Domino Heck–C–H activation reaction of unsymmetrically substituted [3]cumulene†

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The Heck reaction of an unsymmetrically substituted [3]cumulene has been investigated. Although a carbonyl conjugated alkene is present, the arylpalladium species selectively inserts into the C3–4 double bond, and a subsequent C–H activation reaction with a neighboring phenyl group gives the indene derivatives with a tetrasubstituted olefin moiety.

Cumulene derivatives have attracted a lot of attention due to their high reactivity and unique chemical behavior[1] as nucleophiles, electrophiles, and occasionally dienophiles. Most investigations on reactivity have focused on symmetrically substituted cumulene derivatives possessing the same substituents on both sides of the molecule,[2,12] but reports on the reactivity of unsymmetrically substituted cumulene derivatives are limited.[3]

We have recently demonstrated the reaction behavior of 2-methyl-5,5-diphenylpenta-2,3,4-trienal (**1**),[4] a stable unsymmetrically substituted [3]cumulene, in Diels–Alder (DA) and Friedel–Crafts reactions.[5] That study has revealed that the distinct double bonds, which possess different electronic and steric properties, show completely different reactivities. The DA reaction of **1** with cyclopentadiene selectively occurs on the C2–3 double bond to afford tetrasubstituted allenyl adducts. In sharp contrast, the Friedel–Crafts reaction with electron-rich hetero-aromatics yields tetrasubstituted conjugated dienes *via* a conjugate addition–protonation on C3–4.

As part of our continuing investigations on the reaction behavior of **1** in transition metal catalyzed transformations, we have explored the Heck reaction. Initially, we expected a reactivity similar to the DA reaction might provide allene **3** *via* insertion of an arylpalladium species into the carbonyl conjugated C2–3 double bond[6] (path a) and successive β-hydride elimination of **2**. However, the reaction unexpectedly afforded 2,3-diaryl indene derivative **5**. This product is explained by a reaction that proceeds through a domino process, which includes the selective insertion of the arylpalladium species at the C3–4 double bond (path b) and a further C–H activation reaction[7] with a neighboring phenyl moiety to palladacycle **4** (Fig. 1). Herein, we report the details of this domino Heck–C–H activation reaction.

We initially surveyed the appropriate conditions for the Heck reaction with a variety of aryl halides (Table 1). Upon treating **1** and phenyl iodide with 10 mol% of $Pd(OAc)_2$ and *i*-Pr_2NEt, the reaction proceeded smoothly to afford indene derivative **5a** as an *E*–*Z* mixture in 54% yield (entry 1). Using 2.0 equivalent of phenyl iodide improved the chemical yield (entry 2),‡ but adding more phenyl iodide did not afford a remarkable improvement (entry 3).[8]

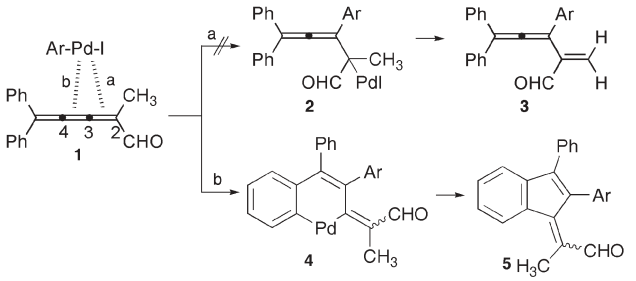
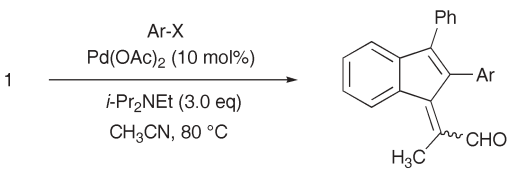
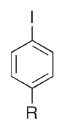
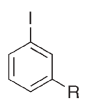


Fig. 1 Domino Heck–C–H activation reaction of **1**.

Table 1 Domino Heck–C–H activation reactions of cumulene **1**



Entry	Ar-X		Equiv.	*t*/h	Product	Yield[a] (%)	Ratio[b] (*Z* : *E*)
1[c]	PhI		1.0	2	**5a**	54	3.7 : 1.0
2	PhI		2.0	1	**5a**	59 (69)[d]	3.6 : 1.0
3	PhI		3.0	1	**5a**	61	3.4 : 1.0
4	PhBr		1.0	3	—	—	—
5		R = OMe	2.0	1	**5b**	46	3.6 : 1.0
6		R = OMs	2.0	1	**5c**	39	2.4 : 1.0
7		R = NO_2	2.0	1	**5d**	66	4.3 : 1.0
8		R = Br	2.0	1	**5e**	55	2.7 : 1.0
9		R = OMe	2.0	2	**5f**	47	2.3 : 1.0
10		R = OMs	2.0	1	**5g**	62	2.3 : 1.0
11		R = NO_2	2.0	1	**5h**	47	2.5 : 1.0

[a] Isolated yields of *E*–*Z* mixtures. [b] Determined by integration of the ^1H NMR spectrum. [c] The reaction mixture was heated to 100 °C. [d] Calculated by integration of the ^1H NMR spectrum of the crude reaction material using dimethyl oxalate as an internal standard.

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† This paper is dedicated to the memory of the late Prof. Kiyoshi Tanaka, who passed away December 8, 2004.

Functionalized phenyl iodides were also applied to this reaction (entries 5–11). The reaction with *p*-methoxyphenyl iodide gave the corresponding indene derivative **5b** in 46% yield (entry 5).[9] In addition, aryl iodides with electron-withdrawing groups were compatible. Although *p*-mesyloxyphenyl iodide gave a moderate result (entry 6),[9] a nitro substituent increased the yield to 66% (entry 7). Because phenyl bromide did not react (entry 4), the transformation with *p*-bromophenyl iodide afforded **5e** without bromo substituent loss (entry 8).

Aryl iodides with both electron-releasing and withdrawing groups at the *meta*-position also yielded the corresponding products in moderate yields (entries 9–11).

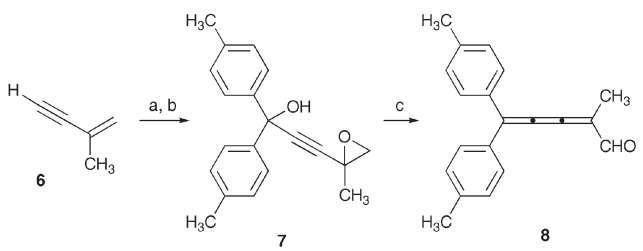
The aromatic region in the NMR spectra for products **5a–5h** was highly overlapped, which made structural confirmations and stereochemistry determinations of the tetrasubstituted double bond problematic. Therefore, we prepared cumulene **8**, an appropriate substrate for structural determination that produced simple NMR signals for the domino products.

Cumulene **8** was prepared in a similar manner to **1**.[4] Lithiation of 2-methyl-1-butene-3-yne (**6**) with *n*-BuLi and subsequent addition of 4,4′-dimethylbenzophenone afforded the alkynyl alcohol. Without further purification, oxidation of the double bond with dimethyldioxirane gave alkynyl epoxide **7** in 74% yield in two steps. Treatment of **7** with $BF_3{\cdot}Et_2O$ afforded desired cumulene derivative **8** (Scheme 1).

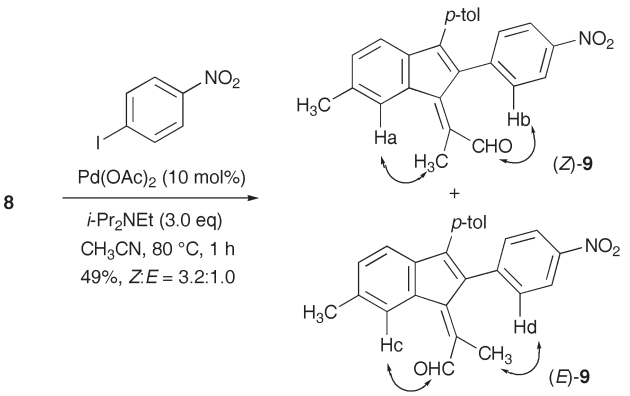
As expected, the domino reaction of **8** with *p*-nitrophenyl iodide proceeded smoothly to give an *E*–*Z* mixture of **9**, which had much simpler signals in the aromatic region than **5a** due to both the methyl and nitro substituents on the phenyl rings. Therefore, a complete assignment of each signal was possible. The NOE correlations between the aromatic (Ha) and the methyl protons and between the aromatic (Hb) and the formyl proton clearly indicate that the *Z*-isomer on the tetrasubstituted olefin is the major product. On the other hand, NOEs between Hc and the formyl proton, and between Hd and the methyl protons were observed in the *E*-isomer (Scheme 2).

Moreover, X-ray crystallographic analysis of **9**, which includes the stereochemistry, was unambiguously determined as shown in Fig. 2.[10]§

Scheme 3 depicts a plausible mechanism for the domino Heck–C–H activation reaction. The first crucial step of the Heck reaction is insertion of arylpalladium iodide into the C3–4 double bond to give intermediate **10**.[11,12] Because β-hydride elimination of **10** is not accessible, C–H activation of the neighboring phenyl moiety proceeds smoothly to afford six-membered palladacycle **4**, which is



Scheme 1 *Reagents and conditions*: (a) *n*-BuLi, Et_2O, −50 °C, 30 min, then 4,4′-dimethylbenzophenone, −50 °C, 24 h; (b) dimethyldioxirane, rt, 1 h, 74% (2 steps); (c) $BF_3{\cdot}Et_2O$, THF, −78 °C, 3 h, 58%.



Scheme 2 NOE correlations of (*E*)- and (*Z*)-**9**.

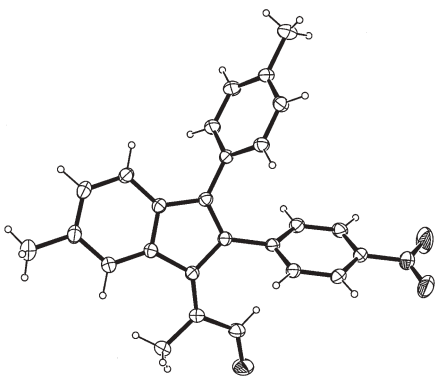
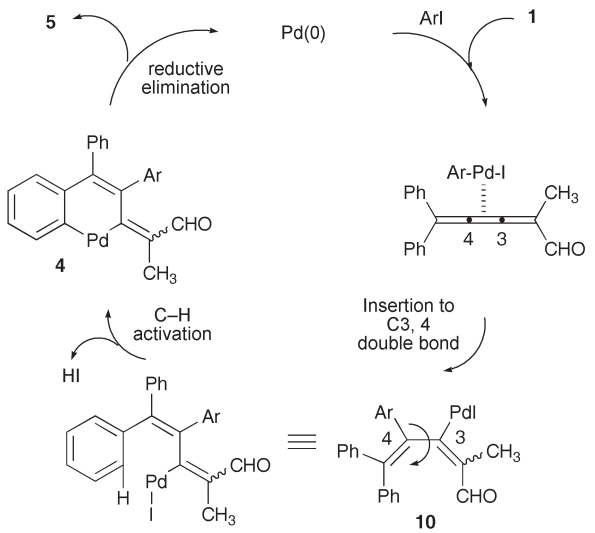


Fig. 2 ORTEP drawing of (*Z*)-**9** with thermal ellipsoids at the 20% probability level.

successively cyclized to give indene derivative **5** *via* reductive elimination of the palladium intermediate.

It is noteworthy that the direction of addition of the arylpalladium iodide to **1** is also regioselective, in which the palladium(II) and aryl group are positioned at C3 and C4, respectively, in **10**.



Scheme 3 Plausible reaction pathway of Heck–C–H activation reaction.

Multiple aryl modified tetrasubstituted alkenes have attracted a lot of attention as key structural elements for bioactive compounds. One of the most prominent examples of such a molecule is tamoxifen,[13] which is a clinically used drug for breast cancer. The Heck–C–H activation reaction of unsymmetrically substituted cumulenes described here might be useful and valuable for constructing such bioactive tetrasubstituted alkenes with appropriate functional groups on both the aromatic and alkene moieties. These bioactive tetrasubstituted alkenes may be key substituents for the interaction with receptors and pivotal in further chemical transformations. Moreover, products **5a–5h** and **9** could be recognized as conformationally locked analogs of tamoxifen, in which one of the aromatic rings is fixed as the partial structure of the indene framework. Using these indene derivatives as bioprobes for tamoxifen related nuclear receptor is also interesting.

In summary, we have found a unique Heck–C–H activation reaction of **1**, which provides indene derivatives with both a functionalized aryl and tetrasubstituted alkene moieties. Furthermore, studies which introduce heteroaromatics such as indole and pyrrole to **1** as well as the biological evaluation of the products are currently under investigation.

Notes and references

‡ Typical procedure for domino Heck–C–H activation reaction (Table 1, entry 2):

Iodobenzene (91 μL, 0.81 mmol), $Pd(OAc)_2$ (9.2 mg, 41 μmol), and *i*-Pr_2NEt (0.21 mL, 1.2 mmol) were added to a solution of **1** (100 mg, 0.41 mmol) in CH_3CN (4 mL) under an argon atmosphere. The mixture was stirred at 80 °C for 1 h and then evaporated. The mixture was washed with saturated aqueous NH_4Cl and brine, extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (*n*-hexane–AcOEt, 9 : 1) to afford 2-(2,3-diphenyl-1*H*-inden-1-ylidene)propanal (**5a**) (78 mg, 59%, $E : Z = 1.0 : 3.6$) as a red solid.

Duplicate reaction was performed to obtain the conversion. The yield was calculated by the ^1H NMR integration of the crude residue using dimethyl oxalate as an internal standard.

^1H NMR (270 MHz, $CDCl_3$, *E*–*Z* mixture): δ = 1.65 (*E*-isomer) (s, CH_3), 2.50 (*Z*-isomer) (s, CH_3), 7.2–7.9 (m, Ar), 9.52 (*Z*-isomer) (s, CHO), 10.88 (*E*-isomer) (s, CHO). ^{13}C NMR (68 MHz, $CDCl_3$, *E*–*Z* mixture): δ = 14.1, 14.2, 121.2, 121.4, 126.2, 126.4, 126.6, 126.8, 127.3, 127.5, 127.6, 127.8, 128.0, 128.1, 128.2, 128.3, 128.5, 128.6, 128.9, 129.1, 129.2, 129.5, 129.95, 130.00, 130.1, 132.3, 133.6, 136.7, 136.8, 137.4, 137.8, 143.6, 145.9, 152.0, 192.5, 193.0. IR (neat, cm^{-1}) 1659. FAB-MS *m*/*z* 323 $(M + H)^+$. HR MS calcd for $C_{24}H_{19}O$ $(M + H)^+$ 323.1436, found 323.1450.

§ Crystallographic data for **9**: $C_{26}H_{21}NO_3$, M = 395.46, triclinic, space group $P\bar{1}$ (#2), T = 298 K, a = 10.7108(14) Å, b = 11.2338(13) Å, c = 10.2696(12) Å, α = 96.444(10)°, β = 110.963(9)°, γ = 110.197(9) Å, V = 1043.0(2) $Å^3$, Z = 2, D = 1.259 g cm^{-3}, λ (Cu Kα) = 1.54178 Å, R = 0.1183, $wR2[F^2]$ = 0.3072 for 833 unique reflections. CCDC 609878. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b607684j

1 One of the most prominent examples is shown in the neocarzinostatin chromophore in which the biradical species generated by a Bergman type cycloaromatization of the enyne[3]cumulene plays a key role in its potent anti-tumor activity. See: (*a*) I. Saito, K. Yamaguchi, R. Nagata and E. Murahashi, *Tetrahedron Lett.*, 1990, **31**, 7469; (*b*) A. G. Myers and P. S. Dragovich, *J. Am. Chem. Soc.*, 1993, **115**, 7021; (*c*) A. L. Smith and K. C. Nicolaou, *J. Med. Chem.*, 1996, **39**, 2103.

2 (*a*) A. Roedig and G. Zaby, *Chem. Ber.*, 1980, **113**, 3342; (*b*) J. K. Crandall, D. M. Coppert, T. Schuster and F. Lin, *J. Am. Chem. Soc.*, 1992, **114**, 5998; (*c*) N. Suzuki, M. Nishiura and Y. Wakatsuki, *Science*, 2002, **295**, 660; (*d*) N. Suzuki, Y. Fukuda, C. E. Kim, H. Takahara, M. Iwasaki, M. Saburi, M. Nishiura and Y. Wakatsuki, *Chem. Lett.*, 2003, **32**, 16; (*e*) P.-H. Liu, L. Li, J. A. Webb, Y. Zhang and N. S. Goroff, *Org. Lett.*, 2004, **6**, 2081.

3 (*a*) J. G. Garcia, B. Ramos, L. M. Pratt and A. Rodriguez, *Tetrahedron Lett.*, 1995, **36**, 7391; (*b*) J. M. Aurrecoechea, E. Pérez and M. Solay, *J. Org. Chem.*, 2001, **66**, 564. See also ref. 2*a*.

4 X. Wang, B. Ramos and A. Rodriguez, *Tetrahedron Lett.*, 1994, **35**, 6977.

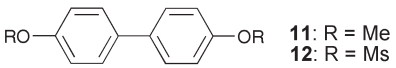
5 T. Asakawa, M. Iinuma, T. Furuta, S. Fujii, T. Kan and K. Tanaka, *Chem. Lett.*, 2006, **35**, 512.

6 It has been reported that the carbonyl conjugated double bond is more reactive than the sterically similar isolated double bonds toward the Heck reaction. This suggests that the reactivity of the C2–3 double bond might be higher than that of the C3–4 or C4–5 double bond in **1**. See R. F. Heck, *Org. React.*, 1989, **27**, 345.

7 For reviews on C–H activation reaction, see: (*a*) A. E. Shilov and G. B. Shul'pin, *Chem. Rev.*, 1997, **97**, 2879; (*b*) S. Ma and Z. Gu, *Angew. Chem., Int. Ed.*, 2005, **44**, 7512; (*c*) K. Godula and D. Sames, *Science*, 2006, **312**, 67.

8 Addition of a phosphine ligand such as $P(o\text{-tol})_3$ was ineffective.

9 Increasing the amount of aryl iodides to a ten times higher concentration afforded biaryl derivatives **11** and **12** as side products.



10 Considering that the chemical shift of the *Z*-isomer aldehyde proton of **9** shifts to a higher-field compared to the corresponding *E*-isomer due to the anisotropic shielding of the neighboring *p*-nitrophenyl moiety (Fig. 2), the major isomer of **5a–5h** should be the *Z*-isomer.

11 Allene derivative **3** was not observed, suggesting that the insertion of arylpalladium iodide into the C2–3 double bond, which leads to palladium intermediate **2**, does not occur (Fig. 1).

12 Considering a previous report, in which the indene derivative was prepared by a related Heck–C–H activation reaction of tetraphenylbutatriene with phenyl iodide, the central and isolated C3–4 double bond might be the most reactive in [3]cumulene derivatives in a Heck reaction. See G. Dyker, S. Borowski, G. Henkel, A. Kellner, I. Dix and P. G. Jones, *Tetrahedron Lett.*, 2000, **41**, 8259.

13 A. S. Levenson and V. C. Jordan, *Eur. J. Cancer*, 1999, **35**, 1628.