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Tuned C–H Functionalization to Construct Aza-Podophyllotoxin/Aza-Conidendrin Derivatives by Means of Domino Cyclization

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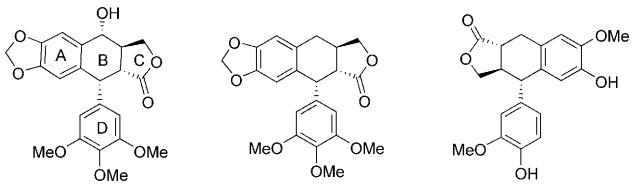
Abstract: An efficient domino cyclization method for the construction of aza-podophyllotoxin/aza-conidendrin derivatives has been established. Reactions of different dienes with aryl halides in the presence of a palladium catalytic system produced different kinds of podophyllotoxin derivatives through a highly regioselective C–H functionalization. Treatment of dienes with aryl halides that have electron-withdrawing substituents on the phenyl ring created aza-podophyllotoxin derivatives by means of the functionalization of the C–H bonds *ortho* to the C–halide bonds of the incoming aryl halides. The reaction of dienes with 1-iodobenzene or aryl halides that incorporate electron-donating groups produced aza-conidendrin derivatives by means of the functionalization of both sp^3 C–H and sp^2 C–H bonds. The regioselective C–H functionalization for the formation of different pseudo-podophyllotoxin/-conidendrin derivatives is proven by analyses of the ^{1}H NMR spectra of the products and selective X-ray analyses of the structures of the products. Thus, the palladium-catalyzed domino cyclization of 1,6-dienes for the preparation of aza-podophyllotoxin/aza-conidendrin derivatives can be controlled by selectively controlling the C–H functionalization.

Keywords: C-H activation · cyclization · dienes · domino reactions · palladium

Introduction

The synthetic methodology for natural products or their analogues has attracted much attention for their medicinal applications. Podophyllotoxin (Scheme 1) is one of the natural products isolated from *Podophyllum peltatum* and *Podophyllum emodi*,[1] as it has long been known to possess antitumor properties in clinical use in the treatment of warts and small-cell lung carcinoma.[2] Various synthetic strategies have been developed for the preparation of podophyllotoxin and its analogues.[3] The groups of Linker and Bach developed the strategies independently by synthesizing (−)-epipodophyllotoxin[4a] and (−)-podophyllotoxin[4b] through enantioselective total synthesis. The total synthesis of (−)-epipodophyllotoxin has also been accomplished in 12 steps starting from the commercially available piperonal, with the final product isolated in 30% overall yield. Sherburn and co-workers constructed the core structure of podophyllotoxin in nine steps with a high regio- and stereoselectivity using a silicon-tethered radical reaction.[4c] In addition, Davies et al. described an efficient C–H activation of primary benzylic positions by means of rhodium carbenoid in the synthesis of (−)-α-conidendrin.[5]



Scheme 1. Selected natural products containing skeletons of aryl tetrahydronaphthalene lactones.

As an analogue of podophyllotoxin, aza-epiisopicropodophyllin has been synthesized by Poli and Giambastiani by

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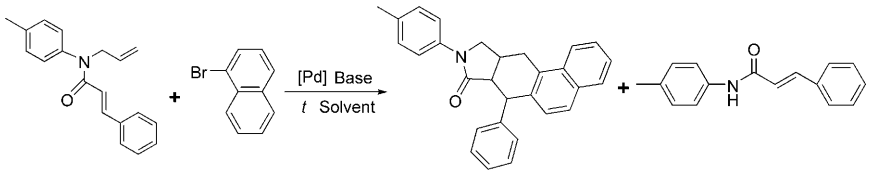
employing two synthetic strategies.[6] In recent years, the tandem reaction has been developed for the synthesis of heterocycles, which are valuable building blocks for the construction of pharmaceuticals.[7] These condensed ring compounds can be constructed by means of the palladium-catalyzed cycloaddition of dienes,[8] Diels–Alder reaction,[9] intramolecular Heck reaction,[10] and C–H functionalization.[11,12] Meanwhile, C–C bond-forming events in established methodologies involve Friedel–Crafts, Michael, and enzyme-assisted reactions.[13,14] Through this approach, enynes can be transformed into cyclic skeletons in a one-pot fashion with an impressive regio- and stereoselectivity.[15,16] Carretero, Ruck, and their co-workers reported a novel tandem Heck/C–H functionalization reaction to generate spiro-oxindoles.[17,18]

Table 1. The palladium-catalyzed reaction for construction of the tetracyclic heterocycles.[a]



a aa j

Entry	[Pd] ([mol%])	Base ([equiv])	Solvent	t [h]	T [°C]	Yield [%][b] aa	j
1	$Pd(OAc)_2/PPh_3$ (1:2)	$(n\mathrm{Bu})_3N$ (1.2)	DMF	15	120	5	–
2	$Pd(OAc)_2/PPh_3$ (2:4)	$(n\mathrm{Bu})_3N$ (1.2)	DMF	24	130	34	–
3	**$Pd(OAc)_2/PPh_3$ (2:4)**	**$(n\mathrm{Bu})_3N$ (1.2)**	**DMF**	**24**	**140**	**82**	**10**
4	$Pd(OAc)_2/PPh_3$ (1:2)	$(n\mathrm{Bu})_3N$ (1.2)	DMF	18	145	60	31
5	$Pd(OAc)_2/PPh_3$ (2:4)	$(n\mathrm{Bu})_3N$ (1.2)	DMF	24	150	45	53
6	$Pd(OAc)_2/PPh_3$ (2:4)	K_2CO_3 (1.2)	dioxane	24	140	58	24
7	$Pd(OAc)_2/PPh_3$ (2:4)	Li_2CO_3 (1.2)	DMF	30	140	24	5
8	$Pd(OAc)_2/PPh_3$ (2:4)	$(n\mathrm{Bu})_3N$ (1.2)	DMF	24	140	61	19
9	$[Pd(PPh_3)_4]$ (2)	$(n\mathrm{Bu})_3N$ (1.2)	DMF	24	140	56	16
10	$PdCl_2$ (2)	$(n\mathrm{Bu})_3N$ (1.2)	DMF	30	140	33	8
11	$[Pd(dba)_2]$ (2)	$(n\mathrm{Bu})_3N$ (1.2)	DMF	24	140	69	12
12	$Pd(OAc)_2$ (2)	Ag_2CO_3 (1.2)	DMF	36	140	5	–
13	2% polymer–Pd (0)	$(n\mathrm{Bu})_3N$ (1.2)	DMF	48	150	4	15
14	1% chitosan–Pd (0)	$(n\mathrm{Bu})_3N$ (1.2)	DMF	24	140	30	–

[a] All reactions were carried out under argon using **a** (1.0 equiv), 1-bromonaphthalene (1.2 equiv), $Pd(OAc)_2$ (2 mol%), PPh_3, base, and solvent (10 mL) at the temperature indicated. [b] Yield of isolated product.

Owing to the many steps required and only moderate yields and stereoselectivities achieved in the synthesis of podophyllotoxin/conidendrin derivatives, the tandem C–C bond formation and different C–H bond functionalization involving a tandem cyclization process to construct aza-podophyllotoxin/aza-conidendrin derivatives is extremely rare. As part of our ongoing studies in this field,[19] we report herein an efficient domino cyclization method for the preparation of different aza-podophyllotoxin/aza-conidendrin by carbopalladation and subsequent regioselectively functionalization of the unactivated C–H bond.

Results and Discussion

The reaction conditions using *N*-allyl-*N*-*p*-tolylcinnamamide (**a**) and 1-bromonaphthalene as a typical reaction in the presence of a palladium catalytic system were surveyed (Table 1). In a test experiment, reaction of **a** with 1-bromonaphthalene in *N*,*N*-dimethylformamide (DMF) in the presence of a catalytic amount of $Pd(OAc)_2$ produced 7-phenyl-9-*p*-tolyl-7,7a,9,10,10a,11-hexahydronaphtho[1,2-*f*]isoindol-8-one (**aa**) in 34% yield at 130°C for 24 h. Altering the experimental conditions indicated that the output of the domino reaction producing product **aa** was greatly affected by the reaction temperature (Table 1, entries 1–5), the additive bases (Table 1, entries 3, 6, 7), the catalytic system (Table 1, entries 6, 9–11), and the solvents (Table 1, entries 3, 6). Thus, the following standard reaction conditions were selected for carrying out the following studies: 1,6-dienes (1 equiv) were treated with different aryl halides (1.2 equiv) in the presence of a palladium(II) catalyst (2 mol%) and Ph_3P (4 mol%) with $(n\mathrm{Bu})_3N$ (1.2 equiv) as an additive in DMF at 140°C.

Tuned C–H Functionalization

To examine the scope of this domino reaction, the reactions of a range of substituted aryl halides with **a** were examined (Table 2). The outputs of the domino reactions of **a** with aryl halides were strongly influenced by the electronic properties of the aryl halides. Functionalization of different C–H bonds with the formation of different cyclic compounds could be achieved by varying the electronic properties of the aryl halides. When substrate **a** reacted with aryl halides with substituents such as $COOC_2H_5$, COOMe, CHO, COMe, SO_2Me, and CN under the selected reaction conditions, the cyclic products **aa**–**ai** were obtained through the functionalization of the C–H bonds *ortho* to the C–halide groups of the incoming aryl halides (Table 2, entries 1–9). It is interesting to note that another type of cyclic products, **aj**–**al**, was isolated during treatment of **a** with aryl halides such as *p*-chlorophenylbromide, *p*-methylphenylbromide, and 1-iodobenzene, respectively. This clearly indicates that the formation of **aj**–**al** is through the functionalization of both sp^3 C–H and sp^2 C–H bonds (Table 2, entries 10–12), although the output of the reaction of **a** with *p*-methylphenylbromide is low. The structures of the different C–H functionalization products could be determined by analysis of their corresponding ^1H NMR spectra. For example, the protons (Ha, Hb) of the N–C*H*– group of product **ai** resonate at $\delta = 3.94$ and 3.63 ppm, whereas the corresponding protons

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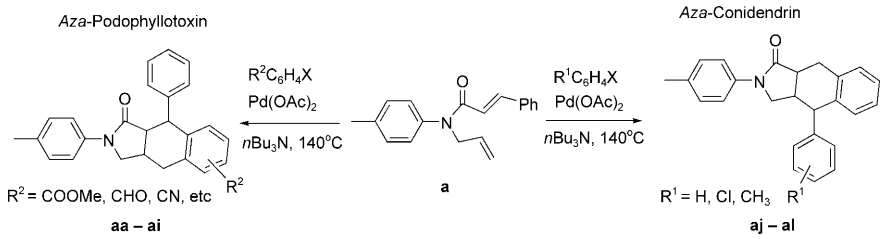
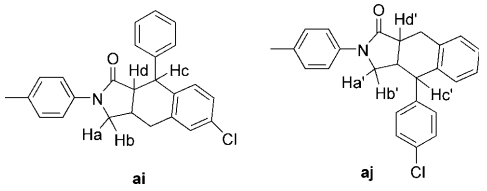
Table 2. Palladium-catalyzed domino reaction of aryl halides with **a**.[a]



Entry	R^n (n = 1,2)	$R^nC_6H_4X$	Product	Yield [%][b]
1	–	α-naphthalenyl–Br	**aa**	82
2	$COOC_2H_5$	p-$CH_3CH_2OOCC_6H_4Br$	**ab**	79
3	COOMe	p-$CH_3OOCC_6H_4Br$	**ac**	70
4	CHO	p-$OHCC_6H_4Br$	**ad**	41
5	CN	p-NCC_6H_4Br	**ae**	45
6	COMe	p-$CH_3OCC_6H_4Br$	**af**	65
7	SO_2Me	p-$CH_3O_2SC_6H_4Br$	**ag**	78
8	CN	m-NCC_6H_4Br	**ah**	55
9	Cl	m-ClC_6H_4Br	**ai**	62
10	Cl	p-ClC_6H_4Br	**aj**	58
11	Me	p-$CH_3C_6H_4Br$	**ak**	5[c]
12	H	C_6H_5I	**al**	54

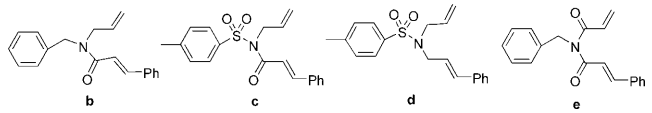
[a] General conditions: **a** (1.0 equiv), $R^nC_6H_4X$ (X = Br, I; 1.1 equiv), $Pd(OAc)_2$ (2 mol %), PPh_3 (4 mol %), (nBu)$_3$N (1.2 equiv), DMF (10 mL), 140 °C. [b] Yield of isolated product after flash column chromatography. [c] Other products of this reaction.



(Ha′, Hb′) of product **aj** resonate at $\delta = 3.86$ and 3.38 ppm. At the same time, the protons (Hc) of the Ar–C*H*– group of product **ai** give signals at $\delta = 4.27$ ppm, whereas the corresponding protons (Hc′) of the Ar–C*H*– group of product **aj** appear at $\delta = 3.23$ ppm. The proton (Hd) of the O=C–C*H*– group in **ai** exhibits a chemical shift at $\delta = 3.10$ ppm, whereas the corresponding proton (Hd′) of the O=C–C*H*– group in **aj** resonates at $\delta = 3.71$ ppm. These differences may result from the different electronic properties of the corresponding protons. The structures of **ae** and **al** were further determined by X-ray crystallography (Figures 1 and 2), and are in agreement with the ^{1}H NMR spectroscopic results. The above results clearly indicate that the C–H bond functionalization can be controlled by selecting treatment of different aryl halides with 1,6-dienes.

Domino Reaction of Different 1,6-Dienes with Aryl Halides

To search for the effect of dienes on C–H functionalization, and to search for the generality of the method for the preparation of the more functionalized aza-podophyllotoxin/aza-conidendrin derivatives, we studied the reactions of different 1,6-dienes (**b**–**e**) with aryl halides. The results are shown in Table 3. The results indicate that different aza-podophyllotoxin could be constructed in 'one pot' with good yields by running the reaction of the corresponding dienes with aryl halides (Table 3, entries 1, 2, and 5–11). However, the reaction of dienes **c** either with α-naphthalenylbromide or with 1-iodobenzene produced the corresponding tricyclic compounds **ca** (30 %) or **cb** (25 %) in relatively low yields (Table 3, entries 3 and 4), thus indicating electronic effects on the outputs



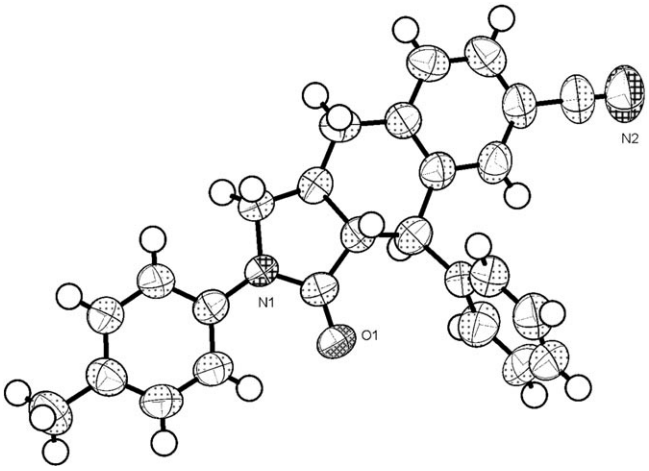


Figure 1. Molecular structure of compound **ae**.

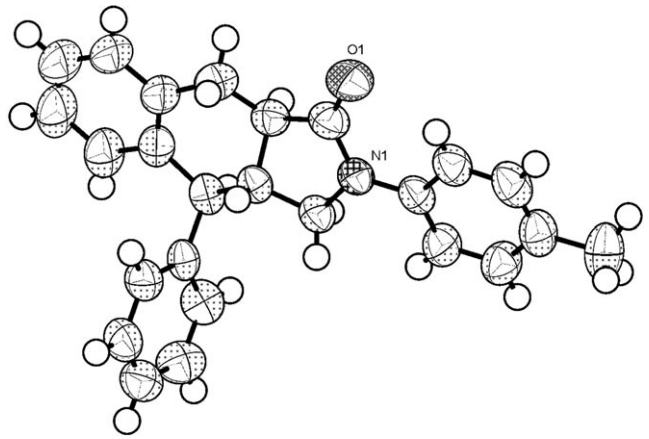
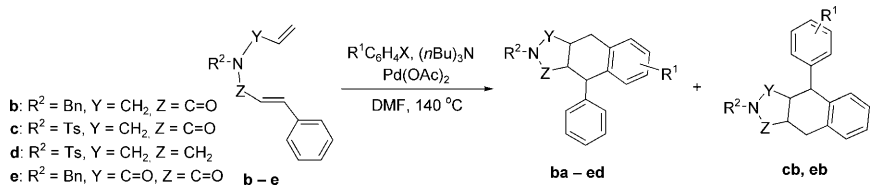


Figure 2. Molecular structure of compound **al**.

Table 3. Domino reaction for the construction of the multicyclic heterocycles.[a]



Entry	Dienes	$R^1C_6H_4X$	*t* [h]	Product	Yield [%][b]
1	**b**	*p*-$CH_3CH_2OOCC_6H_4Br$	20	**ba**	79
2	**b**	α-naphthalenyl–Br	20	**bb**	80
3	**c**	α-naphthalenyl–Br	20	**ca**	30
4	**c**	C_6H_5I	20	**cb**	25
5	**d**	α-naphthalenyl–Br	20	**da**	75
6	**d**	*p*-$CH_3OC_6H_4Br$	20	**db**	60
7	**e**	C_6H_5Br	18	**ea**	82
8	**e**	C_6H_5I	18	**eb**	84
9	**e**	*p*-$CH_3OC_6H_4Br$	18	**ec**	35
10	**e**	*p*-$HOCC_6H_4Br$	18	**ed**	59
11	**e**	*p*-$CH_3CH_2OOCC_6H_4Br$	18	**ee**	75

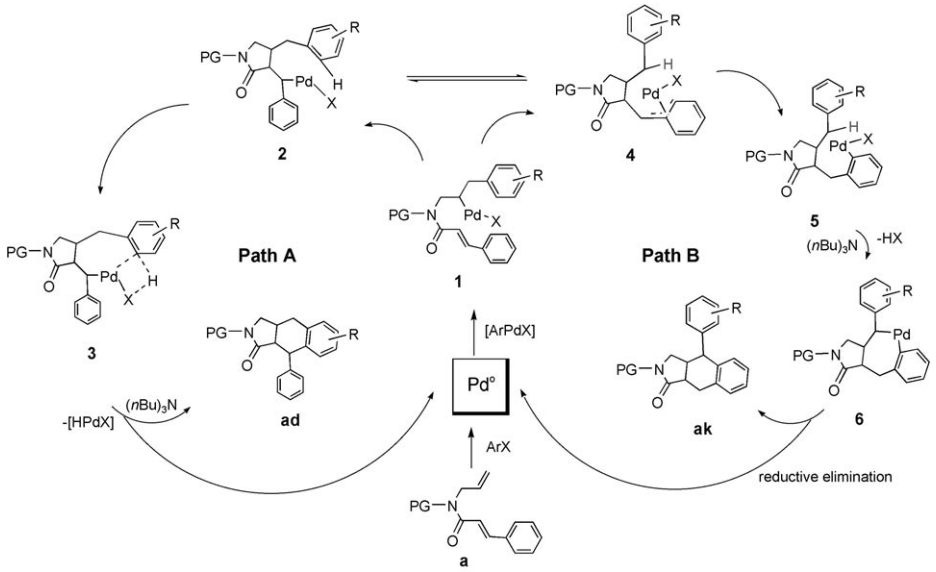
[a] General conditions: **b–e** (1.0 equiv), $R^1C_6H_4X$ (X = Br, I; 1.1 equiv), $Pd(OAc)_2$ (2 mol%), PPh_3 (4 mol%), $(n-Bu)_3N$ (1.2 equiv), DMF (10 mL), 140 °C. [b] Yield of isolated product after flash column chromatography.

All the resulting tri- and tetracyclic compounds were confirmed by one- (^1H, ^{13}C) and two-dimensional (COSY) NMR spectra, and elemental or HRMS analyses. The representative compounds of **ae** and **al** were additionally characterized by X-ray crystallographic analyses (Figures 1 and 2). Further details can be found in the Supporting Information (see also the Experimental Section).[20] Although racemic products were obtained in all cases, it is interesting to note that *trans*-oriented 5,6-ring systems were obtained in all of the reactions of dienes with aryl halides. The X-ray crystal structures proved the stereochemistry.

of the reaction. It was found that the tricyclic compounds were formed by means of functionalization of the C–H bond *ortho* to the C–halide groups of the incoming aryl halides in most cases. However, the formation of products **cb** and **eb** was clearly through the functionalization of both the sp^3- and sp^2-hybridized C–H bonds as shown by the ^1H NMR spectra of the products. Comparison of products **cb** and **ea**, which were formed from the reaction of diene **c** or **e** with 1-iodobenzene, respectively, indicated that the electronic properties of the diene substrate also influenced the regioselectivity of the functionalization of the C–H bond, and produced different C–H bond functionalization products. Again, the electronic effect of the aryl halides that influence the regioselectivity of the functionalization of the C–H bond was found by analyzing the ^1H NMR spectra of products **ea** to **ed**, and the C–H bond functionalization for the formation of product **eb** was clearly different to that of the formation of products **ea**, **ec**, and **ed**. As shown in Table 3, we can also conclude that different diene substrates have a great deal of influence on the domino reaction. The outputs of the reaction of substrates **c** and **d** with aryl halides were much lower than those of the reactions of **b** and **e** with aryl halides, which is probably as a result of the existence of strong electron-withdrawing groups such as *p*-toluenesulfonyl (Ts).

Mechanism

Two proposed catalytic cycle pathways for the formation of the multicyclic compounds are shown in Scheme 2. The selective insertion of aryl–palladium(II) halide into the allyl moiety of **a** produced intermediate **1**, which then reacted with the carbon–carbon double bond through a carbopalladation reaction to afford **2** or **4**. σ-Bond metathesis[20] onto the different C–H bonds in **3** or **5** via intermediates **2** or **4**, which are in equilibrium depending on the electronic properties of the aryl halides, generated the final products **ad** or **ak**, respectively. The reaction of dienes with aryl halides that



Scheme 2. Proposed mechanistic pathways for the formation of different multicyclic compounds (PG = protecting group).

have an electron-withdrawing substituent produced products of type **ad**, whereas the reaction of dienes with 1-iodobenzene or the aryl halides with electron-donating properties gave products of type **ak**. When the less-hindered olefin was used, the Heck reaction as the first step to form the substituted phenyl functionalized 1,6-dienes was proposed. Thus, the C–H bond functionalization[21] could be controlled by selecting differently substituted aromatic halides.

Conclusion

In summary, we have developed an efficient method with good yields for the synthesis of aza-podophyllotoxin/aza-conidendrin derivatives related to natural products through a domino cyclization of 1,6-dienes with aryl halides in the presence of a $Pd(OAc)_2/PPh_3/N(n\text{Bu})_3$ catalytic system under mild conditions. The catalytic system has the advantage of a tolerance towards a wide range of dienes and aryl halides. However, the electronic properties of the substituents on the aryl halides have a great influence on the regioselectivity of the C–H functionalization, thus producing different tricyclic compounds. The C–H functionalization occurred on the phenyl ring (*ortho* to the C–X groups) of incoming aryl halides that incorporate electron-withdrawing groups when they were treated with the corresponding dienes, and the functionalization of both the sp^3- and sp^2-hybridized C–H bonds happened when they were treated with 1-iodobenzene or aryl halides with electron-donating groups on the phenyl ring. Further study of the tandem reaction for the synthesis of more complex products and their biological activity tests are now in progress in our laboratory.

Experimental Section

General

All the catalytic reactions were performed under an argon atmosphere using an oven-dried Schlenk flask. The chemicals were purchased from Alfa Aesar and Acros Chemicals. All solvents and materials were predried, redistilled, or recrystallized before use. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded using a Bruker Avance 300 spectrometer with $CDCl_3$ as the solvent. Chemical shifts are reported in ppm by assigning TMS resonance in the ^{1}H NMR spectra as $\delta = 0.00$ ppm and $CDCl_3$ resonance in the ^{13}C spectra as $\delta = 77.0$ ppm. All coupling constants (J values) were reported in Hz. Column chromatography was performed on silica gel (300–400 mesh). Melting points were determined using a Gallenkamp melting-point apparatus and are uncorrected. The FTIR spectra were recorded with KBr pellets in the 4000–400 cm^{-1} ranges using a Nicolet 5DX spectrometer. Mass spectra were performed using a Micromass GCT-MS. Two-dimensional NMR and HRMS spectroscopy were performed at the State-Authorized Analytical Center at the University of Science and Technology of China. X-ray crystallographic diffraction data of **ab**, **ae**, **al**, and **bb** were collected at room temperature using a Bruker SMART Apex CCD diffractometer with $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å) with a graphite monochromator using the ω-scan mode. Data reductions and absorption corrections were performed with SAINT and SADABS software, respectively.[22] The structure was solved by direct methods and refined on F^2 by full-matrix least squares using SHELXTL.[23] All non-hydrogen atoms were treated anisotropically. The positions of hydrogen atoms were generated geometrically.

Synthesis

A typical procedure for the palladium-catalyzed domino reaction of the linear 1,6-dienes with aryl halides: substrate **a** (1.38 g, 5 mmol), 1-iodobenzene (1.22 g, 6 mmol), $Pd(OAc)_2$ (18.2 mg, 0.05 mmol), and PPh_3 (25.6 mg, 0.1 mmol) were added to the degassed solution of $(n\text{Bu})_3N$ (1.56 mL, 7.5 mmol) in DMF (10 mL). After the mixture was stirred for half an hour at room temperature, it was then heated at 140 °C for 24 h, and then quenched with water and extracted with AcOEt (3×5 mL). The combined organic layers were washed with hydrochloric acid (5%) and sodium carbonate (5%), and saturated with sodium chloride solution. After separation, the organic layer was dried with $MgSO_4$ and then concentrated. The residue was purified by flash column chromatography (6:1 petroleum ether/AcOEt) to give the corresponding product.

X-ray Crystallographic Analysis

CCDC-679144 (**ab**), -679145 (**al**), -679146 (**ae**), and -679148 (**bb**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre at www.ccdc.cam.ac.uk/data_request/cif

Acknowledgements

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