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Highly efficient enantioselective synthesis of optically active dihydropyrones by chiral titanium(IV) (5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-bi-2-naphthol) complexes

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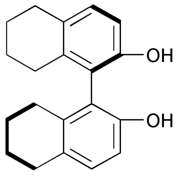
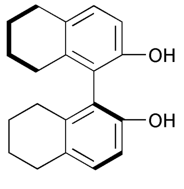
The asymmetric hetero-Diels–Alder reaction of Danishefsky's diene and an aldehyde catalyzed by 20 mol% chiral H_8-BINOL–Ti(IV) affords the corresponding 2-substitutent-2,3-dihydro-4*H*-pyran-4-one with ees of up to 99% under mild reaction conditions.

The formal hetero-Diels–Alder reaction between 1-methoxy-3-(trimethylsilyloxy)buta-1,3-diene and aldehydes provides useful access to dihydropyrones, a class of compounds with extensive utility in organic synthesis.[1] Asymmetric catalysis of this reaction has been previously reported by a number of investigators.[2] Corey *et al.* found that the tryptophan-derived oxazaborolidine catalyst gave good yields and moderate enantioselectivities for the reaction of Danishefsky's diene with representative aldehydes.[2a] Keck *et al.* reported that catalysts generated using 2 : 1 BINOL–Ti(O-i-Pr)$_4$ in the presence of 4 Å MS and 0.0003 equiv. of CF_3CO_2H led to dihydropyrones in Et_2O with good to excellent ee.[2b] Jacobsen and co-workers developed some chiral (Salen)Cr(III) catalysts which afforded cycloadducts with good enantioselectivity.[2c] However, progress in the area of asymmetric hetero-Diels–Alder reactions has been limited. A catalyst that can be used with a wide range of substrates will be pursued.



(*R*)-H_8-BINOL



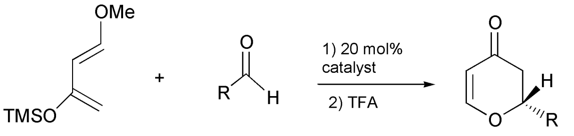
(*S*)-H_8-BINOL

5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-bi-2-naphthol (H_8-BINOL) is a new atropisomeric diol ligand, which possesses a unique structure compared to conventional BINOLs.[3] Chan *et al.* reported its outstanding asymmetric induction ability in the asymmetric alkylation of aromatic aldehydes with triethylaluminium.[4] Herein, we wish to describe that chiral H_8-BINOL–Ti(O-i-Pr)$_4$ complexes are more effective catalysts than BINOL–Ti(O-i-Pr)$_4$ and others for the asymmetric hetero-Diels–Alder reactions.

Our studies started with benzaldehyde as a test substrate. A H_8-BINOL–Ti(O-i-Pr)$_4$–4 Å MS system was found to be the most promising catalyst for this reaction. In toluene solvent and at 0 °C, benzaldehyde gave (*R*)-2-phenyl-2,3-dihydro-4*H*-pyran-4-one in 92% isolated yield with 97% ee (Table 1, entry 1). Further studies showed that several parameters were important for both the reactivity and enantioselectivity of the cycloaddition reaction. The best results were obtained when 1.1 equiv. of (*R*)-H_8-BINOL were used per Ti. A solvent study showed that toluene provided the best overall results.[5] The yield and enantioselectivity were also found to be dependent on temperature. When the reaction was carried out below 0 °C, dihydropyrone was obtained in lower conversion and enantioselectivity. The optimal temperature ranged between 0 and 14 °C depending on the aldehydes used. At rt, high yield (92%) and enantioselectivity (93% ee) were also obtained (Table 1, entry 3). It should be noted that the ee of 93% was particularly high at rt, since most precedent catalytic asymmetric hetero-Diels–Alder reactions require a rather low temperature (−78 to −30 °C) to attain a good level of enantioselectivity. The amount of the catalyst was also revealed to be an important parameter for the attainment of high enantioselectivity. When the amount of catalyst was reduced to 10 mol%, the enantioselectivity of the reaction was decreased considerably (Table 1, entries 1 and 2).

Encouraged by the result obtained for benzaldehyde (Table 1, entry 1), we investigated a number of other aldehydes to probe their behavior under the current catalyst conditions. As shown in Table 1, the aromatic, heteroaromatic, conjugated and aliphatic aldehydes afforded the corresponding product in moderate to high isolated yield with quite high ee. A comparison of the experimental results (Table 1, entries 1, 4–11) revealed the effect on enantioselectivity by *ortho*-substitutents on benzaldehyde. This was probably due to the

Table 1 Asymmetric hetero-Diels–Alder reactions of diene and aldehydes



(predominant enantiomer with (*R*)-H_8-BINOL)

Entry[a]	R	Temp/°C	Time/h	Yield (%)[b]	% ee[c]
1	Ph	0	24	92	97[d]
2[e]	Ph	0	12	75	73[d]
3	Ph	23–25	6	92	93[d]
4	*p*-$MeOC_6H_4$	0	24	52	>99
5	*p*-MeC_6H_4	0	24	60	99
6	*p*-FC_6H_4	0	24	54	98
7	*p*-NCC_6H_4	0	24	64	94
8	*m*-MeC_6H_4	0	24	81	99
9	*m*-ClC_6H_4	0	24	81	94
10	*o*-$MeOC_6H_4$	0	48	54	90[f]
11	*o*-ClC_6H_4	0	24	71	90
12	Furyl	0	30	78	96[g]
13	2-Py	0	24	55	92[f]
14	(*E*)-$CH_3CH{=}CH$	12–14	92	35	98
15	(*E*)-$PhCH{=}CH$	0	30	80	98[g]
16	n-C_8H_{17}	12–14	92	76	94

[a] All reactions were carried out using 20 mol% of catalyst as detail in the experimental procedure,[6] unless otherwise mentioned. [b] All yields are isolated yields. Satisfactory spectral data (^1H NMR, ^{13}C NMR, IR) and C, H, N combustion analyses were obtained for the new compounds. [c] In all cases ee was determined by HPLC using a chiral column (chiracel OD), unless otherwise mentioned. [d] Determined by GC using a chiral column (Cyclodex-β). Absolute configurations were *R*, which were determined by comparison of optical rotations with literature values.[2c] [e] The reactions were carried out using 10 mol% of catalyst as detail in the experimental procedure.[7] [f] Determined by HPLC using a chiral column (chiracel AD). [g] Absolute configurations were *R*, which were determined by comparison of optical rotations with literature values.[2c]

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strong steric hindrance effect of the *ortho*-substitutents, which weakened the coordination of the aldehyde and consequently lowered the enantioselectivity of reaction. These results are consistent with Chan *et al's* report about asymmetric alkylation of aromatic aldehydes with triethylaluminium.[4] The precise structure of the catalyst is not clear at present. An investigation of the mechanism is underway.

In conclusion, we have developed a new, highly efficient method for the synthesis of chiral 2-substitutent-2,3-dihydro-4*H*-pyran-4-one from aldehydes and Danishefsky's diene using chiral H_8-BINOL-Ti(IV).[3] High levels of enantioselectivity in the synthesis of 2-substitutent-2,3-dihydro-4*H*-pyran-4-one with wide substrate generality were obtained according to this reaction.

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5 A series of solvents was screened including toluene, TBME, CH_2Cl_2, DMF, Et_2O and THF.

6 A typical experimental procedure is given for the synthesis of (*R*)-2-phenyl-2,3-dihydro-4*H*-pyran-4-one: a mixture of (*R*)-H_8-BINOL (16.2 mg, 0.055 mmol), 1 M $Ti(O\text{-}i\text{-}Pr)_4$ in CH_2Cl_2 (50 μl, 0.05 mmol), and activated powdered 4 Å molecular sieves (120 mg) in toluene (1 ml) was heated at 35 °C for 1 h. The yellow mixture was cooled to rt, and benzaldehyde (26 μl, 0.25 mmol) was added. The mixture was stirred for 10 min and cooled to 0 °C. Danishefsky's diene (60 μl, 0.30 mmol) was added. The mixture was stirred at 0 °C for 24 h, then it was treated with 5 drops of TFA. After the mixture was stirred for 15 min at 0 °C, saturated $NaHCO_3$ (1.5 ml) was added, the mixture was then stirred for 10 min and filtered through a plug of Celite. The organic layer was separated, and the aqueous layer was extracted with ether (5 × 3 ml), the combined organic layers were dried over Na_2SO_4 and concentrated. The crude residue was purified by flash chromatography (petroleum ether–ethyl acetate, 4 : 1) to yield (*R*)-2-phenyl-2,3-dihydro-4*H*-pyran-4-one (40 mg, 0.23 mmol, 92% yield) as a clear oil. The isolated material was determined to be in 97% ee by chiral GC analysis (cyclodex-β, 159 °C, 20 min, isothermal, t_S(minor) = 14.43 min, t_R(major) = 14.66 min).

7 1-Methoxy-3-(trimethylsilyloxy)buta-1,3-diene was purchased from Lancaster with 95% content.