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A New Cross-Coupling-Based Synthesis of Carpanone

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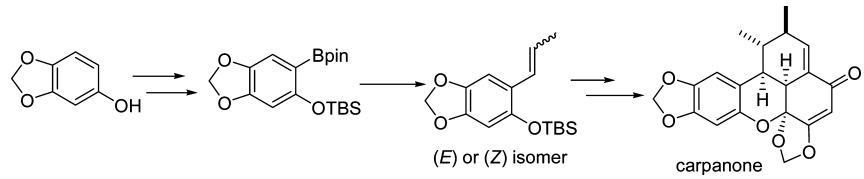
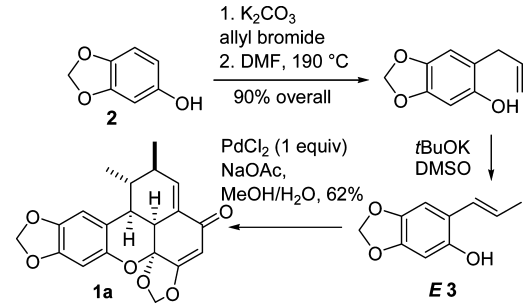
ABSTRACT



Carpanone has been stereoselectively synthesized in 55% yield and six steps from sesamol. The key step of the synthetic sequence is the direct introduction of the propenyl side chain via a Suzuki−Miyaura cross-coupling reaction. The subsequent Pd(II)-catalyzed oxidative coupling yields carpanone as a single diastereoisomer independently of the geometric configuration of the starting precursor. A new mechanism is proposed for this transformation.

Carpanone **1a** is a hexacyclic lignan isolated as a racemic mixture from the bark of the carpano tree found on Bougainville Island and containing five contiguous stereogenic centers.[1] Although carpanone itself displays no interesting biological activity, closely related congeners have shown promising activity such as antihypertensive,[2] antimalarial,[3] antibacterial,[3] and hepatoprotective[4] properties. Thus, the challenging structure of carpanone and the potential biological applications of its analogues make this structure a highly interesting target. Although the synthesis of carpanone has been achieved by quite a few research groups, all reported approaches rely on the elegant biomimetic approach pioneered by Chapman[5] et al. almost 40 years ago.

Scheme 1. Previous Strategy To Obtain Carpanone **1a**



This approach involves a Claisen rearrangement−isomerization sequence followed by a stereoselective oxidative coupling (Scheme 1).[6,7] Although efficient, the Claisen-based route to the cyclization precursor is not straightforward. We thus speculated that an aryl−vinyl cross-coupling reaction could represent a valid and modern alternative to introduce the requisite propenyl moiety directly, possibly in a stereoselective fashion. Structural and geometrical variations on the

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(1) Brophy, G. C.; Mohandas, J.; Slaytor, M.; Sternhell, S.; Watson, T. R.; Wilson, L. A. *Tetrahedron Lett.* **1969**, *10*, 5159–5162.
(2) Wang, E. C.; Shih, M. H.; Liu, M. C.; Chen, M. T.; Lee, G. H. *Heterocycles* **1996**, *43*, 969–975.
(3) (a) Muhammad, I.; Li, X.-C.; Jacob, M. R.; Tekwani, B. L.; Dunbar, D. C.; Ferreira, D. *J. Nat. Prod.* **2003**, *66*, 804–809. (b) Muhammad, I.; Li, X.-C.; Dunbar, D. C.; El Sohly, M. A.; Khan, I. A. *J. Nat. Prod.* **2001**, *64*, 1322–1325.
(4) Sung, S. H.; Kim, Y. C. *J. Nat. Prod.* **2000**, *63*, 1019–1021.

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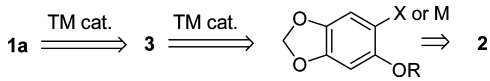
alkene would also provide an interesting diversity-oriented strategy. Furthermore, as the reported oxidative coupling requires stoichiometric amounts of Pd salts,[5] we planned also to develop a greener variant, catalytic in palladium.[8]

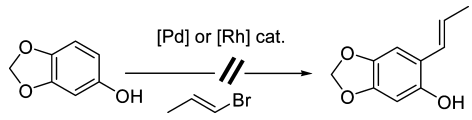
The first step of our retrosynthetic strategy retraces Chapman's seminal paper, wherein carpanone is derived from *carpanization*[9] of propenyl sesamol **3** but as a catalytic variant. Methodological differentiation of our route comes next, deriving **3** from a regioselective cross-coupling based propenylation of sesamol **2** (Scheme 2).

Scheme 2. Envisaged Retrosynthesis of Carpanone



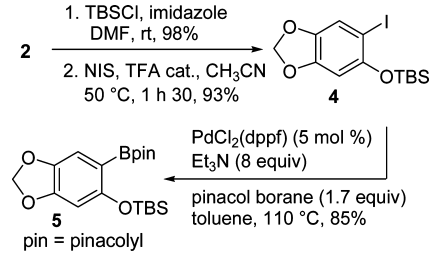
Introduction of the propenyl moiety via transition-metal-catalyzed *ortho*-directed C−H activation was tested first. However, use of Pd- and Rh-catalyzed conditions known to promote *ortho* functionalization of phenols met with failure under a wide range of reported experimental conditions (Scheme 3).[10,11]

Scheme 3. Attempted *Ortho* C−H Activation of Sesamol



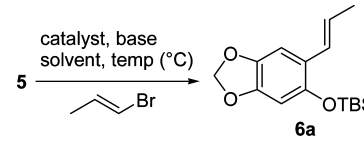
Ortho halogenation of sesamol was next considered.[12] Accordingly, standard *O*-silylation of sesamol and treatment of the resulting ether with NIS gave smoothly iodide **4** in excellent yield and total regioselectivity (Scheme 4).[13] Stille and Negishi cross-coupling reactions with the corresponding metalated propenyl derivative led to unsatisfactory results under a range of conditions. We thus focused on the Suzuki−Miyaura cross-coupling. To this purpose, **4** was initially borylated[14] to give the corresponding boronate **5** in excellent yield.

Scheme 4. Preparation of Boronate **5**



The Suzuki−Miyaura cross-coupling step using (*E*)-1-bromopropene was next studied (Table 1). The influence of the base was first examined using $PdCl_2(PPh_3)_2$ as the palladium source and toluene as the solvent. Only alkoxide bases and KOH allowed formation of some coupled product (entries 1−3), albeit in a low yield, whereas NaOAc, K_2CO_3

Table 1. Optimization of the Suzuki−Miyaura Cross-Coupling



entry	base (3 equiv)	catalyst (10 mol %)	solvent	*T* (°C)	yield[a] (%)
1	KOH	$PdCl_2(PPh_3)_2$	Tol	20	27
2	MeONa	$PdCl_2(PPh_3)_2$	Tol	80	10
3	*t*BuOK	$PdCl_2(PPh_3)_2$	Tol	80	25
4	NaOAc	$PdCl_2(PPh_3)_2$	Tol	80	0
5	K_2CO_3	$PdCl_2(PPh_3)_2$	Tol	80	0
6	Et_3N	$PdCl_2(PPh_3)_2$	Tol	80	0
7	*t*BuOK	$PdCl_2(PPh_3)_2$	Tol	110	24
8	**tBuOK**	**$PdCl_2(PPh_3)_2$**	**Tol**	20	60
9	*t*BuOK	$PdCl_2$(dppf)	Tol	20	20
10	*t*BuOK	$PdCl_2$(dppp)	Tol	20	0
11	*t*BuOK	$Pd(dba)_2$/Xantphos[b]	Tol	20	0
12	*t*BuOK	$PdCl_2(PPh_3)_2$	DME	20	23
13	*t*BuOK	$PdCl_2(PPh_3)_2$	Et_2O	20	13
14	*t*BuOK	$PdCl_2(PPh_3)_2$	THF	20	4
15	*t*BuOK	$PdCl_2(PPh_3)_2$	DMF	20	27

[a] Isolated yields. [b] 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene.

(5) (a) Chapman, O. L.; Engel, M. R.; Springer, J. P.; Clardy, J. C. *J. Am. Chem. Soc.* **1971**, *93*, 6697–6698. See also: (b) Majetich, L. G.; Wheless, K. In *Microwave Heating in Organic Chemistry: An Update*; Kingston, H. M., Haswell, S. J., Eds.; ACS: Washington, D.C., 1997; Chapter 8, pp 455−501.

(6) (a) Lindsley, C. W.; Chan, L. K.; Goess, B. C.; Joseph, R.; Shair, M. D. *J. Am. Chem. Soc.* **2000**, *122*, 422–423. (b) Baxendale, I. R.; Lee, A.-L.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1850–1857. (c) Goess, B. C.; Hannoush, R. N.; Chan, L. K.; Kirchhausen, T.; Shair, M. D. *J. Am. Chem. Soc.* **2006**, *128*, 5391–5403. (d) Daniels, R. N.; Fadeyi, O. O.; Lindsley, C. W. *Org. Lett.* **2008**, *10*, 4097–4100.

(7) During the redaction of this paper, introduction of the propenyl moiety via a Wittig condensation was disclosed: Fadeyi, O. O.; Daniels, R. N.; DeGuire, S. M.; Lindsley, C. W *Tetrahedron Lett.* **2009**, *50*, 3084–3087.

(8) During the course of this work, a paper appeared dealing with a Cu-catalyzed oxidative coupling. See ref 6d.

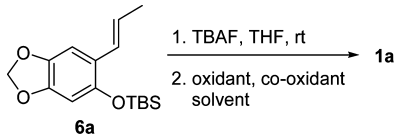
(9) For convenience, we propose to define "carpanization" as the conversion of 2-propenylsesamol into carpanone. This oxidative coupling is the result of more than one elementary step, and its mechanism appears to be reagent dependent (see the text).

(10) (a) Bedford, R. B.; Coles, S. J.; Hursthouse, M. B.; Limmert, M. E. *Angew. Chem., Int. Ed.* **2003**, *42*, 112–114. (b) Bedford, R. B.; Hazelwood, S. L.; Horton, P. N.; Hursthouse, M. B. *Dalton Trans.* **2003**, 4164–4174. (c) Bedford, R. B.; Limmert, M. E. *J. Org. Chem.* **2003**, *68*, 8669–8682. (d) Oi, S.; Watanabe, S.-I.; Fukita, S.; Inoue, Y. *Tetrahedron Lett.* **2003**, *44*, 8665–8668. (e) Satoh, T.; Inoh, J.; Kawamura, T.; Kawamura, Y.; Miura, N.; Masakatsu, N. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2239–2246. (f) Satoh, T.; Kawamura, Y.; Miura, N.; Nomura, M. *Angew. Chem., Int. Ed.* **1997**, *36*, 1740–1742. (g) Dunina, V.; Gorunova, N.; Stepanova, A.; Zykov, A.; Livantsov, V.; Grishin, K.; Churakov, V.; Jyudmila, G. *Tetrahedron: Asymmetry* **2007**, *18*, 2011–2015.

and Et_3N gave no reaction (entries 4−6). Raising the temperature from 80 to 110 °C led to no change (entry 7), whereas running the reaction at rt improved the yield up to 60% yield (entry 8). Bidentate ligands proved less efficient (entries 9−11). Finally, various solvents of increasing polarity were shown to be less efficient than toluene (entries 12−15).

The final steps of the synthesis involve deprotection of the TBS ether and subsequent carpanization.[15] Use of a stoichiometric amount of $PdCl_2$, according to Chapman's protocol,[5] led to carpanone **1a** in 56% yield (Table 2, entry 1). Interestingly, when a catalytic amount of $PdCl_2$ was used together with $CuCl_2$ as the co-oxidant, a comparable yield of carpanone was obtained (48%, entry 2). Use of O_2 as a co-oxidant led to an excellent 82% yield (entry 3). Catalytic $CuCl_2$ under an O_2 atmosphere led to a similar yield (73%, entry 4). Other oxidizing systems such as $FeBr_3/O_2$, $PhI(OAc)_2$,[6a,c,16] or DDQ, led to less satisfactory results (entries 5−8). Much to our surprise, autoxidation of **6a** to carpanone occurred also rather efficiently in O_2 atmosphere in the absence of any transition-metal catalyst (entry 9).

Table 2. Carpanization of (*E*)-Propenyl Sesamol[a]

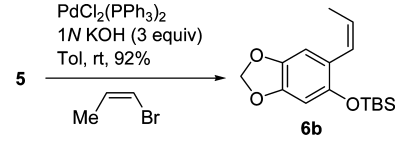


entry	oxidant (equiv)	co-oxidant	solvent	yield[b] (%)
1	$PdCl_2$ (1.0)		$MeOH/H_2O$	56
2	$PdCl_2$ (0.1)	$CuCl_2$	$MeOH/H_2O$	48
3	**$PdCl_2$(0.1)**	**O_2**	**$MeOH/H_2O$**	82
4	$CuCl_2$ (0.1)	O_2	$MeOH/H_2O$	73
5	$FeBr_3$ (0.1)	O_2	$MeOH/H_2O$	0
6	$PhI(OAc)_2$ (0.55)		CH_2Cl_2	36
7	CAN (0.55		MeCN	41
8	DDQ (0.55)		THF	0
9	O_2		$MeOH/H_2O$	55[c]

[a] Reaction conditions: (a) substrate (0.1 mmol), THF (0.5 mL), TBAF (0.3 mmol), rt, 30 min; (b) NaOAc (0.12 mmol), oxidant, MeOH (0.3 mL), H_2O (0.3 mL), O_2, 50 °C, 4 h [b] Isolated yields. [c] Spectroscopic yield from ^1H NMR of the crude mixture with 1,4-dioxane as the internal standard.

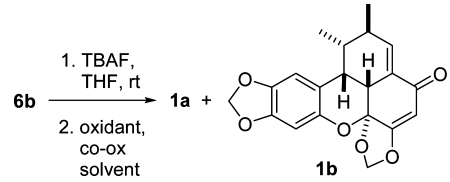
In all cases studied, the relative configuration of the five stereogenic centers appeared to be fully controlled, as carpanone was always isolated as a single diastereoisomer out of the 16 possible. We then wondered if a change of the stereochemistry of the alkene precursor would have modified the outcome of the reaction. If so, this would represent an efficient way to introduce stereochemical diversity into the carpanone core. Accordingly, we decided to apply the above studied cross-coupling protocol to obtain the (*Z*)-alkene **6b** and test it for carpanization. In the event, the Suzuki−Miyaura cross-coupling reaction between boronic ester **5** and (*Z*)-1-bromopropene using aqueous KOH as the base gave the desired (*Z*)-olefin in excellent yield (Scheme 5).[17]

Scheme 5. Preparation of Alkene **6b**



Alkene **6b** was then submitted to *O*-silyl deprotection followed by carpanization (Table 3). Quite unexpectedly, treatment of the in situ obtained ***Z*3** with catalytic $PdCl_2$ in the presence of O_2 gave again natural carpanone **1a** (entry 1). Cu catalysis gave instead an inseparable 63:37 mixture of natural carpanone **1a** and the diastereomeric structure **1b**, as assigned on the basis of NOESY experiments (entry 2). Lastly, $PhI(OAc)_2$ gave only traces of carpanone (entry 3).

Table 3. Carpanization of (*Z*)-Propenyl Sesamol[a]



entry	oxidant (equiv)	co-ox	**1a/1b**	yield[b] (%)
1	$PdCl_2$ (0.1)	O_2	100:0	77
2	$CuCl_2$ (0.1)	O_2	63:37	40
3	$PhI(OAc)_2$ (0.55)			traces

[a] Reaction conditions: **6b** (0.34 mmol), NaOAc (1.26 equiv), oxid., MeOH (0.5 mL), H_2O (0.5 mL), O_2, 50 °C, 4 h. [b] Isolated yields.

The above results add some relevant pieces of information on the mechanism of carpanization, whose state of knowledge is still far from satisfactory (Scheme 6). As to this issue, Chapman[5] postulated for the Pd(II)-promoted transformation involvement of the bis-phenoxy Pd(II) intermediate **I** which would undergo stereoselective phenol β,β-coupling to give

(11) See Supporting Information.

(12) The cross-coupling of unprotected electron-rich phenols is not an efficient process. See for example (a) Jinno, S.; Okita, T.; Inouye, K. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1029–1032. (b) Jinno, S.; Otsuka, N.; Okita, T.; Inouye, K. *Chem. Pharm. Bull.* **1999**, *47*, 1276–1283, See Supporting Informationfor more details on the attempted cross-coupling reactions on the free or protected halogenated sesamol.

(13) Carmen, M.; Jose, C. L.; Ruano, G.; Sanz, G.; Toledo, M. A.; Urbano, A. *J. Org. Chem.* **1995**, *60*, 5328–5331.

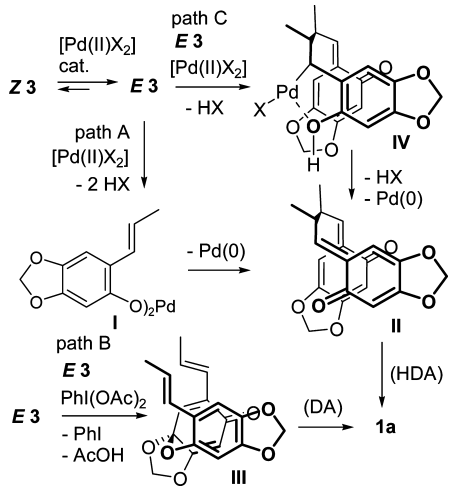
(14) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508–7510.

(15) As the free phenol resulting from the deprotection of **6a** was very sensitive, we carried out the two steps in a single pot.

(16) Although refs 6c and 7 report that $PhI(OAc)_2$ is incapable of bringing about carpanization, in our hands this reagent did produce **1a**, although in modest yield.

(17) Under our previously optimized conditions (Table 1, entry 8), no reaction occurred.

Scheme 6. Proposed Carpanization Mechanisms

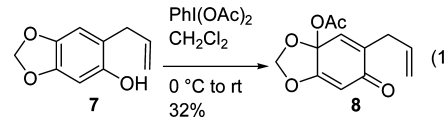


the C_2-symmetric bis-enone **II** (path A). Final *endo*-selective hetero-Diels−Alder cycloaddition (HDA) affords carpanone. On the other hand, on the basis of the results obtained on analogues less electron rich than propenylsesamol, Shair postulated for $PhI(OAc)_2$ a dimerizative addition of the phenolic hydroxyl function *para* to an oxidant-activated substrate molecule to give adduct **III**, followed by an *endo*-selective Diels−Alder (DA) cycloaddition (path B)[6a] Coming back to our results, the stereoconvergence observed in the present study under Pd(II) catalysis suggests a *Z*-to-*E* Pd-catalyzed isomerization prior to carpanization via a common intermediate (Scheme 6).[18,19]

Furthermore, the recent results by Sigman and co-workers[20] on the aerobic hydroalkoxylation of phenol-containing styrenes suggest to us a new appealing mechanistic hypothesis for the Pd(II)-catalyzed carpanization of 2-propenylsesamol, wherein the first C−C bond formation is triggered by a carbopalladative β,β-coupling to give intermediate **IV**[21](Scheme 6, path C).

Loss of HX and Pd(0) would then merge **IV** into the previously evoked Pd(II)-mediated stream.[22] The failure of $PhI(OAc)_2$, as opposed to $PdCl_2$, to cyclize ***Z*3** is compatible with the different mechanisms postulated for the two reagents. Validation of the mechanism associated with $PhI(OAc)_2$ came from submission of an isomer of 2-propenylsesamol to this reagent, so as to obtain an intermediate incapable of undergoing a Diels−Alder cycloaddition reaction. Indeed, treatment of 6-allylsesamol **7**[23,24] with $PhI(OAc)_2$ afforded **8** as the only observable product (Scheme 7), thereby supporting the mechanism associated

Scheme 7. Test To Prove the Mechanism Associated with Path B



with path B. Although further studies will be needed to obtain a more satisfactory picture of the subtle details of the carpanization steps, it is clear that this intriguing transformation follows specific reagent-dependent mechanisms.

In conclusion, we have developed a new synthesis of carpanone. This new approach features the direct and stereoselective incorporation of the propenyl moiety onto sesamol, affording carpanone in six steps and 55% overall yield and lends itself to a diversity-oriented synthesis of analogues. Furthermore, the Pd(II)-promoted carpanization originally developed by Chapman could be rendered catalytic in Pd(II), establishing that the (*E*)- as well as the (*Z*)-propenyl precursors give rise to the same natural product. On the other hand, $PhI(OAc)_2$ was able to carpanize only the *E*-configured precursor. Last, but not least, the mechanism of action of $PhI(OAc)_2$ originally proposed by Shair could be confirmed, whereas a new mechanistic path is proposed for the Pd(II)-catalyzed carpanization.

Acknowledgment. Financial support of this research by UPMC and CNRS is gratefully acknowledged. The sponsorship of COST Action D40 "Innovative Catalysis: New Processes and Selectivities" is kindly acknowledged.

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

OL9017326

(18) For Pd(II). catalyzed isomerization of similar systems. (a) Giles, R. G. F.; Son, V. R. L.; Sargent, M. V. *Aust. J. Chem.* **1990**, *43*, 777–781. (b) Ju, J.; Gaunt, M. J.; Spencer, J. B. *J. Org. Chem.* **2002**, *67*, 4627–4269. (c) Thiery, E.; Chevrin, C.; Le Bras, J.; Harakat, D.; Muzart, J. *J. Org. Chem.* **2007**, *72*, 1859–1862. (d) Fan, J.; Wan, C.; Wang, Q.; Gao, L.; Zheng, X.; Wang, Z. *Org. Biomol. Chem.* **2009**, *7*, 3168–3172.

(19) Performing the experiments of entries 1, 2 or 3 of table 3 in the presence of TEMPO as the radical trap did not allow isolation of a TEMPO adduct. For a carpanization under free-radical conditions, see: Matsumoto, M.; Kuroda, K. *Tetrahedron Lett.* **1981**, *22*, 4437–4440.

(20) Gligorich, K. M.; Schultz, M. J.; Sigman, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 2794–2795.

(21) For a vinylogous nucleophilic behavior of 2-propenyl-phenol see: Cornia, M.; Merlini, L.; Zanarotti, A. *Gazz. Chim. Ital.* **1977**, *107*, 299–304.

(22) Carpanization experiments from *E***3** conducted in the presence of several chiral ligands gave almost racemic material.[11]

(23) Prepared in two steps from sesamol according to described procedures. See refs 5 and 6d.

(24) Attempts to convert **7** into **3**, or directly into carpanone, via a Pd(II) catalyzed process were unsuccessful.