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Novel Method for Synthesizing Spiro[4.5]cyclohexadienones through a Pd-Catalyzed Intramolecular *ipso*-Friedel−Crafts Allylic Alkylation of Phenols

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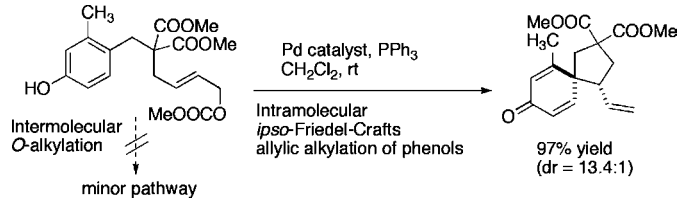
ABSTRACT



The first successful Pd-catalyzed intramolecular *ipso*-Friedel−Crafts allylic alkylation of phenols, which provided a new access to spiro[4.5]cyclohexadienones, is described. The present method could be applied to catalytic enantioselective construction of an all-carbon quaternary spirocenter.

Efficient construction of spirocyclic frameworks is an important topic in synthetic organic chemistry because of their broad distribution in biologically active natural products and pharmaceuticals as well as their usefulness in complex molecule syntheses. Among the various spirocycles, spirocyclohexadienones are the most important class of compounds in organic synthesis.[1] Extensive effort has been focused on the development of an efficient synthetic method based on hypervalent iodine reagents,[2] *ipso*-halocyclization,[3] radical cyclization,[4] arene−Ru complex-mediated dearomatization,[5] and Cu-catalyzed oxygenation of α-azido-*N*-arylamides.[6] The reported reactions, however, are difficult to extend to catalytic enantioselective synthesis, and very limited success has been reported to date.[7,8] This background led us to explore a novel method for synthesizing spirocyclohexadienones that is readily applicable to catalytic asymmetric synthesis. The present

(1) For reviews, see: (a) Sannigrahi, M. *Tetrahedron* **1999**, *55*, 9007. (b) Kotha, S.; Deb, A. C.; Lahiri, K.; Manivannan, E. *Synthesis* **2009**, 165.

(2) For recent representative examples, see: (a) Dohi, T.; Maruyama, A.; Yoshimura, M.; Morimoto, K.; Tohma, H.; Kita, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 6193. (b) Dohi, T.; Maruyama, A.; Minamitsuji, Y.; Takenaga, N.; Kita, Y. *Chem. Commun.* **2007**, 1224. (c) Dohi, Y.; Minamitsuji, Y.; Maruyama, A.; Hirose, S.; Kita, Y. *Org. Lett.* **2008**, *10*, 3559.

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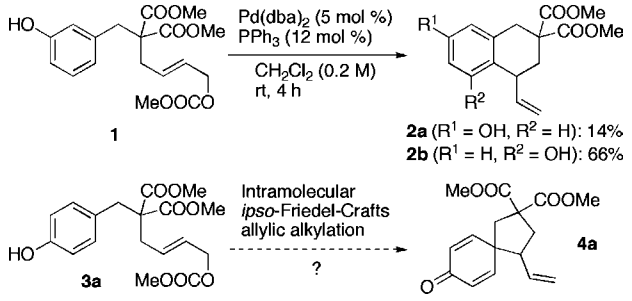
paper describes a new access to spiro[4.5]cyclohexadienone frameworks through a Pd-catalyzed intramolecular *ipso*-Friedel−Crafts allylic alkylation of phenols that can be applied to catalytic enantioselective construction of an all-carbon quaternary spirocenter.

Phenols are generally utilized as oxygen nucleophiles in transition metal-catalyzed allylic alkylation,[9] with very few exceptions of *C*-allylation.[10] In contrast to the general reactivity, we found that Pd-catalyzed intramolecular allylic alkylation of *meta*-substituted phenol derivative **1** occurred on the aromatic carbons to afford the corresponding Friedel−Crafts-type adducts **2a** and **2b** in good conversion (Scheme 1).[11] This surprising

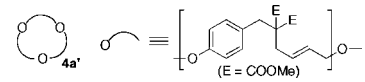
Scheme 1



result led us to hypothesize that *para*-substituted phenol derivatives such as **3a** could be utilized as substrates for intramolecular *ipso*-Friedel−Crafts allylic alkylation, which would provides a new access to spirocyclohexadienones. We initially optimized the reaction conditions using allyl carbonate **3a** as a model substrate (Table 1). First, we investigated the effect of a phosphorus ligand using 5 mol % of $Pd(dba)_2$ in CH_2Cl_2 at room temperature. Compared with bidentate phosphorus ligands, the use of monodentate phosphorus ligands increased the reactivity. Among the examined ligands, triphenylphosphine, tris(4-chlorophenyl)phosphine, and triphenyl

Table 1. Optimization of the Reaction Conditions Using **3a**[a]

entry	catalyst	ligand (mol %)	solvent	yield of **4a** (%)[b]
1	$Pd(dba)_2$	dppm (6)	CH_2Cl_2	33 (84)[c]
2	$Pd(dba)_2$	dppe (6)	CH_2Cl_2	16
3	$Pd(dba)_2$	dppp (6)	CH_2Cl_2	trace
4	$Pd(dba)_2$	dppf (6)	CH_2Cl_2	5
5	$Pd(dba)_2$	PPh_3 (12)	CH_2Cl_2	94 (1)[d]
6	$Pd(dba)_2$	P(*o*-tol)$_3$ (12)	CH_2Cl_2	76
7	$Pd(dba)_2$	P(4-Cl-Ph)$_3$ (12)	CH_2Cl_2	94
8	$Pd(dba)_2$	P(4-MeO-Ph)$_3$ (12)	CH_2Cl_2	30 (93)[c]
9	$Pd(dba)_2$	P(*c*Hex)$_3$ (12)	CH_2Cl_2	trace
10	$Pd(dba)_2$	$P(OPh)_3$ (12)	CH_2Cl_2	95
11	$Pd(dba)_2$	PPh_3 (12)	CH_3CN	90
12	$Pd(dba)_2$	PPh_3 (12)	THF	88
13	$[allylPdCl]_2$	PPh_3 (12)	CH_2Cl_2	84
14	$Pd(OAc)_2$	PPh_3 (12)	CH_2Cl_2	trace
15	$[Ir(cod)Cl]_2$	PPh_3 (6)	CH_2Cl_2	0
16	$[Ir(cod)Cl]_2$	$P(OPh)_3$ (6)	CH_2Cl_2	0



[a] Reaction conditions: metal catalyst (5 mol %), solvent (0.2 M), rt, 3 h. [b] Isolated yield. [c] Yield in 24 h. [d] Isolated yield of **4a′**.

phosphite were suitable ligands for this reaction, and the desired product **4a** with a spiro[4.5]cyclohexadienone framework was obtained in 94−95% yield. For practical reasons, triphenylphosphine was used for further optimization. There was no noticeable solvent effect in this reaction. No reaction occurred when $Pd(OAc)_2$ and $[Ir(cod)Cl]_2$ were used as the catalyst source. When the reaction was performed under the reaction conditions shown in entry 5, **3a** was completely consumed. Careful purification of the reaction mixture revealed the formation of cyclic trimer **4a′** via O-alkylations in 1% yield (3% of **3a** was incorporated).

Having developed efficient conditions, we next examined the scope and limitations of different substrates (Table 2). Intramolecular *ipso*-Friedel−Crafts allylic alkylation of **3a** could be performed even in the presence of 1 mol % of the Pd catalyst, giving **4a** in 89% yield (entries 1−3). Secondary alcohol derivatives **3b** and **3c** were also applicable to this reaction, and the corresponding spiro[4.5]cyclohexadienones with a *trans*-olefin **4b** and **4c** were obtained in 84% yield and 89% yield, respectively (entries 4 and 5). Moreover, intramolecular *ipso*-Friedel−Crafts allylic alkylation of **3d** and **3e**, bearing a dimethyl acetal tether or an *N*-Ts tether connecting the phenol and allyl carbonate moiety, proceeded smoothly to give the corresponding spirocyclic adducts in good yield (entries 6 and 7). In contrast, the use of oxygen-tethered substrate **3f** resulted in a messy reaction, and the desired product **4f** was not obtained at all using the $Pd(dba)_2-PPh_3$ catalyst system. This result indicates that the present spirocyclization process would be facilitated by the Thorpe−Ingold effect. Optimization of the reaction conditions revealed that the reactivity was dramatically affected by the properties of the phosphorus ligand. Spirocyclic adduct **4f** was obtained in 63% yield when triphenyl phosphite was utilized instead of triphenylphosphine (entry 8). Multisub-

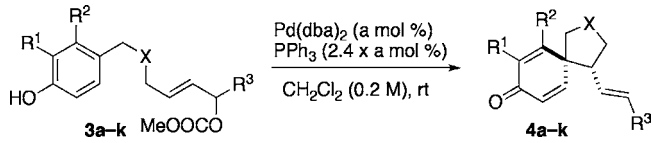
(8) For recent representative examples of catalytic asymmetric construction of a spirocenter, see: (a) Teng, X.; Cefalo, D. R.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 10779. (b) Hatano, M.; Mikami, K. *J. Am. Chem. Soc.* **2003**, *125*, 4704. (c) Tsuchikama, K.; Kuwata, Y.; Shibata, T. *J. Am. Chem. Soc.* **2006**, *128*, 13686. (d) Trost, B. M.; Cramer, N.; Silverman, S. M. *J. Am. Chem. Soc.* **2007**, *129*, 12396. (e) Zhang, E.; Fan, C.-A.; Tu, Y.-Q.; Zhang, F.-M.; Song, Y.-L. *J. Am. Chem. Soc.* **2009**, *131*, 14626. (f) Shintani, R.; Isobe, S.; Takeda, M.; Hayashi, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 3795. (g) Yao, W.; Pan, L.; Wu, Y.; Ma, C. *Org. Lett.* **2010**, *12*, 2422. (h) Wu, Q.-F.; He, H.; Liu, W.-B.; You, S.-L. *J. Am. Chem. Soc.* **2010**, *132*, 11418.

(9) For reviews, see: (a) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921. (b) Lu, Z.; Ma, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 258.

(10) (a) Malkov, A. V.; Davis, S. L.; Baxendale, I. R.; Mitchell, W. L.; Kocovsky, P. *J. Org. Chem.* **1999**, *64*, 2751. (b) Fernández, I.; Hermatschweiler, R.; Breher, F.; Pregosin, P. S.; Veiros, L. F.; Calhorda, M. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 6386. For an example of Pd-catalyzed C-allylation of phenols via an O-allylation−Claisen rearrangement sequence, see: (c) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 815.

(11) For examples of catalytic intramolecular Friedel−Crafts-type allylations using aromatic nucleophiles, see: (a) Ma, S.; Zhang, J. *Tetrahedron* **2003**, *59*, 6273. (b) Bandini, M.; Melloni, A.; Piccinelli, F.; Sinisi, R.; Tommasi, S.; Umani-Ronchi, A. *J. Am. Chem. Soc.* **2006**, *128*, 1424. (c) Cook, G. R.; Hayashi, R. *Org. Lett.* **2006**, *8*, 1045. (d) Namba, K.; Yamamoto, H.; Sasaki, I.; Mori, K.; Imagawa, H.; Nishizawa, M. *Org. Lett.* **2008**, *10*, 1767. (e) Bandini, M.; Elchholzer, A.; Kotrusz, P.; Tragni, M.; Troisi, S.; Umani-Ronchi, A. *Adv. Synth. Catal.* **2009**, *351*, 319.

Table 2. Scope and Limitations



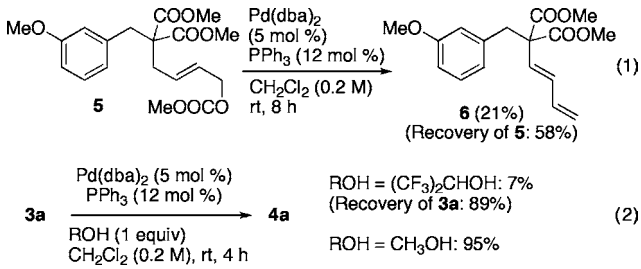
entry	substrate	X	R^1	R^2	R^3	catalyst (mol %)	product	time (h)	yield (%)[a]	dr[b]
1	**3a**	$C(COOMe)_2$	H	H	H	5	**4a**	3	94	-
2[c]	**3a**	$C(COOMe)_2$	H	H	H	2	**4a**	6	96	-
3[d]	**3a**	$C(COOMe)_2$	H	H	H	1	**4a**	24	89	-
4	**3b**	$C(COOMe)_2$	H	H	CH_3	5	**4b**	6	84	-
5	**3c**	$C(COOMe)_2$	H	H	Ph	5	**4c**	6	89	-
6	**3d**	$C(OMe)_2$	H	H	H	5	**4d**	6	93	-
7	**3e**	NTs	H	H	H	5	**4e**	6	86	-
8[e]	**3f**	O	H	H	H	5	**4f**	6	0 (63)[f]	-
9	**3g**	$C(COOMe)_2$	H	CH_3	H	5	**4g**	6	97	13.4:1
10	**3h**	$C(COOMe)_2$	H	Cl	H	5	**4h**	8	92	11.0:1
11	**3i**	NTs	H	CH_3	H	5	**4i**	9	89	7.5:1
12[g]	**3j**	NTs	−CH=CH−CH=CH−		H	5	**4j**	24	97	3.0:1
13	**3k**	$C(COOMe)_2$	CH_3	H	H	5	**4k**	24	95	1.1:1

[a] Isolated yield. [b] Determined by ^{1}H NMR analysis of the crude mixture. [c] [**3a**] = 0.33 M. [d] [**3a**] = 0.5 M. [e] [**3f**] = 0.05 M. [f] Isolated yield using triphenyl phosphite as the ligand. [g] (*R*)-Monophos was used as the ligand. Solvent: CH_3CN.

stituted phenol derivatives were also examined using 5 mol % of the catalyst. Dimethyl malonate-tethered substrates with a methyl group (**3g**) or a chloride group (**3h**) on the *meta*-position to the phenol proceeded under the same reaction conditions, affording the corresponding products with contiguous chiral centers in excellent yield with high diastereoselectivity (entries 9 and 10). The relative stereochemistry of **4g** was determined by the NOE experiment. Similarly, *N*-Ts-tethered-type substrate **3i** was an effective substrate, resulting in the formation of **4i** in 89% yield with relatively high diastereoselectivity (entry 11). Although diastereoselectivity decreased, naphthol-type substrate **3j** was also applicable to this reaction, giving naphthoquinone derivative **4j** in excellent yield (entry 12). On the other hand, there was no significant diastereoselectivity when compound **3k**, bearing a methyl group on the *ortho*-position to the phenol, was utilized as the substrate. To the best of our knowledge, this is the first example of Pd-catalyzed intramolecular *ipso*-Friedel−Crafts allylic alkylation of phenols, which provides new access to spiro[4.5]cyclohexadienones.

To gain preliminary insight into the reaction mechanism, we performed the following experiments (Scheme 2).

Scheme 2



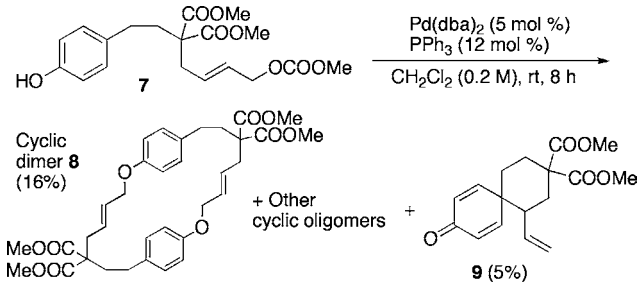
When compound **5**, an anisole variant of **1**, was treated with the optimized reaction conditions, diene **6** was obtained in 21% yield, accompanied by the recovery of **5** (58%) (eq 1). It is noteworthy that no bicyclic compounds were produced by an intramolecular Friedel−Crafts allylic alkylation of **5**, based on an ^{1}H NMR analysis of the crude reaction sample.[12] In addition, there was a significant decrease in the reactivity when 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) was added to the spirocyclization of **3a** (eq 2). Compared with a control experiment using methanol (pK_a 15.5) as the additive (95% yield), **4a** was obtained in 7% yield with the use of 1 equiv of HFIP (pK_a 9.3) as the additive (recovery of **3a**: 89%). These results indicate the importance of phenol deprotonation by the methoxide anion, which was generated during the formation of the π-allylpalladium species, to promote this reaction.[13]

Furthermore, when phenol derivative **7**, a substrate bearing a CH_2 unit-longer tether than **3a**, was reacted under the optimized reaction conditions, conventional O-alkylations occurred dominantly to afford cyclic dimer **8** as the major product (16% yield: 32% of **7** was incorporated) (Scheme 3). Cyclic trimer, tetramer, and pentamer were also observed

(12) Reaction of an anisole derivative prepared from **3a** also gave a similar diene adduct in 88% yield under the same reaction conditions. No bicyclic compounds derived from the postulated spirocyclic oxonium cation intermediate were detected by ^{1}H NMR analysis of the crude reaction mixture.

(13) Base-promoted intramolecular alkylation of phenols to form spirocyclohexadienones is a classical transformation. See: (a) Baird, R.; Winstein, S. *J. Am. Chem. Soc.* **1962**, *84*, 788. (b) Kropp, P. J. *Tetrahedron Lett.* **1965**, *21*, 2183. **4a** was not produced through a S_N2' substitution, however, when **3a** was treated with 1 equiv of KO*t*-Bu in CH_2Cl_2 at room temperature in the absence of Pd catalyst. In contrast, **4a** was obtained in good yield when an allyl bromide derivative corresponding to **3a** was refluxed in *t*-BuOH in the presence of KO*t*-Bu.

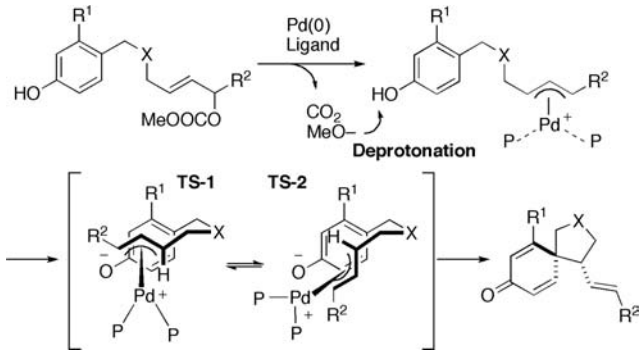
Scheme 3



in ESI−MS analysis. In contrast, spirocyclic adduct **9** was isolated in only 5% yield, indicating that the tether length between the phenol and π-allylpalladium unit was a crucial factor for the present spirocyclization.

These findings led us to propose a plausible reaction pathway for this reaction (Scheme 4). First, oxidative addition of allylic

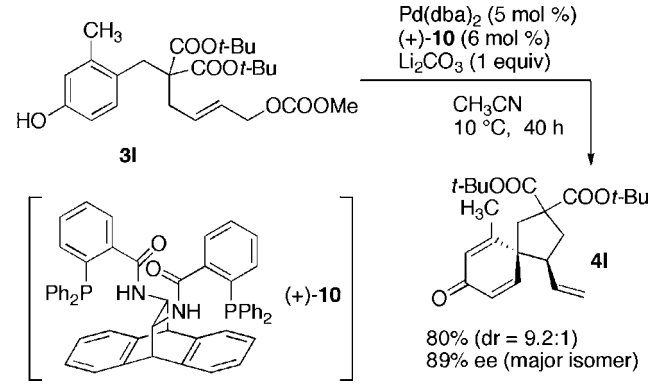
Scheme 4



carbonates to the Pd(0) catalyst forms a π-allylpalladium species. Subsequent deprotonation of the phenol by the endogenous methoxide anion proceeds to increase the nucleophilicity of the *para*-position to the phenol. The carbon−carbon bond formation occurs via transition states **TS-1** or **TS-2**, where the proximal arrangement of both reactive centers is facilitated by the chairlike transition state structure.[14] The observed diastereoselectivity could be explained by steric repulsion between the π-allyl unit and the *ortho*-substituent (R^1) in **TS-1**.

Preliminary attempts to extend the developed reaction to enantioselective construction of an all-carbon quaternary spirocenter were promising (Scheme 5).[15] Using 5 mol %

Scheme 5



of Pd catalyst, 6 mol % of chiral ligand (+)-**10**,[16] and 1 equiv of Li_2CO_3, catalytic asymmetric *ipso*-Friedel−Crafts allylic alkylation of **3l** proceeded in a diastereoselective manner (dr = 9.2:1), providing (*S*,*S*)-**4l** in 80% yield with 89% ee (major diastereomer).[17] Although there is still room for improvement in the enantioselectivity, the asymmetric transformation constitutes a proof of concept and provides a blueprint for the development of a more efficient catalytic system.

In conclusion, we developed a novel method for synthesizing spiro[4.5]cyclohexadienones using a Pd-catalyzed intramolecular *ipso*-Friedel−Crafts allylic alkylation of phenols. Moreover, the potential applicability to catalytic asymmetric synthesis of spirocyclic compounds bearing two contiguous chiral centers was demonstrated for the first time. Further investigations into the catalytic asymmetric version of this process, as well as more detailed studies of the reaction mechanism, are in progress.

Acknowledgment. This work was supported by a Grant-in Aid for Encouragement of Young Scientists (B) from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

Supporting Information Available: Experimental procedures, supplementary data, compound characterization, and NMR charts. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) There might be π-orbital interactions between the electron-deficient cationic π-allylpalladium unit and the electron-rich phenoxide ring in the transition states. Phosphorus ligands with π-acidic properties, such as triphenyl phosphite, could enhance the intramolecular charge transfer interaction, facilitating the carbon−carbon bond formation.

(15) For reviews on catalytic asymmetric construction of quaternary stereocenters, see: (a) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591. (b) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369. (c) Shibasaki, M.; Kanai, M. *Org. Biomol. Chem.* **2007**, *5*, 2027.

(16) For examples of asymmetric reactions using **10**, see: (a) Trost, B. M.; Tsui, H.-C.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, *122*, 3534. (b) Trost, B. M.; Tang, W. *J. Am. Chem. Soc.* **2003**, *125*, 8744. (c) Trost, B. M.; Frederiksen, M. U. *Angew. Chem., Int. Ed.* **2005**, *44*, 308. (d) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 2846. (e) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 17180. (f) Trost, B. M.; Xu, J.; Reichle, M. *J. Am. Chem. Soc.* **2007**, *129*, 282. (g) Trost, B. M.; Thaisrivongs, D. A. *J. Am. Chem. Soc.* **2008**, *130*, 14092. (h) Trost, B. M.; Thaisrivongs, D. A. *J. Am. Chem. Soc.* **2009**, *131*, 12056. (i) Trost, B. M.; Lehr, K.; Michaelis, D. J.; Xu, J.; Buckl, A. K. *J. Am. Chem. Soc.* **2010**, *132*, 8915.

(17) Enantiomeric excess of the minor isomer was 21% ee. For the determination of the absolute configuration of the major isomer, see the Supporting Information. When the reaction was performed in the absence of Li_2CO_3, the product was obtained in 88% yield (dr ratio = 9.2:1; ee: major diastereomer 87% ee, minor diastereomer 18% ee).