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Catalytic Asymmetric Nitroso-Diels–Alder Reaction with Acyclic Dienes**

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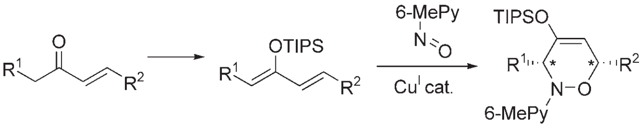
The nitroso-Diels–Alder reaction has long been a valuable synthetic operation for multistep syntheses given that the resulting adducts serve as 1-amino-4-hydroxy-2-ene derivatives after a single step. Subsequent to earlier studies by Kresze and co-workers[1] on the use of simple nitroso derivatives, many research groups have made significant contributions to the steady improvement of this methodology.[2] Recently, we enhanced this transformation to catalytic and enantioselective methods through the use of nitrosopyridine as a dienophile in the presence of a chiral copper catalyst.[3] Unfortunately, the new asymmetric reaction did not proceed as smoothly for acyclic dienes as it did for cyclic systems, which therefore limits its range of application. Herein, we report catalytic regio-, diastereo-, and enantioselective nitroso-Diels–Alder reactions of acyclic 2-silyloxy-1,3-dienes that have a broad substrate scope. The pathway for the present catalytic enantioselective transformation is outlined in Scheme 1.



Scheme 1. The present pathway for the catalytic enantioselective transformation of acyclic 2-silyloxy-1,3-dienes. TIPS = triisopropylsilyl, Py = pyridine.

The nitroso-Diels–Alder reaction of pentadiene and 6-methyl-2-nitrosopyridine in the presence of $[Cu(MeCN)_4$-(segphos)]PF_6 gave a mixture of 1- and 4-amino derivatives in a 3:1 ratio with up to 10 % *ee*. The reactivity of the diene was increased, and (2*Z*,4*E*)-3-trimethylsilyloxy-2,4-hexadiene[4] (**1a**) was examined in the presence of a catalytic amount of

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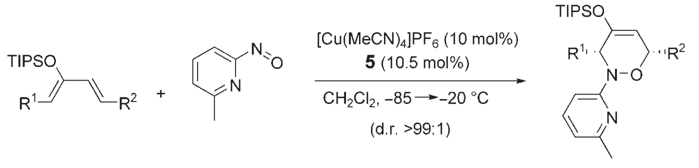
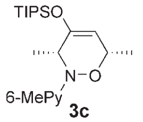
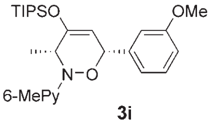
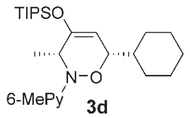
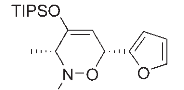
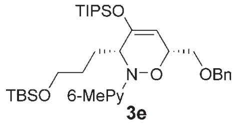
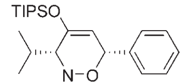
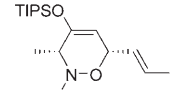
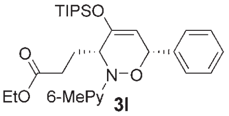
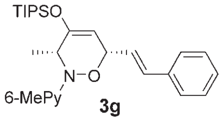
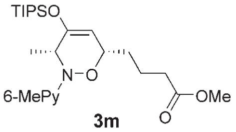
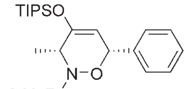
$[Cu(MeCN)_4(segphos)]PF_6$. Although this experiment gave complete regioselectivity[5] (4-silyloxy/5-silyloxy ≥ 99:1), the enantioselectivity (16% *ee* for the 4-silyloxy derivative) remained low. Surprisingly, the low enantioselectivity was improved significantly by simply increasing the size of the silyl group (**1a**γ**1b**γ**1c**): Up to 98% *ee* in the presence of Cu^I–segphos[6] and >99% *ee* with $[Cu(MeCN)_4(difluorophos)]PF_6$[7] were attained in the reaction of the triisopropylsilyl derivative **1c** (Table 1).

The applicability of this reaction was demonstrated for the functionalized dienes **1c–m** (summarized in Table 2). All of the reactions proceeded in high yields and enantioselectivities, with complete regio- and diastereoselectivities. The dialkyl-substituted dienes generally gave high enantioselectivities (Table 2, entries 1–3 and 11). Interestingly, reactions with trienes proceeded in a completely regioselective manner and provided only a single regioisomer (Table 2, entries 4 and 5).[8] Phenyl-substituted alkenes (R^2 = Ph) gave a relatively lower enantioselectivity (Table 2, entries 6 and 10), whereas methoxyphenyl derivitive **1i** and heteroaromatic **1j** gave high enantioselectivities (Table 2, entries 7, 8). Lewis basic substituents such as protected alcohols (Table 2, entry 3) and ester functional groups (Table 2, entries 10 and 11) were also used in the reaction and gave highly functionalized products enantioselectively.

Table 2: Reaction with various dienes.[a]

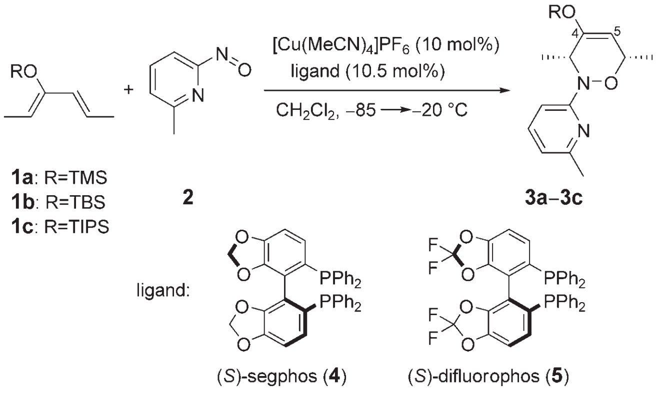


1c–1m **2** **3c–3m**

Entry	Product	Yield [%]	*ee* [%][b]	Entry	Product	Yield [%]	*ee* [%][b]
1	 **3c**	95	99	7	 **3i**	91	99
2	 **3d**	93	91	8	 **3j**	91	95
3	 **3e**	86	95	9	 **3k**	97	95
4	 **3f**	91	96	10	 **3l**	94	88
5	 **3g**	84	85	11	 **3m**	96	93
6	 **3h**	95	81				

[a] The reaction was conducted with catalyst (10 mol%), nitrosopyridine (1 equiv), and silyloxydiene (1.2 equiv) under N_2 at −85 °C and gradually warmed to −20 °C over 5 h. [b] The *ee* values were determined by HPLC analysis (Supporting Information).

Table 1: Effect of size the of the silicon group on the enantioselectivity.[a]



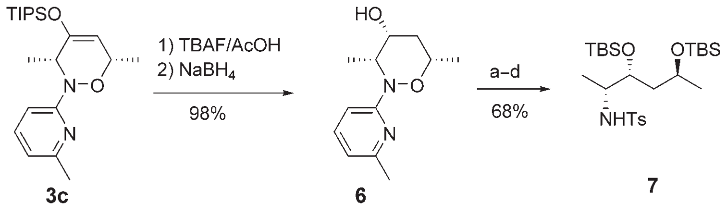
Entry	Diene	Ligand	Yield [%]	*ee* [%][b]
1	**1a**	**4**	86	16
2	**1b**	**4**	88	84
3	**1c**	**4**	93	98
4	**1c**	**5**	95	>99

[a] The reaction was conducted with catalyst (10 mol%), nitrosopyridine (1 equiv), and silyloxydiene (1.4 equiv) in a N_2 atmosphere at −85 °C and gradually warmed to −20 °C over 5 h. [b] The *ee* values were determined by HPLC (Supporting Information). TMS = trimethylsilyl.

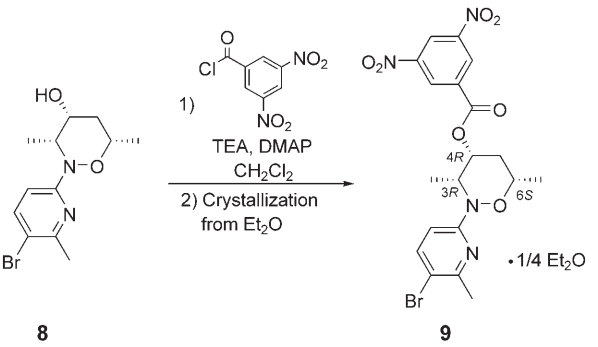
The products **3c–m** can be cleanly converted into the respective protected amino alcohol. For example, after hydrolysis of the silyl enol ether **3c** by TBAF/AcOH, reduction of the ketone gave the corresponding alcohol **6** as a single diastereomer.[8] Further transformations then gave the protected amino alcohol with a defined configuration that is found in several important natural products (Scheme 2).[9]

The absolute and relative configurations of the nitroso-Diels–Alder adducts were assigned by X-ray crystallographic analysis. Compound **8** was prepared under the standard reaction conditions discussed above, then further transformed into the 3,5-dinitrobenzoic acid ester **9**, which was crystallized from Et_2O (Scheme 3, Figure 1).[8]

The absolute stereochemical course of the reaction was found to be in accordance with the mechanistic model we previously reported (Scheme 4).[3] This model strongly supports the importance of the pyridine moiety in the formation of a highly organized chelating intermediate during the reaction. Such an effect could not be expected for nitrosobenzene.[2i]



Scheme 2. Conversion of the nitroso-Diels–Alder adduct into the protected amino alcohol **7**. Reaction conditions: a) Pd/C 10%, H_2, MeOH; then 2,2-dimethoxypropane, TsOH; b) Ts_2O, diethylisopropylamine, 1,2-dichloroethane; c) TsOH, MeOH; then TBSOTf, 2,6-lutidune, CH_2Cl_2; d) MeOTf, CH_2Cl_2; then 10 N KOH, MeOH. TBAF = tetrabutylammonium fluoride, Ts = *p*-toluenesulfonyl, TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl.



Scheme 3. Transformation of the alcohol **8** into the 3,5-dinitrobenzoic acid ester **9**. TEA = triethylamine, DMAP = 4-(dimethylamino)pyridine.

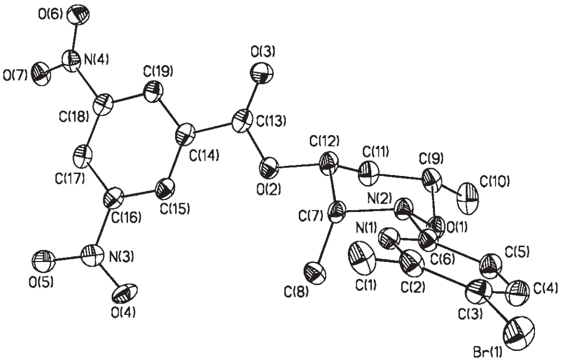
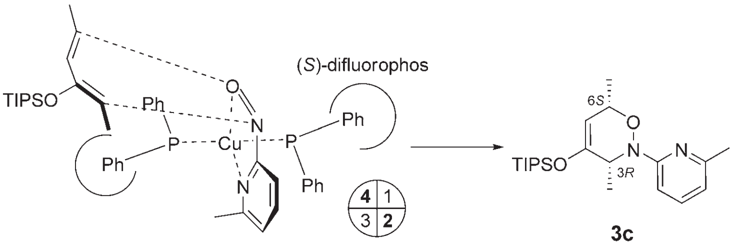
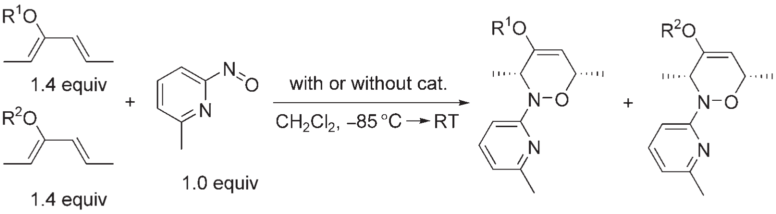


Figure 1. X-ray crystallographic structure of **9**, Et_2O is omitted for clarity. Elipsoids drawn at the 50% probability level



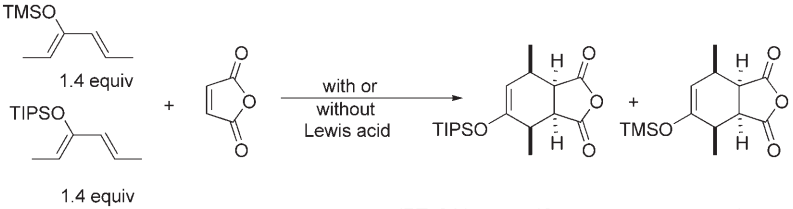
Scheme 4. Model for a plausible chelate intermediate.

The acyclic nitroso-Diels–Alder reaction proceeds exceedingly smoothly with TIPS derivatives, but rather slowly with TMS ethers, a fact that is of great mechanistic interest. 6-Methyl-2-nitrosopyridine (1 equiv) was treated with a 1:1 mixture of two silyloxydienes (1.4 equiv each) in competitive experiments with and without the use of a copper catalyst [Eq. (1)]. The OTIPS diene was clearly shown to be far more reactive than the OTMS or OTBS dienes.[10,11] A similar trend of differences in reactivity was observed for the Diels–Alder reaction of maleic anhydride with and without Lewis acid catalysis [Eq. (2)].

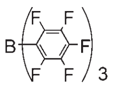


(1)

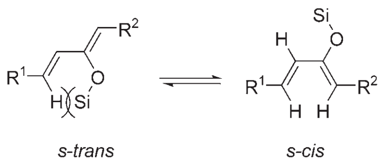
R^1 = TIPS, R^2 = TMS			
no catalysis	>99	:	<1
with $[Cu(MeCN)_4]PF_6$/difluorophos	>99 (99% *ee*)	:	<1
R^1 = TIPS, R^2 = TBS			
no catalysis	3	:	1
with $[Cu(MeCN)_4]PF_6$/difluorophos	11 (99% *ee*)	:	1



(2)

	no cat. (RT, 3 h)	10	:	1
with 2 mol%	 (−78 → 0 °C, 2 h)	15	:	1

The above reactions provide strong evidence that the high reactivity arises from the bulk of the TIPS group, which forces the diene to adopt an *s-cis* configuration in favor of the concerted [4+2] cycloaddition reaction [Eq. (3)].[12] A large



(3)

NOE interaction (10.7%) was observed between H1 and H4 of the OTIPS diene, whereas no significant NOE interaction was observed for the OTMS diene.[13] The difference in reactivity between Me_3Si and iPr_3Si can also be attributed to the exceedingly rapid copper-catalyzed nitroso-Diels–Alder reaction.

In summary, we have developed a highly practical and promising method for the regio-, diastereo-, and enantioselective introduction of oxygen and nitrogen groups into simple acyclic unsaturated ketones.

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[8] CCDC-271386 (**3g**), -271387 (**6**), and -271388 (**9**) contain 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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