JOC*Note*

Intramolecular Triple Heck Reaction. An Efficient Entry to Fused Tetracycles with a Benzene Core

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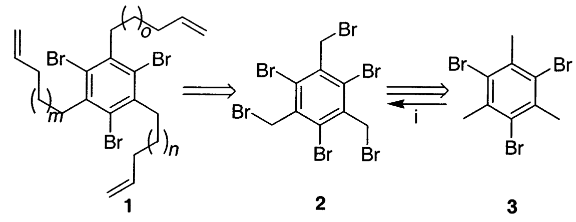
Abstract: Twelve examples of 1,3,5-tribromo-2,4,6-trienylbenzenes were easily synthesized by alkylation, etherification, and amination methods. Under conditions A and B, a series of tetracycles with a benzene core, i.e., fused 5,6,6-, 6,6,6-, and 6,6,7-tetracyclic compounds, were prepared efficiently via this intramolecular triple Heck reaction protocol.

Construction of two or more rings in one synthetic operation is an attractive synthetic strategy. Recently, we have developed a protocol of bicyclic carbopalladation, which can be efficiently applied to the synthesis of fused bicyclic compounds.[1] Over the past decade, carbopalladation of unsaturated carbon−carbon bonds has become one of the most powerful tools for the synthesis of stereodefined substituted alkenes and cyclic compounds via intermolecular and intramolecular reactions.[2] The latter has emerged as a potent new synthetic strategy for construction of oligocyclic systems from acyclic precursors in just one step.[3] Recently, carbon-rich compounds, such as conjugated polyaromatics and dendrimers, have received increasing attention due to their superior electronic, magnetic, or catalytic properties, thus effort has been spent in the synthesis of highly symmetric triannulated benzenes from ketones.[4] So far, there is no report on the synthesis of these analogous compounds using intramolecular triple Heck reaction. Here, we wish to report an efficient and versatile general method of the synthesis of triannulated benzenes. By this protocol, triannulated benzenes with different ring sizes as well as attached functional groups can be simultaneously constructed from the corresponding trialkene precursors in just "one shot".

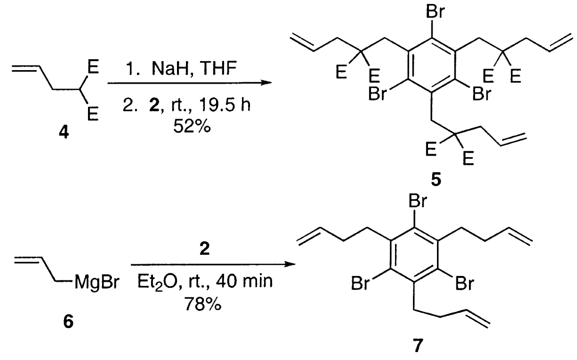
SCHEME 1



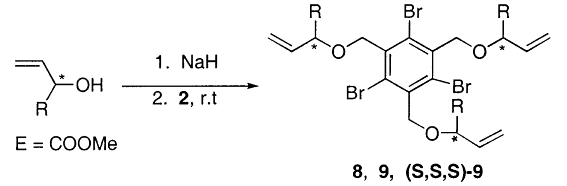
$m, n, o = 0, 1, 2$

i = NBS, BPO, CCl_4, reflux, 5.5 h, 63%

SCHEME 2



SCHEME 3



Conditions	R	Product	Yield (%)
THF, 16 h	H	**8**	50
THF-HMPA, 4.5 h	CH_3	**9**	57
THF-HMPA, 5 h	CH_3	**(S,S,S)-9**	56

Synthesis of Starting Materials. 1,3,5-Tribromo-2,4,6-tris(bromomethyl)benzene (**2**), which could be synthesized by bromination of 1,3,5-tribromo-2,4,6-trimethylbenzene (**3**)[5] with NBS, was used as the key building block for the synthesis of the starting materials **1** (Scheme 1).

1,3,5-Tribromobenzenes having three equal C=C bond fragments, i.e., **5** and **7**, were prepared by the treatment of **2** with dimethyl 2-allyl malonate **4** and allylmagnesium bromide **6**, respectively (Scheme 2). Triethers **8**, **9**, and (*S,S,S*)-**9** were prepared by the reaction of **2** with sodium 2-alkenoxides (Scheme 3).

1,3,5-Tribromobenzenes **12**, (*S,S*)-**12**, **13**, and **15** with different C=C bond-containing fragments were prepared

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[1] (a) Ma, S.; Xu, B. *J. Org. Chem.* **1998**, *63*, 9156. (b) Ma, S.; Xu, B.; Ni, B. *J. Org. Chem.* **2000**, *65*, 8532.

[2] (a) Heck, R. F. *Org. React.* **1982**, *27*, 345. (b) Heck, R. F. *Palladium Reagents in Organic Syntheses*; Academic Press: New York, 1985. (c) Gibson, S. E.; Middleton, R. J. *Contemp. Org. Synth.* **1996**, *3*, 447. (d) Negishi, E.-i.; Copéret, C.; Ma, S.; Liu, F. *Chem. Rev.* **1996**, *96*, 365. (e) Ojima, I.; Tzamarioudaki, M.; Li, Z.-Y.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635. (f) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2. (g) de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379. (h) Ma, S. *Youji Huaxue* **1991**, *11*, 561. (i) Kündig, E. P.; Ratni, H.; Crousse, B.; Bernardinelli, G. *J. Org. Chem.* **2001**, *66*, 1852. (j) Yoshikawa, E.; Radhakrishnan, K. V.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*, 7280. (k) Copéret, C.; Negishi, E.-i. *Org. Lett.* **1999**, *1*, 165.

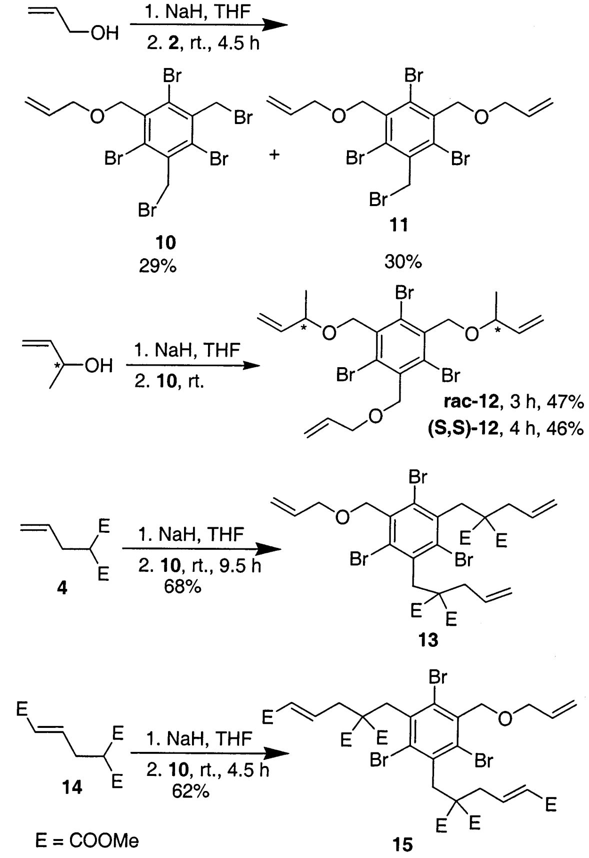
[3] (a) Zhang, Y.; Negishi, E.-i. *J. Am. Chem. Soc.* **1989**, *111*, 3454. (b) Abelman, M. M.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 2328. (c) Grigg, R.; Dorrity, M. J.; Malone, J. F.; Sridharan, V.; Sukirthalingam, S. *Tetrahedron Lett.* **1990**, *31*, 1343. (d) Wu, G. Z.; Lamaty, F.; Negishi, E.-i. *J. Org. Chem.* **1989**, *54*, 2507. (e) Carpenter, N. E.; Kucera, D. J.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 5846. (f) Grigg, R.; Sukirthalingam, S.; Sridharan, V. *Tetrahedron Lett.* **1991**, *32*, 2545. (g) Zhang, Y.; Wu, G. Z.; Agnel, G.; Negishi, E.-i. *J. Am. Chem. Soc.* **1990**, *112*, 8590. (h) Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.* **1991**, *113*, 701. (i) Meyer, F. E.; de Meijere, A. *Synlett* **1991**, 777.

[4] (a) Li, Z.; Sun, W.; Jin, X.; Shao, C. *Synlett* **2001**, 1947. (b) Elmorsy, S. S.; Pelter, A.; Smith, K. *Tetrahedron Lett.* **1991**, *32*, 4175.

[5] Engman, L.; Hellberg, J. S. E. *J. Organomet. Chem.* **1985**, *296*, 357.

10.1021/jo0258094 CCC: $22.00

SCHEME 4



by the etherification of 3-buten-2-ol, (*S*)-3-buten-2-ol,[6] or alkylation of **4** and **14** with **10**, which was prepared from the etherification of **2** with allylic alcohols in 29% yield. In this reaction, **11** was also isolated in 30% yield (Scheme 4).

Compounds **18**−**22** were easily synthesized by alkylation, etherification, or amination starting with the common starting precursor **11** as depicted in Scheme 5.

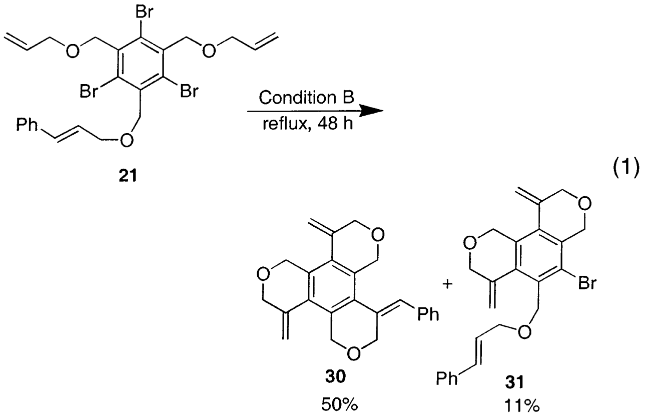
Annulation of 1,3,5-Tribromo-2,4,6-trienylbenzene. 1,3,5-Tribromo-2,4,6-tris (2′,2′-bis(methoxycarbonyl)-pent-4′-enyl)benzene (**5**) was used as the first substrate to test the triannulation reaction under different reaction conditions and the results are summarized in Table 1.

As shown in Table 1, when a mixture of **5** and Et_3N in toluene was stirred in the presence of 10 mol % $Pd_2(dba)_3$−$CHCl_3$ at 85−90 °C for 43 h, the desired tetracyclic compound **23** was not formed in a detectable yield (entry 1, Table 1). Using Et_3N as the base and $Pd(OAc)_2$ as the catalyst, the reaction in DMF did not afford tetracycle **23** (entry 2, Table 1). Under the catalysis of $Pd(OAc)_2$, using CH_3CN as the solvent and Et_3N as the base, **5** cyclized to afford tetracyclic product **23** in low yields (entries 3 and 4, Table 1). However, **23** was formed in moderate yields when using 10 mol % $Pd(PPh_3)_4$ as the catalyst, K_2CO_3 or Et_3N as the base, and DMF or CH_3CN as the solvent (entries 9−12, Table 1). The simplicity of the ^1H NMR and ^{13}C NMR spectra led us to come to the conclusion that there was no isomerization of double bonds forming thermodynamically more favored alkenes, which was observed in many cases.[7] The best results were obtained with 10 mol % $Pd(OAc)_2$, K_2CO_3 (6 equiv), and 40 mol % PPh_3 in CH_3CN under refluxing for 32 h affording fused tetracyclic product **23** in 87% yield (entry 13, Table 1). Here, it is interesting to note that the reaction catalyzed by $Pd(OAc)_2$ is better than that with $Pd(PPh_3)_4$, probably due to the presence of OAc^-.[8]

The Scope of Triannulation Reaction of Substituted Tribromobenzenes. Having established the standard reaction conditions for triannulation reaction of **5**, we tried to investigate the scope and cyclization patterns of this triannulation reaction. Some typical examples are summarized in Table 2. From Table 2, it is obvious that a series of tetracycles, i.e., fused 5,6,6- (entry 10, Table 2), 6,6,6- (entries 1−9, Table 2), and 6,6,7-triannulated benzenes (entry 11, Table 2), can be efficiently prepared.

To study the stereochemistry of products with chiral centers **25** and **26**, the optically active starting materials (*S*,*S*,*S*)-**9** and (*S*,*S*)-**12** were cyclized under similar reaction conditions. The ^1H and ^{13}C NMR data of corresponding products, i.e., (*S*,*S*,*S*)-**25** and (*S*,*S*)-**26**, led us to assign the complete stereochemistry of each diastereomer of **25** and **26** (entries 2−5, Table 2).

To explore the influence of steric effects on the reactivity of C=C double bonds, the triannulation reaction of three additional precursors in which the double bonds were substituted with one phenyl or methoxycarbonyl group or two methoxycarbonyl groups was studied. Product **29** could be synthesized in CH_3CN under conditions A in 35% yield, respectively (entry 8, Table 2), while under conditions B, **21** gives tetracyclic product **30** in 50% yield together with tricyclic product **31** in 11% yield (eq 1). The stereochemistry of the substituted double



(1)

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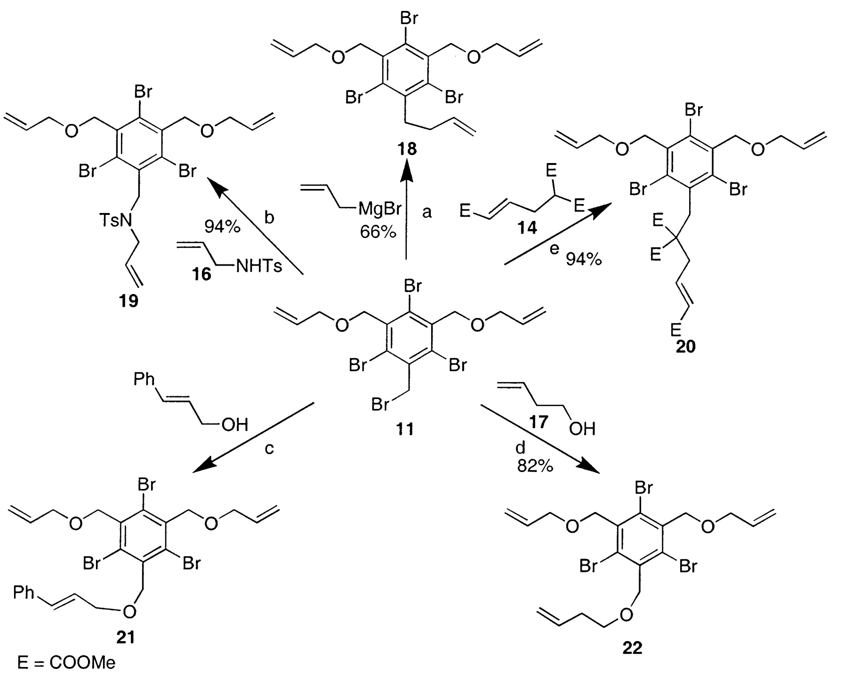
[6] Balmer, E.; Germain, A.; Jackson, W. P.; Lygo, B. *J. Chem. Soc., Perkin Trans. 1* **1993**, 399.

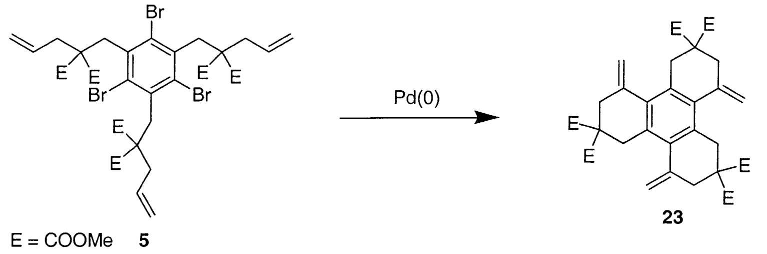
[7] For isomerization see: (a) Larock, R. C.; Babu, S. *Tetrahedron Lett.* **1987**, *28*, 5291. (b) Odle, R.; Blevins, B.; Ratcliff, M.; Hegedus, L. S. *J. Org. Chem.* **1980**, *45*, 2709. (c) Wu, G.; Lamaty, F.; Negishi, E.-i. *J. Org. Chem.* **1989**, *54*, 2507. For the suppression of isomerization by silver salt additives, see: (d) Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4130. (e) Abelman, M. M.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 2328. (f) Larock, R. C.; Song, H.; Baker, B. E.; Gong, W. H. *Tetrahedron Lett.* **1988**, *29*, 2919. (g) Larock, R. C.; Gong, W. H. *J. Org. Chem.* **1990**, *55*, 407. (h) Jeffery, T. *Tetrahedron Lett.* **1993**, *34*, 1133. (i) Sato, Y.; Sodeoka, M.; Shibasaki, M. *J. Org. Chem.* **1989**, *54*, 4738. (j) Jeffery, T. *Tetrahedron Lett.* **1991**, *32*, 2121. (k) Nilsson, K.; Hallberg, A. *J. Org. Chem.* **1992**, *57*, 4015. (l) Nilsson, K.; Hallberg, A. *J. Org. Chem.* **1990**, *55*, 2464. For the suppression of isomerization by thallium salt, see: (m) Carfagna, C.; Musco, A.; Sallese, G. *J. Org. Chem.* **1991**, *56*, 261. (n) Grigg, R.; Loganathan, V.; Santhakumar, V.; Sridharan, V.; Teasdale, A. *Tetrahedron Lett.* **1991**, *32*, 687.

SCHEME 5[a]



[a] Conditions: (a) Et_2O-THF, rt, 0.5 h; (b) NaH, THF-DMF, rt, 5.5 h; (c) NaH, THF, rt, 14 h; (d) NaH, THF, rt, 12 h; (e) NaH, THF, rt, 4.5 h.

TABLE 1. Triannulation of 5 under Different Reaction Conditions



entry	catalyst[a]	solvent	base	PPh_3 (%)	T (°C)	time (h)	yield of **23** (%)
1	10 mol % A	toluene	Et_3N	0	85−90	43	0
2	10 mol % B	DMF	Et_3N	40	85−90	38	0
3	10 mol % B	CH_3CN	Et_3N	40	reflux	51	15
4	10 mol % B	CH_3CN	Et_3N[b]	40	reflux	22	33
5	5 mol % B	CH_3CN	K_2CO_3	40	reflux	63	76
6	5 mol % B	CH_3CN	K_2CO_3	20	reflux	63	59
7	10 mol % B	CH_3CN	Cs_2CO_3	40	reflux	35	89
8	10 mol % B	CH_3CN	K_2CO_3[c]	20	reflux	41	64
9	10 mol % C	DMF	Et_3N	0	85−90	45	42
10	10 mol % C	DMF	K_2CO_3	0	85−90	45	64
11	10 mol % C	CH_3CN	Et_3N	0	reflux	45	49
12	10 mol % C	CH_3CN	K_2CO_3	0	reflux	45	40
13	10 mol % B	CH_3CN	K_2CO_3	40	reflux	32	87

[a] A = $Pd_2(dba)_3 \cdot CHCl_3$; B = $Pd(OAc)_2$; C = $Pd(PPh_3)_4$. [b] $AgNO_3$ (1 equiv) was added. [c] n-Bu_4NBr (1 equiv) was added.

bond product **29** was unambiguously detemined by the X-ray diffraction study.[9] From precursor **15**, in which the two C=C bonds were substituted with methoxycarbonyl groups, the tetracyclic product **32** can also be prepared in reasonable yield (entry 9, Table 2). The configurations of two C=C bonds were determined by the NOE study.

Under conditions B, the precursor **18** gives 5,6,6-triannulated benzene **33** in 61% yield (entry 10, Table 2). When **22** was submitted to conditions A, the corre-

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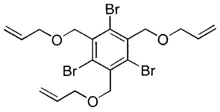
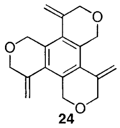
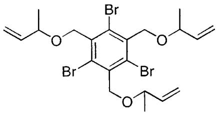
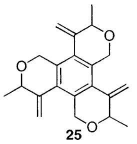
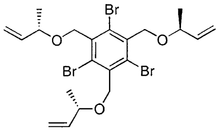
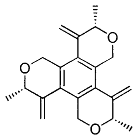
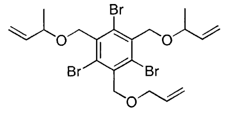
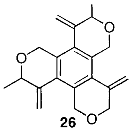
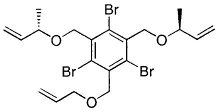
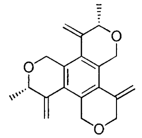
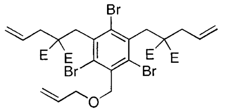
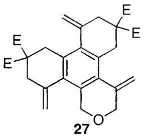
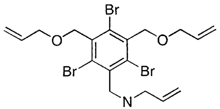
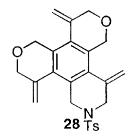
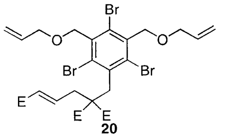
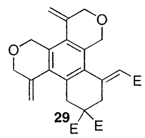
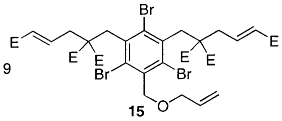
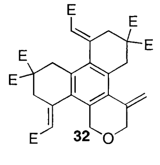
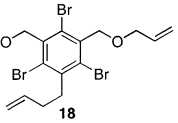
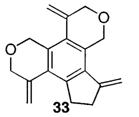
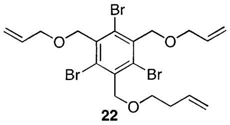
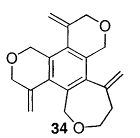
(8) Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314.

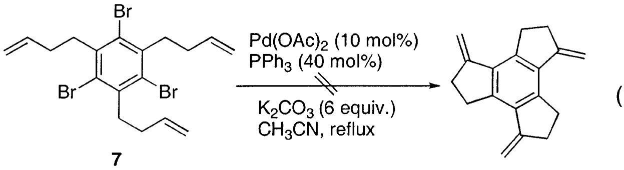
(9) Crystal data for **29**: $C_{25}H_{26}O_8$, mw = 454.46, triclinic, space group $P\bar{1}$, Mo Kα, final R indices [$I > 2\sigma(I)$], R1 = 0.0469, wR2 = 0.0875, a = 8.9173(8) Å, b = 9.8623(9) Å, c = 14.4631(13) Å, α = 81.585(2)°, β = 83.561(2)°, γ = 64.417(2)°, V = 1133.20 (18) Å^3, T = 293 (2) K, Z = 2, reflections collected/unique 6797/4840 [R(int) = 0.0363], no observation ($I > 2.0\sigma(I)$), parameters 403.

TABLE 2. Synthesis of Triannelated Benzenes[a]

entry	substrate	conditions	time (h)	product	isolated yield (%)
1	 **8**	A	48	 **24**	72
2	 **9**	B	54	 **25** (S*,S*,S*) : (R*,R*,S*) = 1 : 3	82
3	 **(S,S,S)-9**	B	48	 **(S,S,S)-25**	83
4	 **12**	B	54	 **26** (S*,S*) : (R*,S*) = 1 : 1	71
5	 **(S,S)-12**	B	46	 **(S,S)-26**	72
6	 **13**	B	48	 **27**	23
7	 **19**	B	47	 **28**	50
8	 **20**	A	46	 **29**	35
9	 **15**	A	50	 **32**	28
10	 **18**	B	46	 **33**	61
11	 **22**	A	44	 **34**	49

sponding tetracyclic product **34** also formed smoothly in 49% yield (entry 11, Table 2).

Apart from the results given above, we failed to construct fused 5,5,5-triannulated benzene **35** from **7**, probably due to the ring constrain of the benzo-fused five-membered cycle (eq 2). This reaction was complicated by the complete consumption of **7**.



7 **35** (2)

In conclusion, a new and highly convenient triannulation reaction was developed. By this protocol, a series of triannulated benzenes, i.e., 5,6,6-, 6,6,6-, and 6,6,7-tetracyclic compounds, can be efficiently prepared via a triple Heck reaction. With optically active starting compounds optically active tetracyclic compounds were easily prepared. Due to the easy availability of the starting materials, the potentials of the products, and the high stereoselectivity, this methodology will show its utility in organic synthesis.

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Supporting Information Available: Experimental Section and the analytical data for all the starting materials and products, the ORTEP presentation of **29**, and the NOE results of **32**. This material is available free of charge via the Internet at http://pubs.acs.org.

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