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Tetrahedron Letters
Tetrahedron Letters 47 (2006) 2141–2145

Phosphine-catalyzed enantioselective [3+2] annulations of 2,3-butadienoates with imines

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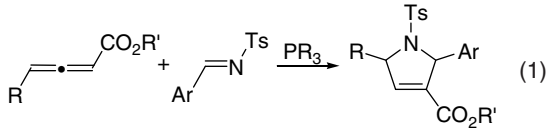
Received 29 November 2005; revised 20 January 2006; accepted 24 January 2006
Available online 10 February 2006

Abstract—The first systematic screening of chiral phosphines in the cycloaddition reaction between 2,3-butadienoates and arylimines has led to the identification of fairly efficient catalysts. 2-Aryl-3-pyrrolines have been obtained with enantiomeric excesses up to 64%. In one instance, the enantiomeric excess could be increased to 91% ee by combining the enantioselective cyclization reaction with a crystallization step.

Tertiary phosphines are known to be effective nucleophilic catalysts for a number of organic transformations[1] including the cycloadditions of 2,3-butadienoates and other electron-poor allenes with imines. The outcome of these last annulation processes appears to be dependent on the substitution scheme of the allene moiety: allenes bearing enolizable α-carbons lead to tetrahydropyridine derivatives,[2,1g] while other allenes afford 3-pyrrolines, as shown in Scheme 1.[3]

The last reaction provides a potentially convenient, nevertheless underdeveloped tool for the synthesis of functionalized pyrrolines, which are useful intermediates for the synthesis of natural products[3b] and pharmaceutically relevant compounds[4] bearing five-membered nitrogen heterocycles. Due to its significant synthetic potential, the development of an enantioselective version of reactions (1) by using chiral phosphines as catalysts,[5] might be an important objective. We report here on a preliminary screening of both commercially available chiral phosphines and chiral phosphetanes from our previous studies,[6] as nucleophilic catalysts for the 3-pyrroline synthesis shown in Scheme 1.



Scheme 1.

The [3+2] cycloaddition reaction was initially explored by reacting, in standard conditions, ethyl 2,3-butadienoate with either *N*-*p*-toluenesulfonylbenzaldimine or *N*-*p*-toluenesulfonyl-1-naphthaldimine[7] in dichloromethane, at room temperature, in the presence of a 10% amount of representative chiral phosphines (Table 1).

From these preliminary tests, BINAP (entry 1) and ferrocenylphosphetanes[8] (entries 8 and 9) emerged as catalysts giving comparatively high enantioselectivities, with ees up to about 30% and 45%, respectively, for the two substrates. Other chiral phosphines, including Me-BPE which is known to afford significant enantioselectivity in analogous cycloaddition reactions,[1g] afforded ees lower than 20%.

Further studies have been run then in order to evaluate the effects of various parameters and reaction conditions on both conversion rate and selectivity.

Changing the ester group in the 2,3-butadienoates[9,10] has an appreciable influence on the enantioselectivity: as shown in Table 2 for the FerroTANE promoted reactions, higher ees are generally obtained with bulkier ester groups. A *tert*-butyl group decreases, however, the observed conversion rates.

Keywords: [3+2] Cycloadditions; Enantioselective organocatalysis; Phosphines; 3-Pyrrolines.
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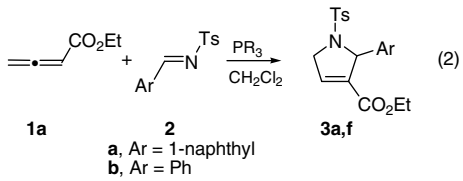
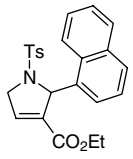
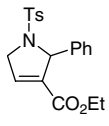
doi:10.1016/j.tetlet.2006.01.122

Table 1. Survey of chiral phosphine catalysts for the asymmetric [3+2] cycloadditions of imines with allenes





3a

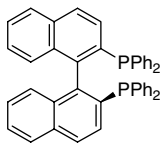


3f

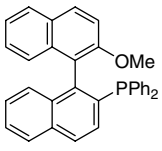
Entry	Catalyst	ee[b]	Yield[a] (%)	ee	Yield (%)
1	(*S*)-BINAP	**45%** (+)	13	18% (+)	12
2	(*R*)(+)-MOP	11% (+)	45		
3	(*R*,*R*)-Trost ligand	19% (−)	60		
4	(*R*)-PHOX	0%	18		
5	(*R*,*R*)-Me-BPE	0%	70		
6	(*R*,*R*)-Me-DuPHOS			7% (−)	21
7	(*R*,*S*)-Josiphos			15% (+)	27
8	(*R*,*R*)-Et-FerroTANE	22% (+)	47	**28%** (+)	32
9	(*S*,*S*)-*i*Pr-**A**	**44%** (+)	34	**29%** (+)	23

[a] Conditions: room temperature, reaction time 24 h; substrate concentration 0.2 M, 0.5 mmol scale.

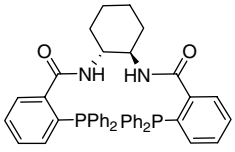
[b] Enantiomeric excesses have been obtained by HPLC. For **3a**: Chiracel AD column, hexane/*i*-PrOH 80/20, 1 mL/min, UV detection at 224 nm. retention times 12.0 ((+)-enantiomer) and 13.6 min. For **3f**: Chiracel OD column, hexane/*i*-PrOH 80/20, 1 mL/min, retention times 9.6 and 12.0 ((+)-enantiomer) min. The absolute configurations of the final 3-pyrrolines are unknown: they are specified only by the sign of optical rotation ($c = 1$, $CHCl_3$).



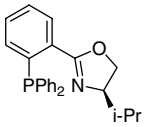
BINAP



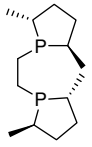
MOP



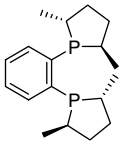
Trost ligand



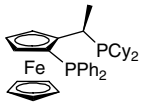
PHOX



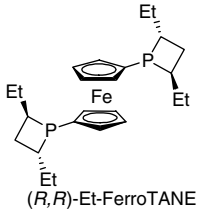
(*R*,*R*)-Me-BPE



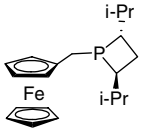
(*R*,*R*)-Me-DuPHOS



(*R*)(*S*)-Josiphos



(*R*,*R*)-Et-FerroTANE



(*S*,*S*)-iPr-**A**

Results in Table 2 also show that the nature of the R-substituents of FerroTANEs modulates as well conversion rates and enantioselectivities. Thus, simultaneous tuning of both ester groups and FerroTANE substituents are required to optimize the enantioselectivity while retaining acceptable conversion rates. In the (ferrocenylmethyl)phosphetanes series R-**A**, changing the R-substituent from *tert*-butyl to *i*-propyl and cyclohexyl increases slightly the enantiomeric excess of the cycloaddition leading to **3a** (up to 48% ee).[11]

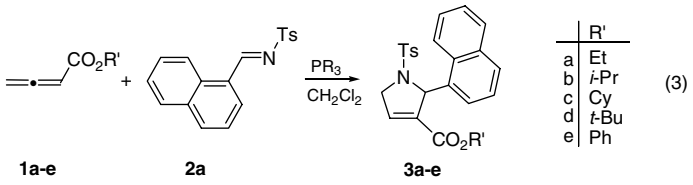
Solvent displays a dramatic effect on the enantioselectivity of the model reaction leading to pyrroline **3a** (Eq. 2). For instance, when using the P-ferrocenylmethylphosphetane (*S*,*S*)-*i*Pr-**A** as the catalyst, dichloromethane and acetone are the best suited solvents, which give ees of 44% and 41%, respectively, while in toluene,[12] ethyl acetate and THF ees lower than 10% were obtained. Moreover, an inversion of configuration was observed for the final 3-pyrroline **3a** when MeOH or toluene were used as the solvents.

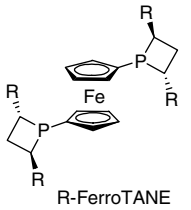
The role of solvents cannot be rationalized easily: it should be related to the relative stabilizing effects and/or charge separation in the zwitterionic intermediates of the catalytic cycle.[3]

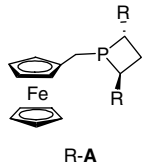
Based on the preliminary results in Table 1, the screening of chiral catalysts has been extended then to additional atropisomeric phosphines, ferrocene-based phosphines as well as to PHANEPHOS whose three-dimensional structure, with two aromatic rings facing each other, somewhat reminds that of ferrocene moieties (Table 3).

Results in Table 1 show that BINAP can afford significant ees, its catalytic activity is however very low. Thus, with the aim of improving the catalytic activity, two additional atropoisomeric phosphines, QUINAP and MeO-BIPHEP, have been evaluated. The use of MeO-BIPHEP improves, to some extent, both the catalytic activity and the enantioselectivity (up to 53% ee), conversion rates are however still moderate. QUINAP displays comparatively high activity but low enantioselectivities.

Table 2. Tuning of the substrate ester groups and substituents of the phosphetane rings







Substrate	(*R*,*R*)-Et-FerroTANE		(*S*,*S*)-*i*Pr-FerroTANE		R-**A**		
					(*S*,*S*)-*i*Pr	(*S*,*S*)-Cy	(*R*,*R*)-*t*Bu
	ee	Conv.[b] (%)	ee[c]	Conv. (%)	ee	ee	ee
1a, R′ = Et	22 (+)	60	37 (+)	82	44% (+)	**48% (+)**	28% (−)
1b, R′ = *i*-Pr	**52 (+)**	44	44 (+)	27			
1c, R′ = Cy	31 (+)	72 (98[a])	**46 (+)**	77 (96[a])		n.d.[d]	
1d, R′ = *t*-Bu	**60 (+)**	36	48 (+)	10			
1e, R′ = Ph	2 (+)	63	44 (+)	48			

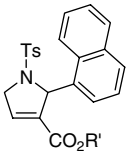
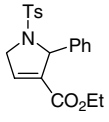
[a] Substrate concentration = 0.6 M.
[b] In addition to **3**, unreacted **2a** and, sometimes small amounts of the corresponding aldehyde are observed in the reaction mixtures.
[c] Enantiomeric excesses have been determined by HPLC, Chiracel AD column, hexane/*i*-PrOH 80/20, 1 mL/min, UV detection at 224 nm. For **3c**: retention times 9.7 ((+)-enantiomer) and 11.9 min. For **3e**: retention times 14.9 and 16.5 min. For **3b**: WHELK column, hexane/*i*-PrOH 90:10, 1 mL/min, retention times 25.4 ((+)-enantiomer) and 28.1 min. For **3d**: Chiracel OD column, hexane/*i*-PrOH 90/10, 1 mL/min, retention times 11.1 and 13.2 ((+)-enantiomer) min.
[d] Conversion rates <10%.

The use of the aminoethyl-ferrocenylphosphine **B**, which displays planar chirality, did not improve the enantioselectivity, while MandyPhos, a rather efficient chiral auxiliary for Baylis-Hillman-type reactions,[13] was totally inactive in these cycloaddition reactions, probably due to its steric bulk.

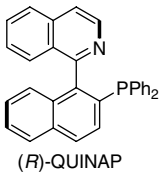
PHANEPHOS afforded comparatively high enantiomeric excesses with ees up to 64% in the synthesis of **3a**. Yields are however still moderate.

For comparison purposes, yields and conversions in Tables 1–3 have been measured mostly under the

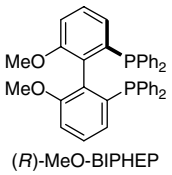
Table 3. Screening of additional chiral phosphines

Entry	Catalyst	 **3a,c** **3a**, R' = Et		 **3f**	
		ee	Yield (%)	ee	Yield (%)
1	(*R*)-QUINAP	28% (−)	61	19% (−)	60
2	(*R*)-MeO-BIPHEP	53% (−)	22	25% (−)	21
3	(*R*,*S*)-**B**			5% (−)	21
4	(*S*,*S*)(*R*)-MandyPhos	—	0	—	0
5	(*S*)-Phanephos	**64% (+)**	32	26% (+)	30
		3c, R′ = Cy			
6		50% (+)	28[a]		

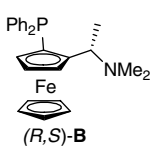
[a] Substrate concentration = 0.6 M.



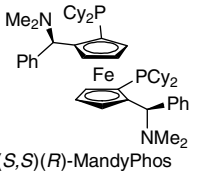
(*R*)-QUINAP



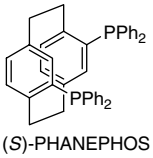
(*R*)-MeO-BIPHEP



(*R*,*S*)-**B**



(*S*,*S*)(*R*)-MandyPhos

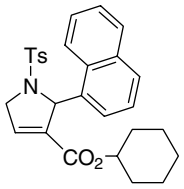


(*S*)-PHANEPHOS

initially defined, non-optimized conditions. They can be improved however by increasing the concentration of the reactants. Thus, for instance, the cycloaddition reactions of entry 9 in Table 1, leading to **3a**, gives a conversion rates of 50% when performed at a 0.2 M concentration, while a 72% conversion is obtained for a 0.6 M concentration. Addition of molecular sieve may also be beneficial. Under such optimized conditions, quantitative conversion of **1c** into **3c** is observed by using FerroTANEs as the catalysts (Table 2), while PHANEPHOS and atropoisomeric diphosphines give conversion rates still lower than 50%.

Taken together, the preliminary results reported here show that among the chiral phosphines considered so far, only a few, namely atropoisomeric diphosphines, phosphetanes bearing ferrocenyl moieties and PHANEPHOS, afford significant ees in the cycloaddition reactions of Eqs. 2 and 3. α-Naphthyl substituted 3-pyrrolines have been obtained in this way in 48–64% enantiomeric excesses.

Among the enantiomerically enriched pyrrolines **3**, the cyclohexyl ester **3c**[14] retained our attention most particularly because it came out to be a crystalline solid whose enantiomeric purity is likely to be improved by applying recrystallization techniques.



3c

This proved to be the case: crystallization was performed by slow cooling to room temperature of a saturated solution of **3c** (46% ee, obtained via *i*Pr-Ferrotane promoted cyclization, see Table 2) in boiling hexane–ethyl acetate. According to HPLC analysis, the crystalline solid thus recovered contains racemic **3c** while the filtrate contains **3c** in 91% enantiomeric excess ($[\alpha]_D$ +107 (*c* 1, $CHCl_3$); 31% total yield from **1c**).

In summary, the preliminary results above demonstrate the potential utility of selected chiral phosphines in the enantioselective synthesis of 2-aryl-3-pyrrolines via the [3+2] cyclizations of imines with allenic esters. The 2-naphthyl-substituted pyrrolinic esters **3a–d** have been obtained with ees going from 46% to 64%, in moderate to good yields.

The method proved particularly useful for the synthesis of the 3-pyrroline **3c**, which has been obtained in 31% yield and 91% enantiomeric excess by combining the enantioselective [3+2] cyclization reaction with a crystallization step.

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5. The specific use of phosphines as nucleophilic catalysts seems to be required for this cycloaddition reaction. The same starting materials are known to afford either azetidines or dihydropyridine derivatives, when combined in the presence of nucleophilic amines such as DMAP or DABCO: Zhao, G.-L.; Huang, J.-W.; Shi, M. *Org. Lett.* **2003**, *5*, 4737; See also: Shi, Y.-L.; Shi, M. *Org. Lett.* **2005**, *7*, 3057–3060.
6. (a) Marinetti, A.; Labrue, F.; Genêt, J.-P. *Synlett* **1999**, 1975; (b) Marinetti, A.; Jus, S.; Labrue, F.; Lemarchand, A.; Genêt, J.-P.; Ricard, L. *Synthesis* **2001**, 2095.
7. The starting materials have been prepared according to Ref. 3b.
8. Phosphetanes bearing other aryl or alkyl substituents on phosphorus have also been evaluated.
9. These initial studies have been restricted to unsubstituted allenic esters. 2-Butynoates are known to be suitable substrates as well (see Ref. 3). They display however lower reactivity. The few cycloaddition tests performed so far on methyl 2-butynoate show that Et-FerroTANE is inactive at room temperature while Josiphos and Me-Duphos give low conversion rates and enantioselectivities.
10. Allenes have been prepared as described: Lang, R. W.; Hansen, H.-J. *Org. Synth.* **1984**, *62*, 202–209; Compounds **1b** and **1d**: Zhu, X.-F.; Henry, C. E.; Wang, J.; Dudding, T.; Kwon, O. *Org. Lett.* **2005**, *7*, 1387–1390; Compound **1e**: Himbert, G.; Fink, D. *Tetrahedron Lett.* **1985**, *26*, 4363–4366.
11. The P-ferrocenylmethylphosphetanes (*S*,*S*)-Cy-**A** and (*R*,*R*)-^{t}Bu-**A** have been prepared from (ferrocenylmethyl)phosphine and the cyclic sulfate of (*R*,*R*)-1,3-dicyclohexylpropanediol (38% yield) and (*S*,*S*)-2,2,6,6-tetramethyl-3,5-heptanediol (15% yield), respectively, according to Ref. 6b.
12. Aromatic solvents, typically benzene, are often used in these cycloaddition reactions (see Refs. 1 and 2).
13. Pereira, S. I.; Adrio, J.; Silva, A. M. S.; Carretero, J. C. *J. Org. Chem.* **2005**, *70*, 10175–10177.
14. Experimental procedure for the cycloaddition reaction leading to **3c**: cyclohexyl 2,3-butadienoate **1c** (54 mg, 0.33 mmol) was added to a solution containing *N*-tosyl-1-naphthaldimine **2a** (93 mg, 0.3 mmol) and (*S*,*S*)-*i*Pr-FerroTANE (15 mg, 0.030 mmol) in 0.5 mL of degassed CH_2Cl_2. The mixture was stirred at room temperature for 24 h under argon. After evaporation of the solvent, the crude product was purified by column chromatography on silica gel with heptane/ethyl acetate (7:3) as the eluent. Pure **3c** was obtained in 77% yield (110 mg) and 46% ee

(determined by HPLC, see Table 2) as a white powder. Dropwise addition of ethyl acetate to a suspension of **3c** in boiling hexane afforded a clear solution, which was allowed to cool down slowly to room temperature. The crystalline solid was established to be a racemate while evaporation of the filtrate gave 45 mg of **3c** having a 91% ee ($[\alpha]_D$ +107, $c = 1$, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 0.65 (br, 1H), 1.0 (2H), 1.15 (4H), 1.3 (1H), 1.4 (1H), 1.6 (1H), 2.26 (s, Me), 4.4–4.5 (m, 1H, CH–O), 4.53 (ddd, $^2J = 16.9$ Hz, $^4J = 6.2$ Hz, $^3J = 1{,}8$ Hz, 1H, CH_2–N), 4.75 (dt, $^2J = 16.9$ Hz, $^4J = {}^3J = 2.3$ Hz, 1H, CH_2–N), 6.57 (br m, 1H, NCH), 6.89 (d, $J = 8.0$ Hz, 2H, Ts), 6.93 (br, 1H, CH═), 7.18 (d, $J = 8.0$, 2H, Ts), 7.22 (d, $J = 8$ Hz, 1H, naph), 7.27 (d, $J = 6.2$ Hz, 1H, naph), 7.43–7.53 (m, 2H, naph), 7.71 (d, $J = 7.6$ Hz, 1H, naph), 7.79 (d, $J = 8.4$ Hz, 1H, naph), 8.23 (d, $J = 8.0$ Hz, 1H, naph); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.3 (Me), 22.9, 23.2, 25.0, 30.6, 31.1 (CH_2), 54.9 (NCH_2), 64.6 (NCH), 73.1 (OCH), 123.4, 124.9, 125.4, 126.1, 126.7 (CH), 126,9 (CH, Ts), 128.4, 128.5 (CH), 128.9 (CH, Ts), 131.5, 133.7 (C), 135.0 (HC═), 135.1, 135.7, 137.4, 142.8 (C), 161.3 (CO_2–) ppm. HRMS: Calcd for $C_{28}H_{29}NO_4SNa$: 498.1715. Found: 498.1719.