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Tetrahedron Letters 46 (2005) 8213-8216

Tetrahedron Letters

A correlation study of bisphosphine ligand bite angles with enantioselectivity in Pd-catalyzed asymmetric transformations

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Received 9 August 2005; revised 15 September 2005; accepted 16 September 2005 Available online 11 October 2005

Abstract—Among the bisphosphine ligands, we have previously developed C_n -TunePhos (n = 1-6) as a family of ligands with tunable bite angles. The increase in spacer –CH₂– groups in this family of ligands causes changes in ligand dihedral angle, which in turn causes P–Pd–P bite angle variation. Pd-catalyzed asymmetric alkylations and cycloadditions have been tested with C_n -TunePhos ligands. This study aims at a possible correlation between ligand bite angles with enantioselectivity of the Pd-catalyzed asymmetric products.

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Development of chiral bisphosphine ligands¹ is important for asymmetric catalysis. Asymmetric reactions are sensitive to the substrate and ligand environment. Hence, subtle changes in the geometric, steric, and/or electronic properties of chiral ligands can lead to dramatic variations in reactivity and enantioselectivity. Conformationally rigid, yet tunable chiral ligands² offer a great advantage in optimizing reaction conditions. It is usually achieved by maximizing the possibility of a low energy enantiotopic approach of substrates in the stereochemistry defining step. Chiral atropisomeric biaryl bisphosphines such as BINAP, BIPHEMP, and MeO-BIPHEP (Fig. 1) are effective in catalyzing many asymmetric reactions.^{3,4} Bis-phosphine ligands are characterized by their bite angles, which is the (P–metal–P) angle made when the two phosphorus atoms chelate to the central metal. The bite angle is closely related to the inherent dihedral angle made by the P atoms in ligand. The dihedral angle is known to influence the catalytic activity and enantioselectivity in many asymmetric



Figure 1. Dihedral angles of some chiral bisphosphine ligands.

Keywords: C_n-TunePhos ligands; Asymmetric catalysis.

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^{0040-4039/\$ -} see front matter @ 2005 Published by Elsevier Ltd. doi:10.1016/j.tetlet.2005.09.093

transformations.⁵ The sp²-sp² rotation in these chiral biaryl ligands causes only a small energy change within a wide range of bite angles with transition metals. While these ligands have been proven effective, sometimes they are not efficient for certain substrates due to lack of ligand rigidity. To overcome this drawback, prior work in our group focused on introducing a bridge with variable length to link the diaryl groups, such that the new ligands are rigid with tunable bite angles. The resulting family of Cn-TunePhos was produced with n = 1-6 ligands.⁶ The dihedral angle of the series was calculated with CAChe⁷ MM2 calculations and is listed (Fig. 1). Based on its structural features, it was postulated that the C_n -TunePhos ligands would be less flexible than BINAP as their sp^2-sp^2 bond rotation is restricted. The ligands were put to test for the well-known Ru-catalyzed asymmetric hydrogenation of β -keto esters. The results demonstrated the influence of ligand dihedral angle upon % ee, with the maximum enantioselectivity obtained with C₄-TunePhos.⁶ The current work is an extension toward studying the influence of ligand dihedral angle on C-C bond formation reactions, such as Pd-catalyzed asymmetric allylic alkylations (AAA)⁸ and asymmetric cycloadditions.⁹

Mechanistically, the Pd-catalyzed AAA is one of the best studied asymmetric C-C bond forming reactions.¹⁰ We first chose the reaction of 1,3-diphenylpropenyl acetate 1 with dimethyl malonate 2, the standard test reaction for asymmetric allylation chemistry (Table 1). Under the standard conditions: catalyst formed in situ from 2 mol % of $[(\pi-allyl)PdCl]_2$ and 5 mol % chiral ligand; a mixture of N,O-bis(trimethylsilyl)acetamide (BSA) and catalytic amounts of KOAc (5%), the product 3 was afforded in high yields. THF solvent and BSA/KOAc was discovered as the optimum reaction condition and all the Cn-TunePhos ligands were screened. As observed from the results, C₆-TunePhos gave the best result (Table 1, entry 6). This result showed an alignment of the enantioselectivity with the increasing ligand dihedral angle. Further optimization studies were not included due to the simplicity of this substrate and it sufficed to demonstrate the effectiveness of C_n-TunePhos ligands for AAA reaction. It is to be noted that our results of dihedral angle correlation sharply contrast the results obtained by Trost et al.¹¹ For the

chiral pocket-type ligands described by Trost, the concept of 'buttressing effect' of ligands is invoked to explain the trend in enantioselectivity.

Our next goal was to extend the scope of C_n -TunePhos ligands to more challenging substrates. Butadiene monoepoxide **4** is an inexpensive four-carbon building block and has been extensively used toward several natural product syntheses.¹² We were interested in the reaction of **4** with phthalimide **5** under the catalysis of Pd/C_n-TunePhos. Under the conditions mentioned by Trost et al.,¹³ catalyst formed in situ from 1 mol% of [(π -allyl)PdCl]₂ and 2.2 mol% chiral ligand in CH₂Cl₂ with Na₂CO₃ as base afforded the product **6** in 67– 90% yields and low % ee's (Table 2, entries 2–7). Switching to THF as reaction solvent significantly improved the % ee with a maximum of 82% for C₄-TunePhos (Table 2, entries 9–14).

Further optimization with varying reaction temperature was done with C_4 -TunePhos, which gave higher enantioselectivity at the cost of lower yields (Table 3, entry 3 vs entry 4). The reaction yields and % ee's could not be improved significantly by altering other reaction parameters such as base or Pd(0)-precursors or additives.

Having achieved a modest success with Pd-catalyzed AAA reaction of butadiene monoepoxide **4**, we wished to explore this substrate for asymmetric cycloadditions with heterocumulenes viz. phenyl isocyanate **7** and diphenyl carbodiimide **8**. Both these reactions have been well studied by Alper et al.⁹ and once again, our goal was to evaluate the C_n -TunePhos ligands' performance (Table 4). In the case of cycloadditions of heterocumulenes, Pd₂(dba)₃·CHCl₃ precursor and THF solvent were better choices. It was found that the enantioselectivities were highly substrate dependent. The C₄-TunePhos worked best for phenyl isocyanate, while C₁-TunePhos worked the best for carbodiimide **8** substrate. As evidenced in Table 4, for most parts, the C_n-TunePhos seem to give good yields and enantioselectivities.

In bisphosphine ligands like those developed by Trost et al.,¹⁴ the depth of such pockets correlates with the (P-Pd-P) bite angle. Larger the bite angle, deeper the pocket, better is the enantioselectivity of product. In

Table 1.	C _n -TunePhos	ligands for	AAA of	the standard	substrate	1
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	OAc MeO ₂ C、_CO ₂ Me	2.5 mol% [Pd (allyl) Cl] ₂ ; 5 mol% ligand	
	Ph +	BSA; KOAc; CH ₂ Cl ₂ ; RT; 12 hrs	
	1 2	3	
Entry	Ligand	% Yield ^a	% ee ^b
1	C ₁ -TunePhos	89	77
2	C ₂ -TunePhos	86	82
3	C ₃ -TunePhos	90	84
4	C ₄ -TunePhos	91	87
5	C ₅ -TunePhos	91	92
6	C ₆ -TunePhos	90	95

^a Isolated yields.

^b Determined by chiral HPLC.

Table 2. Cn-TunePhos for AAA with butadiene monoepoxide 1



			-	
Entry	Ligand	Solvent	% Yield ^a	% ee ^b
1	PPh ₃	CH ₂ Cl ₂	60	_
2	C ₁ -TunePhos	CH_2Cl_2	76	43
3	C ₂ -TunePhos	CH_2Cl_2	90	49
4	C ₃ -TunePhos	CH_2Cl_2	67	48
5	C ₄ -TunePhos	CH_2Cl_2	70	40
6	C ₅ -TunePhos	CH_2Cl_2	65	30
7	C ₆ -TunePhos	CH_2Cl_2	60	<10
8	PPh ₃	THF	75	_
9	C ₁ -TunePhos	THF	83	65
10	C ₂ -TunePhos	THF	92	75
11	C ₃ -TunePhos	THF	88	76
12	C ₄ -TunePhos	THF	90	82
13	C ₅ -TunePhos	THF	85	70
14	C ₆ -TunePhos	THF	82	68

^a Isolated yields.

^b Determined by chiral HPLC.

 Table 3. Effect of temperature



^a Isolated yields.

^b Determined by chiral HPLC.

the case of C_n -TunePhos ligands from n = 1-6, there is an increase in the ligand dihedral angle that in turn causes an increase in (P-metal-P) bite angle. The increase in spacer -CH2- groups, however, allows for greater sp^2-sp^2 bond rotation. As evidenced from the results (Table 1), for the simple AAA substrate 1,3-diphenyl prop-2-enyl acetate 1, the effect of ligand bite angle correlates well with the product enantioselectivity. Extending this to other AAA systems such as butadiene monoepoxide 4 and phthalimide 5 does not correlate the bite angles with % ee. As evidenced by the results (Table 2), the highest % ee's are obtained with C₄-TunePhos. With increase in the number of spacer $-CH_{2}$ groups, the rigidity of the ligand is compromised while the bite angle increases. Indeed, for this substrate, it has been found by Trost et al.¹³ that curbing rotational freedom

brings higher % ee. It is plausible that an optimized bite angle is required and is obtained with C₄-TunePhos. The reaction of butadiene monoepoxide **4** with heterocumulenes **7** and **8** also follows very similar Pd(0)-catalyzed mechanism. However, once again, there was no particular correlation of ligand bite angles and % ee. Furthermore, the highest enantiodiscriminating ligand was found to be different for the two heterocumulenes **7** and **8**. For phenyl isocyanate **7**, C₄-TunePhos was found to give the best ee (70%) while C₁-TunePhos gave 83% ee for carbodiimide **8**.

Among the types of ligands that can effectively catalyze AAA reaction is one, which creates chiral space or pocket within an array of groups. The C_n -TunePhos ligands have been identified with these characteristics. The

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Table 4. Cycloadditions with Pd(0)-TunePhos catalyst

	/ + X	=C=Y Pd(0)-Cn-Tunephos	-Y	
	4	rt	- X	
	7 X=C	; Y=C ₆ H ₅ N	9 X=O; Y=C ₆ H ₅ N	
	8 X=Y	=C ₆ H ₅ N	10 X=Y=C ₆ H ₅ N	
Entry	Cycloadduct	Ligand	% Yield ^a	% ee ^b
1	9	PPh ₃	84	_
2	9	C ₁ -TunePhos	80	45
3	9	C ₂ -TunePhos	88	50
4	9	C ₃ -TunePhos	89	58
5	9	C ₄ -TunePhos	95	70
6	9	C ₅ -TunePhos	90	60
7	9	C ₆ -TunePhos	88	50
8	10	PPh ₃	55	_
9	10	C ₁ -TunePhos	96	83
10	10	C ₂ -TunePhos	85	79
11	10	C ₃ -TunePhos	76	70
12	10	C ₄ -TunePhos	65	60
13	10	C ₅ -TunePhos	62	58
14	10	C ₆ -TunePhos	60	57

^a Isolated vields.

^b Determined by chiral HPLC.

results show that these asymmetric transformations are substrate dependent and changes in ligand bite angles have a dramatic effect on the enantioselectivities. The current study of C_n-TunePhos ligands is a step in this direction. Future optimization studies will be performed so that highly enantioselective and reactive systems can be realized.

Acknowledgments

The authors wish to thank the National Institute of Health for financial support (GM-58832).

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