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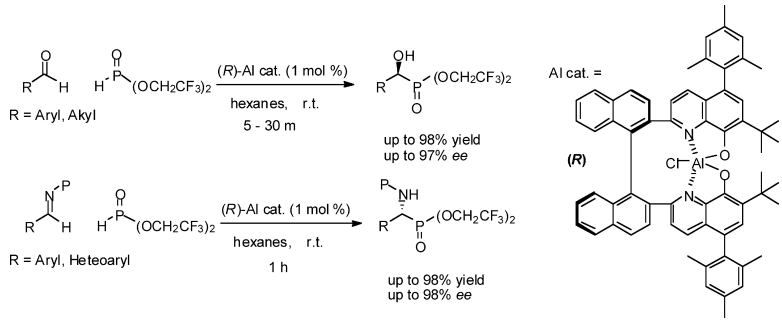

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Catalytic Enantioselective Pudovik Reaction of Aldehydes and Aldimines with Tethered Bis(8-quinolinato) (TBOx) Aluminum Complex

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The addition of dialkylphosphites to carbonyl compounds to generate α-hydroxyphosphonates, known as the Pudovik reaction, is a powerful and direct method for construction of C−P bonds. With the potential to synthesize biologically important phosphoderivatives of α-hydroxycarboxylic acids, this reaction has received deserved attention lately to make the process highly enantioselective.[1] To date several organocatalysts including Cinchona alkaloids[2] and chiral phosphoric acids,[3] Lewis acids including titanium,[4] late transition metals,[5] aluminum[6a] SALALEN,[6b] SALEN,[7] SALAN,[7] BINOL,[8] and chiral vanadium catalyst[9] have been utilized for this reaction. Unfortunately, these catalysts typically require high catalyst loading and long reaction times, usually ≥5 mol % or greater and several days.

Due to the recent success using the ligand **1** developed in our laboratory,[10] we envisaged that our ligand, when complexed with aluminum, could prove to be a highly selective and active catalyst for the Pudovik reaction. With the chiral tethered bis(8-quinolinato) (TBOxH) ligand in hand, complexation took place smoothly at room temperature by addition of a solution of Et_2AlCl (Scheme 1). This catalyst **2** was used under previously reported conditions; however, only low yields and enantioselectivities were observed (Table 1, entries 1−4). With these positive results we set out to find a more reactive system.

While the actual mechanism has not been experimentally confirmed, it is believed that the first step is deprotonation of the phosphite to generate a more highly nucleophilic species.[1d] The proton on the phosphite was found to be crucial for the enantioselectivity of the reaction.[11] Using a more electron withdrawing alkyl group on the phosphite the yield could be improved to synthetically useful levels. As shown in Table 1, the bis(2,2,2-trifluoroethyl) phosphite increased the yield to 94% and the enantioselectivity to 48% (entry 5).[12] With efforts now focused on increasing the enantioselectivity, increasing the size of the alkyl group only decreased the yield and selectivity (entry 6), possibly due to decreased nucleophilicity of the phosphite and increased steric environment. Decreasing the reaction temperature only decreased the reactivity while not increasing the enantioselectivity (entry 7). Interestingly, after screening the reaction conditions, decreasing the catalyst loading of the reaction increased the enantioselectivity while maintaining the same reactivity and yield (entry 8). This phenomenon was also observed with the work of North in the enantioselective silylcyanation reaction[13] and more closely related with Kee's hydrophosphonylation reaction.[7] Furthermore, it was found that nonpolar solvents gave higher enantioselectivity, with hexanes giving the highest reactivity and selectivity (entry 9).

With the influence of the phosphite and solvent now established, the ligand structure was examined (Table 2). The ligand structure was found to be highly influential on the enantioselectivity of the product. Simply attaching a phenyl substituent at the 5,5′-position of the quinoline ring led to a dramatic increase in enantioselectivity (entry 2). Pleased with this result we further examined other derivatives and found catalysts **4** and **5** to be most reactive and selective (entries 3 and 4). Since there was no change in yield and enantioselectivites of the most selective catalysts, catalyst **4** was chosen for further examination.

Having optimized reaction conditions, the substrate scope of the reaction was explored (Table 3). It was found that electron rich compared to electron poor aromatic aldehydes proved to be more reactive and selective (entries 6, 7, 9, 10). Aliphatic aldehydes could also be used, further establishing the utility of our system (entries 11,12). All reactions proceeded very quickly, with high yields and enantioselectivity. Furthermore, the catalyst loading could be decreased to 0.5 mol % with essentially no loss in enantioselectivity or yield with slightly prolonged reaction times (entries 1, 3, 7).

Upon further investigation of this ligand system with previously synthesized ligands by our group, it was found that the substitution at the 5,5′-position of the quinoline ring had a dramatic increase on the rate of the reaction. To demonstrate

Scheme 1. Synthesis of (*R*)-TBOxAlCl

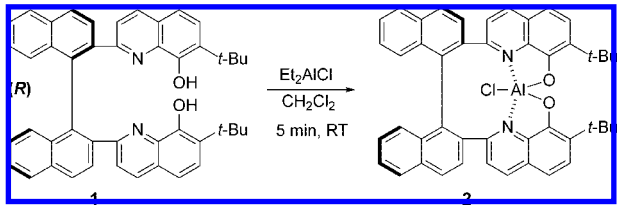
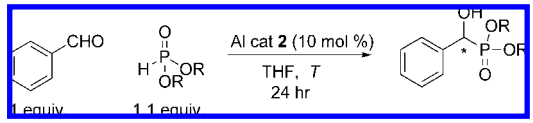


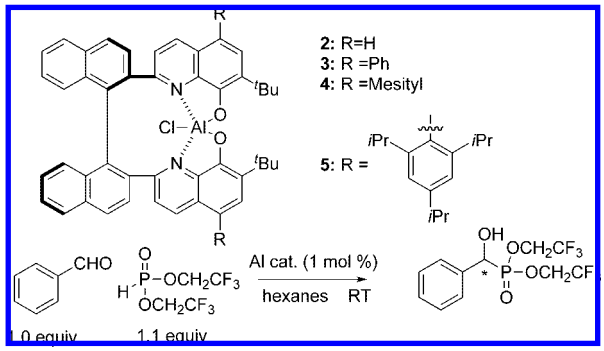
Table 1. Reaction Optimization



entry	R	*T*(°C)	yield (%)[a]	*ee* (%)[b]
1	Me	RT	20	24
2	Et	RT	18	23
3[c]	Me	RT	94	20
4	Ph	RT	48	<5
5[d]	CH_2CF_3	RT	94	48
6	$CH(CF_3)_2$	RT	30	<5
7[e]	CH_2CF_3	−15	27	50
8[f]	CH_2CF_3	RT	93	65
9[g]	CH_2CF_3	RT	94	78

[a] Isolated yield after column chromatography. [b] Determined by HPLC analysis. [c] 5.0 equiv of phosphite was employed. [d] Reaction was completed after 1 h. [e] Reaction not complete after 24 h. [f] 1 mol % catalyst employed. [g] Hexanes used as solvent.

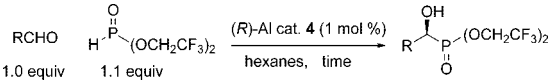
Table 2. Catalyst Optimization



entry	catalyst	yield (%)[a]	*ee* (%)[b]
1	2	94	78
2	3	95	91
3	4	96	96
4	5	95	96

[a] Isolated yield after column chromatography. [b] Determined by HPLC analysis.

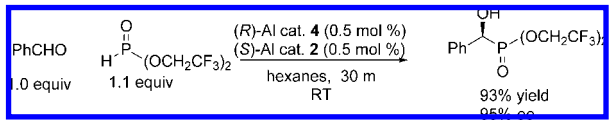
Table 3. Aldehyde Reaction Scope[d]



entry	R	time (min)	yield (%)[a]	*ee* (%)[b]
1	Ph	10	95 (94)	96 (95)[c]
2	2-naphthyl	15	98	95
3	4-ClC_6H_4	15	94 (93)	95 (93)[c]
4	4-BrC_6H_4	15	96	95
5	4-$NO_2C_6H_4$	10	93	92
6	4-$MeOC_6H_4$	10	93	97
7	4-MeC_6H_4	5	94 (94)	94 (94)[c]
8	3-$MeOC_6H_4$	20	93	95
9	2-$MeOC_6H_4$	10	93	93
10	2-MeC_6H_4	5	95	95
11[e]	*c*-hexyl	25	95	82
12[e]	*n*-hexyl	20	91	82

[a] Isolated yield after column chromatography. [b] Determined by HPLC analysis. [c] 0.5 mol % was employed in parentheses. [d] Absolute configuration determined by X-ray analysis of entry 4. [e] *Ee* determined after conversion to benzoate ester.

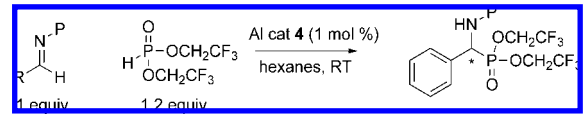
Scheme 2. Ligand Competition Experiment



the difference in reactivity, the enantiopure 5,5′-substituted ligand ((*R*)-Al cat. **4**) and an enantiopure unsubstituted oppositely stereoconfigured ligand ((*S*)-Al cat. **2**) were added in equal catalytic amounts to a reaction vessel and subjected to the typical reaction conditions (Scheme 2). It was found that the product was favored for the substituted ligand in the same enantioselection as the same ligand alone.

In light of the recent success with the simple synthesis of α-hydroxyphosphonates we expected that our aluminum catalyst could also be applicable to other electrophiles and the natural extension of aldehydes is aldimines. Synthesis of optically active α-aminophophonates has been the pursuit of several research groups.[12,14] Their potential use as proteinase inhibtors[15] as well

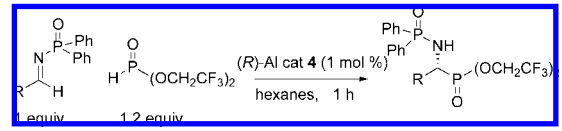
Table 4. Aldimine Protection Group Screening



entry	P	yield (%)[a]	*ee* (%)[b]
1	Boc	trace	ND
2	Bn	62	<5
3	Ph	35	15
4	DPP[c]	95	96

[a] Isolated yield after column chromatography. [b] Determined by HPLC analysis. [c] DPP = diphenylphosphinoyl.

Table 5. Aldimine Reaction Scope[c]



entry	R	yield (%)[a]	*ee* (%)[b]
1	Ph	98	96
2	4-ClC_6H_4	85	90
3	4-$BrC6_6H_4$	88	92
4	4-$NO_2C_6H_4$	90	88
5	4-$MeOC_6H_4$	91	90
6	4-MeC_6H_4	92	96
7	3-$MeOC_6H_4$	93	98
8	2-MeC_6H_4	90	90
9	2-MeC_6H_4	96	92
10	2-furyl	89	91
11	2-thienyl	93	94

[a] Isolated yield after column chromatography. [b] Determined by HPLC analysis (see Supporting Information). [c] Absolute configuration determined by optical rotation in comparison with previously reported α-amino phosphonic acid.

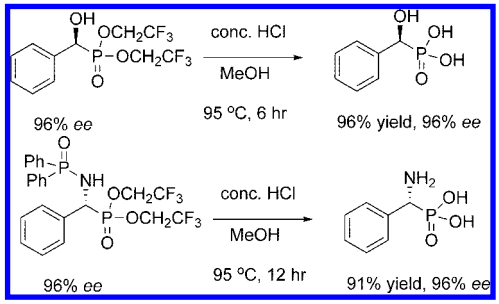
as antifungal[16] and antibacterial[16] agents highly depends on the absolute configuration of the α-carbon. To date only a few examples of catalyzed hydrophosphonylation to aldimines with a direct C−P bond formation exist.[12,17,18] Still improvements in the area of catalyst loading and reaction times can be made.

After screening several imines it was found that *N*-diphenylphosphinoyl imines provided the highest enantioselectivity and yield (Table 4). *N*-Diphenylphosphinoyl imines have been demonstrated previously as versatile electrophiles in a number of asymmetric reactions.[19] This labile nitrogen protection group is easily cleaved in mildly acidic conditions.

Using the typical reaction conditions the substrate scope of this reaction was established (Table 5). A variety of imines are well suited for this catalyst system including a number of subsituents and hetereoatoms. Electron rich aldimines showed higher reactivity (entries 5−9), while electron poor aldimines showed slightly diminished reactivity but still high yields of the protected amines (entries 2−4). This high enantioselection using both aldehydes and aldmines has been shown previously, albeit with longer reaction times and higher catalyst loadings.[17]

The use of optically active α-hydroxy- and α-aminophophonates to test for biological activity requires that the phosphorus moiety be deprotected to the free acid. Serveral reported procedures utilize either TMSBr,[1,20] TMSCl, and NaI[1,21] at room temperature or BBr_3[22] at elevated temperatures to deprotect the phosphonate ester; however, in our hands these procedures

Scheme 3. Synthesis of α-Hydroxy- and α-Aminophosphonic Acids



resulted in either no reaction or undesired side products. Although, simple acid hydrolysis was reported to be highly effective to generate the desired phosphonic acid.[14d] Attempting to deprotect the product in methanolic concentrated HCl at room temperature resulted in no reaction, but no loss in enantiopurity of the original substrate is observed. However, increasing the temperature to refluxing conditions provides the desired product almost quantitatively (Scheme 3). Subsequent protection of the hydroxy/amino moiety and reprotection of the acid to the methyl phosphonates provided the fully reprotected methyl phosphonates (see Supporting Information). We were pleased to find that no erosion in enantioselectivity is observed during the hydrolysis of the bis(2,2,2-trifluoroethyl) phosphonate ester moiety. Another unique feature of this system is that, with the protected amine in hand, both protecting groups can be removed in a single pot with acidic hydrolysis or selective deprotection of the phosphinoyl moiety using mildly acidic conditions. In addition, it was observed that the absolute configurations of the hydroxyl and amino products were oppositely stereoconfigured, presumably due to the single coordination of the aldehyde and the double coordination of the aldimine to the aluminum catalyst.

In conclusion, α-hydroxy- and α-aminophosphonates were synthesized in high yield and high enantioselectivies using low catalyst loading (0.5 to 1 mol %) and expedient reaction times. This is a significant improvement over other catalysts in that they usually require higher catalyst loading, typically ≥5 mol % or more and long reaction times. The ligand can be easily recycled after purification without any loss in reactivity or selectivity. The utility of this catalyst is currently under investigation for other asymmetric reactions.

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Supporting Information Available: Experimental procedures, spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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