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First Asymmetric Synthesis of Quinoline Derivatives by Inverse Electron Demand (IED) Diels–Alder Reaction Using Chiral Ti(IV) Complex

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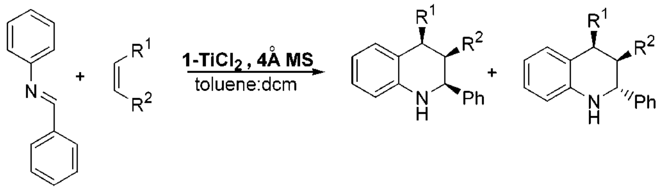
ABSTRACT



R^1, R^2 = (-OCH_2CH_2-), (-$OCH_2CH_2CH_2$-), (-CH=CH-CH_2-), (-OCH_2CH_3, H)

(*R,R*)-3-Aza-3-benzyl-1,5-dihydroxy-1,5-diphenylpentane (1) ligated Ti(IV) complex (1-$TiCl_2$) is used as a chiral Lewis acid catalyst for promoting asymmetric IED Diels–Alder reaction between electron-rich dienophiles and electron-poor dienes. Here we introduce a facile route for the synthesis of asymmetric tetrahydroquinoline derivatives using the above-mentioned chiral catalyst reagent in the presence of 4 Å molecular sieves. The reactions proceed with moderate yields and at times high enantioselectivty.

Inverse electron demand Diels−Alder (IED-DA) reactions are important in synthetic organic chemistry as they allow regio- and stereo-controlled formation of adducts in a single operation.[1] Though recently much work has been devoted to the diastereoselective IED Diels−Alder reaction, only a few asymmetric IED-DA reactions have been reported[2].

In nature quinoline ring systems are widely distributed. For synthesizing quinoline products various methods[3] are available, but reports on the synthesis of asymmetric quinoline derivatives are limited.[4] In the literature[5] we found IED-DA reactions could be used to synthesize quinoline derivatives[6] where cycloaddition of electron-poor 2-azadiene with electron-rich dienophiles could be facilitated by chiral Lewis acid catalysts.[6b] Here the reversible complexation with Lewis acids would make the 2-azadiene system more reactive in a concerted Diels−Alder process, because this will decrease the energy gap between the lowest unoccupied molecular orbital (2-azadiene) and highest occupied molecular orbital (dienophile).[7]

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In this context, we noted that the enantioselective addition of electron-rich dienophiles to benzylidene aniline with chiral Lewis acids as catalyst is still a relatively unexplored field. Earlier our group used **1-TiCl$_2$** complex as a Lewis acid promoter in the Diels–Alder reaction.[8a,b] As an extension of this work, in this paper, we explore the possibility of using this chiral Lewis acid catalyst as promoter in IED-DA reactions for synthesizing chiral heterocyclic compounds.

The preparation of chiral ligand **1** from benzylamine and homochiral styrene oxide was reported earlier.[8] We confirmed the structure of the ligand by its single-crystal XRD (Figure 1).

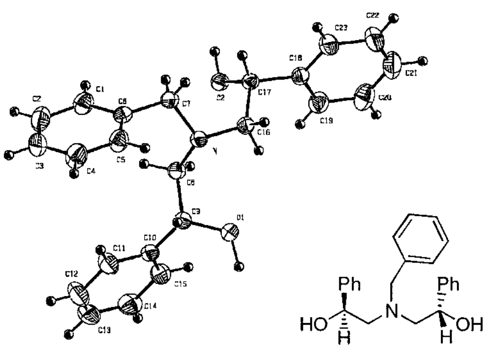


Figure 1. Single-crystal XRD of amino diol **1**.

On reacting **1** with the in situ formed titanium di(isopropoxide)dichloride, a solid was precipitated in hexane. The isolated complex, in mass spectrometry, showed the M$^+$ ion peak, which confirmed the formation of the catalyst. The study of single-crystal XRD of the **1-TiCl$_2$** complex is in progress. The titanium complex was used for accelerating the IED-DA reactions.

The electron-poor diene benzylidene aniline was prepared and recrystallized as per literature[9] and was used for further reaction. The dienophiles used were dihydrofuran, dihydropyran, ethylvinyl ether, and cyclopentadiene. It is known that in these reactions, the reaction conditions, as well as the combination of diene/dienophile, play important role in determining the exact course of addition. For example, in the reaction with enol ethers, acid catalysis leads to the tetrahydroquinoline derivative, whereas under neutral conditions with ketenes it afforded azetidinones.[10] Interestingly, however, neither the tetrahydroisoquinoline nor the Michael adducts formed in these reactions.[11] In total agreement with these results, we also obtained only the tetrahydroquinoline derivatives.

The proposed mechanism of formation of tetrahydroquinoline is shown in (Figure 2), where the nitrogen of the 2-azadiene group is coordinated to the **1-TiCl$_2$** complex and the reaction becomes faster.[7]

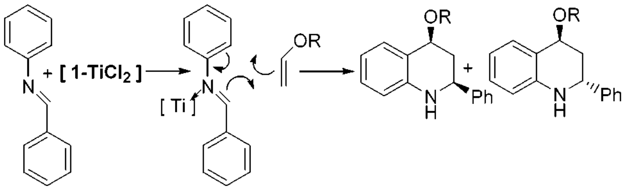
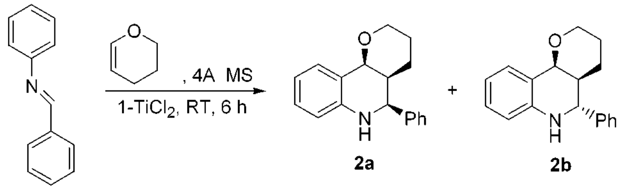


Figure 2. Proposed mechanism for the IED Diels–Alder reaction.

On examining the role of the solvents toward improving the efficiency of this reaction, we found that in dichloromethane medium alone the products were obtained in poor yield. With pure toluene, there was no reaction and the catalyst also decomposed over standing for a couple of hours. On switching to dichloromethane/toluene (1:1) mixture, the amount of conversion of the starting material improved but the enantiomeric excesses were still comparatively low. With dichloromethane/toluene (2:1) as solvent mixture, however, we noted better yields and better enantiomeric excesses (vide Table 1). From this one could infer that in low polarity solvents the catalyst is not stable. On going to a more polar solvent, the catalyst is less active, possibly as a result of a high degree of solvation leading to delinking of the ligand from the metal. We also attempted a three-component coupling reaction[12] in toluene, by preparing 2-azadiene in situ (by adding amine and aldehyde) in the presence of the dienophile, but this was not successful.

Table 1. Effect of Solvent in the IED Diels–Alder Reaction



			ee %	
solvent	% conversion	**2a/2b**	**2a**	**2b**
DCM	25	0.56	49	9
DCM:toluene (1:1)	43	0.54	52	13
DCM:toluene (2:1)	43	0.43	76	20
toluene				

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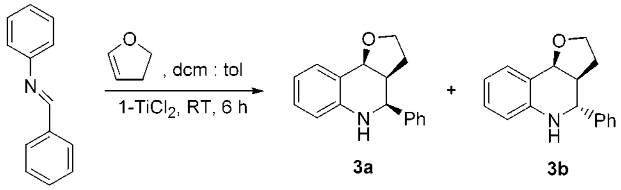
It is well-known[13] that addition of molecular sieves to the reaction mixture sometimes increases the enantiomeric excesses of the products obtained. Therefore to observe the effect of molecular sieves in the IED-DA catalyzed by the **1-TiCl$_2$** complex, we added various mol % of molecular sieves into the reaction mixture of dihydrofuran and benzylidene aniline and observed some increase in the enantiomeric excess. This may be due to absorption of water molecule present in the medium or the formation of certain active species with the molecular sieves in the presence of **1-TiCl$_2$** complex (Table 2).

Table 2. Effect of Molecular Sieves in the IED Diels−Alder Reaction



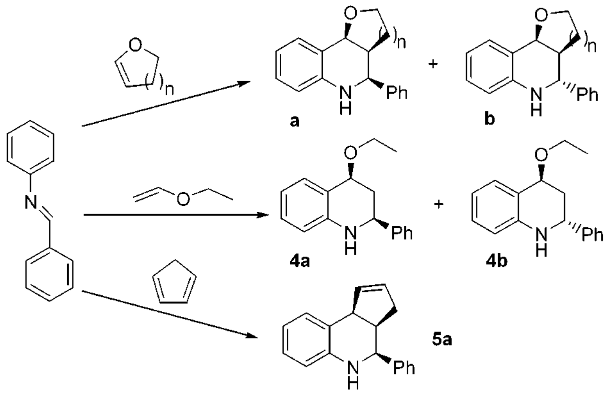
4 Å mol sieves (mol %)	% conversion	3a/3b	ee % 3a	ee % 3b
	47	0.67	13	5
10	49	1.86	47	17
20	48	0.67	34	18

As the product yields were poor in these reactions, we tried to increase the yield by adding indium chloride to the reaction mixture. The positive role of indium chloride in the imino Diels−Alder reaction has been reported earlier.[14] We hence surmized that **1-TiCl$_2$** complex can be activated by indium chloride. The effect of added external Lewis acid on the product yield and enantiomeric excess was studied by varying the ratio of InCl$_3$/**1-TiCl$_2$**, and the results are detailed in (Table 3). The results are not very encouraging, and the addition of InCl$_3$, while increasing the yields of the products, reduced the ee's considerably. We presume that both indium and titanium act independently as catalysts for the IED-DA reaction and do not lend to cooperative behavior between them.

Table 3. Effect of Indium Chloride with **1-TiCl$_2$** Complex

InCl$_3$ (mol %)	% conversion	3a/3b	ee % 3a	ee % 3b
0.0	49	1.80	47	17
0.5	66	1.94	5	10
1.0	70	0.67	10	18
1.5	70	0.67	14	5

Table 4. IED Diels−Alder Reactions with Various Dienophiles



no.	dienophile	*T* (°C)	% conversion	a/b	ee % a	ee % b
2	dihydropyran (*n* = 2)	0	60	0.25	92	10
3	dihydrofuran (*n* = 1)	0	50	2.33	82	90
3	dihydrofuran (*n* = 1)	−40	60	2.33	56	18
4	ethylvinyl ether	35	65	0.67	90	50
5	cyclopentadiene	35	58		51	

An obvious technique to increase the ee in such Lewis acid catalysis would be to lower the temperature, which could enhance the observed ee albeit with lower conversions. However, we found that at −78 °C the reaction failed to proceed, and at higher temperature (70 °C) the catalyst

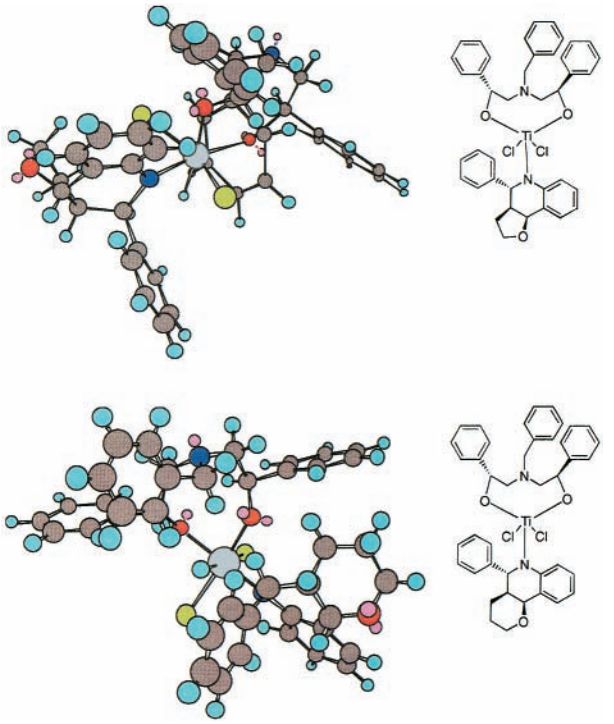


Figure 3. MMX energy minimized structure of **3b** (top) and **2b** (bottom). Blue, N; red, O; gray, Ti; brown, C; green, Cl; cyan, H.

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decomposed. Intermediate temperatures allowed the reaction to occur at varying rates. Reactions with different dienophiles such as cyclopentadiene[15] and ethylvinyl ether[16] were carried out using dichloromethane/toluene (2:1) solvent, 10 mol % of molecular sieves, and 20 mol % of catalyst. The results are given in Table 4.

The above results were rationalized by carrying out energy minimization studies using CS Chem3D modeling software available from Cambridge Software Corporation, U.S. The MMX energy minimized structures for the Lewis acid coordinated intermediates containing furan or pyran dienophiles (**2a**, **2b**, **3a**, **3b**) were chosen for the analysis and to provide better understanding of the enantioselectivities of the adducts at 0 °C.

MMX minimization and conformational search for models of enantioselection show that the planes of the furan ring and of the 2-phenyl in quinoline derivative occupy a disposition parallel[17] to the plane of the 1,5-diphenyl in **1-TiCl$_2$** as shown in Figure 3 (top) for **3b**. Also the energy minimization shows more steric energy for **3b** than **2b**, which confirms the presence of high steric hindrance in the formation of the **3b** adduct and leading to higher enantiomeric excess. However, in the case of **2b** (Figure 3, bottom) the plane of the pyran ring is perpendicular to the plane of 2-phenyl in the quinoline derivative, which is again perpendicular to the plane of the 1,5-diphenyl ring in **1-TiCl$_2$**, which might be the origin for the low enantioselectivity in the formation of **2b**.

In conclusion, **1-TiCl$_2$** complex is quite effective for asymmetric the IED Diels−Alder reaction of benzylidine aniline. The reaction conditions were optimized to give moderate yields and enantioselectivities. On adding molecular sieves into the reaction mixture we observed some increase in the enantioselectivity in the IED-DA reactions.

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Supporting Information Available: Experimental details and characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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