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One-Pot Construction of Aza- or Oxa-Bridged Benzocycloheptanes from Readily Available 2,3-Allenyl Malonates or 2,3-Allenols and *o*-Iodobenzaldehyde or Imine

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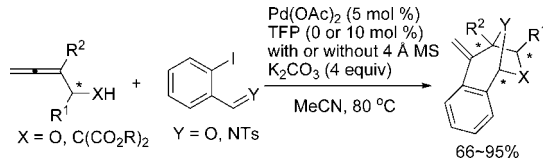
ABSTRACT



A $Pd(OAc)_2$-catalyzed reaction of 2,3-alkadienyl malonates or 2,3-allenols with *o*-iodobenzaldehyde or its *N*-tosyl imine occurred smoothly in MeCN at 80 °C to form the oxa- or aza-bridged benzocycloheptane derivatives with important biological potential. With the optically active 2,3-allenols, the absolute configurations of all the three chiral centers have been conveniently established.

Aza- or oxa-bridged benzocycloheptane compounds **A** are core structures in a class of compounds with interesting pharmacological activities for type II diabetes (**A1** and **A2**)[1] and ALK- or c-Met-mediated diseases (**A3** and **A4**)[2] (Figure 1). Very limited methods have been developed for the synthesis of these type of products;[3] thus, new methodologies for the efficient synthesis of this type of skeleton are highly desirable.

On the other hand, Pd-catalyzed cyclization of allenes has been extensively developed as an efficient methodology for the synthesis of simple cyclic products via the intermediacy of

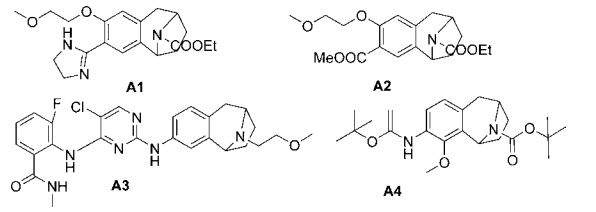


Figure 1. Pharmaceutically active aza-bridged benzocycloheptanes.

π-allylic palladium species (Scheme 1) by Cazes, Cheng, Grigg, Ibuka, Larock, Negishi, Walkup, us, etc.[4] Thus, we envisioned that the **A**-type compounds may be efficiently constructed via the intramolecular allylic substitution of π-allylic palladium

(1) Ammenn, J.; Paal, M.; Ruehter, G.; Schotten, T.; Stenzel, W. PCT Int. Appl. WO 2000078724, 2000.

(2) Ahmed, G.; Bohnstedt, A.; Breslin, H. J.; Burke, J.; Curry, M. A.; Diebold, J. L.; Dorsey, B.; Dugan, B. J.; Feng, D.; Gingrich, D. E.; Guo, T.; Ho, K.-K.; Learn, K. S.; Lisko, J. G.; Liu, R.-Q.; Mesaros, E. F.; Milkiewicz, K.; Ott, G. R.; Parrish, J.; Theroff, J. P.; Thieu, T. V.; Tripathy, R.; Underiner, T. L.; Wagner, J. C.; Weinberg, L.; Wells, G. J.; You, M.; Zificsak, C. A. PCT Int. Appl. WO 2008051547, 2008.

(3) (a) Curphey, M.; Lennon, M.; Murphy, E.; Proctor, G. R. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2013. (b) Grunewald, G. L.; Sall, D. J.; Monn, J. A. *J. Med. Chem.* **1988**, *31*, 433. (c) Nicolas, T. E.; Franck, R. W. *J. Org. Chem.* **1995**, *60*, 6904.

(4) For related reviews, see: (a) Zimmer, R.; Dinesh, C. U.; Nandanan, E.; Khan, F. A. *Chem. Rev.* **2000**, *100*, 3067. (b) Yamamoto, Y.; Radhakrishnan, U. *Chem. Soc. Rev.* **1999**, *28*, 199. (c) Bates, R. W.; Satcharoen, V. *Chem. Soc. Rev.* **2002**, *31*, 12. (d) Ma, S. *Chem. Rev.* **2005**, *105*, 2829.

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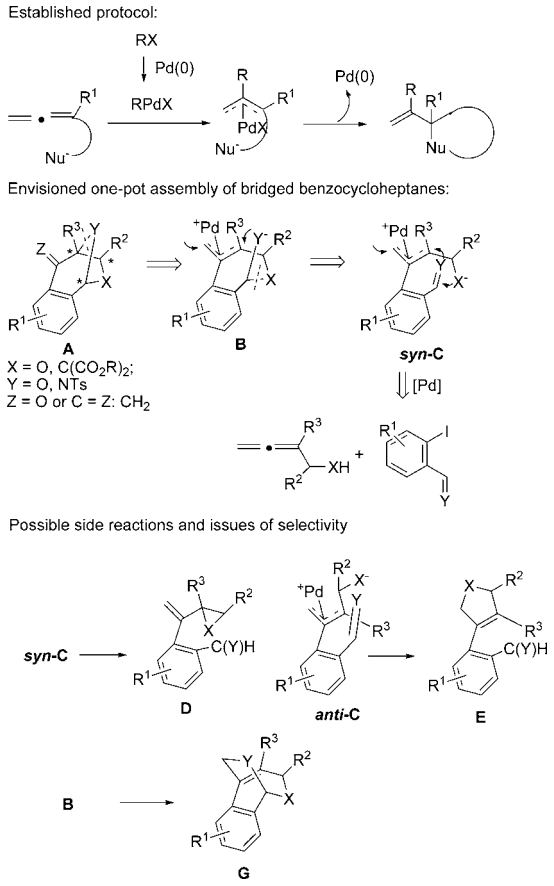
Scheme 1. Concept for the One-Step Construction of Oxa-Bridged Benzocycloheptanes

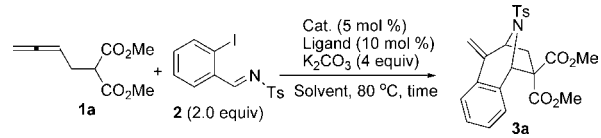


intermediate **B**, in which the nucleophilic Y anion may be generated from the intramolecular 1,2-addition of the X anion to the C═Y moiety of intermediate *syn*-**C**; the π-allylic palladium moiety in *syn*-**C** may be easily generated from the intermolecular carbopalladation of allenes (Scheme 1).[5] If these sequential transformations are feasible, it may provide one of the most straightforward pathways for the synthesis of the **A**-type of relatively complicated skeletons with biological potential. With this notion in mind, although there is a report on a three-component cyclization of 2-(2′,3′-dienyl)malonates, organic halides, and imines forming simple *cis*-pyrrolidine derivatives,[6] we realized that the challenge here would be the expected ring strain in the target skeleton, which requires the sequential smooth match of the reactivities of all the in situ generated intermediates or leading to the easy formation of three- or five-membered products **D** or **E**;[7,8] the regioselectivity of Pd-catalyzed allylation (forming bridged product **G** by attacking at the less-sterically hindered carbon terminal of **B**); and the diastereoselectivity and the final construction of the absolute configurations of the chiral centers in target **A**.

In this paper, we wish to report our recent achievement in the realization of such a multistep one-pot transformation with the convenient establishment of the absolute configurations of all the three chiral centers by using the optically active alcohols, showing the beauty and efficiency of allene chemistry.

We started this project by using dimethyl 2,3-butadienyl malonate **1a** and *o*-iodobenzaldehyde *N*-tosyl imine **2** to develop the reaction conditions with K_2CO_3 as the base (Table 1).

Table 1. Pd-Catalyzed Cyclization of Dimethyl 2,3-Butadienyl Malonate **1a** and *o*-Iodobenzaldehyde *N*-Tosyl Imine **2**: Optimization of Reaction Conditions[a]



entry	catalyst/ligand/additive	solvent	time(h)	yield of **3a** (%)[b]
1	$Pd(OAc)_2/PPh_3$	dioxane	10.5	0
2	$Pd(OAc)_2/PPh_3$	toluene	17.5	17
3	$Pd(OAc)_2/PPh_3$	MeCN	5.5	38
4	$Pd(OAc)_2$/TFP	MeCN	3	49
5	$Pd(dba)_2$/TFP	MeCN	47	30
6[c]	$Pd(OAc)_2$/TFP/4 Å MS	MeCN	7.5	62
7[c]	$Pd(OAc)_2$/4 Å MS	MeCN	3.5	80
8[d]	$Pd(OAc)_2$/4 Å MS	MeCN	3.5	80
9[d,e]	$Pd(OAc)_2$/4 Å MS	MeCN	3.5	80
10[d,e,f]	$Pd(OAc)_2$/4 Å MS	MeCN	3.5	80(77[g])

[a] [**1a**] = 0.033 mmol/mL. [b] NMR yield determined by using CH_2Br_2 as the internal standard. [c] 4 Å MS (61.3 mg/mL) was added. [d] 4 Å MS (12.2 mg/mL) was added. [e] [**1a**] = 0.067 mmol/mL. [f] 1.5 equiv of **2** were used. [g] Isolated yield.

However, with $Pd(OAc)_2$-PPh_3 as the catalyst, the reaction in dioxane failed to afford the expected product **3a** (entry 1); interestingly, it was observed that the solvent effect is obvious: the reaction in toluene and MeCN yielded **3a** in 17% and 38%, respectively (entries 2 and 3); with TFP (TFP = tri-(2-furyl)phosphine) as the ligand instead of PPh_3, the yield in MeCN was improved to 49% (entry 4); furthermore, we reasoned that the trace amount of water may be critical to the reaction since all the anionic intermediates are sensitive to water; thus, 4 Å MS was added to remove moisture, and the yield was improved to 62% (entry 6); to our surprise, with the addition of 4 Å MS, TFP is not required and the yield was further improved to 80% (Compare entry 6 with entry 7); the concentration of the starting materials has no effect on the yield

(5) For a seminal report on a Pd-promoted insertion reaction of allenes forming π-allylic palladium species, see: Schultz, R. G. *Tetrahedron Lett.* **1964**, *5*, 301. For a recent review on carbopalladation of allenes, see: Bai, T.; Ma, S.; Jia, G. *Coord. Chem. Rev.* **2009**, *253*, 423.

(6) Ma, S.; Jiao, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 4737.

(7) Ma, S.; Zhao, S. *J. Am. Chem. Soc.* **1999**, *121*, 7943.

(8) (a) Ahmar, M.; Cazes, B.; Gore, J. *Tetrahedron Lett.* **1985**, *26*, 3795. (b) Ahmar, M.; Cazes, B.; Gore, J. *Tetrahedron* **1987**, *43*, 3453. (c) Besson, L.; Bazin, J.; Gore, J.; Cazes, B. *Tetrahedron Lett.* **1994**, *35*, 2881. (d) Gamez, P.; Ariente, C.; Gore, J.; Cazes, B. *Tetrahedron* **1998**, *54*, 14835. (e) Ma, S.; Zhao, S. *Org. Lett.* **2000**, *2*, 2495. (f) Ma, S.; Jiao, N.; Zhao, S.; Hou, H. *J. Org. Chem.* **2002**, *67*, 2837.

of **3a**, and 1.5 equiv of **2** are sufficient. The structure of **3a** was confirmed by an X-ray single crystal diffraction study (Figure 2).[9]

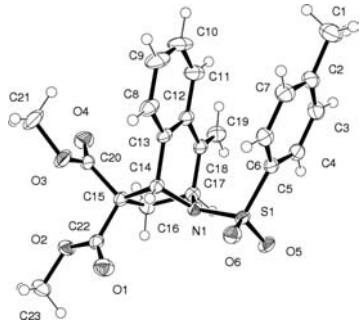
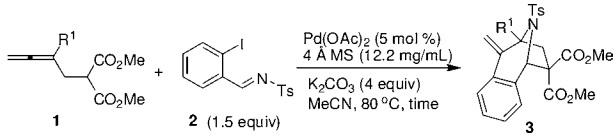


Figure 2. ORTEP representation of **3a**.

With this set of optimized reaction conditions, a different R^1 group may be introduced to the allylic position of the C═C bond in **3** in 91−95% yields (entries 2−5, Table 2).

Table 2. $Pd(OAc)_2$-Catalyzed Synthesis of Aza-Bridged Benzo[*a*,*d*]cycloheptenes **3**[a]



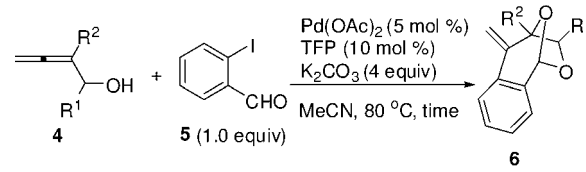
	1		
entry	R^1	time(h)	isolated yield of **3** (%)
1	H (**1a**)	3.5	77 (**3a**)
2	Ph (**1b**)	7	94 (**3b**)
3	Bn (**1c**)	6.2	95 (**3c**)
4	n-C_4H_9 (**1d**)	4	94 (**3d**)
5	Allyl (**1e**)	3	91 (**3e**)

[a] [**1**] = 0.067 mmol/mL.

In all the cases, only the bridged product **3** was formed as judged by ^{1}H NMR analysis of the crude product before chromatographic purification on silica gel; the three- or five-membered **D**- or **E**-type products and bridged products **G** were not formed.

With these results in hand we started to expand the scope of the reaction by using 2,3-allenols and *o*-iodobenzaldehyde as the starting materials. A control experiment showed that the addition of 4 Å MS was not required here. However, the reaction with TFP afforded the product **6a** in a much higher yield (70% vs 56%). In addition, it should also be noted that 1 equiv of the aldehyde is sufficient with an even higher yield (Table 3, entry 1). Under these optimized reaction conditions,

Table 3. $Pd(OAc)_2$-TFP-Catalyzed Cyclization of 2,3-Allenols and *o*-Iodobenzaldehyde[a]



	4			
entry	R^1	R^2	time(h)	isolated yield of **6** (%)
1	H	H (**4a**)	4.5	75 (**6a**)
2	H	n-C_7H_{15} (**4b**)	10.5	73 (**6b**)
3	H	Ph (**4c**)	52.8	87 (**6c**)
4	H	Bn (**4d**)	11	68 (**6d**)
5	H	allyl (**4e**)	19	66 (**6e**)
6	Ph	H (**4f**)	2.5	92 (**6f**)
7	2-BrC_6H_4	H (**4g**)	13.5	90 (**6g**)
8	2-$MeOC_6H_4$	H (**4h**)	21	88 (**6h**)
9	n-C_6H_{13}	H (**4i**)	6	90 (**6i**)
10	4-ClC_6H_4	H (**4j**)	6.5	77 (**6j**)

[a] [**4**] = 0.1 mmol/mL.

the scope was then studied. Different R^1 and R^2 may be introduced to the allylic and homoallylic positions of the C═C bond in **6** (Table 3). Gratifyingly, only one diastereomer was observed to form even with the R^1 substituent as determined by ^{1}H NMR analysis of the crude reaction mixture before chromatographic separation on silica gel (entries 6−10). The relative configurations in these products **6f**−**j** were determined by the X-ray single crystal diffraction study of **6f** (Figure 3).[10] Again, it should be noted that the three- or five-membered **D**- or **E**-type products and bridged products **G** were not formed.

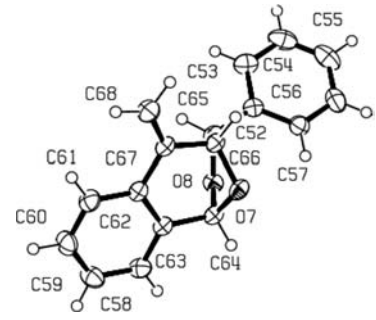


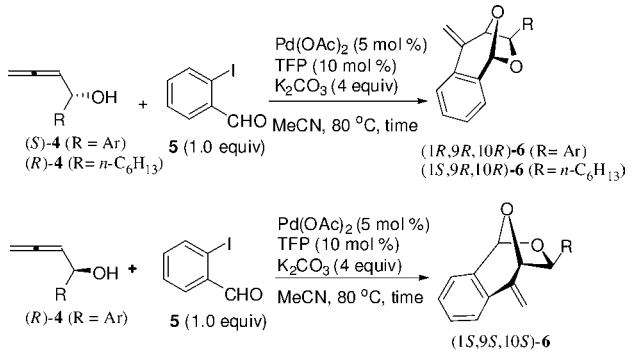
Figure 3. ORTEP representation of **6f**.

Optically active 2,3-allenols are readily available from optically active propargylic alcohol.[11] With these optically active alcohols **4f**, **4g**, **4i**, and **4j** as the starting materials, the absolute

(9) Crystal data for compound **3a**: $C_{23}H_{23}NO_6S$, MW = 441.48, Triclinic, space group P-1, final R indices [$I > 2\sigma(I)$], R1 = 0.0578, wR2 = 0.1489; R indices (all data), R1 = 0.0593, wR2 = 0.1517; a = 10.2477(5) Å, b = 10.6579(5) Å, c = 11.7877(6) Å, α = 97.6360(10)°, β = 99.7840(10)°, γ = 117.3550(10)°, V = 1093.62(9) Å^3, T = 173(2) K, Z = 2, reflections collected/unique 12886/3836 (R_{int} = 0.1482), number of observations [> 2$\sigma(I)$] 3635, parameters: 288. Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Centre, CCDC 779702.

configurations of the other two chiral centers in optically active products **6f**, **6g**, **6i**, and **6j** have been efficiently established with excellent de in >97% ee (Table 4). The absolute configurations

Table 4. $Pd(OAc)_2$-TFP-Catalyzed Cyclization of Optically Active 2,3-Allenols with *o*-Iodobenzaldehyde[a]



entry	4 R	time (h)	isolated yield of **6** (%)	ee of **6** (%)
1	Ph ((*S*)-**4f**)	2.5	92 ((1*R*,9*R*,10*R*)-**6f**)	98.0
2	Ph ((*R*)-**4f**)	2	91 ((1*S*,9*S*,10*S*)-**6f**)	97.9
3	2-BrC_6H_4 ((*S*)-**4g**)	13.5	91 ((1*R*,9*R*,10*R*)-**6g**)	99.8
4	*n*-C_6H_{13} ((*R*)-**4i**)	6.5	90 ((1*S*,9*R*,10*R*)-**6i**)	99.8
5	4-ClC_6H_4 ((*S*)-**4j**)	3.5	84 ((1*R*,9*R*,10*R*)-**6j**)	99.8

[a] [**4**] = 0.1 mmol/mL.

in these products were determined by an X-ray single crystal diffraction study of (1*R*,9*R*,10*R*)-**6j** (Figure 4).[12] Obviously, no reracemization occurred here.

The diastereoselectivity may be explained as follows: Carbopalladation of allenols in the presence of K_2CO_3 would favor the formation of π-allylic palladium intermediate *syn*-**8** due to the steric interaction of Pd and the substituent containing the hydroxyl group in *anti*-**8**. Intramolecular 1,2-addition of the alkoxyl anion to the aldehyde functionality would form **9** or **10**. However, the subsequent intramolecular allylation of **10** forming **6′** would be largely disfavored due to the steric interaction of the *endo*-H with the formed oxa-bridge and the R group with the exocyclic methylene group. Thus, diastereoisomer **6** was formed exclusively via the intermediacy of **9**. The regioselectivity of allylation has been controlled by the fact

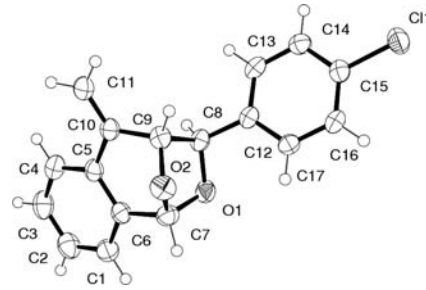
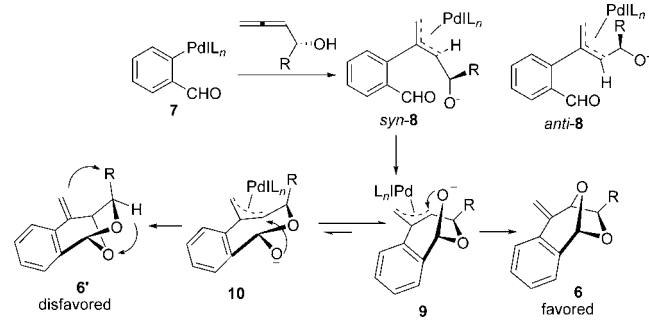


Figure 4. ORTEP representation of (1*R*,9*R*,10*R*)-**6j**.

that the terminal position attack would form a seven-membered ring instead of the current much more favored five-membered ring in **6** (Scheme 2).

Scheme 2



In conclusion, we have developed an efficient and high-yielding synthesis of aza or oxa-bridged benzocycloheptanes from readily available 2,3-allenyl malonates or 2,3-allenols and *o*-iodobenzaldehyde or *N*-tosyl imine. This one-pot reaction is clean and highly diastereoselective. With optically active 2,3-allenols, smooth double stereoinductions led to the formation of highly optically active oxa-bridged benzocycloheptanes. Due to the efficiency of the one-pot process, potential of the products, easy availability of these starting materials, and the excellent diastereoselectivity, this chemistry will be of high interest for organic and medicinal chemists. Further studies including the scope and application are being conducted in our laboratory.

Acknowledgment. Financial support from the Major State Basic Research & Development Program (2011CB808700) and National Natural Science Foundation of China (20732005) are greatly appreciated. We thank Mr. Bo Chen in this group for reproducing the preparation of **3d** in Table 2, **6e** in Table 3, and (1*R*, 9*R*, 10*R*)-**6g** in Table 4. Shengming Ma is a Qiu Shi Adjunct Professor at Zhejiang University.

Supporting Information Available: General procedure and spectroscopic data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Crystal data for compound **6f**: $C_{68}H_{56}O_8$, MW = 1001.13, monoclinic, space group *P*2(1)/*c*, final R indices [$I > 2\sigma(I)$], R1 = 0.0496, wR2 = 0.0934; R indices (all data), R1 = 0.1132, wR2 = 0.1131; *a* = 10.6114(6) Å, *b* = 10.5287 (6) Å, *c* = 46.396(3) Å, α = 90°, β = 98.255(2)°, γ = 90°, *V* = 5129.8(5) Å^3, *T* = 173(2) K, *Z* = 4, reflections collected/unique 68695/12248 (R_{int} = 0.0818), number of observations [> $2\sigma(I)$] 6982, parameters: 717. Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Centre, CCDC 779703.

(11) (a) Xu, D.; Li, Z.; Ma, S. *Tetrahedron Lett.* **2003**, *44*, 6343. (b) Kuang, J.; Ma, S. *J. Org. Chem.* **2009**, *74*, 1763. (c) Ma, S.; Hou, H.; Zhao, S.; Wang, G. *Synthesis* **2002**, 1643.

(12) Crystal data for compound (1*R*,9*R*,10*R*)-**6j**: $C_{2.27}H_{1.73}Cl_{0.13}O_{0.27}$, MW = 37.96, monoclinic, space group *P*2(1), final R indices [$I > 2\sigma(I)$], R1 = 0.0234, wR2 = 0.0632; R indices (all data), R1 = 0.0239, wR2 = 0.0637; *a* = 8.1646(3) Å, *b* = 5.2885(2) Å, *c* = 16.1885(6) Å, α = 90°, β = 99.2100(10)°, γ = 90°, *V* = 689.98(4) Å^3, *T* = 173(2) K, *Z* = 15, reflections collected/unique 7972/2408 (R_{int} = 0.0164), number of observations [> $2\sigma(I)$] 2362, parameters: 189. Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Centre, CCDC 779701.