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Asymmetric Allylic Alkylation Catalyzed by Palladium Complexes with Atropisomeric Quinazolinone Phosphine Ligands

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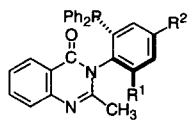
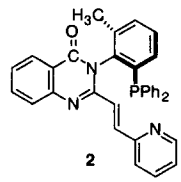
Abstract: Asymmetric inductions up to 52% ee and 87% ee have been achieved with palladium catalyzed allylic alkylation reactions using a new class of atropisomeric monodentate ((*R*)-**1b**) and chelate (**2**) quinazolinone phosphine ligands, respectively.
Keywords: 3-Aryl-4(3*H*)-quinazolinone, atropisomeric, phosphine ligands, asymmetric allylic alkylation.

Palladium-catalyzed asymmetric allylic alkylation reactions (AAA reactions) have recently been the subject of a great deal of interest from the synthetic community due to their wide synthetic scope, practical simplicity and potential for asymmetric synthesis through the use of chiral ligands.[1] This type of reaction is also a convenient model reaction for the evaluation of new ligands. The successful chiral ligands developed to date can be either monodentate[2] or bidentate structures[3] such as diphosphines, diamines, and ligands containing electronically different donor centers.[4] Both categories have given impressive results. In this paper, we report the preliminary results from catalytic AAA reaction studies on a new class of atropisomeric monophosphine ligands **1a-c** and a mixed phosphorus/nitrogen ligand **2**.



(*R*)-**1a**: R^1 = H, R^2 = H
(*R*)-**1b**: R^1 = CH_3, R^2 = H
(*R*)-**1c**: R^1 = CH_3, R^2 = CH_3



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We have reported earlier the synthesis and resolution of ligand **1a-c**.[5] The asymmetric induction ability of monophosphine ligands **1a-c** towards the palladium-catalyzed AAA reaction was evaluated using ligand (*R*)-**1b**. The catalyst was generated *in situ* by mixing ligand (*R*)-**1b** and the chloro-bridged palladium precursor ($[Pd(\pi\text{-}C_3H_5)Cl]_2$) at room temperature. A solution of racemic substrate (1,3-diphenyl-2-propenyl acetate, **3a**) was then added followed by the addition of the base and the additive. The resulting mixture was stirred at room temperature for a given period of time before the product was isolated and analyzed. The reaction results are shown in Table 1.

The sodium dimethylmalonate anion generated by sodium hydride (NaH) gave better enantioselectivity than the potassium dimethylmalonate anion generated by *N,O*-bis(trimethylsilyl)acetamide (BSA) and potassium acetate (Table 1, entry 1 and 2). The increased enantiomeric excess (ee) obtained by removal of chloride ion using silver (I) perchlorate ($AgClO_4$)

0040-4039/99/$ - see front matter
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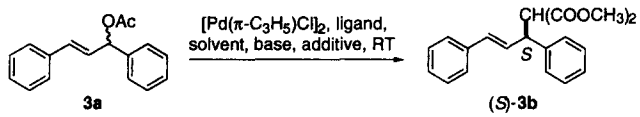
suggested that chloride remained in the coordination sphere of the palladium (Table 1, entry 2 and 3). The reaction rate was slow for all entries, particularly in toluene (Table 1, entry 4). By adding a crown ether (15-crown-5) to improve the solubility of sodium dimethylmalonate, the enantiomeric excess increased to 52%.

Based on these encouraging preliminary studies with monophosphine (*R*)-**1b**, we decided to modify the structure of **1b** into a phosphorus-nitrogen chelate ligand related to ligand **2** in the hope of achieving higher enantioselectivity for this reaction.

Table 1: Palladium-Catalyzed AAA reaction with quinazolinone Ligands.[a]



3a (*S*)-**3b**

Entry	[Pd] (mol%)	Ligand (mol%)	Solvent	Time (h)	Base[b]	Additive	Yield[c] (%)	% ee[d]
1	2.5	10.0 (**1b**)	CH_2Cl_2	96	1.5 equiv. BSA	3 mol% KOAc	40	28 (*S*)-(-)
2	2.5	10.0 (**1b**)	THF	48	1.1 equiv. NaH	–	37	37 (*R*)-(+)
3	2.5	5.0 (**1b**)	THF	48	3.0 equiv. NaH	5.0% mol% $AgClO_4$	27	44 (*R*)-(+)
4	2.0	4.8 (**1b**)	Toluene	48	3.0 equiv. NaH	–	8	44 (*R*)-(+)
5	2.0	4.0 (**1b**)	CH_2Cl_2	96	3.0 equiv. NaH	3.0 equiv. 15-crown-5	30	**52** (*S*)-(-)
6	2.5	6.0 (**2**)	THF	48	3.0 equiv. BSA	3 mol% KOAc	64	68 (*R*)-(+)
7	2.5	6.0 (**2**)	Toluene	48	3.0 equiv. BSA	3 mol% KOAc	53	73 (*R*)-(+)
8	2.5	5.5 (**2**)	CH_2Cl_2	48	3.0 equiv. BSA	3 mol% KOAc	90	80 (*R*)-(+)
9	2.5	5.5 (**2**)	THF	24	3.0 equiv. NaH	3.0 equiv. 15-crown-5	75	56 (*R*)-(+)
10	2.5	5.5 (**2**)	Toluene	48	3.0 equiv. NaH	3.0 equiv. 15-crown-5	44	67 (*R*)-(+)
11	2.5	6.0 (**2**)	CH_2Cl_2	36	3.0 equiv. NaH	3.0 equiv. 15-crown-5	65	**87** (*R*)-(+)
12	2.5	6.0 (**5**)	CH_2Cl_2	36	3.0 equiv. NaH	3.0 equiv. 15-crown-5	68	78 (*R*)-(+)

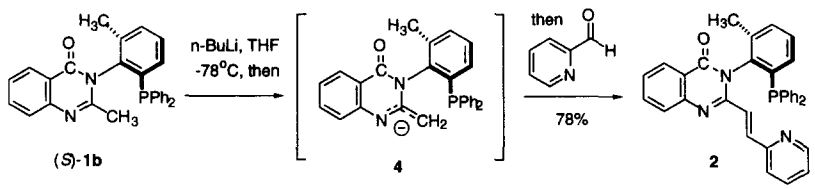
a) Reactions were carried out at room temperature under argon using 1,3-diphenyl-2-propenyl acetate as the substrate, dimethylmalonate (1 equiv. with respect to the base) with the base as the nucleophile, additive, solvent, [Pd] (allylpalladium chloride dimer: $[Pd(\pi\text{-ally})Cl]_2$), and ligand **2a**. b) BSA: *N,O*-bis(trimethylsilyl)acetamide. c) Isolated yield by flash chromatography. d) For values lower than 60%, % ee was determined by ^1H NMR using $Eu(hfc)_3$ as a chiral shift reagent in $CDCl_3$; for values higher than 60%, % ee was determined by HPLC using a Chiralcel OD-H column (98:2 Hexane:*i*-PrOH, 0.3 mL/min). The absolute configuration was determined by comparing the optical rotation with literature values.[6]

Lithiation of the 2-methyl group of the 3-aryl-4(3*H*)-quinazolinones with sodium hydride, lithium diisopropylamide, or *n*-butyllithium has been used frequently in the preparation of quinazolinone derivatives.[7] The facile deprotonation of this methyl group is presumably due to

resonance-stabilization of the resulting anion by the neighboring nitrogen at the 1-position (Scheme 1). The anion can be quenched with a variety of electrophiles to afford substitution products.[8]

The 2-methyl group of (*S*)-**1b** reacted smoothly with 1.2 equivalents *n*-BuLi in THF at -78 °C to yield a dark red solution of anion **4** (Scheme 1). Claisen-Schmidt reaction of anion **4** with pyridinecarboxaldehyde afforded bidentate ligand **2** in 78% yield after aqueous workup. Only the thermodynamically more favored product with the *trans* double bond was formed based on ^{1}H NMR analysis.[9]

Scheme 1

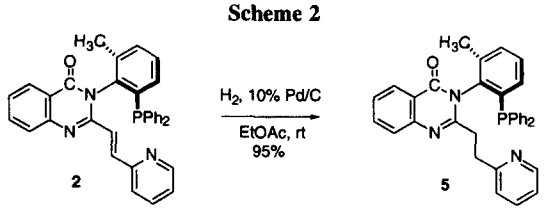


When bidentate ligand **2** was used for the palladium catalyst under the asymmetric allylic alkylation conditions described above, the reaction rate was faster than that of the reactions catalyzed by the palladium catalyst with monophosphine ligand (*R*)-**1b** (Table 1). Unlike the monophosphine ligand, which gave variable ee and configurations of the product **3b**, chelate ligand **2** consistently afforded product **3b** in higher ee's and in the *R* configuration. In THF and toluene, the reaction was slower than in methylene chloride (Table 1, entry 6, 7, 9, and 10). In methylene chloride, deprotonation of dimethylmalonate with the BSA-KOAc combination gave satisfying enantiomeric excess (80%, based on HPLC analysis) (Table 1, entry 8). However, use of sodium hydride in the presence of crown ether (15-crown-5) gave the highest enantiomeric excess (87%) (Table 1, entry 11).

The consistent configuration of the product as well as the increase in the reaction rates, enantiomeric excesses, and yields are consistent with a reaction catalyzed by a more ordered palladium complex. The large distance between nitrogen and phosphorus in ligand **2** provides a large bite angle for metal coordination to form a deep chiral "pocket". Trost proposed that an increase in the bite angle of chelate ligands would enhance the chiral recognition of the "pocket" for the substrate in AAA reactions.[10] The higher enantiomeric excess induced by the palladium catalyst with ligand **2** is in good agreement with this idea.

To confirm that the *trans* double bond in ligand **2** was necessary for high chiral induction, ligand **2** was easily hydrogenated in 95% yield to produce the new ligand **5** with an ethylene group linkage (Scheme 2).[11]

Scheme 2



When ligand **5** was subjected to the optimized conditions of asymmetric allylic alkylation, product (*R*)-**3b** was obtained in good yield and 78% ee (Table 1, entry 12). This result suggests that the palladocycle formed from the palladium center and ligand **5** is more flexible, decreasing the control of the enantiomeric excess.

In conclusion, our studies demonstrate that monophosphine ligand (*R*)-(-)-**1b** and its chelate analog **2** are effective in the palladium catalyzed asymmetric allylic alkylation reaction. The facile modification of the 2-methyl group of ligand (*R*)-**1b** by electrophilic substitution should allow easy structural tuning of this class of ligand for a variety of substrates and catalytic reactions.

References and Notes:

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9. Data for ligand **2**: mp 99-101°C; R_f = 0.22 (silica, 1:2 ethyl acetate/hexane); FTIR (thin film, cm^{-1}) 3052, 1680, 1580, 1551, 1470, 1432, 1346, 1338, 777, 742, 696; $[\alpha]_D^{23}$ = -113 (*c* = 1.27, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.51 (dd, 1H, *J* = 1.46, 4.88 Hz), 8.23 (d, 1H, *J* = 7.81 Hz), 7.75-7.81 (m, 3H), 7.58 (dt, 1H, *J* = 1.71, 7.69 Hz), 7.31-7.46 (m, 4H), 7.01-7.25 (m, 12H), 6.75 (d, 1H, *J* = 15.14 Hz), 2.16 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_c 161.35 (C4), 159.03, 153.65, 151.66, 149.83, 148.01, 140.72 (d, *J* = 25.28 Hz), 138.93, 137.66 (d, *J* = 13.2 Hz), 136.61 (d, *J* = 3.08 Hz), 136.31, 136.16 (d, *J* = 10.35 Hz), 135.26 (d, *J* = 12.15 Hz), 134.45, 134.31, 134.06, 133.60, 133.37, 132.49, 129.74, 128.74, 128.56, 128.38, 128.26, 127.59, 127.43, 126.55, 124.14, 123.52, 123.38, 121.33, 18.48. $^{31}P\{^1H\}$ NMR (121.4 MHz, $CDCl_3$): -16.91 (s); HRMS: 523.18143 (calcd for $C_{34}H_{26}N_3OP$ 523.18135).
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11. Data for ligand **5**: R_f = 0.21 (silica, 1:2 ethyl acetate/hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 8.43 (dd, 1H, *J* = 1.46, 4.71 Hz), 8.04 (d, 1H, *J* = 7.65 Hz), 7.66-7.77 (m, 2H), 7.46-7.56 (m, 1H), 7.01-7.42 (m, 16H), 3.30-3.44 (m, 1H), 3.02-3.14 (m, 1H), 2.66-2.75 (m, 2H), 2.04 (s, 3H, CH_3).