ORGANIC LETTERS

2012
Vol. 14, No. 3
812–815

Enantioselective Acylation of 1,2- and 1,3-Diols Catalyzed by Aminophosphinite Derivatives of (1*S*,2*R*)-1-Amino-2-indanol

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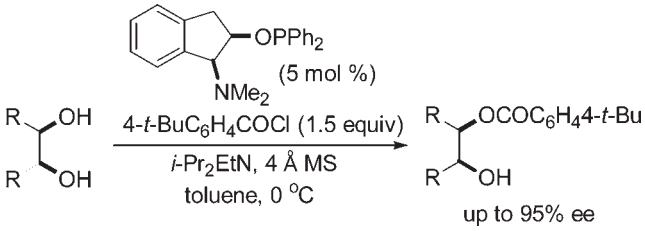
Received December 15, 2011

ABSTRACT



A phosphinite derivative that can be easily prepared in two steps from commercially available aminoindanol was found to be an effective catalyst for enantioselective acylation of diols. For the asymmetric desymmetrization of *meso*-1,2-diols, the corresponding monoester was obtained in up to 95% ee from the reaction in the presence of 5 mol % catalyst.

Asymmetric desymmetrization of diols, which has a plane of symmetry in the molecule, is an effective methodology for obtaining chiral multifunctional organic compounds.[1] Enantioselective acylation of alcohols has been frequently used as an effective transformation reaction for both asymmetric desymmetrization and kinetic resolution of racemic alcohols.[2] To date, nonenzymatic enantioselective acylation of alcohols for asymmetric desymmetrization has primarily been achieved by a strategy based on activation of acylating reagents by nucleophilic organocatalysts[3] or molecular recognition of diols by chiral metal complexes.[4] In particular, for the organocatalytic process, excellent catalysts in which a wide variety of nucleophilic functional groups serve as reactive sites have been reported.[5] In addition, the asymmetric desymmetrization of diols by silylation catalyzed by the nucleophilic organocatalyst has also been achieved.[6] Although these catalysts produce the desired chiral alcohol derivatives

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10.1021/ol2033459
Published on Web 01/19/2012

with a high level of enantioselectivity, multiple steps were occasionally needed for the preparation of the catalysts, and in some cases, only one of the enantiomers can be synthesized because of limitations to the available chiral reagent pool. We previously reported that phosphinite derivatives of cinchona alkaloids, such as **1** and **2** (Figure 1), are promising organocatalysts for asymmetric benzoylation of diols.[7] These catalysts can be prepared by one-step synthesis from cinchona alkaloids and effectively catalyze acylation of 1,2-diaryl-1,2-diols, a reaction having limited successful examples. For the acylation reaction, these

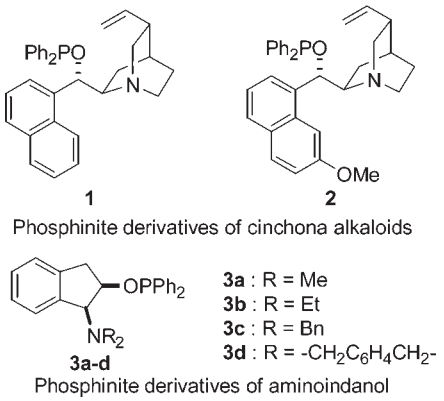

Figure 1. Phosphinite derivatives as acylation catalysts.

catalysts were assumed to be a bifunctional catalyst in which an amino and a phosphinite group cooperatively promote the reaction as a Brönsted and Lewis base, respectively. However, more than 30 mol % of catalyst loading was necessary for the reaction with many substrates, and the catalysts needed to be used immediately after their preparation because the tertiary phosphorus group is susceptible to oxidation. Therefore, we attempted to identify more reactive, tractable, and accessible small molecule organocatalysts, maintaining the effectiveness of the bifunctional catalyst.

Note that, after screening the available chiral aminoalcohols, *N,N*-dimethyl *cis*-aminoindanol phosphinite derivative **3a** (Figure 1), whose both enantiomers are commercially available, was found to be a more reactive and tractable aminophosphinite catalyst for enantioselective acylation of diols. Compound **3a** was easily synthesized in two steps from (1*S*,2*R*)-aminoindanol in high yield (Scheme 1), and its relatively stable crystals can be purified by standard column chromatography and stored under an argon atmosphere in the refrigerator for more than three months.

Initially, the reaction of *meso*-hydrobenzoin with benzoyl chloride in the presence of 20 mol % catalyst, diisopropylethylamine, and 4 Å molecular sieves was conducted

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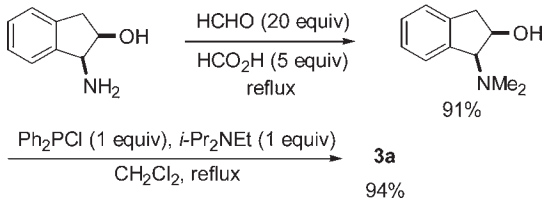
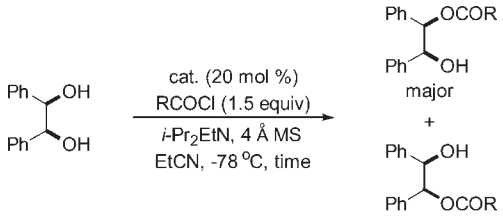
Scheme 1. Synthesis of Aminophosphinite **3a**



at −78 °C in propionitrile (Table 1). As a result, the corresponding ester was obtained with promising enantioselectivity (84% ee, Table 1, entry 1). On the other hand, similar aminophosphinite derivatives **3b**–**d** (Figure 1) with various nitrogen substituents provided the product

Table 1. Asymmetric Acylation of Hydrobenzoin Catalyzed by Aminophosphnites **3a**–**d**



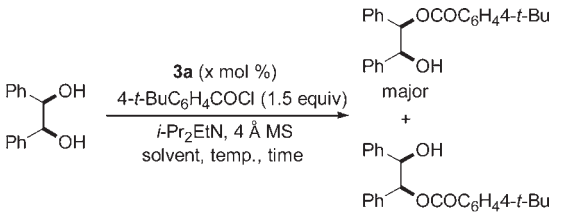
entry	cat.	R	time(h)	yield (%)[a]	ee (%)[b]
1	**3a**	Ph	5	77	84
2	**3b**	Ph	24	34	31
3	**3c**	Ph	24	49	6
4	**3d**	Ph	24	9	35
5	**3a**	4-*t*-BuC_6H_4	25	50	93

[a] Isolated yield. [b] Determined by chiral HPLC analysis.

in lower yield and with lower enantioselectivity. In addition, when 4-*tert*-butylbenzoyl chloride replaced benzoyl chloride as the acylating reagent for the reaction catalyzed by **3a**, the enantioselectivity of the product increased to 93% ee (Table 1, entry 5). The configuration of the major product was assigned to be (1*R*,2*S*) on the basis of the specific rotation of (*R*,*R*)-hydrobenzoin derived from the product via a Mitsunobu reaction using benzoic acid followed by hydrolysis (see Supporting Information).

Moreover, we evaluated other reaction solvents to further improve the stereoselectivity of acylation, and found that aromatic hydrocarbons were more effective solvents for the present reaction. In particular, the reaction using toluene as a solvent afforded the desired product in 97% yield and 95% ee even if the reaction was executed under reduced catalyst loading (5 mol %) at 0 °C (Table 2, entry 5). Benzene was also an effective solvent, and high stereoselectivity was retained even for the reaction with 2.5 mol % catalyst (Table 2, entry 8). Other hydrocarbons, such as mesitylene, cyclohexane, and chlorobenzene gave the product in lower yield as well as with low

Table 2. Screening of Reaction Conditions



entry	X	solvent	temp (°C)	time (h)	yield (%)[a]	ee (%)[b]
1	20	EtCN	−78	25	50	93
2	20	EtCN	0	12	82	74
3	20	toluene	0	12	93	95
4	10	toluene	0	12	98	94
5	5	toluene	0	12	97	95
6	2.5	toluene	rt	24	62	90
7[c]	5	toluene	rt	48	4	69
8	2.5	benzene	rt	24	71	93
9	2.5	mesitylene	rt	48	16	81
10	2.5	cyclohexane	rt	45	19	68
11	5	chlorobenzene	rt	45	54	78

[a] Isolated yield. [b] Determined by chiral HPLC analysis. [c] Reaction in the absence of 4 Å MS.

enantioselectivity (entries 9, 10, and 11, respectively). In the absence of 4 Å molecular sieves and under the optimized reaction conditions, drastic reduction in the yield and enantioselectivity of the product was observed (Table 2, entry 7). The effect of molecular sieves was originally investigated by Oriyama et al. in enantioselective acylation of alcohols catalyzed by chiral diamines, which were developed by his group.[5n] Similarly, molecular sieves were essential additives for the present reaction catalyzed by aminophosphinite derivatives.

Enantioselective acylation of 1,2-diols catalyzed by **3a** could be realized for aliphatic diols (Table 3). For example, the reaction of a 2,3-butandiol gave the corresponding ester with 89% ee (Table 3, entry 2). Furthermore, cyclic diol of 1,2-cyclohexanediol was converted to its ester with high enantioselectivity (93% ee), whereas the stereoselectivity of the reaction using 1,2-cyclopentanediol was moderate.

Compared to 1,2-disubstituted-1,2-diols, fewer examples of asymmetric desymmetrization of 2-substituted 1,3-propanediols have been reported.[8] This is possibly due to the fact that the pro-chiral center locates at a carbon atom adjacent to the carbinol groups and that primary hydroxyl groups are more reactive than secondary ones. We also previously attempted enantioselective acylation of 1,3-propanediol derivatives catalyzed by cinchona alkaloid phosphinite derivatives such as **1** and **2**; however, asymmetric induction was not observed in these reactions.[7a] For exploring versatility of catalyst **3a**, enantioselective acylation of 1,3-propanediol derivatives was attempted under

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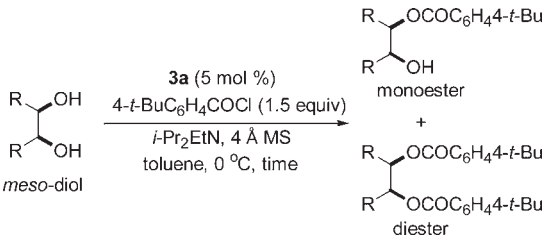
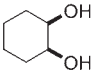
Table 3. Enantioselective Acylation of *meso*-1,2-Diols



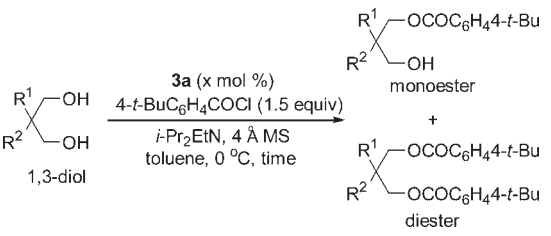
entry	*meso*-diol	time (h)	monoester yield (%)[a]	monoester ee (%)[b]	diester yield (%)[a]
1		12	97	95	nd[c]
2		24	82	89	< 1
3		12	83	93	2
4		12	96	59	< 1

[a] Isolated yield. [b] Determined by chiral HPLC analysis. [c] Not detected.

the optimized reaction conditions (Table 4). Although a substantial amount of diester was generated along with the desired monoester for all reactions, enantioselectivity for the acylation reaction was observed. In particular, for the reactions of aromatic or allyl 1,3-propanediol derivatives (Table 4, entries 1, 2, and 4), the yield and enantioselectivity of the products were maintained even though a reduced amount of catalyst (2.5 mol %) was employed. Meanwhile, the reaction of alkyl 1,3-propanediol or a substrate containing a quaternary center gave the monoester with lower enantioselectivity.

As described above, aminophosphinite derivatives were designed as Brönsted-Lewis dibasic bifunctional organocatalysts. For the acylation reaction catalyzed by aminophosphinite derivatives, the phosphinite moiety and not the amino group is assumed to serve as a Lewis base to activate the acylating reagent. Although we have no direct evidence for the reaction mechanism, aminoindanol derivative **4**, in which the phosphorus group is detached from the original catalyst and the oxygen atom of aminoindanol is acylated, was often isolated from the acylation reaction of alcohols catalyzed by **3a**. Derivative **4** was isolated as a single stereoisomer, and its configuration was in accordance with that of the original aminophosphinite derivative **3a**. In fact, the reaction of **3a** with 4-*tert*-butylbenzoyl chloride in the absence of alcohols afforded **4** having the same stereochemistry in 70% yield (Scheme 2). ^{1}H NMR and specific rotation of **4** was completely consistent with that of the product obtained from the reaction of *N*,*N*-dimethylaminoindanol with 4-*tert*-butylbenzoyl chloride in the presence of Hünig's base. The mechanism for the

Table 4. Enantioselective Acylation of 1,3-Diols



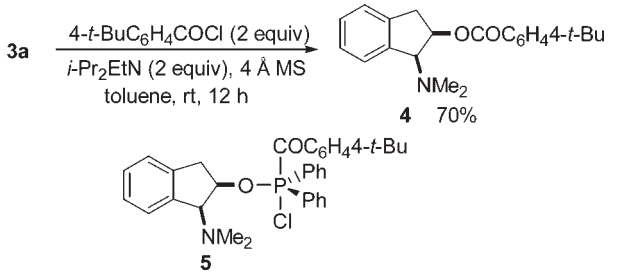
entry	1,3-diol	X	time (h)	monoester yield (%)[a]	monoester ee (%)[b]	diester yield (%)[a]
1	Ph, OH, H, OH	5	7	78	64 (*R*)	19
		2.5	8	71	63 (*R*)	11
2	4-ClC$_6$H$_4$, OH, H, OH	5	6	72	67 (nd)[c]	13
		2.5	8	77	66 (nd)[c]	11
3	Me, OH, H, OH	5	9	75	47[d] (*R*)	13
		2.5	11	51	45[d] (*R*)	8
4	OH, H, OH	5	8	76	60 (*R*)	11
		2.5	9	73	60 (*R*)	6
5	Ph, OH, Me, OH	5	12	55	42 (nd)[c]	7
		2.5	24	37	27 (nd)[c]	9

[a] Isolated yield. [b] Determined by chiral HPLC analysis. Symbols in parentheses indicate the absolute configuration of the major products. [c] Absolute configuration was not determined. [d] From chiral HPLC analysis of the acetate derivative of the monoester.

preparation of **4** cannot be clearly explained, but considering the retention of stereochemistry observed for **4**, a possible scenario would be ligand coupling[9] via pentacoordinated hypervalent phosphorus compound **5**. Although **5** and chlorodiphenylphosphine, which should be extruded from **5** through ligand coupling, could not be detected at present, it is implied that the phosphinite moiety could react with acyl chloride. On the other hand, the acylation reaction of *meso*-hydrobenzoin using **4** as a catalyst instead of **3a** gave only a trace amount of the racemate of the corresponding ester. Therefore, **4** was not a catalyst for the present acylation reaction.

(9) For a review on ligand-coupling reactions, see:Oae, S.; Uchida, Y. *Acc. Chem. Res.* **1991**, *24*, 202.

Scheme 2. Reaction of Acylating Reagent with Catalyst **3a**



In summary, aminophosphinite derivative **3a** was found to be an effective organocatalyst for asymmetric acylation of diols. In particular, the catalyst can be easily prepared from *cis*-aminoindanol, whose both enantiomers are commercially available, and can effectively catalyze asymmetric desymmetrization of *meso*-1,2-diols. The kinetic resolution of monoalcohols using the catalyst and studies on the reaction mechanism including the mechanism for the generation of **4** are in progress.

Acknowledgment. This work was supported by JSPS KAKENHI (Grant-in-Aid for Scientific Research (C), 21550102).

Supporting Information Available. Experimental procedure, compound characterization data, and NMR spectra for catalysts **3a**–**d** and products. This material is available free of charge via the Internet at http://pubs.acs.org.