The Oxidative Acylnitroso Hetero-Diels–Alder Reaction Catalyzed by Dirhodium Caprolactamate

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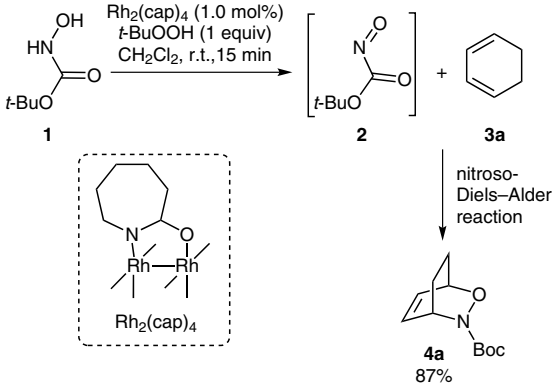
Abstract: An effective protocol is described for the generation and in situ Diels–Alder trapping of acylnitroso derivatives. In this procedure, the oxidation of hydroxamic acid is efficiently catalyzed by dirhodium(II) caprolactamate with *tert*-butyl hydroperoxide (TBHP) in the presence of dienes at room temperature. Using this approach we obtained a variety of hetero-Diels–Alder cycloadducts in yields of up to 96% at 0.1 mol% catalyst loading.

Key words: catalysis, oxidation, acylnitroso, Diels–Alder reaction, dirhodium(II)

Since Kirby's pioneering work was reported in 1973,[1] the hetero-Diels–Alder (HDA) reaction of acylnitroso compounds has been recognized as a useful tool in direct 1,4-functionalizations of conjugated dienes, and it provides easy access to a number of nitrogen- and oxygen-containing natural products.[2] Acylnitroso compounds are traditionally generated in situ by oxidizing hydroxamic acids using oxidants such as periodates,[3,4] due to the high reactivity of acylnitroso species, these reactions are usually conducted in the presence of trapping agents to ensure formation of the desired products. In recent years, mild protocols have been developed in which these oxidations are catalyzed by transition metals in conjunction with TBHP,[5–9] H_2O_2,[10–13] and dioxygen.[14,15] The combination of ruthenium(II) complexes and *tert*-butyl hydroperoxide (TBHP) has been reported to promote the oxidation of hydroxamic acids and subsequent HDA reactions, although poor to moderate yields of 19–42% were obtained for noncyclic dienes.[6] Here, we report that dirhodium(II) caprolactamate [$Rh_2(cap)_4$] exhibits similar oxidative reactivity toward hydroxamic acids when TBHP is the terminal oxidant; this catalytic combination in the presence of dienes provides HDA cycloadducts in high efficiency under mild reaction conditions. The present study provides the first example of the $Rh_2(cap)_4$-catalyzed oxidation of hydroxamic acids and extends the potential utility of this important catalyst, which has already been used for efficient catalytic oxidation of activated C–H bonds,[16–22] phenols, and anilines.[23]

We began our studies by examining the reaction of hydroxamic acid **1** and 1.2 equivalents of 1,3-cyclohexadiene **3** in the presence of 1 mol% $Rh_2(cap)_4$ and 1.0 equivalent of TBHP in CH_2Cl_2 at room temperature. The HDA reaction proceeded smoothly to completion in 15 minutes, providing the cycloadduct **4** in 87% isolated yield (Scheme 1).



Scheme 1 Initial experimental results

Since the reaction proceeded quite fast, we investigated the possibility of reducing the catalyst loading. Indeed, the catalyst loading could be reduced to 0.1 mol% without obvious loss of yield (Table 1), though excess TBHP was required (Table 1, entry 1, 2.0 equiv TBHP). When 4.0 equivalents of TBHP were used, hydroxamic acid **1** in CH_2Cl_2 was completely consumed within two hours and an even higher yield of 92% was obtained (Table 1, entry 2). Notably, less expensive T-HYDRO® (70 wt% TBHP in water) is also a suitable terminal oxidant, however, in this case a prolonged reaction time (38 h) is required for complete conversion of **1** (Table 1, entry 3). Further investigations indicated that methanol is not a suitable solvent for this reaction. In the presence of methanol (Table 1, entry 4), relatively small amount of **1** reacted and only trace amounts of **4a** were detected, even after a reaction time of 24 hours, in addition, unwanted byproducts were observed. Both TBHP and $Rh_2(cap)_4$ were essential, since reactions lacking either one gave poor to moderate yields (Table 1, entries 5 and 6). Moreover, attempts to replace TBHP with hydrogen peroxide or $Rh_2(cap)_4$ with $Rh_2(OAc)_4$ resulted in sluggish reactions with incomplete conversion of hydroxamic acid **1** (Table 1, entries 7 and 8).

Using the optimized reaction conditions of 0.1 mol% $Rh_2(cap)_4$, 4.0 equivalents of TBHP, 1.0 equivalents of

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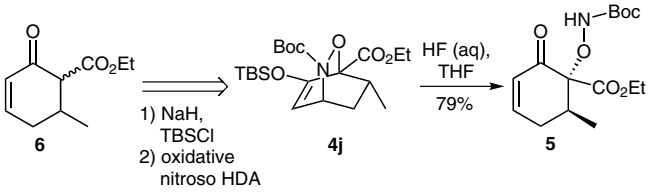
Table 1 Optimization and Control Experiments (**1** + **3a** → **4a**)[a]

Entry	Catalyst (0.1 mol%)	Oxidant	Temp (°C)	Time (h)	Yield (%)[b]
1[c]	$Rh_2(cap)_4$	TBHP	r.t.	20	84
2	$Rh_2(cap)_4$	TBHP	r.t.	2	92
3	$Rh_2(cap)_4$	T-HYDRO	r.t.	38	92
4[d]	$Rh_2(cap)_4$	TBHP	r.t.	24	–[e]
5	$Rh_2(cap)_4$	none	r.t.	24	14
6	none	TBHP	r.t.	56	61
7	$Rh_2(cap)_4$	H_2O_2	40	78	50
8	$Rh_2(OAc)_4$	TBHP	r.t.	24	37

[a] Reactions were performed using **1** (1.0 equiv), **3** (1.2 equiv), catalyst (0.1 mol%), and oxidant (4.0 equiv) in CH_2Cl_2 (0.2 M/[substrate]) unless otherwise noted.
[b] Isolated yields after silica gel chromatography.
[c] Conditions: 2.0 equiv of TBHP were used.
[d] MeOH was used as solvent.
[e] A complex mixture with low conversion was obtained.

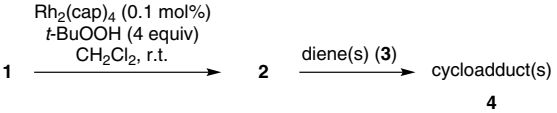
hydroxamic acid, and 1.2 equivalents of diene in CH_2Cl_2 at room temperature, we investigated the scope of the reaction with different 1,3-dienes. The dienes were those commonly used to test the scope of the nitroso-Diels–Alder (NDA) reaction (Table 2). Cyclic dienes **3a**–**c** were good NDA-trapping substrates and gave the corresponding cycloadducts **4a**–**c** in excellent yields (Table 2, entries 1–3), while 1,3-cyclooctadiene (**3d**), 9,10-dimethylanthracene (**3e**), and acyclic dienes (**3f**–**i**) generally gave moderate yields (Table 2, entries 4–9).[24,25] The yields obtained by our $Rh_2(cap)_4$-catalyzed oxidative protocol are generally higher than that using ruthenium(II) complexes.[5–9] Exposing the densely functionalized cyclic diene **3j** to the reaction conditions resulted in a complex mixture, while adding 2.0 equivalents $NaHCO_3$ to the reaction in order to avoid the hydrolysis of the silyl ether made the NDA cycloaddition feasible and furnished the desired product **4j** in 47% yield with complete regio- and diasteroselectivity.[26] Desilylation of **4j** mediated by HF and subsequent β-elimination of the amino group afforded the *O*-nitroso aldol product **5** of the β-keto-γ,δ-unsaturated ester **6**,[27] the precursor of diene **3j** (Scheme 2).



Scheme 2 Desilylation–β-elimination cascade

It has been well documented that the *tert*-butylperoxy radical can be generated from TBHP in the presence of dirhodium caprolactamate and that the *tert*-butylperoxy radical tends to abstract a proton from substrates and subsequently initiate transformations.[21] It is therefore possible that the reaction described here proceeds via H-atom abstraction from the hydroxamic acid mediated by the *tert*-butylperoxy radical, producing the acyl nitroxyl radical.[35] This radical is further oxidized to the acylnitroso compound by an oxidative species such as the *tert*-butylperoxy radical or Rh_2^{5+} species, which is a one-electron oxidation product derived from $Rh_2(cap)_4$. Another possibility that cannot be ruled out is that the acylnitroso compound is furnished through dismutation of the acyl nitroxyl radical.[36] Further studies are needed to elucidate the detailed mechanism of this reaction.

Table 2 Hetero-Diels–Alder Trapping of Acylnitroso by Dienes



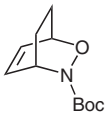
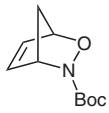
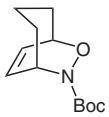
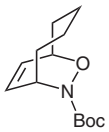
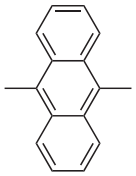
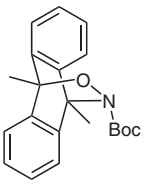
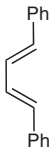
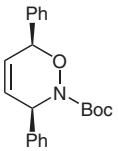
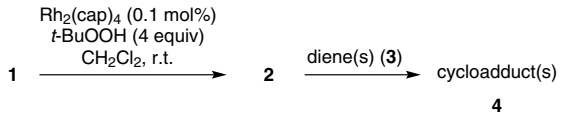
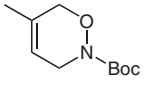
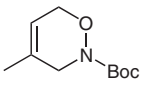
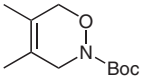
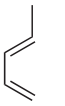
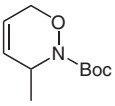
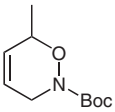
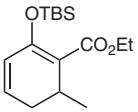
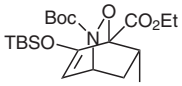
Entry	Diene (**3**)	Time (h)	Product (**4**)	Yield (%)[a]
1	 **3a**	2	 **4a**	92
2	 **3b**	14	 **4b**	92
3	 **3c**	6	 **4c**	96
4	 **3d**	24	 **4d**	68
5	 **3e**	24	 **4e**	61
6	 **3f**	14	 **4f**	68

Table 2 Hetero-Diels–Alder Trapping of Acylnitroso by Dienes (continued)



Entry	Diene (**3**)	Time (h)	Product (**4**)	Yield (%)[a]
7	 **3g**	12	 **4g** +  **4g′**	65[b]
8	 **3h**	10	 **4h**	57
9	 **3i**	8	 **4i** +  **4i′**	81[c]
10[d]	 **3j**	14	 **4j**	47

[a] Isolated yields after silica gel chromatography.
[b] Obtained as a 1:1 mixture of inseparable regioisomers.
[c] Obtained as a 2:1 mixture of inseparable regioisomers.
[d] Conditions: 2.0 equiv of $NaHCO_3$ were used.

In summary, dirhodium caprolactamate in the presence of TBHP is effective at catalyzing the oxidation of hydroxamic acid to the acylnitroso derivative at catalyst loadings as low as 0.1 mol% under mild reaction conditions. The generated acylnitroso derivative is trapped in situ by dienes, providing a variety of hetero-Diels–Alder cycloadducts. The catalytic reaction reported here serves as the first example for the dirhodium(II)-catalyzed oxidation of hydroxamic acid derivatives and significantly extends the utility of this unique catalyst.

Acknowledgment

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(24) **General Procedure for the Oxidative Acylnitroso Hetero-Diels–Alder Reaction Catalyzed by Dirhodium Caprolactamate**
A 0.0020 M solution of $Rh_2(cap)_4 \cdot 2MeCN$ in CH_2Cl_2 (0.25 mL, 0.0005 mmol, 0.1 mol%) and diene **3** (0.6 mmol, 1.2 equiv) were sequentially added to a solution of BocNHOH (66.6 mg, 0.5 mmol) in CH_2Cl_2 (2.5 mL). Then TBHP (5–6 M solution in decane; 2 mmol, 4 equiv) was added dropwise to the resulting mixture. The reaction mixture was stirred at r.t. and monitored by TLC. Reaction completion was confirmed by the disappearance of the starting material. The solvent was removed by evaporation to give the crude product, which was purified by silica gel chromatography to afford the desired products. Analysis of the cycloadducts **4a–e** and **4g–i** gave results identical to those previously reported.[6,28–33]

(25) ***tert*-Butyl 3,6-diphenyl-3,6-dihydro-2*H*-1,2-oxazine-2-carboxylate (4f)**
The general procedure described above was followed using BocNHOH (66.6 mg, 0.5 mmol), 1,4-diphenyl-1,3-butadiene (123.8 mg, 0.6 mmol), $Rh_2(cap)_4$·2MeCN (0.0005 mmol), and TBHP (5–6 M solution in decane, 2 mmol). The reaction mixture was stirred for 12 h and purified by silica gel chromatography using PE–EtOAc (5:1) as eluent to give cycloadduct **4f** (114 mg, 68%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.55 (m, 10 H), 6.11–6.17 (m, 2 H), 5.59 (br, 2 H), 1.52 (s, 9 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 154.4, 139.4, 137.3, 129.1, 128.8, 128.6, 128.4, 127.94, 127.88, 127.86, 126.6, 81.6, 79.2, 52.3, 28.5. ESI-HRMS: *m/z* calcd for $C_{21}H_{23}NO_3$ $[M + H]^+$: 338.1756; found: 338.1756.

(26) **3-*tert*-Butyl-4-ethyl-5-(*tert*-butyldimethylsilyloxy)-8-methyl-2-oxa-3-azabicyclo[2.2.2]oct-5-ene-3,4-dicarboxylate (4j)**
To a solution of BocNHOH (146.5 mg, 1.1 mmol) in CH_2Cl_2 (2.5 mL) were sequentially added $Rh_2(cap)_4$·2MeCN (0.8 mg, 0.0011 mmol), followed by $NaHCO_3$ (184.4 mg, 2.2 mmol) and then diene **3j**[34] (390.7 mg, 1.32 mmol). The resulting solution was stirred for 10 min, after which TBHP (5–6 M solution in decane, 4.4 mmol) was added dropwise. The reaction mixture was stirred at r.t. for 14 h, solvent was removed by evaporation, and the residue was purified by silica gel chromatography using PE–EtOAc (10:1) as eluent to give cycloadduct **4j** (221 mg, 47%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.38 (d, *J* = 6.8 Hz, 1 H), 4.69–4.72 (m, 1 H), 4.19–4.28 (m, 2 H), 2.55–2.58 (m, 1 H), 2.26–2.28 (m, 1 H), 1.47 (s, 9 H), 1.33 (t, *J* = 6.8 Hz, 3 H), 1.07 (d, *J* = 6.8 Hz, 3 H), 1.01–1.05 (m, 1 H), 0.91 (s, 9 H), 0.20 (s, 3 H), 0.18 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.4, 158.7, 150.2, 101.8, 84.4, 81.9, 61.6, 51.8, 34.3, 32.2, 28.4, 25.5, 20.4, 18.1, 14.2, –4.6, –4.8. ESI-HRMS: *m/z* calcd for $C_{21}H_{37}NO_6SiNa$ $[M + Na]^+$: 450.2288; found: 450.2284.

(27) **Desilylation–β-Elimination Product 5**
To a solution of cycloadduct **4j** (51.0 mg, 0.12 mmol) in THF (2.0 mL) was added aq HF (40 wt%) (20 μL), and the resulting mixture was vigorously stirred for 90 min at r.t. The reaction was quenched with sat. aq $NaHCO_3$ and treated by usual workup. Purification by silica gel chromatography using PE–EtOAc (5:1) as eluent to give the product **5** as a colorless oil (29.7 mg, 79%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (s, 1 H), 6.99–7.03 (m, 1 H), 6.13 (dd, *J* = 1.6, 10.0 Hz, 1 H), 4.22–4.30 (m, 2 H), 2.54–2.69 (m, 2 H), 2.37–2.45 (m, 1 H), 1.46 (s, 9 H), 1.28 (t, *J* = 6.8 Hz, 3 H), 1.28 (d, *J* = 6.8 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.8, 166.0, 156.3, 151.2, 129.2, 91.2, 82.2, 62.1, 35.8, 33.2, 28.3, 15.7, 14.3. ESI-HRMS: *m/z* calcd for $C_{15}H_{23}NO_6Na$ $[M + Na]^+$: 336.1423; found: 336.1415.

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