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Highly Diastereoselective Pd-Catalyzed Carboetherification Reactions of Acyclic Internal Alkenes. Stereoselective Synthesis of Polysubstituted Tetrahydrofurans

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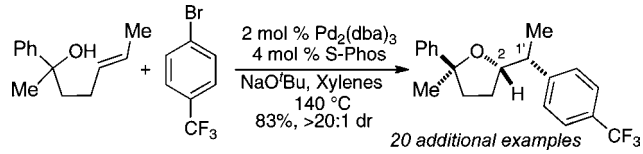
ABSTRACT



A highly diastereoselective synthesis of substituted tetrahydrofurans bearing stereocenters at C2 and C1′ via Pd-catalyzed carboetherification reactions of acyclic internal alkenes is described. Use of an improved catalyst composed of $Pd_2(dba)_3$/S-Phos provides products with up to >20:1 dr. The stereoselective preparation of tetrahydrofurans containing three stereocenters, including a molecule structurally related to simplakidine A, is also reported.

The prevalence of tetrahydrofuran units in natural products and other biologically active molecules has inspired the invention of numerous methods for the construction of these heterocycles.[1] For the past several years, our group has investigated a new approach to the stereoselective synthesis of tetrahydrofurans via Pd-catalyzed cross-coupling reactions between γ-hydroxy alkenes and aryl or alkenyl halides.[2−5] These reactions exhibit several attractive, synthetically useful features: simple starting materials are employed, both a C−O and a C−C bond are generated, and control of relative stereochemistry around the tetrahydrofuran ring is generally high. For example, the coupling of **1** with 1-bromo-4-*tert*-butylbenzene afforded **2** in 69% yield with >20:1 dr (Scheme 1).[3b] Although Pd-catalyzed carboetherifications have considerable utility, this method currently suffers from a significant limitation: transformations of substrates such as **3** that contain acyclic internal alkenes afford products bearing stereocenters adjacent to the ring (e.g., **4**) with only modest stereoselectivity (ca. 3−5:1 dr).[3a,c]

(1) For reviews on the synthesis of tetrahydrofurans, see: (a) Jalce, G.; Franck, X.; Figadere, B. *Tetrahedron: Asymmetry* **2009**, *20*, 2537–2581. (b) Wolfe, J. P.; Hay, M. B. *Tetrahedron* **2007**, *63*, 261–290. (c) Muzart, J. *Tetrahedron* **2005**, *61*, 5955–6008. (d) Harmange, J. -C.; Figadere, B. *Tetrahedron: Asymmetry* **1993**, *4*, 1711–1754.

(2) Reviews : (a) Wolfe, J. P. *Eur. J. Org. Chem.* **2007**, 571–582. (b) Wolfe, J. P. *Synlett* **2008**, 2913–2937.

(3) (a) Hay, M. B.; Wolfe, J. P. *J. Am. Chem. Soc.* **2005**, *127*, 16468–16476. (b) Wolfe, J. P.; Rossi, M. A. *J. Am. Chem. Soc.* **2004**, *126*, 1620–1621. (c) Hay, M. B.; Wolfe, J. P. *Tetrahedron Lett.* **2006**, *47*, 2793–2796. (d) Hay, M. B.; Hardin, A. R.; Wolfe, J. P. *J. Org. Chem.* **2005**, *70*, 3099–3107. (e) Ward, A. F.; Wolfe, J. P. *Org. Lett.* **2009**, *11*, 2209–2212.

(4) (a) For related reactions of hydroxy dienes, see: Yeh, M. -C. P.; Tsao, W -C.; Tu, L. -H. *Organometallics* **2005**, *24*, 5909–5915. For related reactions of allylic alcohols that generate oxiranes, see: (b) Hayashi, S.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2009**, *131*, 2052–2053.

(5) For recent, complementary alkene difunctionalization reactions of unsaturated alcohols that generate disubstituted tetrahydrofurans with formation of both a C−C and a C−O bond, see: (a) Zhang, G.; Cui, L.; Wang, Y.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 1474–1475. (b) Nicolai, S.; Erard, S.; Gonzalez, D. F.; Waser, J. *Org. Lett.* **2010**, *12*, 384–387. (c) Protti, S.; Dondi, D.; Fagnoni, M.; Albini, A. *Eur. J. Org. Chem.* **2008**, 2240–2247. (d) Yang, X.; Fang, X.; Yang, X.; Zhao, M.; Han, Y.; Shen, Y.; Wu, F. *Tetrahedron* **2008**, *64*, 2259–2269.

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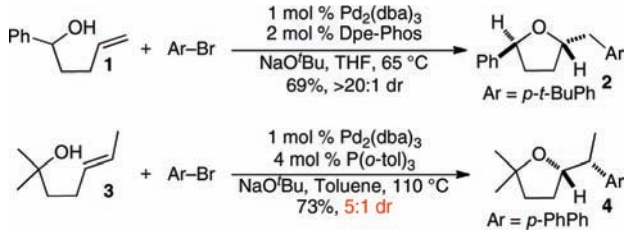
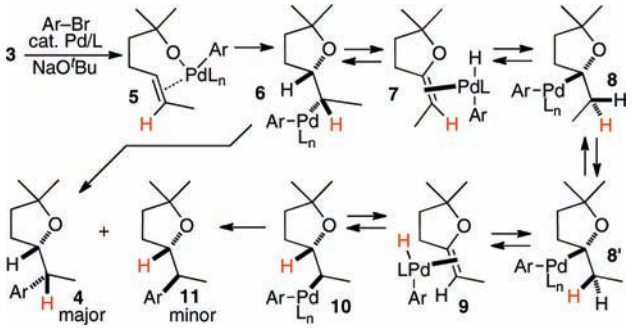
Scheme 1. Prior Studies



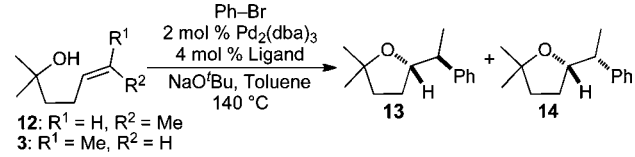
Through a series of deuterium labeling experiments we found that both diastereomers (e.g., **4** and **11**) formed in carboetherification reactions of substrates such as **3** arise from a common intermediate (**6**) (Scheme 2).[3a] The mechanism of these transformations involves oxidative addition of the aryl halide to Pd(0) followed by substitution of alkoxide for bromide to provide **5**. A key *syn*-oxypalladation of **5** generates intermediate **6**, which can undergo C−C bond-forming reductive elimination to afford tetrahydrofuran product **4**. *However, the reductive elimination from complex* ***6*** *is not fast enough to avoid competing* β*-hydride elimination*. Thus, partial isomerization of **6** occurs via β-hydride elimination/hydridopalladation to provide **8**, which undergoes σ-bond rotation (**8** → **8′**) followed by a second β-hydride elimination/hydridopalladation to yield **10**. Reductive elimination from **10** affords the minor stereoisomer **11**, leading to the modest diastereoselectivity observed with substrates such as **3**.

Scheme 2. Mechanism



In recent years, a number of new phosphine ligands have been developed for Pd-catalyzed carbon−carbon and carbon−heteroatom bond-forming reactions that accelerate reductive elimination.[6] It seemed that one of these ligands could potentially improve the diastereoselectivity in Pd-catalyzed carboetherifications of internal alkenes by increasing the rate of reductive elimination from intermediate **6**. In order to probe this hypothesis, we investigated the Pd-catalyzed coupling of (*Z*)-2-methylhept-5-en-2-ol (**12**) with bromobenzene using a number of different ligands known to promote rapid reductive elimination.[7] As shown in Table 1, P(*o*-tol)$_3$, which was employed in our initial studies,[3a] provided **13** in good yield but only 4:1 dr. Chelating ligands with wide bite angles, such as Dpe-Phos and xantphos, failed to provide satisfactory results. However, considerably improved diastereoselectivity was obtained using Buchwald's S-Phos ligand (entry 9, 9:1 dr). In addition, the Pd/S-Phos catalyst transformed *E*-alcohol stereoisomer **3** to tetrahydrofuran **14** in good yield and excellent diastereoselectivity (entry 10, 20:1 dr).[8,9]

Table 1. Ligand Optimization[a]



entry	substrate	ligand	**13**:**14**	yield[b] (%)
1	**12**	P(*o*-tol)$_3$	4:1	76
2	**12**	Dpe-Phos	1:1	55
3	**12**	Xantphos	2:1	17
4	**12**	X-Phos	3:1	40
5	**12**	RuPhos	9:1	68
6	**12**	Dave-phos	2:1	49
7	**12**	John-phos	2:1	18
8	**12**	Brett-phos		0
9	**12**	S-Phos	9:1	84
10	**3**	S-Phos	1:20	86

[a] Conditions: 1.0 equiv of alcohol, 2.0 equiv of ArBr, 2.0 equiv of NaO^{t}Bu, 2 mol % of Pd$_2$(dba)$_3$, 4 mol % of ligand, xylenes, 140 °C. [b] Isolated yields (average of two or more experiments).

With a much more effective catalyst system in hand, we investigated Pd-catalyzed carboetherification reactions between several different γ-hydroxyalkene substrates and a range of aryl or alkenyl bromides.[10] As shown in Table 2, both electron-donating and electron-withdrawing groups on the aryl bromide were tolerated. In all cases examined, the major diastereomer resulted from *syn*-addition of the arene and the oxygen atom across the double bond, which is consistent with our prior results.[3]

(6) (a) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338–6361. (b) Van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Reek, J. N. H.; Dierkes, P. *Chem. Rev.* **2000**, *100*, 2741–2770.

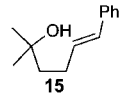
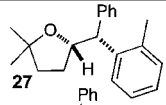
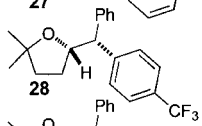
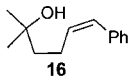
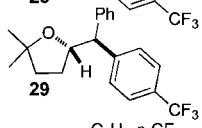
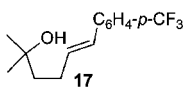
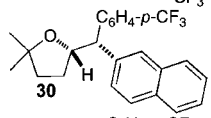
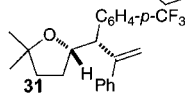
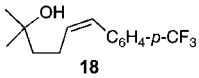
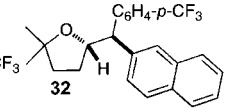
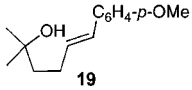
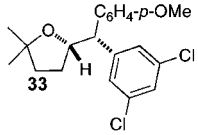
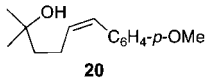
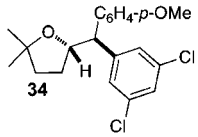
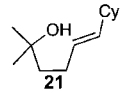
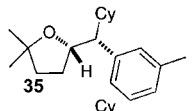
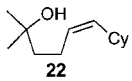
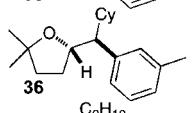
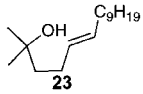
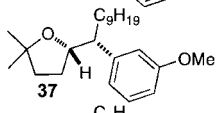
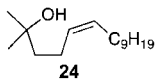
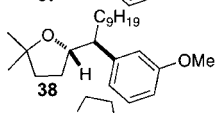
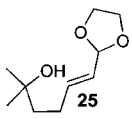
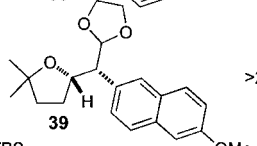
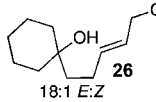
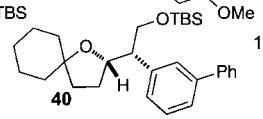
(7) Ligand definitions: Dpe-Phos = bis(2-diphenylphosphinophenyl) ether; Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene; X-Phos = 2-(dicyclohexylphosphino)-2′,4′,6′-triisopropyl-1,1′-biphenyl; Ru-Phos = 2-dicyclohexylphosphino-2′,6′-diisopropoxy-1,1′-biphenyl; Dave-phos = 2-dicyclohexylphosphino-2′(*N*,*N*-dimethylamino)biphenyl; John-phos = 2-(di-*tert*-butylphosphino)biphenyl; Brett-phos = 2-(dicyclohexylphosphino)-3,6-dimethoxy-2′,4′,6′-triisopropyl-1,1′-biphenyl; S-Phos = 2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl.

(8) Diastereomeric ratios observed in crude reaction mixtures were identical to those obtained upon isolation.

(9) The precise origin of the efficacy of S-Phos in these transformations is not entirely clear but is likely related to features that have been ascribed to its utility in Suzuki coupling reactions. See: Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871–1876.

(10) Reaction temperatures of 140 °C were employed to ensure transformations proceeded to completion. Use of lower reaction temperatures did not have a significant influence on diastereoselectivity.

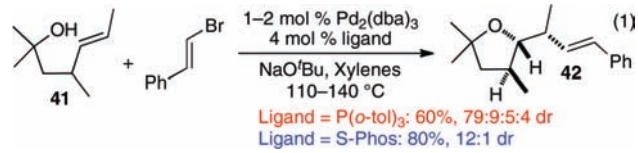
Table 2. Synthesis of Tetrahydrofurans[a]

entry	substrate	product	dr	yield (%)[b]
1	 **15**	 **27**	>20:1	82
2	**15**	 **28**	>20:1	87
3	 **16**	 **29**	9:1	74
4	 **17**	 **30**	>20:1	89
5	**17**	 **31**	>20:1	55
6	 **18**	 **32**	>20:1	96
7	 **19**	 **33**	>20:1	51
8	 **20**	 **34**	>20:1	60
9	 **21**	 **35**	>20:1	90
10	 **22**	 **36**	2:1	23[c,d]
11	 **23**	 **37**	>20:1	94
12	 **24**	 **38**	4:1	43[d]
13	 **25**	 **39**	>20:1	42
14	 **26** 18:1 *E*:*Z*	 **40**	12:1	86

[a] Conditions: 1.0 equiv of alcohol, 2.0 equiv of ArBr, 2.0 equiv of NaO^{t}Bu, 2 mol % of $Pd_2(dba)_3$, 4 mol % of S-Phos, xylenes, 140 °C. [b] Isolated yields (average of two or more experiments). [c] NMR yield. This material was contaminated with ca. 15% of an inseparable unidentified side product. [d] Formation of a side product tentatively assigned as a regioisomer was also observed.

In most instances *E*-alkene substrates bearing aryl or alkyl substituents were converted to the desired products with high diastereoselectivities (entries 1, 2, 4, 5, 7, and 11). In addition, the coupling reaction of a sterically hindered cyclohexyl-substituted alkene was also efficient (entry 9). An *E*-alkene bearing an acetal was transformed into the desired tetrahydrofuran **39** with good diastereoselectivity, but only modest yield (entry 13). In contrast, the conversion of cyclohexanol derivative **26** to spirocyclic tetrahydrofuran **40** proceeded with good yield (entry 14), but slightly lower stereoselectivity (12:1).

Although reactions of *Z*-alkenes substituted with methyl or phenyl groups proceeded with only 9:1 dr (Table 1, entry 9, and Table 2, entry 3), substrates bearing either electron-rich or electron-poor aryl substituents on the alkene were converted to products with excellent diastereoselectivity (Table 2, entries 6 and 8). However, chemical yields were lower with the electron-donating aryl substituent (entry 8). Unfortunately, *Z*-alkene substrates bearing either a long alkyl chain (entry 12) or a bulky substituent (entry 10) were transformed with poor diastereoselectivity, and the formation of side products tentatively assigned as regioisomers was also observed.[11]



Our prior efforts to effect carboetherification reactions of internal alkene substrates bearing stereocenters led to the formation of complicated mixtures of stereoisomers.[3c] For example, we had previously shown the Pd/P(*o*-tol)$_3$-catalyzed coupling of **41** with β-bromostyrene proceeded in 60% yield and afforded an inseparable mixture of four diastereomers (eq 1). In contrast, use of the S-Phos ligand provided **42** in 80% yield with 12:1 dr.[12] As shown in Table 3, *E*-alkene substrates bearing stereocenters at C1 (entry 1) or C3 (entry 3) were efficiently converted to polysubstituted tetrahydrofurans with good to excellent stereocontrol. The conversion of *Z*-alkene **44** to tetrahydrofuran **47** proceeded with 7:1 *syn*/*anti* addition selectivity, which is similar to results obtained for carboetherification of (*Z*)-2-methylhept-5-en-2-ol **12** (Table 1, entry 9).[13] Although the coupling of **45** with 4-bromotoluene provided a 4:1 mixture of tetrahydrofuran diastereomers epimeric at C4, complete selectivity for *syn*-addition was observed.[14] Nonetheless, all four transformations illustrated in Table 3 afforded products with significantly better diastereoselectivities than were obtained in related transformations with P(*o*-tol)$_3$ as ligand.[3c] Although this method is very effective with tertiary alcohol substrates

(11) For a discussion of the mechanism for regioisomer formation, see ref 3a.

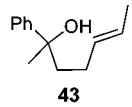
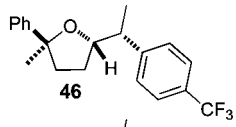
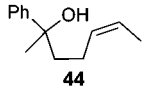
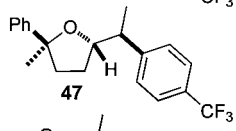
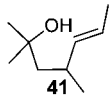
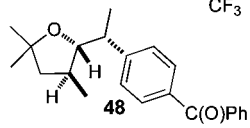
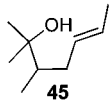
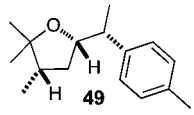
(12) The two diastereomers are epimeric at C3.

(13) A reaction that was halted at 30% conversion showed no evidence for *Z* to *E* isomerization of the alkene starting material.

(14) Use of P(*o*-tol)$_3$ for the coupling of β-bromostyrene with **45** afforded a 65:17:14:4 mixture of diastereomers. See ref 3c.

bearing internal alkenes, efforts to employ secondary alcohols failed to generate tetrahydrofuran products. Instead, oxidation of the secondary alcohol to the corresponding ketone was observed.[15]

Table 3. Synthesis of Polysubstituted Tetrahydrofurans[a]

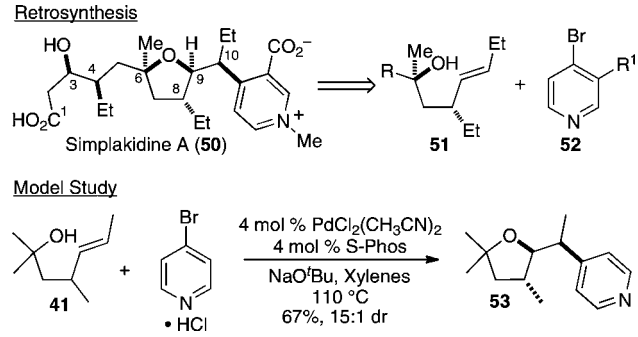
entry	substrate	product	dr	yield (%)[b]
1	 **43**	 **46**	>20:1	83
2	 **44**	 **47**	7:1[c]	87
3	 **41**	 **48**	20:1	83
4	 **45**	 **49**	4:1[d]	84

[a] Conditions: 1.0 equiv of alcohol, 2.0 equiv of ArBr, 2.0 equiv of NaO^{t}Bu, 2 mol % of $Pd_2(dba)_3$, 4 mol % of S-Phos, Xylenes, 140 °C. [b] Isolated yields (average of two or more experiments). [c] The two diastereomers are epimeric at C1′. [d] The two diastereomers are epimeric at C4.

The results illustrated in Table 3 prompted us to model the feasibility of applying our method to the synthesis of simplakidine A (**50**).[16] This polysubstituted tetrahydrofuran natural product exhibits cytotoxic activity and has not previously been synthesized. As shown in Scheme 3, the tetrahydrofuran core of this molecule could potentially be generated through a Pd-catalyzed carboetherification between a tertiary alcohol bearing a pendant *E*-alkene (**51**) and a suitably substituted 4-bromopyridine derivative (**52**). The ring-closing reaction would form the C9 and C10 stereocenters with concomitant installation of the heteroaryl group.

The two substituents on C6 of the natural product are fairly close in size (approximately Me vs *i*-Bu), which suggests the diastereotopic face selectivity of the alkene carboetherification reaction will likely be controlled by the stereochemical configuration at C8 of substrate **51** rather than C6. Thus, the simple tertiary alcohol **41** seemed to be a reasonable approximation to **51** for an initial model study. As such, we examined the Pd/S-Phos-catalyzed coupling of **41** with 4-bromopyridine hydrochloride. We were gratified to find that this transformation provided **53** with 15:1 dr in 67% yield.

Scheme 3. Strategy for the Synthesis of Simplakidine A



In conclusion, we have developed significantly improved conditions for the synthesis of tetrahydrofurans bearing stereocenters at C2 and C1′ via Pd-catalyzed carboetherification. The Pd/S-Phos catalyst system minimizes isomerization after the key *syn*-oxypalladation event in the catalytic cycle by facilitating rapid C−C bond-forming reductive elimination. This significantly expands the range of tetrahydrofuran products that can be generated efficiently by coupling aryl or alkenyl halides with unsaturated alcohol substrates. In addition, the experiments illustrated in Table 1 provide a measure of the relative facility of sp^3C-C_{Ar} bond-forming reductive elimination with a series of different ligands, which may be useful in the development of other metal-catalyzed reactions.[16] Further studies on applications of this method are currently underway.

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Supporting Information Available: Experimental procedures, spectroscopic data, and copies of ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Analogous reactions of secondary alcohol substrates bearing terminal alkenes (e.g., **1**) provide *trans*-2,5-disubstituted products in good yield with >20:1 dr. See refs 3b, 3d and 3e.

(16) Campagnuolo, C.; Fattorusso, C.; Fattorusso, E.; Ianaro, A.; Pisano, B.; Taglialatela-Scafati, O. *Org. Lett.* **2003**, *5*, 673–676.