2-Aryl-4,4,8-trimethyl-2-phosphabicyclo[3.3.0]octanes: Reactive Chiral Phosphine Catalysts for Enantioselective Acylation

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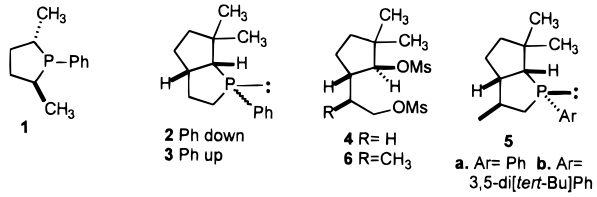
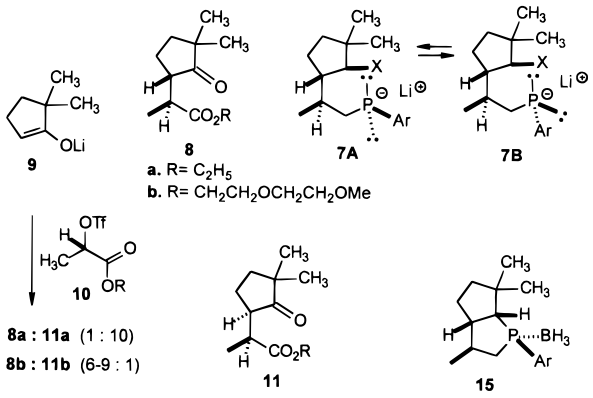
Exploratory studies stimulated by the discovery of chiral phosphine catalysis using **1** for enantioselective acylation[1] have encountered exceptional catalysts based on the 2-phosphabicyclo-[3.3.0]octane ("PBO") skeleton. The first member of this catalyst family (**2**) was found to activate *m*-chlorobenzoic anhydride for aroyl transfer in the kinetic resolution of phenyl *tert*-butyl carbinol. While the enantioselectivity was promising, (s = 14 at rt), we were intrigued to find that the reaction was >100-fold faster than with the original catalyst **1**, and that **2** was sufficiently active to induce acyl transfer with other anhydrides. However, the key cyclization step in the synthesis gave only 7% of **2** from the bis-mesylate **4** and $PhPH_2$/BuLi, together with 53% of the unreactive *exo*-phenyl isomer **3**. We therefore considered modifications of



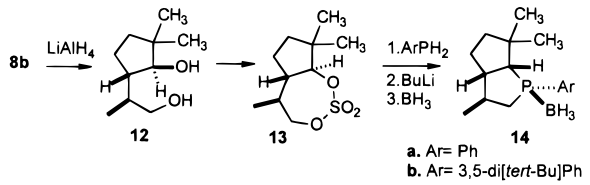
catalyst structure that might improve phosphorus diastereoselectivity in the cyclization, and that might also be convenient for enantiocontrolled synthesis of the bicyclic phosphine.

Catalyst **5** was selected as the target on the basis of the following considerations. Cyclization from **6** should reflect the relative stability of transition states similar to monoalkylated lithiophosphide rotamers **7A** and **7B**. If the methyl branch point destabilizes rotamer **7A** by 1,3-interactions vs **7B**, then the correct phosphorus configuration could be favored. Ester **8**, a logical precursor of **7**, should be accessible in nonracemic form if the alkylation of 2,2-dimethylcyclopentanone enolate **9** with the lactate triflate **10** can be controlled to give the correct diastereomer. This requires enantiofacial selectivity in the enolate alkylation, and stereospecific displacement of the triflate.

Alkylation of **9** with **10a** gave temperature-dependent mixtures of **8a** and the undesired **11a** (1:1 at rt; 1:10 at −60 °C) in THF. Similar product ratios, but poor conversions, were obtained in toluene. In an attempt to favor a more highly ordered transition state and to increase reactivity in toluene by incorporating greater lithium ion affinity in the ester, the methoxyethoxyethyl lactate triflate **10b** was tested in the alkylation. This experiment gave an inverted 9:1 ratio of **8b:11b** on millimole scale (7−8:1 ratio on multigram scale). The complementary selectivity of **10a** and **10b** toward the enolate **9** allows either enantiotopic face of **9** to be alkylated, a finding that may have other synthetic applications.



Diastereoselective reduction of **8b** to **12** followed by treatment with CH_3SO_2Cl/Et_3N afforded the bis-mesylate **6**, and reaction with $PhPH_2$/BuLi gave an encouraging 3:1 ratio in favor of the desired **5a** (36% yield). When the sequence was performed via the precedented[2] cyclic sulfate **13** in place of **6**, followed by BH_3 complexation, the ratio of **14a**:**15a** increased to 36:1 (85% isolated, 99.7% ee, using recrystallized **13**), and a similar experiment with 3,5-di[*tert*-Bu]$PhPH_2$/BuLi afforded the corresponding diastereomers **14b**:**15b** with a remarkable isomer ratio of 91:1 (85%). The stable borane adduct **14a** (Ar = Ph) was fully characterized, including confirmation of relative and absolute configuration by X-ray crystallography. Thus, **8** is formed with inversion of lactate configuration in the alkylation step.



Phosphines **5a** or **5b** were released by warming **14** with pyrrolidine and were evaluated as catalysts in the kinetic resolutions of alcohols **16** (Table 1).[3] The match of anhydride, catalyst, and substrate proved important. In the unique case of phenyl *tert*-butyl carbinol **16f**, catalyst **5a** was best, and the combination with benzoic anhydride gave the highest enantioselectivity **s**.[4] For a variety of other aryl alkyl carbinols, catalyst **5b** in combination with $(i\text{-PrCO})_2O$ in heptane was most effective.[5]

A striking improvement in enantioselectivity became possible when it was observed that acylations catalyzed by **5b** have an unusual temperature/reactivity profile (Table 1).[6] A temperature drop of 60 °C (rt to −40 °C) decreased typical acylation rates by less than a factor of 10! The spectacular enantioselectivities summarized in Table 1 result from the extraordinary range of accessible reaction temperatures in combination with relatively

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(2) Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1993**, *115*, 10125.

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(5) For less soluble alcohols, acylations with **5b** can be performed in toluene with a 2−3-fold decrease in rate and some loss in enantioselectivity, or less well in oxygenated or chlorinated solvents.

(6) One possible explanation is that lower temperature increases the equilibrium concentration of **17**, but other possibilities will need to be evaluated by kinetic studies.

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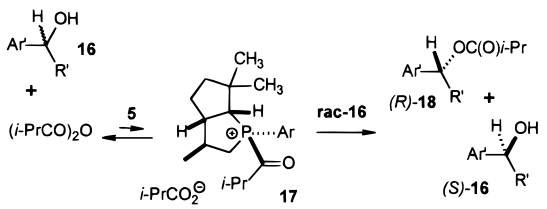
Table 1. Catalytic Kinetic Resolution of **16** Using 5/$(i\text{-PrCO})_2O$[a]

entry	Ar′, R′	struct	*s*	temp	h	% cat	conv	ee **18**[b]	ee **16**[c]
1	C_6H_5, CH_3	**16a**	22	rt	1	4	42.4	84.0	61.9
2	C_6H_5, CH_3	**16a**	42	−20 °C[d]	4	2.5	29.2[d]	93.3	38.4
3	1-*c*C_6H_9,[e]CH_3	**16b**	10	rt	5	5.5	41.0	72.3	50.2
4	1-*c*C_6H_9,[e]CH_3	**16b**	49	−40 °C	14	6.6	50.4	88.2	89.8
5	C_6H_5, *n*-C_4H_9	**16c**	18	rt	2	3.7	39.3	83.0	53.6
6	C_6H_5, *n*-C_4H_9	**16c**	57	−40 °C	8	3.9	51.3	88.6	93.3
7	C_6H_5, *i*-C_4H_9	**16d**	14	rt	2.5	3.9	46.4	76.1	65.9
8	C_6H_5, *i*-C_4H_9	**16d**	31	−40 °C[d]	7	3.5	41.9[d]	88.2	63.6
9	C_6H_5, *i*-C_3H_7	**16e**	20	rt	10	3.3	33.5	85.9	43.2
10	C_6H_5, *i*-C_3H_7	**16e**	100	−40 °C	42	2.8	46.9	94.8	83.8
11	C_6H_5, *t*-C_4H_9	**16f**	24[f,g]	rt	12	4.0	53.1	78.5	88.7
12	C_6H_5, *t*-C_4H_9	**16f**	67[f,g]	−40 °C	65	4.9	45.8	93.1	78.7
13	*o*-$CH_3C_6H_4$, CH_3	**16g**	39	rt	1	3.2	44.4	89.6	71.6
14	*o*-$CH_3C_6H_4$, CH_3	**16g**	145	−40 °C	4	3.5	50.1	94.9	95.3
15	*o*-$CH_3OC_6H_4$, CH_3	**16h**	38	rt	1.5	5.6	36.5	91.5	52.5
16	*o*-$CH_3OC_6H_4$, CH_3	**16h**	81[g]	−40 °C	9.5	6.8	28.7	96.5	38.8
17	α-naphthyl, CH_3	**16i**	41	rt	1	2.7	42.0	90.9	65.8
18	α-naphthyl, CH_3	**16i**	99[g]	−40 °C	7	3.9	29.8	97.0	41.2
19	mesityl, CH_3	**16j**	15[g,h]	rt	10	3.8	40.2	79.2	53.4
20	mesityl, CH_3	**16j**	369[g,h,i]	−40 °C	16	12.1	44.4	98.7	78.8

[a] All reactions with 99.7% ee **5b** in heptane, 0.1 M substrate, unless noted; rt reactions were done without positive temperature control; −40 °C experiments were controlled; absolute configuration by comparison with the sign of optical rotation for the known alcohols; ee determination by HPLC or GLC (entries 3, 4); empirical *s* values; see Supporting Information for *s* values corrected for 99.7% ee catalyst. [b] Product ee after saponification. [c] Unreacted substrate ee. [d] Reaction at 0.05 M substrate. [e] 1-Cyclohexenyl. [f] Catalyst = **5a**; anhydride = Bz_2O. [g] Toluene solvent. [h] **5b** with >99.9% ee was used. [i] *s* = 389 in a duplicate run.

typical temperature effects on $\Delta\Delta G^*$. Preliminary experiments indicate that some of the unhindered substrates can be acylated even at −78 °C. Especially rapid acylations were observed using acetic anhydride, but enantioselectivities were significantly lower.[7]

Acylation rates are qualitatively proportional to the concentration of the anhydride as well as the catalyst, consistent with reversible formation of transient **17** and rate-determining conversion to **18**. This information can be useful for designing preparative scale experiments using <1% catalyst. However, the data in Table 1 underestimate catalyst reactivity because no special precautions were taken to exclude oxygen (nitrogen bypass system; 3−6% **5b**). In a typical experiment, this results in 15−30% loss of catalyst due to phosphine oxide formation (NMR assay). For extrapolation to preparative scale, a more rigorous test experiment is recommended to establish % conversion vs time. Thus, entry 14 was repeated on 0.1 mmol scale in deoxygenated heptane using 0.8 ± 0.1 mol % **5b**, resulting in 51.2% conversion to **18g** after 14h. A gram-scale (7.5 mmol) kinetic resolution of *o*-methylphenyl-1-ethanol, (*rac*)-**16g**, was then performed under similar conditions (deoxygenated heptane), but using 0.6 mol % catalyst (16 mg; 0.045 mmol). After 14 h at −40 °C, isopropylamine was added to quench the anhydride, and ester *(R)*-**18g** (48.5% conversion) was obtained with 95.7% ee (48% isolated), while 46% of *(S)*-**16g** was recovered (90.2% ee; *s* = 142, preparative scale). According to NMR assay, **5b** survived acylation and workup (<10% phosphine oxide formation), but catalyst recovery was not explored because **5b** has been prepared on multigram scale.[8]



The data in Table 1 were obtained using **5b** prepared from **13** with 99.7% ee. According to a recent mathematical analysis, even this small level of catalyst contamination can result in substantially underestimated values for *s* when selectivities are high.[9] To test this proposition, **5b** was repurified (99.7% ee material recrystallized twice). The ee for the resulting **5b** could not be measured with precision, but a repeat of entry 14 gave *(R)*-**18g** with 95.2% ee at 50.7% conversion, and *(S)*-**16g** was recovered with 98.0% ee, values clearly improved over the original results and corresponding to *s* = 188! The value predicted[9] if **5b** has been upgraded from 99.7% ee to ≫99.9% ee is *s* = 186. The corrected number is highly sensitive to assay error in catalyst ee while the experimental *s* is also dependent on assay precision, and on predictable kinetic behavior in the resolution. Therefore, reliance on corrected *s* values would not be advisable unless experimental data are available for the purified catalyst. Furthermore, the exact value of *s* is not important when selectivities are so high. Nevertheless, the mathematical correction is relevant now that there are examples where chiral phosphine catalysts can be compared favorably with enzymatic catalysts.[10] The latter presumably have ≫99.9% ee, so that comparisons with the nonenzymatic catalyst having 99.7% ee would be misleading. Of course, yields and ee values near 50% conversion provide a more meaningful way to evaluate exceptionally enantioselective catalysts for practical use.

One added example **16j** was studied using twice recrystallized **5b** and isobutyric anhydride (entries 19,20). Despite the modest *s* = 15 measured in toluene at room temperature, the −40 °C experiment gave *s* = 369 and 389 in duplicate runs. A promising value of *s* = 21 was measured in heptane at room temperature, but the corresponding experiment at −40 °C was not feasible due to solubility limitations. Alcohol **16j** also proved to be an excellent substrate for kinetic resolution when **5b** was used in combination with acetic anhydride, and *s* = 112 was measured at −40 °C in toluene (51.8% conversion; **16j**, 98.6% ee, product **18j**, 91.6% ee after saponification).

Further studies are planned to explore the promising allylic alcohol substrates (entry 4), to probe structure/enantioselectivity correlations of Ar−PBO catalysts for a variety of applications, and to better understand transition state preferences.[11]

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Supporting Information Available: Experimental procedures, characterization of new compounds, ee assay data, and X-ray data for **14b** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) For example, *s* = 10 for **16a** using **5b**/Ac_2O in toluene at −40 °C.

(8) Upon request from North American research groups, 15 mg samples of **14b** can be provided on a limited basis to test new alcohol resolutions in exchange for data.

(9) Ismagilov, R. F. *J. Org. Chem.* **1998**, *63*, 3772. The correction can become quite large if s is large because the contaminating catalyst enantiomer has high reactivity toward the (*S*)-alcohol, and because the (*S*):(*R*) ratio increases as conversion approaches 50%.

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(11) Early results suggest that cyclic analogues of **16** (Ar′ joined to R′) do not match the transition-state requirements for good selectivity with **5b**/(*i*-PrCO)$_2$O: *s* < 2 for α-indanol or α-tetralol at rt.