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Niobium-Catalyzed Highly Enantioselective Aza-Diels–Alder Reactions

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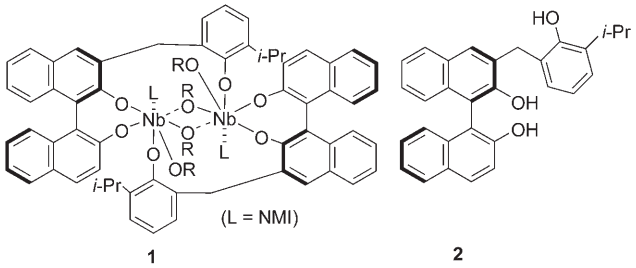
Abstract: Niobium-based chiral Lewis acid was found to be highly effective catalyst for aza-Diels–Alder reactions of imines with Danishefsky's dienes. The reactions proceed in high yield with high enantioselectivity for both aromatic and aliphatic imines. The developed methodology was applied to total synthesis of (+)-anabasine.

Keywords: anabasine; aza-Diels–Alder reaction; Lewis acid; niobium

The enantioselective aza-Diels–Alder reactions of Danishefsky's diene with imines[1] represent a useful route to chiral piperidine-enones, which themselves are important intermediates in the synthesis of highly functionalized piperidines.[2] Although remarkable progress has been made in the field of Lewis acid-catalyzed Diels–Alder reactions in recent years,[3] in the case of the aza-Diels–Alder reaction, an additional hurdle that must be overcome is the tendency of the Lewis acid to bind to the nucleophilic nitrogen atom of the reactants or product, leading to catalyst deactivation and low catalyst turnover, which makes the catalytic reaction difficult. Indeed, early attempts to catalyze aza-Diels–Alder reactions were plagued by this problem, which led to the requirement for stoichiometric use of catalyst/activator in some instances.[4] We have previously reported the first truly catalytic enantioselective aza-Diels–Alder reaction of imines with Danishefsky's diene using catalyst systems based on complexes of substituted 2,2′-binaphthol (BINOL) and Zr(IV).[5] Some other catalyst systems for the aza-Diels–Alder reactions of Danishefsky's diene based on Cu,[6] Ag[7] and Zn[8] as well as organocatalytic versions[9] of these reactions have been reported.



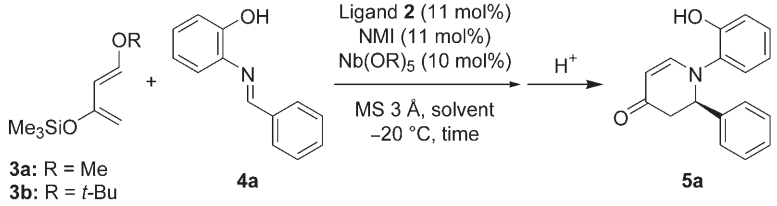
1 2

Figure 1. Tridentate ligand and proposed catalyst structure.

We have recently developed a highly functionalized chiral Nb(V) catalyst system **1** (Figure 1) generated from tridentate ligand **2** and related systems as catalysts for Mannich reactions[10] and the desymmetrization of *meso*-epoxides and *meso*-aziridines with aniline nucleophiles.[11] These catalysts are characterized not only by their ability to activate both oxygen-centered and nitrogen-centered electrophiles, but also by their ability to distinguish between small steric differences in substrates arising from their well defined asymmetric environments, which are believed to be due to a highly organized dinuclear bridged structure. We sought to investigate the chemical scope of this catalyst, and herein we report the first enantioselective aza-Diels–Alder reaction catalyzed by a niobium Lewis acid.

We initially prepared the catalyst from ligand **2** and $Nb(OMe)_5$ as the niobium source in the presence of *N*-methylimidazole (NMI) for 3 h at room temperature in dichloromethane (DCM). Gratifyingly we discovered that the catalyst prepared under these conditions efficiently promoted the reaction of Danishefsky's diene **3a**[12] with imine **4a**, where at −20 °C for 36 h, and following protic work-up the corresponding piperidine-enone **5a** was isolated in 76% yield with 81% *ee* (Table 1, entry 1). The *tert*-butyl-substituted diene **3b**, also reacted smoothly giving **5a** in 80% yield and 72% *ee* (entry 2). The absolute configura-

Table 1. Effect of solvents.



Entry	Diene	Conc. [M]	Solvent	Nb source	*t* (h)	Product **5a** Yield [%][a]	*ee* [%][b]
1	**3a**	0.2	DCM	$Nb(OMe)_5$	36	76	81
2	**3b**	0.2	DCM	$Nb(OMe)_5$	36	80	72
3	**3a**	0.2	PhMe/DCM[c]	$Nb(OMe)_5$	48	84	94
4	**3a**	0.1	PhMe/DCM[c]	$Nb(OMe)_5$	48	81	96
5	**3b**	0.1	PhMe/DCM[c]	$Nb(OMe)_5$	48	79	96
6	**3b**	0.1	PhMe/DCM[c]	$Nb(OEt)_5$	48	84	70
7	**3b**	0.1	PhMe/DCM[c]	$Nb(O\text{-}i\text{-}Pr)_5$	48	63	64

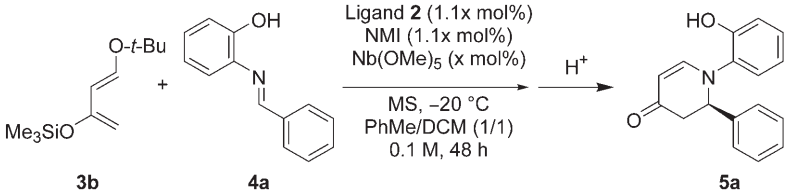
[a] Isolated yield.
[b] Determined by chiral HPLC. The absolute configuration assigned by X-ray analysis of the camphanic ester.
[c] PhMe/DCM = 1/1.

tion was established as *R* by reference to the single crystal X-ray diffraction analysis of the corresponding camphanic ester.[13]

Encouraged by these results we next set about optimizing the conditions for catalyst generation. After careful examination, we found catalyst generation in toluene at 60 °C for 3 h, followed by addition of the substrates **3a** and **4a** in DCM at −20 °C gave the corresponding product in 84% yield with 94% *ee* (entry 3). By performing the reaction under more dilute conditions, we were able to obtain **5a** in 81% yield and slightly improved *ee* (96%) (entry 4). Similar results were obtained with **3b** (entry 5). We next probed the effect of niobium sources from which catalyst may be generated, but soon discovered that the use of $Nb(OEt)_5$ or $Nb(O\text{-}i\text{-}Pr)_5$ gave the cycloaddition product with significantly lower enantioselectivity (entries 6 and 7).

We next turned our attention to the effect of desiccants and catalyst loadings. A range of experiments

Table 2. Effect of loadings and desiccants on the Nb catalyzed aza-Diels–Alder reaction.



Entry	**4a** [mmol]	Cat. **x** [mol%][a]	MS [mg]	Product **5a** Yield [%][b]	*ee* [%][c]
1	0.3	10[d]	3 Å (50)	81	96
2[e]	0.3	5	3 Å (50)	70	84
3	0.3	5	3 Å (25)	82	96
4	0.6	2.5	3 Å (25)	67	93
5	0.6	2.5	3 Å (12.5)	59	92
6	0.3	5	4 Å (25)	77	96
7	0.3	5	5 Å (25)	83	86

[a] 0.015 mmol catalyst used unless otherwise stated.
[b] Isolated yield.
[c] Determined by chiral HPLC.
[d] 0.03 mmol catalyst used.
[e] Reaction carried out at 0.2 M.

revealed that the ratio of the substrate to molecular sieves (MS) exerted a profound influence on the efficiency of the reaction. For example, in the reaction using 10 mol% catalyst (0.03 mmol) with 50 mg 3 Å MS the yield and *ee* were 81% and 96% respectively (Table 2, entry 1). However, reducing the catalyst loading to 5 mol% (0.015 mmol) whilst maintaining the amount of 3 Å MS at 50 mg led to a noticeable decrease in both yield and selectivity (70%, 84%, entry 2). Pleasingly, we discovered that by reducing the amount of molecular sieves to 25 mg and using 0.015 mmol catalyst (5 mol%), (i.e., the same ratio of MS to the catalyst to that of entry 1), both yield and selectivity were restored to the levels observed with 10 mol% catalyst loading (82% and 96%, respectively, entry 3). Reducing the catalyst loading still further to 2.5 mol% (0.015 mmol on an overall scale of 0.6 mmol) with 25 mg 3 Å MS resulted in a drop in yield to 67% although the product was still obtained in very high enantioselectivity (entry 4). Cutting the amount of molecular sieves further to 12.5 mg *versus* 0.015 mmol of catalyst had no positive effect, as the yield dropped still further although the *ee* was maintained (92%). Interestingly, use of other types of MS in the reaction (4 Å, 5 Å) in the ratio 25 mg/0.015 mmol also permitted the generation of the desired product with excellent enantioselectivity although with no advantage in yield compared with the procedure employing 3 Å MS.

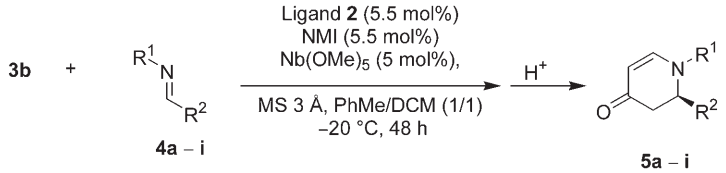
Having established optimum conditions for the reaction we turned our attention to probing the scope of the reaction with respect to the imine fragment. Reactions proceed smoothly with aromatic imines (Table 3, entries 1 and 2), and those bearing electron-donating (Table 3, entry 3) and electron withdrawing groups (Table 3 , entries 4 and 5), as well as heteroaromatic imines (entry 6). To our delight, the reactions of aliphatic imines generated *in situ* also proceeded in good yields with high enantioselectivities (entries 7–9).

The phenolic OH group *ortho* to the nitrogen atom is necessary for high yields and selectivities. When the OH group was substituted by a methoxy group, the reaction barely turned over and the piperidine-enone was formed in very low yield and enantiomeric excess (9%, 34% *ee*). The *ortho*-hydroxyphenyl group can be converted to the *o*-methoxyphenyl (OMP) group, a common nitrogen protecting.

To demonstrate the applicability of the developed methodology, we have synthesized the minor nicotine alkaloid (+)-anabasine (Scheme 1). First, the aza-Diels–Alder product (**5f**) was transformed to the corresponding methyl ether using methyl iodide/NaH in THF at 0 °C. After reduction using L-Selectride and free radical deoxygenation, the OMP protecting group was removed using CAN, giving the (+)-anabasine as a single enantiomer.

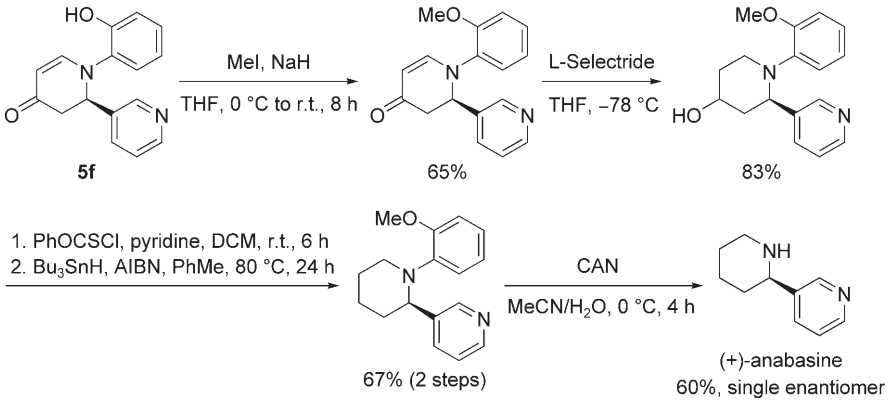
Based on several observations as well as single crystal X-ray diffraction data,[10] we tentatively assume a transition state for the reaction in which the imine is coordinated to niobium in a bidentate fashion displacing the NMI and one alkoxy group from the catalyst.

Table 3. Scope of the Nb(V)-catalyzed asymmetric aza-Diels–Alder reaction.



Entry	Imine	Solvent	R^1	R^2	Product	Yield [%][a]	*ee* [%][b]
1	**4a**	PhMe/DCM (1:1)	2-OH-C_6H_4	Ph	**5a**	81	96
2	**4b**	PhMe/DCM (1:1)	2-OH-C_6H_4	1-Naphthyl	**5b**	89	92
3	**4c**	PhMe/DCM (1:1)	2-OH-C_6H_4	4-Me-C_6H_4	**5c**	90	94
4	**4d**	PhMe/DCM (1:1)	2-OH-C_6H_4	2-CF_3-C_6H_4	**5d**	94	99
5	**4e**	PhMe/DCM (1:1)	2-OH-C_6H_4	2-Cl-C_6H_4	**5e**	89	91
6	**4f**	PhMe/DCM (1:1)	2-OH-C_6H_4	3-Pyridyl	**5f**	74	92
7[c,d]	**4g**	DCM	2-OH-5-Me-C_6H_3	*c*-Hex	**5g**	67	90
8[c,e]	**4h**	PhMe	2-OH-5-Me-C_6H_3	*i*-Pr	**5h**	63	92
9[c,e]	**4i**[f,g]	PhMe	2-OH-5-Me-C_6H_3	$CH_2CH(CH_3)_2$	**5i**	47	90

[a] Isolated yield.
[b] Determined by chiral HPLC.
[c] Imine generated *in situ* by condensation of the corresponding aldehyde and *o*-amino-*p*-cresol in the presence of $MgSO_4$.
[d] 4 Å MS used instead of $MgSO_4$.
[e] Reaction carried out at 0 °C.
[f] Imine added over 25 h.
[g] Reaction time 96 h.



Scheme 1. Synthesis of (+)-anabasine.

The rigid stereochemical environment generated by the ligand field then forces attack by the Danishefsky's diene approaching from the *re* face to give the piperidine-enone product with the observed *R* enantiomer with very high stereofidelity.

In conclusion, we have developed highly enantioselective aza-Diels–Alder reactions of imines with Danishefsky's diene, catalyzed by a chiral Nb(V) Lewis acid. It should be noted that high yields and enantioselectivities were obtained using both aliphatic and aromatic imines and that the reaction was applied to the synthesis of (+)-anabasine. Further studies aimed at broadening the scope of the reaction and elucidating the precise mechanism of the reaction are currently underway in our laboratories.

Experimental Section

Typical Procedure for the Aza-Diels–Alder Reaction Catalyzed by Niobium

To a solution of ligand **2** (7.8 mg, 0.018 mmol) in PhMe (1.0 mL), NMI (1.5 μL, 0.018 mmol) was added. After 5 minutes stirring, $Nb(OMe)_5$ (3.7 mg, 0.015 mmol) was added as a solid with gentle stream of argon. A trace of $Nb(OMe)_5$ which remained on the wall was washed with additional portion of PhMe (0.5 mL). The reaction mixture was heated to 60 °C for 3 h. After cooling to room temperature, molecular sieves 3 Å (25 mg) were added. The catalyst solution was cooled to appropriate temperature and a solution of imine (0.3 mmol) in DCM (1.5 mL) was added, followed by diene (0.4 mmol, 100 μL). After 48 h, the reaction mixture was quenched by addition of saturated $NaHCO_3$ solution (3 mL) and the resulting mixture was extracted with EtOAc (4 × 5 mL). The combined organic fractions were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was cooled to 0 °C and treated with 0.1 M HCl in THF (10 mL). After 15 min., the mixture was basified by addition of satutated $NaHCO_3$ solution and the product was extracted with EtOAc (4 × 5 mL). The combined organic fractions were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude mixture was purified by preparative TLC (hexane/EtOAc, 1/1) to give the product as a solid.

Three-Component Aza-Diels–Alder Reaction

The reaction was conducted in the same manner as described in the typical procedure. An imine was generated in DCM or PhMe (1.0 mL) from 2-amino-*p*-cresol (0.30 mmol) and an aldehyde (0.30 mmol) using $MgSO_4$ or 4 Å MS as a drying agent. After 2 h at room temperature, $MgSO_4$ was filtered off by inverse filtration using cotton wool on the top of a syringe needle, and the solution of the imine was added to the cooled solution of the catalyst. Another portion of the solvent (0.5 mL) was used to wash the $MgSO_4$ and then was added to the reaction mixture. The reaction was quenched and worked up in the same manner as in the typical procedure.

Acknowledgements

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