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Benzylic Phosphates as Electrophiles in the Palladium-Catalyzed Asymmetric Benzylation of Azlactones

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Supporting Information

ABSTRACT: Palladium-catalyzed asymmetric benzylation has been demonstrated with azlactones as prochiral nucleophiles in the presence of chiral bisphosphine ligands. Benzylic electrophiles are utilized under two sets of reaction conditions to construct a new tetrasubstituted stereocenter. Electron density of the phenyl ring dictates the reaction conditions, including the leaving group. The reported methodology represents a novel asymmetric carbon−carbon bond formation in an amino acid precursor.

Palladium-catalyzed benzylation has become an active area of research in the construction of carbon−carbon and carbon−heteroatom bonds.[1] The proposed catalytic cycle for the transformation invokes a cationic η^3-benzyl-palladium intermediate. Ionization of the electrophile can be challenging since the π-benzyl intermediate is dearomatized. Electrophiles containing a naphthalene or heteroaromatic moiety, to which the barrier to ionization and dearomatization is lower, are often employed in benzylation methodology. We recently disclosed an asymmetric process for benzylation of 3-aryloxindoles.[2] This method, in which asymmetric induction occurs during nucleophilic attack, was demonstrated to proceed with high yield and enantioselectivity with naphthyl and heteroaryl electrophiles (Figure 1a,b). Monocyclic benzylic electrophiles, however, were not reactive. We were interested in expanding the scope of asymmetric benzylation to this new class of less reactive electrophiles in the reaction with prochiral nucleophiles (Figure 1c).

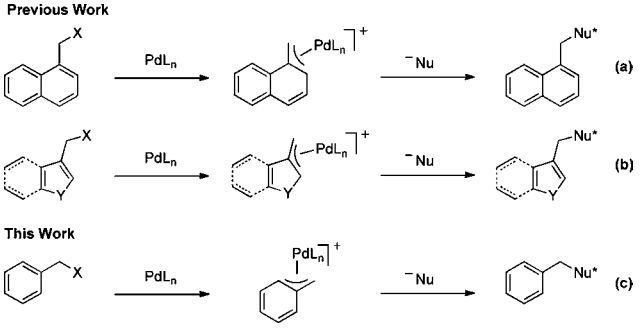


Figure 1. Asymmetric benzylation with (a) naphthyl and (b) heteroaryl electrophiles (previous work). Asymmetric benzylation with (c) benzyl electrophiles (this work).

Azlactones, derived from amino acids, were selected as the nucleophilic partner. The benzylated azlactones could be hydrolyzed to yield quaternary amino acids, which are prevalent in biologically active molecules. The synthesis of enantioenriched quaternary amino acids has been addressed via resolution and asymmetric processes.[3] Azlactones have been utilized as nucleophiles in various asymmetric reactions,[4] including phase-transfer-catalyzed alkylation,[5] conjugate addition,[6] and allylic alkylation.[7] We now report a process for asymmetric benzylation of azlactones using benzylic electrophiles with chiral bisphosphine ligands (Figure 2). To the best

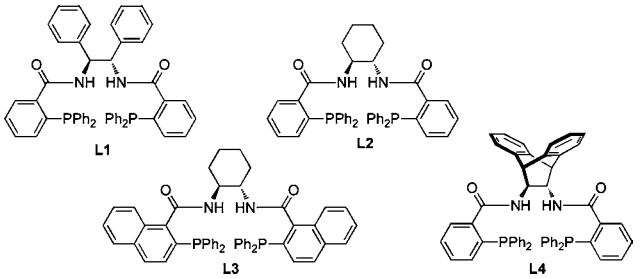
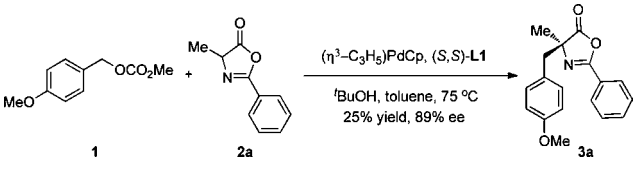


Figure 2. Chiral ligands utilized in asymmetric benzylation.

of our knowledge, this represents the first utilization of monocyclic benzylic electrophiles in an asymmetric benzylation.

Initial experiments employed benzylic carbonates as electrophiles. However, modest reactivity was observed when *p*-methoxybenzyl methyl carbonate (**1**) was treated with alanine-derived azlactone **2a** in toluene at 75 °C under catalytic conditions. Encouragingly, an enantioselectivity of 89% of **3a** was observed (Scheme 1).

Scheme 1. Initial Experiment



Reasoning that the low isolated yield was due to slow ionization of **1**, the leaving group was changed to a more labile diethyl phosphate.[8] Low reactivity was observed, and

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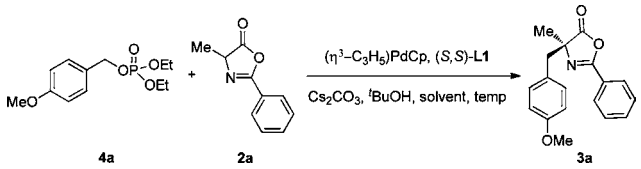
Table 1. Selected Optimization Experiments



4a 2a 3a

entry	equiv Cs_2CO_3	solvent	temp (°C)	yield[b] (%)	ee[c] (%)
1	0	toluene	75	10	78
2	0.1	toluene	75	25	91
3	0.1	DCM	25	23	97
4	0.5	DCM	25	63	97
5	0.6	DCM	25	90[d]	96
6	0.6	DCM	25	17[e]	88

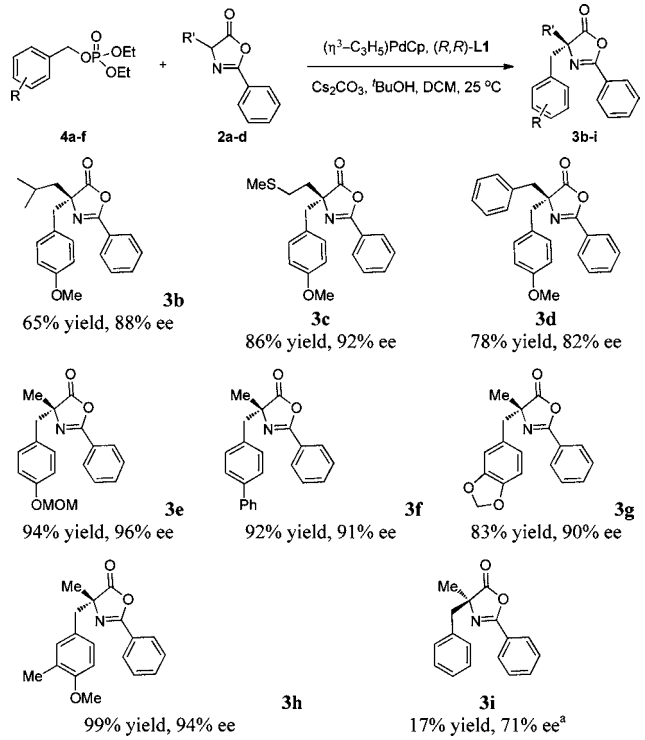
[a]Reactions performed on 0.2 mmol scale at 0.4 M using 1.0 equiv of **4a**, 1.0 equiv of **2a**, 5.0 mol % (η^3-C_3H_5)PdCp, 6.0 mol % **L1**, and 5.0 equiv of ^{t}BuOH for 20 h. [b]Isolated yield. [c]Determined by chiral HPLC. [d]Reaction run with 1.5 equiv of **2**. [e]Reaction run without ^{t}BuOH.

enantioselectivity decreased to 78% using electrophile **4a** (Table 1, entry 1). The isolated yield improved and enantioselectivity was restored upon addition of Cs_2CO_3 as catalytic base to deprotonate the nucleophile (Table 1, entry 2). A further increase in enantioselectivity was observed when dichloromethane (DCM) was used as the solvent and the reaction temperature lowered (Table 1, entry 3). Noticing that the isolated yield correlated to the amount of base utilized (0.2 equiv of basic sites for 0.1 equiv of Cs_2CO_3), we increased the amount of base to 0.5 equiv (Table 1, entry 4). The isolated yield increased to 63%, and enantioselectivity remained high. An increase in the equivalents of **2a** to 1.5 and Cs_2CO_3 to 0.6 furnished benzylated azlactone **3a** in 90% yield and 96% ee (Table 1, entry 5). In the absence of ^{t}BuOH, **3a** was isolated in 17% yield and 88% ee, confirming the beneficial effect of the additive. Additionally, under the optimized reaction conditions, no product was observed when **1** was used as the electrophile, highlighting the importance of the more labile phosphate leaving group.

The scope of asymmetric benzylation was investigated with respect to the nucleophile and electrophile (Table 2). Benzylation of nucleophiles derived from leucine (**3b**), methionine (**3c**), and phenylalanine (**3d**) proceeded in high yield and enantioselectivity. A methoxymethyl (MOM)-protected phenol was tolerated under the reaction conditions, and **3e** was isolated in 94% yield and 96% ee. A *p*-phenyl electrophile furnished **3f** in 92% yield and 91% ee. 3,4-Disubstituted electrophiles were competent reaction partners, providing azlactones **3g**,**h** in 83 and 99% yield, respectively. High reactivity was limited to electron-rich electrophiles; an unsubstituted benzylic phosphate reacted to give **3i** in only 17% isolated yield.

Studies were performed to increase the electrophile scope to less electron-rich benzyl groups as in **3i**. From a survey of exogenous bases, it was found that using 1.2 equiv of TEA increased the isolated yield of **3i** to 38% and the ee to 95%. To further promote ionization, a more labile diphenyl phosphate (**5a**) was utilized as the leaving group. An increase in isolated yield to 55% was observed upon this change in leaving group (Table 3, entry 1). Other chiral bisphosphine ligands (Figure 2) were investigated, but **L1** furnished the highest enantioselectivity (Table 3, entries 2−4). Screening various solvents indicated that yield and enantioselectivity were highest in dioxane (Table 3, entries 5−8). Performing the reaction at 50 °C increased the yield to 77% while maintaining high levels of

Table 2. Asymmetric Benzylation with Electron-Rich Phosphates[a]



[a]Reactions performed on 0.2 mmol scale at 0.4 M using 1.0 equiv of **4a**−**f**, 1.5 equiv of **2a**−**d**, 5.0 mol % (η^3-C_3H_5)PdCp, 6.0 mol % **L1**, 0.6 equiv of Cs_2CO_3, and 5.0 equiv of ^{t}BuOH for 20 h. All yields are isolated, and ee determined by chiral HPLC. [b]Reaction run with (*S*,*S*)-**L1**.

enantioselectivity (Table 3, entry 9). An increase in reaction concentration to 0.67 M with respect to **5a** provided **3i** in 83% isolated yield and 93% ee (Table 3, entry 10). A decrease in yield was observed in the absence of ^{t}BuOH (Table 3, entry 11).

With optimized conditions for an electron-neutral electrophile in hand, attention was turned to investigation of reaction scope (Table 4). Using azlactones **2b**,**c**, benzylation products **3j**,**k** were formed in high yield and enantioselectivity. Substitution at the *para*-position with a fluorine atom furnished **3l** in 74% yield and 94% ee at ambient temperature. The *p*-tolyl electrophile furnished **3m** in 91% yield and 95% ee. 3,4-

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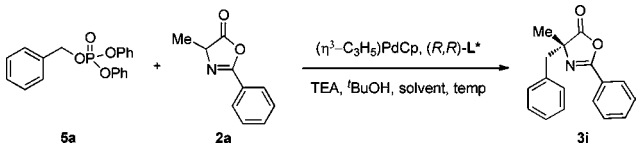
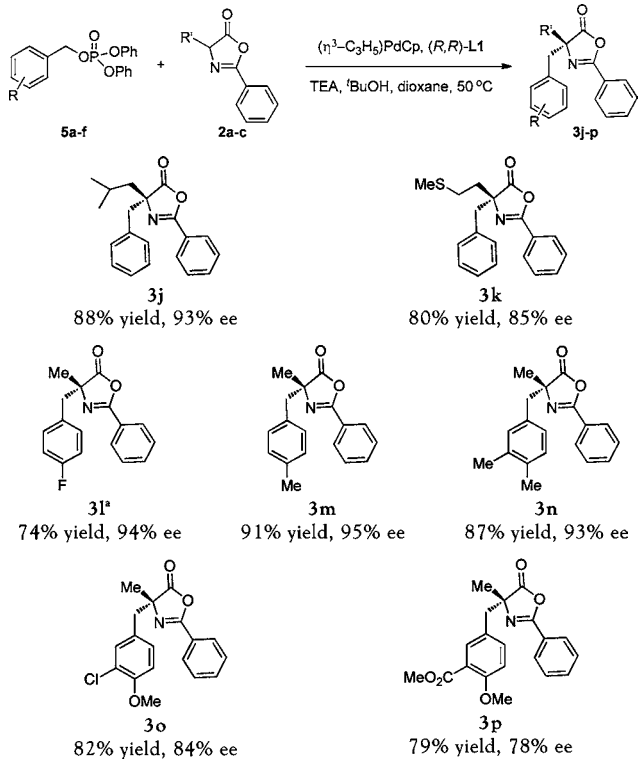
Table 3. Optimization of Electron-Neutral Phosphate



entry	L*	solvent	temp (°C)	yield[b] (%)	ee[c] (%)
1	**L1**	DCM	25	55	−94[d]
2	**L2**	DCM	25	53	−54[d]
3	**L3**	DCM	25	47	83
4	**L4**	DCM	25	28	59
5	**L1**	toluene	25	40	96
6	**L1**	DME	25	23	96
7	**L1**	THF	25	42	95
8	**L1**	dioxane	25	57	96
9	**L1**	dioxane	50	77	93
10	**L1**	dioxane	50	83[e]	93
11	**L1**	dioxane	50	34[e,f]	93

[a]Reactions performed on 0.2 mmol scale at 0.4 M using 1.0 equiv of **5a**, 1.5 equiv of **2a**, 5.0 mol % (η^3-C_3H_5)PdCp, 6.0 mol % **L***, 1.2 equiv of TEA, and 5.0 equiv of ^{t}BuOH for 16 h. [b]Isolated yield. [c]Determined by chiral HPLC. [d]Reaction run with (*S,S*)-**L***. [e]Reaction run at 0.67 M with respect to **5a**. [f]Reaction run without ^{t}BuOH.

Table 4. Asymmetric Benzylation with Electron-Neutral Phosphates[a]

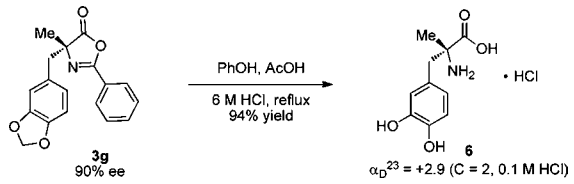


[a]Reactions performed on 0.2 mmol scale at 0.67 M using 1.0 equiv of **5a−f**, 1.5 equiv of **2a−c**, 5 mol % (η^3-C_3H_5)PdCp, 6 mol % **L1**, 1.2 equiv of TEA, and 5.0 equiv of ^{t}BuOH for 16 h. All yields are isolated, and ee's are determined by chiral HPLC. [a]Reaction run at 25 °C.

Dimethyl substitution provided **3n** in 87% yield and 93% ee. An electron-withdrawing halogen or ester subsituent could be placed at the *meta*-position of the electrophile, but an electron-donating group was required at the *para*-position to balance electronics and achieve high reactivity (**3o**,**p**).

To illustrate the utility of the asymmetric benzylation for the synthesis of quaternary amino acids, azlactone **3g** was hydrolyzed under acidic conditions to furnish α-methyl-D-dopa (**6**) as its hydrochloride salt (Scheme 2).[9] α-Methyl-L-dopa (methyldopa) is an antihypertensive drug. Syntheses of enantioenriched methyldopa have relied upon resolution of the racemate[10] or have utilized chiral precursors.[11] Palladium-catalyzed asymmetric benzylation can be used to synthesize either enantiomer of methyldopa in two steps from readily available **2a**. This route represents the first catalytic asymmetric synthesis of methyldopa. The optical rotation of **6** was used to assign the absolute stereochemistry of the benzylation. Comparison of the optical rotation of **3i** to the known value corroborated the assignment.[12]

Scheme 2. Hydrolysis to α-methyl-D-dopa



Ionization to the η^3-benzyl-palladium cationic intermediate could proceed through two different pathways (Figure 3). The first, analogous to that of allylic alkylation, invokes coordination of Pd(0) to the π-system followed by ionization to the η^3-benzyl-palladium cation (Figure 3, path a). Alternatively, S_N2 displacement of the leaving group by palladium leads to the σ-bound cation, which can isomerize to the π-benzyl cation

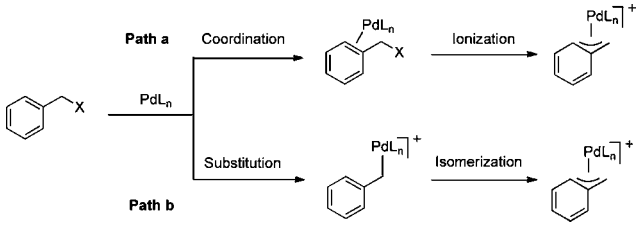


Figure 3. Ionization modes in palladium-catalyzed benzylation.

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(Figure 3, path b). An S_N2 displacement with palladium has been proposed in studies on oxidative addition to benzyl chloride.[13] Based on our studies, we feel that substitution followed by isomerization is occurring. Electron-rich benzyl electrophiles are more reactive, requiring a less labile leaving group. Increased electron density would stabilize the transition state in an S_N2 reaction, leading to charged intermediates.[14] On the other hand, low-valent palladium would better coordinate to an electron-poor π system, which should have led to increased reactivity. The lower reactivity of less electron-rich electrophiles under identical conditions (Table 2) further supports S_N2 displacement as opposed to pre-coordination.

In conclusion, we have expanded the scope of asymmetric benzylation to monocyclic benzylic electrophiles. Using phosphate leaving groups to render benzyl groups more reactive, we have developed a method for benzylating azlactones. A tetrasubstituted stereocenter is generated in high enantiomeric excess with a variety of electron-rich and electron-neutral elecrophiles. The methodology provides access to enantioenriched quaternary amino acids via hydrolysis of the azlactone, which has been illustrated in the synthesis of α-methyl-D-dopa. Further studies into asymmetric benzylation scope are underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and spectral data for unknown compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Kuwano, R. *Synthesis* **2009**, *7*, 1049. (b) Legros, J.-Y.; Fiaud, J.-C. *Tetrahedron Lett.* **1992**, *33*, 2509. (c) Kuwano, R.; Konda, Y.; Matsuyama, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12104.

(2) Trost, B. M.; Czabaniuk, L. C. *J. Am. Chem. Soc.* **2010**, *132*, 15534.

(3) (a) Cataviela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2007**, *18*, 569. (b) Cataviela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517.

(4) Alba, A.-N. R.; Rios, R. *Chem. Asian J.* **2011**, *6*, 720.

(5) Uraguchi, D.; Asai, Y.; Seto, Y.; Ooi, T. *Synlett* **2009**, 658.

(6) (a) Cabrera, S.; Reyes, E.; Aleman, J.; Milelli, A.; Kobbelgaard, S.; Joergensen, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 12031. (b) Hayashi, Y.; Obi, K.; Ohta, Y.; Okamura, D.; Ishikawa, H. *Chem. Asian J.* **2009**, *4*, 246. (c) Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051. (d) Aleman, J.; Milelli, A.; Cabrera, S.; Reyes, E.; Jorgensen, K. A. *Chem. Eur. J.* **2008**, *14*, 10958. (e) Balaguer, A. N.; Companyo, X.; Calvet, T.; Font-Bardia, M.; Moyano, A.; Rios, R. *Eur. J. Org. Chem.* **2009**, 199. (f) Alba, A.-N. R.; Companyo, X.; Valero, G.; Moyano, A.; Rios, R. *Chem. Eur. J.* **2010**, *16*, 5354.

(7) (a) Trost, B. M.; Ariza, X. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2635. (b) Trost, B. M.; Ariza, X. *J. Am. Chem. Soc.* **1999**, *121*, 10727. (c) Trost, B. M.; Dogra, K. J. *J. Am. Chem. Soc.* **2002**, *124*, 7256. (d) Trost, B. M.; Jakel, C.; Plietker, B. *J. Am. Chem. Soc.* **2003**, *125*, 4438.

(8) Selected examples of allylic phosphates in Pd-catalyzed allylic substitution: (a) Tanigawa, Y.; Nishimura, K.; Kawasaki, A.; Murahashi, S.-I. *Tetrahedron Lett.* **1982**, *23*, 5549. (b) Hanzawa, Y.; Ishizawa, S.; Kobayashi, Y. *Chem. Pharm. Bull.* **1988**, *36*, 4209. (c) Murahashi, S.-I.; Taniguchi, Y.; Imada, Y.; Tanigawa, Y. *J. Org. Chem.* **1989**, *54*, 3292.

(9) *Merck Index*, 14th ed.; Merck: Whitehouse Station, NJ, 2007; p 6055.

(10) Tristram, E. W.; ten Broeke, J.; Reinhold, D. F.; Sletzinger, M.; Williams, D. E. *J. Org. Chem.* **1964**, *29*, 2053.

(11) (a) Reinhold, D. F.; Firestone, R. A.; Gaines, W. A.; Chemerda, J. M.; Sletzinger, M. *J. Org. Chem.* **1968**, *33*, 1209. (b) Kawabata, T.; Suzuki, H.; Nagae, Y.; Fuji, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 2155. (c) Leon-Romo, J. L.; Virues, C. I.; Avina, J.; Regla, I.; Juaristi, U. *Chirality* **2002**, *14*, 144. (d) Seebach, D.; Aebi, J. D.; Naef, R.; Webber, T. *Helv. Chim. Acta* **2004**, *68*, 144.

(12) Stierli, F.; Obrecht, D.; Heimgartner, H. *Chimia* **1984**, *38*, 432.

(13) Wong, P. K.; Lau, K. S. Y.; Stille, J. K. *J. Am. Chem. Soc.* **1974**, *96*, 5956.

(14) (a) Swain, C. G.; Langsdorf, W. P. Jr. *J. Am. Chem. Soc.* **1951**, *73*, 2813. (b) Kim, S. H.; Yoh, S.-D.; Lim, C.; Mishima, M.; Fujio, M.; Tsuno, Y. *J. Phys. Org. Chem.* **1998**, *11*, 254.