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Catalytic Asymmetric Vinylation of Ketone Enolates

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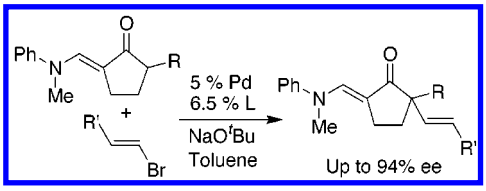
ABSTRACT



A protocol for the catalytic asymmetric vinylation of ketone enolates has been developed. Key to the success of this process was the development of new electron-rich chiral monodentate ligands.

We recently reported the catalytic asymmetric arylation of ketone enolates employing Pd(0)/(S)-BINAP as catalyst. This reaction, in several instances, proceeded in good yields and with high levels of enantioselectivity.[1,2] When we attempted an analogous coupling reaction using a vinyl bromide, the desired product was formed in low yield and low ee. Catalysts derived from the aminophosphine ligand 2-(*N*,*N*-dimethylamino)-2′-(dicyclohexylphosphino)-biphenyl (**1a**)[2b] as well as the simpler desamino ligands (**1b**−**e**)[3] are extremely active for a number of palladium-catalyzed cross-coupling reactions, including the α-arylation of ketones.[2b,c] As such, we focused our efforts on the preparation of enantiomerically pure analogues of these (Figure 1)[4,5] and investigated their use in the asymmetric vinylation of ketone enolates.[6]

To develop a useful protocol, we first studied the reaction of 2-methyl-5-(*N*-methyl-anilinomethylene)cyclopentanone (**4a**)[7] with *trans*-1-bromopropene under a variety of conditions. Using 2.5 mol % $Pd_2(dba)_3$/6.5 mol % **2a** with NaO^{t}Bu as base, the desired product (**5a**) was produced in high yield (95%) with high enantioselectivity (90% ee) when the reaction was performed in toluene at room temperature.[8,9] We also found that we could increase the enantioselectivity by lowering the reaction temperature. At 0 °C the ee increased to 94%, and at −20 °C the ee was 96%. However,

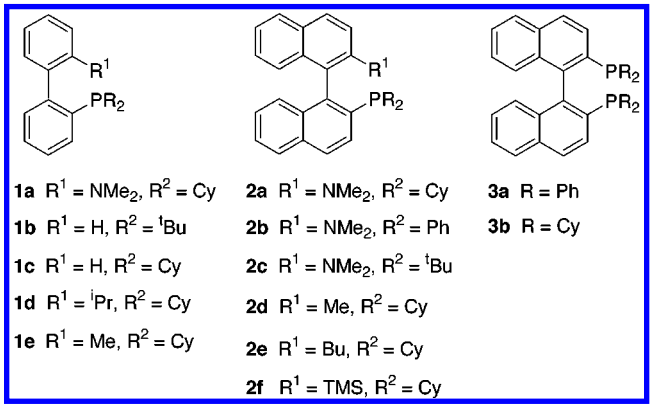


Figure 1.

(1) Åhman, J.; Wolfe, J. P.; Troutman, M. V.; Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 1918.

(2) For a racemic version, see: (a) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108. (b) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722. (c) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360. (d) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382. (e) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473. For catalytic intramolecular vinylations of ketones, see: (f) Piers, E.; Renaud, J. *J. Org. Chem.* **1993**, *58*, 11. (g) Solé, D.; Piedró, E.; Bonjoch, J. *Org. Lett.* **2000**, *2*, 2225. (h) Wang, T.; Cook, J. M. *Org. Lett.* **2000**, *2*, 2057.

(3) (a) Aranyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4369. (b) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413. (c) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550.

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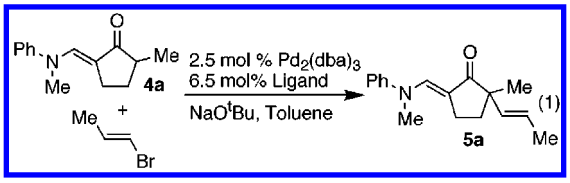
at temperatures below 0 °C the reaction was quite slow (Table 1, entries 1−3). Using 0.1 mol % $Pd_2(dba)_3$ the reaction proceeded to 90% conversion after 2 days at room temperature with the enantioselectivity of the reaction still high (86% ee). Upon increasing the temperature to 50 °C, the coupling product was obtained in 83% yield after 24 h, but the enantioselectivity was lower (74% ee). However, at 50 °C with Pd:L 1:3 (0.1 mol % $Pd_2(dba)_3$), **5a** was formed in 71% yield and 85% ee.[10]

Table 1[a]



entry	ligand	temp	time	conversion[b]	ee (%)[c]
1	**2a**	rt	3 h	100%	90
2	**2a**	0 °C	24 h	98%	94
3	**2a**	−20 °C	24 h	75%	96
4	**2a**	40 °C	2 h	100%	74
5	**2b**	rt	24 h	40%	56
6	**2c**	rt	24 h	<10%	nd[d]
7	**2d**	rt	3 h	100%	65
8	**2d**	0 °C	24 h	93%	80
9	**2e**	0 °C	24 h	90%	82
10	**2f**	0 °C	24 h	60%	35
11	**3a**	rt	24 h	trace	nd
12	**3a**	50 °C	24 h	trace	nd
13	**3b**	rt	24 h	<10%	nd
14	**3b**	50 °C	24 h	85%	56

[a] Reactions were run at 0.2 M (**4a**), with 2 equiv of 1-bromopropene and NaO*t*-Bu. [b] Conversion was determined by GC. [c] The ee was determined by chiral HPLC. [d] Not determined.

Next, we extended our investigation to a series of α′-blocked α-alkylcycloalkanones. As illustrated in Table 2, the asymmetric vinylation of cyclic ketones using $Pd_2(dba)_3$/**2a** provides a general method for obtaining a variety of α-vinyl cyclopentanones in good yields and with moderate to high levels of enantioselectivity.

The enantioselectivity of the coupling process was strongly influenced by the structure of the vinyl bromide. The coupling of vinyl bromide and *trans*-bromoalkenes proceeded with high enantioselectivity (>90% ee). When *cis*-1-bromopropene was used as a substrate, the enantiomeric excess dropped to 76% (Table 2, entry 6). The coupling of a 2,2-disubstituted alkene, 1-bromo-2-methylpropene (entry 4), showed approximately the same level of enantioselectivity as that of *cis*-1-bromopropene (entry 6). We also briefly examined the reaction using vinyl chlorides. Under the same conditions as those described for 1-bromo-2-methylpropene, use of the corresponding chloride provided the product in lower yield but with the same enantiomeric excess (entry 5). In contrast to what was observed for the asymmetric ketone arylation reactions with BINAP, the size of the α-alkyl substitutent of **4** did not significantly influence the reaction rate or enantioselectivity (entries 2, 7, and 8).

The vinylation of 1-methylindanone and 1-methyltetralone with vinyl bromide and *trans*-1-bromopropene also proceeded in very good yield and with good enantioselectivity (Table 2, entries 10 and 11). In these cases, similar results were obtained in the coupling of a cyclohexanone and cyclopentanone derivative. However, a considerable difference in the enantioselectivity was observed when **4a** and the corresponding cyclohexanone derivative **4d** were coupled with *trans*-1-bromopropene under identical conditions (entries 1 and 9). While the reaction of **4a** proceeded in very high yield in a highly enantioselective fashion (90% ee), the product from **4d** was formed in lower yield and considerably lower enantiomeric purity (50% ee). Similar differences in enantioselectivity were observed for the reactions of five- and six-membered-ring cyclic ketones in the asymmetric arylation of ketones.[1]

When 2-alkyl-5-(*N*-methyl-anilinomethylene)cycloalkanones were used as coupling partners, the corresponding α-vinyl ketones were obtained after hydrolysis of the coupled product followed by a retro-Claisen reaction (Figure 2).[11] This

(4) Ligands **2a**−**2c** were prepared in several steps from (*rac*)-2, 2′-dibromo-1,1′-binaphthyl. Ligands **2d**−**2f** were prepared in several steps from (*R*)-(+)-2,2′-diiodo-1,1′-binaphthyl. Ligand **2a** has recently been used in catalytic asymmetric Suzuki couplings to give axially chiral biaryls: Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 12051.

(5) Three groups have prepared optically pure **2b** by methods different than the one reported here: (a) Vyskočil, Š.; Smrčina, M.; Hanuš, V.; Polášek, P.; Kočovský, P. *J. Org. Chem.* **1998**, *63*, 7738. (b) Sumi, K.; Ikariya, T.; Noyori, R. *Can. J. Chem.* **2000**, *78*, 697. (c) Ding, K.; Wang, Y.; Yun, H.; Liu, J.; Wu, Y.; Terada, M.; Okubo, Y.; Mikami, K. *Chem. Eur. J.* **1999**, *5*, 1734. In addition, the racemic form of **2a** was reported: 216th Meeting of the American Chemical Society, August 23−27, 1998, Buchwald, S. L.; Wagaw, S.; Yang B. H. *ORGN-004*. For applications of **2b**, see: (d) Kočovský, P.; Vyskočil, Š.; Císařová, I.; Sejbal, J.; Tišlerová, I.; Smrčina, M.; Lloyd-Jones, G. C.; Stephen, S. C.; Butts, C. P.; Murray, M.; Langer, V. *J. Am. Chem. Soc.* **1999**, *121*, 7714. (e) Kočovský, P.; Malkov, A.; Vyskočil, Š.; Lloyd-Jones, G. C. *Pure Appl. Chem.* **1999**, *71*, 1425. (f) Lloyd-Jones, G. C.; Stephen, S. C.; Murray, M.; Butts, C. P.; Vyskočil, Š.; Kočovský, P. *Chem. Eur. J.* **2000**, *6*, 4348.

(6) For the Pd-catalyzed asymmetric alkylation of ketone enolates: (a) Trost, B. M.; Schroeder, G. M. *J. Am. Chem. Soc.* **1999**, *121*, 6759. (b) You, S.-L.; Hou, X.-L.; Dai, L.-X.; Zhu, X.-Z. *Org. Lett.* **2001**, *3*, 149.

(7) 2-Methyl-5-(*N*-methyl-anilinomethylene)cyclopentanone was prepared in 82% yield by the Claisen condensation of 2-methylcyclopentanone with ethyl formate followed by reaction with *N*-methylaniline.

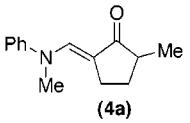
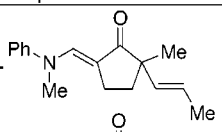
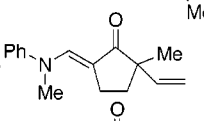
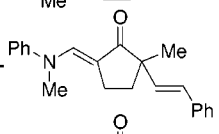
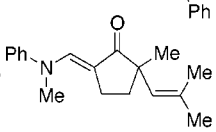
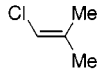
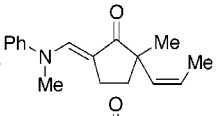
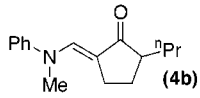
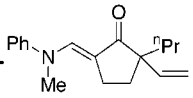
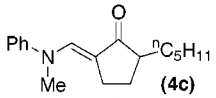
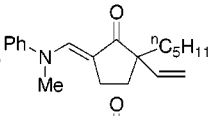
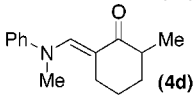
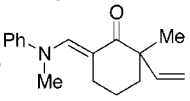
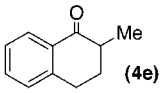
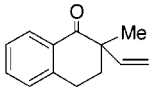
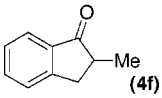
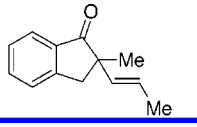
(8) **Typical Procedure.** An oven-dried Schlenk tube was capped with a rubber septum and cooled under argon. The tube was then charged with tris(dibenzylideneacetone)dipalladium(0) (9.2 mg, 0.01 mmol, 1 mol %), **2a** (12.4 mg, 0.025 mmol, 2.5 mol %), and 2-methyl-5-(*N*-methyl-anilinomethylene)-cyclopentanone (216 mg, 1.0 mmol). Toluene (2 mL) was added, and the mixture was stirred for 15 min at room temperature. 1-Bromopropene (0.17 mL, 2.0 mmol) and sodium *tert*-butoxide (192 mg, 2.0 mmol) were added, and the tube was capped with the septum and purged with argon. Additional toluene (4 mL) was added through the septum, and the mixture was stirred at room temperature until the starting ketone had been completely consumed, as judged by GC analysis. The reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL) and diluted with ether (20 mL). The layers were separated, the aqueous layer was extracted with ether (20 mL), and the combined organics were washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated. Chromatography gave 242 mg (95%) of the desired compound, which was judged to be 90% ee by chiral HPLC analysis.

(9) Although we optimized the conditions using toluene as solvent and $Pd_2(dba)_3$ as the palladium source, similar results were obtained using $Pd_2(dba)_3$ in Et_2O and $Pd(OAc)_2$ in toluene.

(10) For the reaction at room temperature, neither the yield nor the enantioselectivity of the reaction is very sensitive to the Pd:L ratio; the same result was obtained using ratios of 1/1.25, 1/2, or 1/3.

(11) The lower yields of **6c** and **6d** are due to difficulties during the isolation and purification steps due to their high volatility.

Table 2. Coupling between Ketone Enolates and Vinyl Halides Catalyzed by $Pd_2(dba)_3$/(*R*)-(−)-**2a**[a]

entry	ketone	vinyl halide	product	yield (%)[b]	ee (%)[c]
1	 (**4a**)		(*S*)-(+)- 	95[d]	90
2			(*S*)-(+)- 	94[d]	92
3[f]			(+)- 	92[d,g]	89[h]
4			(−)- 	95[e]	71
5				76[e]	71
6			(−)- 	84[e]	76
7	 (**4b**)		(+)- 	86[e]	90
8[i]	 (**4c**)		(−)- 	84[e]	92
9	 (**4d**)		(−)- 	78[e]	50
10	 (**4e**)		(−)- 	96[d]	80
11	 (**4f**)		(+)- 	95[d]	74

[a] Reactions were run at 0.2 M (ketone), with 2 equiv of 1-bromopropene and NaO*t*-Bu and with Pd/L ratio = 1:1.25. [b] Yields are an average of two isolated yields of >95% purity as determined by GC, ^{1}H NMR, and elemental analysis. [c] The ee was determined by chiral HPLC. [d] Reactions were run with 1 mol % $Pd_2(dba)_3$. [e] Reactions were run with 2.5 mol % $Pd_2(dba)_3$. [f] 4:1 mixture of *E*/*Z* isomers of the vinyl bromide was used. [g] Yield is for a mixture of *E*/*Z* isomers. [h] Enantiomeric excess reported is for the *E* isomer. [i] (*S*)-(−)-**2a** was used.

provides the first general route to cyclopentanone derivatives of this sort in highly enantiomerically enriched form.[12]

The absolute configurations of the new ligands introduced here, and of α-vinyl ketones **6a** and **6b**, were determined as follows. Levorotatory **2a** and **2c** and dextrorotatory 2-bromo-2′-*N*,*N*-(dimethylamino)-1,1′-binaphthyl were shown to have the (*R*)-configuration, as the last compound, when treated with *n*-BuLi and Ph_2PCl, gives (*R*)-(−)-**2b**.[5a] The (*R*)-configuration was also assigned to the quaternary chiral carbons of dextrorotatory **6a** and **6b**, both of which were obtained from reactions of (*S*)-(+)-**2a**.[13] The same sense of chirality was induced by monophosphines that lack the

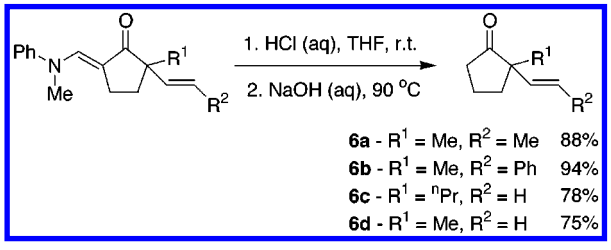


Figure 2.

(12) For a review on the preparation of chiral quaternary centers, see: Fuji, K. *Chem. Rev.* **1993**, *93*, 2037.

(13) Upon treatment with O_3/Me_2S, **6a** and **6b** gave (+)-2-formyl-2-methylcyclpentanone. Subsequent reaction with trimethylphosphono acetate/NaH gave (+)-2-methyl-2-(2-*trans*-methoxycarbonyl-1-ethenyl)cyclopentanone, which is known to have the (*R*)-configuration. See: (a) Tori, M.; Miyake, T.; Hamaguchi, T.; Sono, M. *Tetrahedron Asymmetry* **1997**, *8*, 2731. (b) Pfau, M.; Revial, G.; Guingant, A.; d'Angelo, J. *J. Am. Chem. Soc.* **1985**, *107*, 273.

dimethylamino group of **2b**; ligands **2d**−**f** with the (*R*)-configuration gave (*S*)-(+)-**5a**.

The mechanism of the vinylation reaction presumably follows a pathway similar to the one proposed for the nonasymmetric arylation of ketones.[2] It is not clear at this time which step in the catalytic cycle determines the enantioselectivity of the process. Our view is that the dimethylamino moiety of **2a** does not bind to the Pd complex to form a four-coordinate intermediate or that, if it does, this binding is not necessary for an efficient reaction. This belief is due to several findings. First, we have recently disclosed that reactions utilizing **1b**−**e** as ligands are similar in efficiency to those which use **1a**.[2c,3] Second, reactions that employed monodentate ligands such as **2d** and **2e** provided only slightly lower levels of enantioselectivity than those using **2a**.[14,15] In contrast, bidentate ligands such as **3b** produced the coupled product with significantly lower ee.

In summary, we have prepared a class of chiral electron-rich monodentate phosphines and have used them for the catalytic asymmetric vinylation of ketones. This reaction proceeds in very good yields and with high enantioselectivity. Work on the application of these and related novel ligands, including P chiral ligands, in a variety of catalytic asymmetric processes is currently in progress.

Acknowledgment. We thank the National Institutes of Health (GM 34917) for funding this research. Additional unrestricted support from Pfizer, Merck, and Novartis is also gratefully acknowledged. We thank Strem Chemical for providing (*R*)-(+)-2,2′-diiodo-1,1′-binaphthyl. A.C. was supported by a FAPESP postdoctoral fellowship. K.K. thanks Japan Society for the Promotion of Science for a postdoctoral fellowship. J. Å. was a Wallenberg Foundation Postdoctoral Fellow. J.M.F. thanks the NIH for a postdoctoral fellowship. We are indebted to Professor S. K. Kang for experimental assistance.

Supporting Information Available: Complete experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) It is likely that the enantioselectivity induced by **2a** is greater than that by **2d** or **2e** because the dimethylamino group is larger than either Me or *n*-Bu. That changing the size of the R^1 substituent of ligands **2** can dramatically alter the enantioselectivity is further illustrated by the low ee that is obtained with ligand **2f**. Unfortunately, our efforts to prepare the isopropyl analogue of these ligands (which would be similar to **2a** in terms of sterics) have thus far been unsuccessful.

(15) For the use of chiral monodentate phosphine MOP-ligands in asymmetric catalysis: (a) Hayashi, T. *Acc. Chem. Res.* **2000**, *33*, 354.