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Palladium-catalyzed asymmetric coupling cyclization of terminal γ-allenols with aryl iodides†

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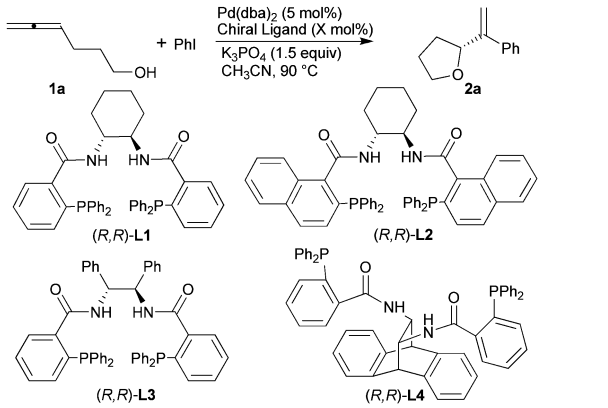
A Pd-catalyzed asymmetric coupling cyclization of γ-allenols has been developed. Styrenyl derivatives can be prepared in 60–86% yields with ee values ranging from 85–92%.

Transition metal-catalyzed asymmetric allylic substitution of allylic acetates or carbonates is a powerful and versatile method for the construction of optically active chiral organic molecules in a non-racemic form. This reaction has been well-established and the nucleophile scope has been expanded to allow for the use of carbon, nitrogen, oxygen, sulfur, and phosphorus nucleophiles to construct C–C, C–N, C–O, C–S, and C–P bonds.[1] It is known that the carbometallation of allenes would result in the formation of 2-substituted allylic metallic intermediates,[2] which could, in principle, also undergo the asymmetric allylic substitution reaction. However, successful reports on this reaction with a 2-substitued π-allylic palladium intermediate are very limited.[3] Hiroi *et al.* reported that the carbopalladation of 1-phenyl-1,2-butadiene with sodium malonate using (*R*)-(*S*)-bppfOAc[4a] afforded allylic malonate with 96% ee although we have not been able to reproduce this result; the carbopalladation of 2-(*N*-allenyl)-aminophenyl iodides and subsequent intramolecular amination using (*S*)-Tol-BINAP afforded cyclic indole derivatives up to 88% ee.[4b] Larock and Zenner developed the palladium-(*R*,*R*)-Bn-Box-catalyzed asymmetric hetero- and carboannulation of allenes using functionally substituted aryl or vinyl iodides in 21–95% yields and 46–88% ee.[5] Our group has also used the same chiral ligand to synthesize other heterocycles such as butenolides[6a] and pyrazolidines[6b] with 80–84% ee. In 2009, this group reported the development of two new ligands, *i.e.*, α- or β-naphthylmethyl spiro-Box, which has been demonstrated for the enantioselective Pd-catalyzed cyclization of 2-iodoanilines with allenes and the enantioselective cyclization of 3,4-allenyl hydrazines with organic halides affording 2*H*-indolines in good yields with 94–98% ee[7a] and the 3-substitued pyrazolidines with 92–95% ee,[7b] respectively. Thus, we have a strong interest in the application of readily commercially available bidentate phosphine ligands to the cyclization of functionalized allenes. In this communication, we report the palladium-catalyzed asymmetric coupling cyclization of γ-allenols with aryl iodides using bisphosphine ligand (*R*,*R*)-**L1** developed by Trost *et al.* with the observation of a very unique effect of mixed solvents.

We started our investigation on the reaction of 4,5-hexadien-1-ol **1a** with iodobenzene and K_3PO_4 as the base in CH_3CN catalyzed by $Pd(dba)_2$ and a chiral ligand. The chiral diphenylphosphinobenzoic

Table 1 The effect of catalyst and ligand on the Pd(0)-catalyzed enantioselective cyclization of **1a** with iodobenzene[a]



Entry	**L** (*X* mol%)	*t* (h)	Yield[b] (ee) of **2a** (%)	Recovery of **1a**[b] (%)
1[c,d]	(*R*,*R*)-**L1** (5.5)	72	38 (80)	44
2	(*R*,*R*)-**L2** (7.5)	48	71 (20)	0
3	(*R*,*R*)-**L3** (7.5)	24	0	71
4[c,d,e]	(*R*,*R*)-**L4** (5.5)	67	41 (2)	42
5[d]	(*R*,*R*)-**L1** (6.5)	51	80 (88)	5
6	**(*R*,*R*)-L1 (7.5)**	**45**	**87 (88)**	**0**
7[f]	(*R*,*R*)-**L1** (7.5)	31	84 (79)	0
8[g]	(*R*,*R*)-**L1** (7.5)	31	81 (80)	4

[a] The reaction was carried out with **1a** (0.2 mmol), iodobenzene (1.5 mmol), $Pd(dba)_2$ (5 mol%), (*R*,*R*)-**L1** (*X* mol%) and base (1.5 equiv.) in 2 mL of CH_3CN at 90 °C. [b] Determined by NMR analysis. [c] The reaction occurred at 80 °C. [d] 1.2 mmol of iodobenzene was used. [e] 3 mL of CH_3CN was used. [f] 2.5 mol% $Pd_2(dba)_3{\cdot}CHCl_3$ was used. [g] 2.5 mol% $[(C_3H_5)PdCl]_2$ was used.

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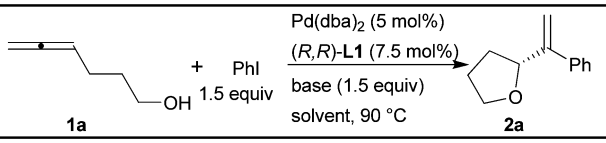
acid-based ligand (*R*,*R*)-**L1** (Table 1, entry 1) provided the desired product **2a** in 80% ee. Use of other commonly employed Trost ligands (Table 1, entries 2–4) offered no improvements in terms of stereocontrol and yield. Gratifyingly, the ee value reached 88% when the amount of ligand (*R*,*R*)-**L1** was increased to 6.5 mol% (Table 1, entry 5). Because of the observation of not-easily-reproducible enantioselectivity under these conditions, the amount of ligand was further increased to 7.5 mol% (Table 1, entry 6). Examination of the palladium source showed that both $Pd_2(dba)_3{\cdot}CHCl_3$ and $[(C_3H_5)PdCl]_2$ had no positive influence on the ee value (Table 1, entries 7 and 8).

With $Pd(dba)_2$ and (*R*,*R*)-**L1** being identified as the optimized catalyst system, a systematic examination of bases and solvents was conducted (Table 2). Bases, such as Na_3PO_4, K_2CO_3, Et_3N and KOAc, all failed to improve the enantioselectivity and yield (Table 2, entries 1–4). Only K_2CO_3 gave a decent ee value with a lower conversion (Table 2, entry 2). Several solvents were also tested. Reactions in polar solvents such as dioxane and DMF gave moderate enantioselectivities (Table 2, entries 5 and 7). In a less polar solvent such as toluene, enantioselectivity was almost the same (Table 2, entry 6). CH_3CN resulted in the full conversion and best enantioselectivity.

Table 2 Base and solvent effects on the $Pd(dba)_2$-(*R*,*R*)-**L1**-catalyzed asymmetric coupling cyclization of **1a** with iodobenzene[a]

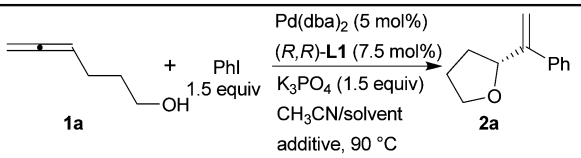


Entry	Solvent	Base	t (h)	Yield[b] (ee) of **2a** (%)	Recovery of **1a**[b] (%)
1	CH_3CN	Na_3PO_4	27	7 (76)	66
2	CH_3CN	K_2CO_3	33	12 (87)	67
3	CH_3CN	KOAc	10	85 (35)	0
4	CH_3CN	Et_3N	35	10 (25)	49
5	Dioxane	K_3PO_4	39	53 (80)	28
6	Toluene	K_3PO_4	42	74 (77)	8
7	DMF	K_3PO_4	37	18 (67)	18

[a] The reaction was carried out with **1a** (0.2 mmol), iodobenzene (0.3 mmol), $Pd(dba)_2$ (5 mol%), (*R*,*R*)-**L1** (7.5 mol%) and base (1.5 equiv.) in 2 mL of solvent at 90 °C. [b] Determined by NMR analysis.

We then examined some binary solvent systems and additives in this reaction. When CH_3CN was mixed with other solvents (1/1 by volume), for instance, dioxane, toluene, $CH_3(CH_2)_3CN$, the ee value remained the same as that obtained with CH_3CN (Table 3, entries 1–3). But when $(CH_3)_3CCN$ was used, the ee value was increased to 89% (Table 3, entry 4). By considering the effect of water on this reaction, fortunately, the addition of 4 Å molecular sieves into the mixed solvent CH_3CN–$(CH_3)_3CCN$ further improved the ee value to 90% (Table 3, entry 5). After screening the volume ratio of these two solvents, it showed that the best ee value was realized when the ratio of $CH_3CN/(CH_3)_3CCN$ was 1.5 : 1 (Table 3, entry 6) with full conversion of the starting material. After replacing the 4 Å molecular sieves with 3 Å molecular sieves, the ee value was improved slightly to 92% (Table 3, entry 9). Overall, the best results were obtained by using 1.5 equiv. of K_3PO_4 as the base in CH_3CN–$(CH_3)_3CCN$ in the presence of 3 Å molecular sieves under the catalysis of 5 mol% $Pd(dba)_2$ and 7.5 mol% (*R*,*R*)-**L1**.

Table 3 Effect of mixed solvent and molecular sieves on the $Pd(dba)_2$-(*R*,*R*)-**L1** catalyzed asymmetric coupling cyclization of **1a** with iodobenzene[a]

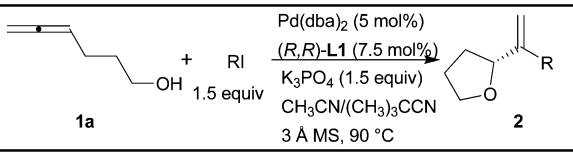


Entry	CH_3CN/solvent (volume ratio)	MS	t (h)	Yield[b] (ee) of **2a** (%)	Recovery of **1a**[b] (%)
1	Dioxane(1 : 1)	/	24	72 (87)	12
2	Toluene(1 : 1)	/	26	55 (88)	21
3	*n*-BuCN(1 : 1)	/	26	24 (88)	34
4	Me_3CCN(1 : 1)	/	25	72 (89)	5
5	Me_3CCN(1 : 1)	4 Å	22	81 (90)	0
6	Me_3CCN(1.2 : 0.8)	4 Å	24	76 (91)	0
7	Me_3CCN(1.5 : 0.5)	4 Å	21	47 (91)	31
8	Me_3CCN(0.8 : 1.2)	4 Å	24	78 (84)	0
9	Me_3CCN(1.2 : 0.8)	3 Å	22	79 (92)	3

[a] The reaction was carried out with **1a** (0.2 mmol), iodobenzene (0.3 mmol), $Pd(dba)_2$ (5 mol%), (*R*,*R*)-**L1** (7.5 mol%), base (1.5 equiv.), MS (80 mg) in 2 mL of solvent at 90 °C. [b] Determined by NMR analysis.

With the optimized reaction conditions in hand, a range of aryl iodides were investigated. The results are listed in Table 4. Aryl iodides bearing electron-withdrawing (Table 4, entries 4–9) and electron-donating groups (Table 4, entries 1–3) proceeded smoothly to afford the corresponding 2-alkenyltetrahydrofurans in moderate to good yields and enantioselectivities at 90 °C within 24–67.7 h. The substitution pattern and electronic property of the phenyl ring has an obvious effect on the enantioselectivity, the reaction time and the concentration needed for the reaction to reach completion: those bearing electron-donating groups usually required less reaction time and lower concentration as compared to the electron-withdrawing ones.

Table 4 Coupling cyclization of **1a** with different aryl halides[a]

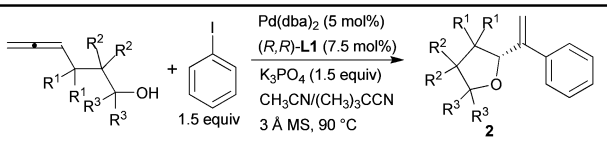


Entry	R	t (h)	Conc. (mol L^{-1})	Yield of **2**[b] (%)	ee of **2** (%)
1	C_6H_5	26	0.100	78	(*R*)-92 (**2a**)
2	4-$MeOC_6H_4$	24	0.125	82	(*R*)-88 (**2b**)
3	3,5-$Me_2C_6H_3$	32	0.125	76	(*R*)-89 (**2c**)
4	4-$Et_2NCOC_6H_4$	40	0.167	75	(*R*)-90 (**2d**)
5	3-$Et_2NCOC_6H_4$	67.7	0.167	86	(*R*)-91 (**2e**)
6[c]	4-IC_6H_4	45	0.250	60	(*R*)-88 (**2f**)
7	4-BrC_6H_4	43	0.250	78	(*R*)-85 (**2g**)
8	4-$CH_3COC_6H_4$	47	0.167	72	(*R*)-87 (**2h**)
9[d]	4-$EtOCOC_6H_4$	39	0.167	67	(*R*)-89 (**2i**)

[a] The reaction was carried out with **1a** (1.0 mmol), aryl iodide (1.5 mmol), $Pd(dba)_2$ (5 mol%), (*R*,*R*)-**L1** (7.5 mol%), 3 Å molecular sieves (400 mg) and K_3PO_4 (1.5 equiv.) in CH_3CN–$(CH_3)_3CCN$ (1.5/1 by volume). [b] Isolated yield. [c] 1.2 equiv. of 1,4-diiodobenzene were used. [d] The reaction was carried out on a 0.5 mmol scale.

We next examined the scope of the γ-allenols with the reaction of iodobenzene. Methyl groups were well tolerated at several positions, including the α, β and γ positions of the allenols (Table 5, entries 1–3). The closer the methyl substituents to the allene moieties, longer reaction time and higher concentration were required.

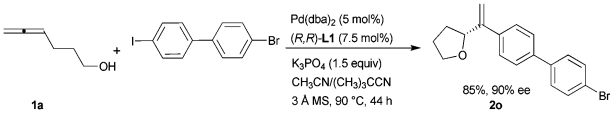
Table 5 Reaction of phenyl iodide with different allenols[a]



Entry	R^1	R^2	R^3	Time (h)	Conc. (mol L^{-1})	Yield of **2**[b] (%)	ee of **2** (%)
1	CH_3	H	H	50	0.250	78((*R*)-**2j**)	88
2	H	CH_3	H	22	0.167	81((*R*)-**2k**)	85
3	H	H	CH_3	27.5	0.149	79((*R*)-**2l**)	86

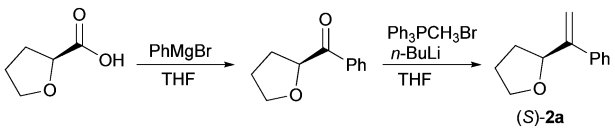
[a] The reaction was carried out with γ-allenol (0.5 mmol), iodobenzene (0.75 mmol), $Pd(dba)_2$ (5 mol%), (*R*,*R*)-**L1** (7.5 mol%), 3 Å molecular sieves (200 mg) and K_3PO_4 (1.5 equiv.) in CH_3CN–$(CH_3)_3CCN$ (1.5/1 by volume). [b] Isolated yield.

The one gram-scale of this reaction has also been demonstrated (Scheme 1), affording the desired product in 85% yield with 90% ee.



Scheme 1 One gram-scale synthesis of (*R*)-2-(1-(4′-bromobiphenyl-4-yl)-vinyl)tetrahydrofuran.

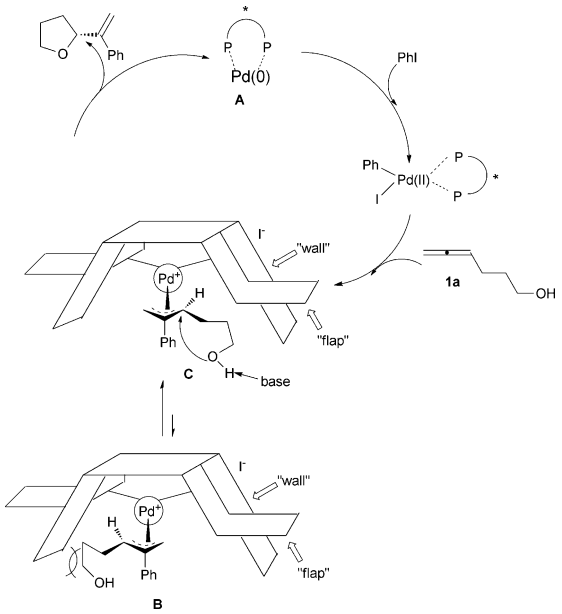
The absolute configuration of **2a** was determined to be *R* by comparison of the t_R and specific rotation of the authentic (*S*)-**2a** (Scheme 2), which was prepared in situ by the Wittig methenylation of (*S*)-phenyl(tetrahydrofuran-2-yl)methanone[8] derived from the reaction between (*S*)-tetrahydrofuran-2-carboxylic acid and phenylmagnesium bromide.[9]



Scheme 2 Preparation of (*S*)-2-(1-phenylvinyl)tetrahydrofuran.

A mechanistic proposal for the prediction of the absolute configuration[10] in the products with the Trost ligand is shown in Scheme 3. The regioselective carbopalladation of PhPdI, which is formed *in situ* from the oxidative addition of Pd(0) with iodobenzene, with γ-allenols at the center carbon atom forms the π-allylic palladium complex *syn*-**C**, not *syn*-**B** due to the unfavorable steric interactions between the $(CH_2)_3OH$ and the coordinated palladium as well as the chiral ligand. Subsequent nucleophilic attack of the hydroxyl group leads to the product with the observed absolute configuration along with regeneration of Pd(0) catalyst **A**.

In summary, we have successfully developed a facile access to enantioenriched tetrahydrofurans *via* Pd(0)-catalyzed asymmetric coupling cyclization of terminal γ-allenols with aryl iodides in 60–86% yields with 85–92% ee with the observation of a unique solvent effect. Further investigations in this area, especially the scope of different organic halides and nucleophiles, as well as the development of new chiral ligands for such reactions are ongoing in our laboratory.



Scheme 3 Proposed mechanism and prediction of the absolute configuration of the product.

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Notes and references

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