	Et_3Si	**1**	24	85	90

[a] All reactions were performed on a 0.3 mmol scale (0.5 M) with 1.5 equivalents of **3a**. [b] Yields of isolated product **5a**. [c] Determined by HPLC on a Daicel Chiralpak AD-H (see ESI for details).



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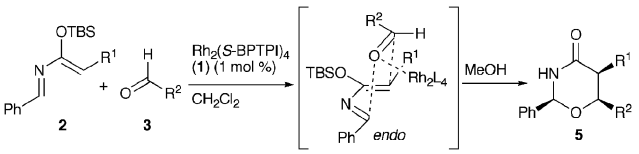
‡ Electronic supplementary information (ESI) available. See DOI: 10.1039/c2cc32876c

(*c*, 1.03, $CHCl_3$) for 98% ee] was assigned as 2*S*,6*S* by its transformation (HCl, MeOH)[3a] to the known methyl 3-hydroxy-3-phenylpropanoate [$[\alpha]_D^{22}$ −51.6 (*c*, 0.95, $CHCl_3$); lit.,[12] $[\alpha]_D^{20}$ +46.9 (*c*, 1.2, $CHCl_3$) for (*R*)-enantiomer]. In the present reaction, the ^{1}H NMR spectrum of the crude reaction mixture obtained prior to methanolysis revealed the exclusive formation of 2,6-*cis*-dihydro-1,3-oxazine **4a** (SiR_3 = TBS). This result suggests that Rh_2(*S*-BPTPI)$_4$-catalyzed cycloaddition with 2-azadiene **2a** proceeds through the same concerted [4+2] mechanism in an *endo* mode as those with Danishefsky-type dienes[11a] and Rawal's diene[11d] (*vide infra*).[6] A survey of solvents revealed that dichloromethane was the optimal solvent for this transformation.[13] We next evaluated the performance of chiral dirhodium(II) carboxylates, Rh_2(*S*-PTTL)$_4$ (**6a**),[14] Rh_2(*S*-TFPTTL)$_4$ (**6b**),[15] and Rh_2(*S*-TCPTTL)$_4$ (**6c**) (entries 2–4).[16] Compared with the catalysis with Rh_2(*S*-BPTPI)$_4$, the use of these catalysts required significantly longer reaction times to reach completion and substantially diminished the product yields because of competitive degradation of **2a**. Although perfect *endo* diastereoselectivity was observed in every case, cycloadditions with **6a–6c** brought about a reversal in enantioselection to give (2*R*,6*R*)-*cis*-1,3-oxazinan-4-one *ent*-**5a** with 34–77% ee. Clearly, Rh_2(*S*-BPTPI)$_4$ (**1**) proved to be the catalyst of choice for the HDA reaction in terms of the rate and product yield as well as enantioselectivity.[17,18] We also examined the effect of silicon substituents of 2-azadienes **2a–2c** on enantioselectivity. Variation in the silyl group revealed that the *tert*-butyldimethylsilyl functionality was optimal for this process (entries 1 *vs*. 5 and 6).

With optimized conditions in hand, we then investigated the scope of the reaction with respect to the aldehyde component (Table 2). High yields and enantioselectivities were consistently observed with aromatic aldehydes bearing a methyl group or electron-withdrawing groups at the *para* or *meta* position on the benzene ring (90–96% ee, entries 1–7). A high enantioselectivity (92% ee) was maintained with electron-rich *p*-anisaldehyde (**3i**), though a marked drop in product yield was observed owing to the decreased reactivity of **3i** (entry 8). The use of highly reactive aldehydes such as α,β-acetylenic aldehydes **3j,k** and benzyloxyacetaldehyde (**3l**) afforded the corresponding HDA adducts **5j–l** in high yields and with high levels of asymmetric induction when the reactions were conducted at 0 °C (95–97% ee, entries 9–11). 2-Furfural (**3m**), 2-thiophenecarbaldehyde (**3n**), *trans*-cinnamaldehyde (**3o**) and straight-chain aliphatic aldehydes **3p,q** were also effective dienophiles for this reaction (92–96% ee, entries 12–16). We next explored the possibility of using 4-methyl substituted 2-azadiene **2d**. Although the scope of the reaction is limited to α,β-acetylenic aldehydes, the HDA reaction with **2d** produced all-*cis* 1,3-oxazinan-4-ones **5r,s** as the sole products in high yields and with high levels of enantioselectivity (91 and 92% ee, entries 16, 17). These results confirmed the exclusive preference for a concerted HDA mechanism in an *endo* mode.

To illustrate the utility of the present catalytic protocol, we conducted an asymmetric synthesis of *syn*-β-hydroxy-α-methyl amide **7**, the amide terminus of F-ATPase inhibitor cruentaren A (Scheme 1).[20] The HDA reaction between **2d** and 2-butynal (**3r**) with the use of 1 mol% of Rh_2(*R*-BPTPI)$_4$ (**8**) proceeded

Table 2 Asymmetric HDA reaction between 2-aza-3-siloxy-1,3-butadines and aldehydes **3** catalyzed by Rh_2(*S*-BPTPI)$_4$ (**1**)[a]



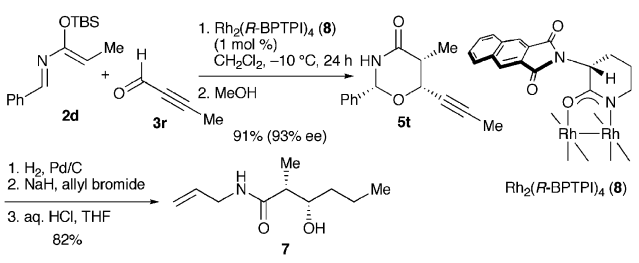
Entry	Diene R^1	Aldehyde R^2	*T*/°C	*t*/h	Product	Yield[b] (%)	ee[c] (%)
1	**2a** H	**3b** 4-$NO_2C_6H_4$	0	12	**5b**	98	91
2	**2a** H	**3c** 4-$CF_3C_6H_4$	23	7	**5c**	96	94
3	**2a** H	**3d** 4-$MsOC_6H_4$	23	24	**5d**	97	90
4	**2a** H	**3e** 4-ClC_6H_4	23	16	**5e**	93	94
5	**2a** H	**3f** 4-MeC_6H_4	23	48	**5f**	97	96
6	**2a** H	**3g** 3-MeC_6H_4	23	48	**5g**	84	92[d]
7	**2a** H	**3h** 3-ClC_6H_4	23	16	**5h**	92	92
8	**2a** H	**3i** 4-$MeOC_6H_4$	30	48	**5i**	64	92
9	**2a** H	**3j** $C_6H_5C{\equiv}C$	0	3	**5j**	99	95
10	**2a** H	**3k** $^nC_5H_{11}C{\equiv}C$	0	8	**5k**	94	96
11	**2a** H	**3l** $BnOCH_2$	0	12	**5l**	86	97
12	**2a** H	**3m** 2-furyl	23	24	**5m**	93	95
13	**2a** H	**3n** 2-thienyl	23	48	**5n**	81	96
14	**2a** H	**3o** (*E*)-PhCH=CH	23	48	**5o**	88	96
15	**2a** H	**3p** $PhCH_2CH_2$	23	48	**5p**	95	92[d]
16	**2a** H	**3q** $^nC_3H_7$	23	12	**5q**	92	93
17	**2d** CH_3	**3j** $C_6H_5C{\equiv}C$	0	10	**5r**	95	91
18	**2d** CH_3	**3k** $^nC_5H_{11}C{\equiv}C$	0	36	**5s**	89	92

[a] All reactions were performed on a 0.3 mmol scale (0.5 M) with 1.5 equivalents of **3**. [b] Yields of isolated product **5**. [c] Determined by HPLC unless otherwise stated (see ESI for details). [d] Determined by HPLC after conversion to the corresponding β-hydroxy methyl ester (see ESI for details).

uneventfully at −10 °C to give, after methanolysis, all-*cis*-1,3-oxazinan-4-one **5t** in 91% yield with 93% ee. Catalytic hydrogenation of the triple bond followed by *N*-allylation and hydrolysis furnished **7** as a single *syn*-isomer in 82% yield.

The observed sense of asymmetric induction (approach of **2** from the less hindered *Si*-face of the aldehyde in an *endo* mode) is consistent with the proposed model for HDA reactions catalyzed by Rh_2(*S*-BPTPI)$_4$,[11a,b,d] which contains a hydrogen bond between the formyl hydrogen atom and the carboxamidate oxygen atom in the rhodium catalyst–aldehyde complex (Fig. 1).[21]

In summary, we have developed the first catalytic asymmetric HDA reaction between 2-aza-3-silyloxy-1,3-butadienes and aldehydes. The cycloaddition reaction catalyzed by 1 mol% of Rh_2(*S*-BPTPI)$_4$ proceeded exclusively in an *endo* mode to give, after methanolysis, all-*cis*-substituted 1,3-oxazinan-4-ones in high yields and with high levels of enantioselectivity



Scheme 1 Synthesis of *syn*-β-hydroxy-α-methyl amide **7**.

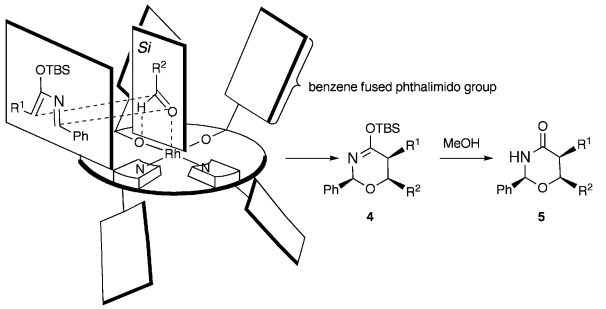


Fig. 1 Plausible stereochemical course.

(up to 98% ee). Using this catalytic protocol, we developed a novel approach to *syn*-β-hydroxy-α-methyl amide terminus of cruentaren A. Further application of this method to catalytic asymmetric synthesis of biologically active natural products is currently in progress.

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17 The reaction between **2a** and **3a** at room temperature in the presence of chiral bis(oxazoline)copper(II) complex, which has previously been shown to be an effective catalyst for the asymmetric Diels–Alder reaction between 2-aza-3-silyloxy-1,3-butadienes and 3-(2-alkenoyl)-1,3-oxazolidin-2-ones, led to a complex mixture of products arising from degradation of **2a** along with a quantitative recovery of **3a**. See: E. Jnoff and L. Ghosez, *J. Am. Chem. Soc.*, 1999, **121**, 2617–2618. Furthermore, the use of $ZnCl_2$, $Yb(OTf)_3$ or $Sc(OTf)_3$ also met with little success.

18 The reaction of **2a** with **3a** at room temperature using 1 mol% of $Rh_2(pfb)_4$ (pfb = perfluorobutyrate) went to completion in 48 h and gave **5a** as the sole product in 64% yield, while Rh(II) complexes such as $Rh_2(OAc)_4$, $Rh_2(tpa)_4$,[19] $Rh_2(piv)_4$, $Rh_2(oct)_4$ and $Rh_2(cap)_4$ (tpa = triphenylacetate, piv = pivalate, oct = octanoate, cap = caprolactamate) were less effective.

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