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Studies on Pd^0-Catalyzed Cyclization of *N*-3,4-Alkadienyl Toluenesulfonamides with Organic Halides: Selective Synthesis of 2,3-Dihydropyrroles, 1,2,3,6-Tetrahydropyrridines, and Azetidines

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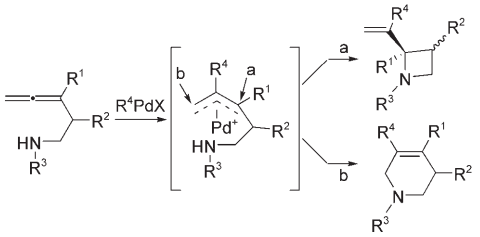
Abstract: The palladium-catalyzed coupling–cyclization of β-amino allenes with organic halides ranging from aryl halide to 1-alkenyl halide was studied. 2,3-Dihydro-1*H*-pyrroles were obtained by reaction of 3-substituted-5-unsubstituted-3,4-allenyl amides under conditions A, while the reaction of 5-substituted-3,4-allenyl amides afforded 1,2,5,6-tetrahydropyridines and/or azetidines with high *de* under conditions B or C. The skeleton and relative configuration of the six-membered products were established by the X-ray diffraction studies of **10ka**. Allenyl amide **4q** reacted with 1,4-diiodobenzene **6r** to afford double cyclization product **15**. The structure of its major stereoisomer was also determined by the X-ray diffraction study.

Keywords: allenes · amines · cross-coupling · cyclization · palladium

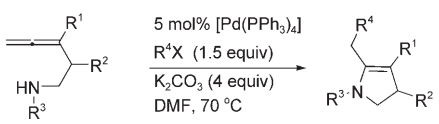
Introduction

Recently, much attention has been paid to the chemistry of allenes.[1,2] During the course of our systematic study on the chemistry of allenes[3] we noted that Hiemstra, Tanaka, Ibuke, and Kang reported on the palladium-catalyzed coupling–cyclization reaction of 3,4-dienyl amide derivatives with organic halides[4,5] or hypervalent iodonium salts[6] leading to the formation of azetidines and/or tetrahydropyridines with considerable selectivity. In these reactions, amino allenes undergo highly regioselective carbopalladation affording a π-allylic palladium intermediate,[7] which was followed by the intramolecular nucleophilic attack of the nitrogen group to give cyclic products (Scheme 1).



Scheme 1.

Recently, we have reported our own results on the Pd^0-catalyzed coupling–cyclization reaction of β-amino allenes with organic halides forming five-membered products, in which the substituent of the allene moiety as well as the nitrogen atom is a decisive factor for the determination of the reaction pathways for this intramolecular amination reaction, that is, with the introduction of R^1 group the reaction afforded 2,3-dihydropyrroles (Scheme 2).[8] Since many azetidines, dihydropyrroles or tetrahydropyridines show interesting biological activities[9] and are important building blocks in organic chemistry,[10] we wish to disclose our recent detailed study on the selective synthesis of these compounds via the Pd-catalyzed coupling cyclization of differently substituted β-amino allenes with organic halides.



Scheme 2.

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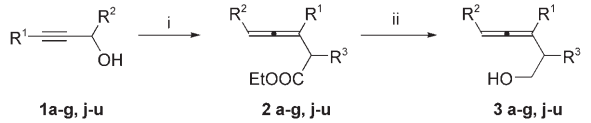
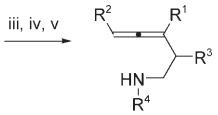
Results and Discussion

Preparation of the starting materials 4a–z: 3,4-Allenyl amides **4a–z** used in this study were prepared by Mitsunobu amination of the related 3,4-allenols,[11] which were prepared from the oxy-Cope rearrangement reaction of the corresponding propargylic alcohols (Table 1).[12]

Table 1. 3,4-Allenyl amides **4a–z** used in this study.



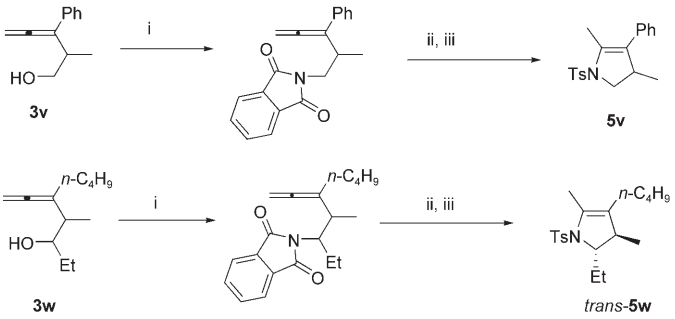


i) $R^3CH_2C(OEt)_3$, R^3CH_2COOH(cat), 140°C;
ii) $LiAlH_4$, THF, 0 °C – RT; iii) phthalimide, DEAD, PPh_3, THF, 0°C - RT; iv) $N_2H_4.H_2O$, MeOH, reflux;
v) NEt_3,CH_2Cl_2, R^4Cl, 0°C - RT

4	R^1	R^2	R^3	R^4
4a	*n*-C_4H_9	H	CH_3	Ts
4b	*n*-C_4H_9	H	H	Ts
4c	CH_3	H	CH_3	Ts
4d	*n*-C_7H_{15}	H	CH_3	Ts
4e	*t*-C_4H_9	H	CH_3	Ts
4f	*t*-C_4H_9	H	H	Ts
4g	*n*-C_4H_9	H	*n*-C_3H_7	Ts
4h	*n*-C_4H_9	H	CH_3	Ns
4i	*n*-C_4H_9	H	CH_3	Bz
4j	allyl	H	CH_3	Ts
4k	H	*n*-C_4H_9	CH_3	Ts
4l	H	*n*-C_3H_7	CH_3	Ts
4m	H	*n*-C_7H_{15}	CH_3	Ts
4n	H	CH_3	CH_3	Ts
4o	H	*i*-C_3H_7	CH_3	Ts
4p	H	*t*-C_4H_9	CH_3	Ts
4q	H	*n*-C_3H_7	C_2H_5	Ts
4r	H	*n*-C_3H_7	*n*-C_3H_7	Ts
4s	H	*i*-C_3H_7	C_2H_5	Ts
4t	H	*i*-C_3H_7	*n*-C_3H_7	Ts
4u	H	Bn	CH_3	Ts
4v	H	*n*-C_7H_{15}	CH_3	Ms
4w	H	*n*-C_7H_{15}	CH_3	Ac
4x	H	*n*-C_7H_{15}	CH_3	Bn
4y	H	*n*-C_7H_{15}	CH_3	Ns
4z	H	*n*-C_7H_{15}	CH_3	Bz

However, when 2-methyl-3-phenyl-3,4-pentadienol (**3v**) or 4-methyl-5-butyl-5,6-heptadien-3-ol (**3w**) were used, the cycloisomerization products, that is, 2,3-dihydropyrroles **5v** and *trans*-**5w** were formed directly (Scheme 3). The stereochemistry of *trans*-**5w** was unambiguously determined by the single crystal X-ray diffraction study (Figure 1).[14]

Palladium-catalyzed coupling–cyclization of 3-substituted-5-unsubstituted-3,4-allenyl amides with organic halides: Our initial study began with the reaction of *N*-(2-methyl-3-(*n*-butyl)-3,4-pentadienyl)toluenesulfonamide (**4a**) with 1.5 equiv of iodobenzene **6a** under conditions A for 7.5 h (conditions A = 5 mol% $[Pd(PPh_3)_4]$, 4 equiv K_2CO_3,



Scheme 3. i) Phthalimide, DEAD, PPh_3, THF, 0°C–RT; ii) $N_2H_4{\cdot}H_2O$, MeOH, reflux; iii) NEt_3, CH_2Cl_2, TsCl, 0°C–RT. DEAD = diethyl azodicarboxylate.

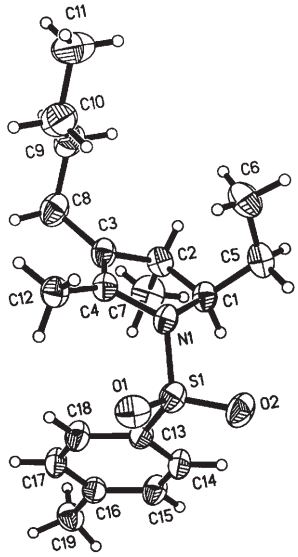
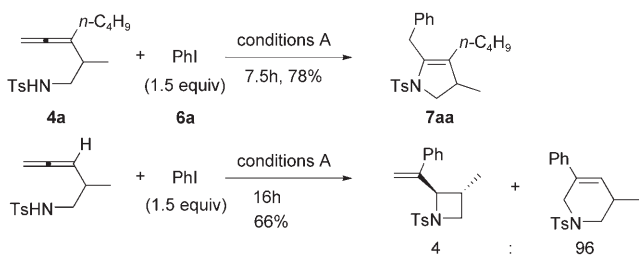


Figure 1. Molecular structure of **5w**.

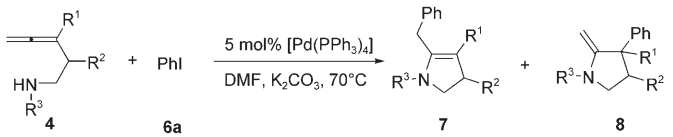
DMF, 70°C), which afforded five-membered product **7aa** in 78% yield together with less than 3% of other isomers.[8] This result is quite different from what was observed for *N*-(2-methyl-3,4-pentadienyl)toluenesulfonamide, where a mixture of the *trans*-four-membered and six-membered product with a ratio of 4:96 was formed,[4,5] indicating a dramatic effect of the substituent at the 3-position of 3,4-dienyl amides (Scheme 4).

Subsequently, the Pd^0-catalyzed coupling cyclization of 3-substituted-5-unsubstituted-3,4-allenyl amides with iodobenzene was performed under conditions A (Table 2). All reactions afforded five-membered products in good selectivity



Scheme 4.

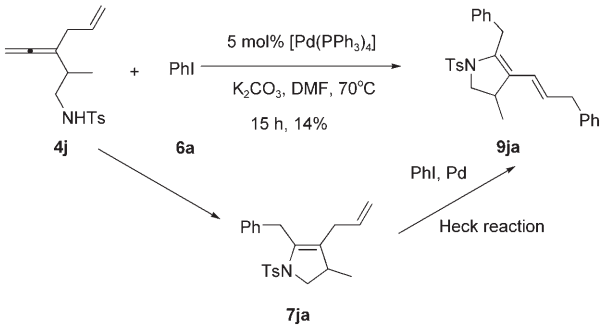
Table 2. Pd-Catalyzed coupling cyclization reaction of allenyl amides **4** with iodobenzene **6a**.[a]



Entry	R^1	R^2	R^3		t [h]	Yield isolated **7** [%]	Yield isolated **8** [%]
1	n-C_4H_9	CH_3	Ts	**4a**	7.5	78 (**7aa**)	–[b]
2	n-C_4H_9	H	Ts	**4b**	8	55 (**7ba**)	10 (**8ba**)
3	CH_3	CH_3	Ts	**4c**	12	66 (**7ca**)	11 (**8ca**)
4	n-C_7H_{15}	CH_3	Ts	**4d**	42	77 (**7da**)	6 (**8da**)
5	t-C_4H_9	CH_3	Ts	**4e**	16	76 (**7ea**)	0
6	t-C_4H_9	H	Ts	**4f**	48	65 (**7fa**)	0
7	n-C_4H_9	n-C_3H_7	Ts	**4g**	24	74 (**7ga**)	0
8	n-C_4H_9	CH_3	Ns	**4h**	5	55 (**7ha**)	0

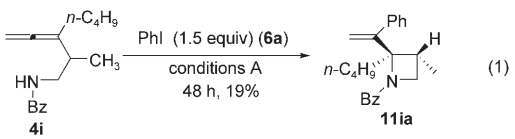
[a] The reaction was carried out with 0.30 mmol of allenyl amides **4**, 0.45 mmol of iodobenzene **6a**, 1.20 mmol of K_2CO_3, and 5 mol% $[Pd(PPh_3)_4]$ in DMF. [b] Other isomers was isolated in less than 3% yield.

and yields. It should be noted that the reactions of **4a–d** afforded a mixture of 2-methylenetetrahydropyrrole products **8aa–8da** and 2,3-dihydropyrrole products **7aa–7da** (entries 1–4, Table 2). With the increased steric hindrance of R^1 or R^2, the regioselectivity increased affording 2,3-dihydropyrroles **7ea–7ga** as the only products (entries 5–7, Table 2). However, prolonged reaction time was necessary to achieve a high conversion due to the increased steric hindrance. Furthermore, it is interesting to note that when we used 2-methyl-3-allyl-3,4-pentadienyl amide (**4j**), the coupling–cyclization-Heck reaction product **9ja** was formed instead of the anticipated product **7ja** in 14% yield (Scheme 5). However, some of the compounds **7** are unstable.



Scheme 5.

Further studies showed that the protecting group of the amine functionality can also determine the reaction pathway. The reaction of N-Ns (Ns = 4-nitrobenzenesulfonyl) substituted β-allenyl amide **4h** afforded five-membered product **7ha** in 55% yield as the only product (compare entry 1 with 8, Table 2) while the reaction of N-Bz substituted 3,4-allenyl amide **4i** (Bz = benzoyl) afforded *trans*-azetidine **11ia** as the only product albeit in a low yield [Eq. (1)].

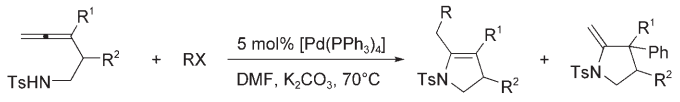


(1)

The coupling–cyclization reactions of 3-substituted-3,4-allenyl amides with different organic halides were performed with the results summarized in Table 3. Both electron-donating and electron-withdrawing aryl iodides can react with 3-substituted-3,4-allenyl amides to afford the corresponding 2,3-dihydropyrrole products **7** (and 2-methylenetetrahydropyrroles **8**) in good yields. The steric effect of the substituent in aryl iodides has limited influence on the outcome of the reaction: the reactions of 2-iodotoluene, 4-iodotoluene and 1-iodonaphthalene with **4a** produced the corresponding 2,3-dihydropyrroles in high yields (entries 4–6, Table 3). When the corresponding aryl bromides were applied, the corresponding products **7** (and **8**) were also isolated in good yields (entries 13–16, Table 3). Heteroaromatic halides, such as 2-iodothiophene, 2-bromopyridine, and alkenyl iodides, could also be used in this transformation (entries 17–21, Table 3). However, 1-alkynyl halides and aryl chlorides failed to react with the 3,4-allenyl amides to afford the expected products.

Palladium-catalyzed coupling–cyclization of 5-substituted-3,4-allenyl amides with organic halides: When we turned our attention to the 5-substituted-3-unsubstituted-3,4-allenyl amides, the reaction of the *N*-(2-methyl-3,4-nonadienyl)-toluenesulfonamide (**4k**) with iodobenzene **6a** under conditions A was firstly performed to afford a mixture of six-membered cyclic product **10ka** (60% *de*) and four-membered cyclic **11ka** in a combined 87% yield with a ratio of **10ka**/**11ka** being 96:4 (entry 1, Table 4). Further screening was performed in order to increase the diastereoselectivity for 2,5-disubstituted-1,2,5,6-tetrahydropyridine **10ka**.[13] In MeOH, **10ka** was formed in a good yield with a low diastereoselectivity (entry 2, Table 4). When we used CH_2Cl_2, acetonitrile, 1,4-dioxane, or THF as the solvent, better diastereoselectivity was observed (entries 3–6, Table 4). It is surprising that only the *cis*-1,2,3,5-tetrahydropyridine **10ka** was formed in triethylamine, though the yield was very low (entry 7, Table 4). The effect of the base on the reaction in toluene at 50°C was also studied (entries 9–14, Table 4). At last, after many screenings it was observed that **10ka** was formed in 41% yield with 97% *de* together with *trans*-*Z*-**11ka** in 12% yield with 100% *de* under conditions B (5 mol% $[Pd(PPh_3)_4]$, 4 equiv NaOH, toluene, 80°C) (entry 15, Table 4). The stereochemistry of the major isomer of **10ka** was unambiguously determined by the single crystal X-ray diffraction study (Figure 2).[15] The relative configuration of **11ka** was determined by an NOE study (Figure 3).[16] However, the yield of this reaction was low; therefore, we tried the reaction in some mixed solvents with NaOH as the

Table 3. Pd-Catalyzed coupling cyclization reaction of allenyl amides **4** with organic halides.[a]

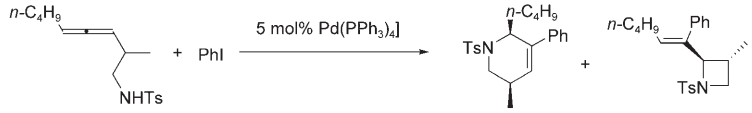


4 6 7 8

Entry	R^1	R^2		RX (**6**)	*t* [h]	Yield **7** [%]	Yield **8** [%]
1	*n*-C_4H_9	CH_3	**4a**	*p*-$MeOC_6H_4I$ (**6b**)	5.5	79 (**7ab**)	0
2	*n*-C_4H_9	CH_3	**4a**	*p*-$MeO_2CC_6H_4I$ (**6c**)	24	73 (**7ac**)	0
3	*n*-C_4H_9	CH_3	**4a**	*p*-BrC_6H_4I (**6d**)	10	82 (**7ad**)	0
4	*n*-C_4H_9	CH_3	**4a**	*o*-MeC_6H_4I (**6e**)	10	84 (**7ae**)	0
5	*n*-C_4H_9	CH_3	**4a**	*p*-MeC_6H_4I (**6f**)	8	83 (**7af**)	0
6	*n*-C_4H_9	CH_3	**4a**	1-iodonaphthalene (**6g**)	12	80 (**7ag**)	0
7	*n*-C_4H_9	H	**4b**	*p*-$MeOC_6H_4I$ (**6b**)	5.5	68 (**7bb**/**8bb**:86:14)[b]	
8	*n*-C_4H_9	H	**4b**	*p*-$MeO_2CC_6H_4I$ (**6c**)	10	77 (**7bc**/**8bc**:86:15)[b]	
9	*t*-C_4H_9	H	**4f**	*p*-$MeOC_6H_4I$ (**6b**)	60	77 (**7fb**)	0
10	*t*-C_4H_9	H	**4f**	*p*-$MeO_2CC_6H_4I$ (**6c**)	96	45 (**7fc**)	0
11	*n*-C_7H_{15}	CH_3	**4d**	*p*-NCC_6H_4I (**6h**)	60	61 (**7dh**)	0
12	*n*-C_7H_{15}	CH_3	**4d**	*p*-$CH_3COC_6H_4I$ (**6i**)	52	77 (**7di**)	0
13	*n*-C_7H_{15}	CH_3	**4d**	PhBr (**6j**)	16	64 (**7da**)	10 (**8da**)
14	*n*-C_7H_{15}	CH_3	**4d**	*o*-ClC_6H_4Br (**6j**)	58	80 (**7dj**)	0
15	*n*-C_7H_{15}	CH_3	**4d**	*p*-$MeOC_6H_4Br$ (**6k**)	36	63 (**7dk**)	0
16	*n*-C_7H_{15}	CH_3	**4d**	*p*-$NO_2C_6H_4Br$ (**6l**)	30	55 (**7dl**)	0
17	*n*-C_4H_9	CH_3	**4a**	2-iodothiophene (**6m**)	36	68 (**7am**)	0
18	*n*-C_4H_9	CH_3	**4a**	2-bromopyridine (**6n**)	12	68 (**7an**)	0

[a] The reaction was carried out at 70 °C with 0.30 mmol of allenyl amides **4**, 0.45 mmol of organic halide **6**, 1.20 mmol of K_2CO_3, and 5 mol % $[Pd(PPh_3)_4]$ in DMF. [b] Ratios were determined by ^1H NMR spectra (300 MHz).

Table 4. Pd-Catalyzed coupling cyclization reaction of *N*-(2-methyl-3,4-nonadienyl)toluenesulfonamide **4k** with iodobenzene **6a**.[a]



4k 6a 10ka 11ka

Entry	Base	*T* [°C]	Solvent	*t* [h]	Yield **10ka** [%]	*de* **10ka**	Yield **11ka** [%][b]	Recovered **4k** [%]
1	K_2CO_3	70	DMF	20	84	61	3	0
2	K_2CO_3	70	CH_3OH	100	76	65	0	0
3	K_2CO_3	70	CH_2Cl_2	100	64	73	7	trace
4	K_2CO_3	70	CH_3CN	100	68	71	7	0
5	K_2CO_3	70	1,4-dioxane	100	67	81	8	0
6	K_2CO_3	70	THF	100	58	89	6	0
7	Et_3N	70	Et_3N	100	5	>99:1	0	91
8	K_2CO_3	70	toluene	100	57	90	15	0
9	K_2CO_3	50	toluene	100	68	91	11	0
10	Et_3N	50	toluene	100	3	>99:1	0	81
11	NaH	50	toluene	100	28	97	7	0
12	KOH	50	toluene	100	42	92	39	0
13	Cs_2CO_3	50	toluene	100	48	89	6	15
14	NaOH	50	toluene	100	53	95	6	23
15	NaOH	80	toluene	100	41	97	12[c]	0
16	NaOH	30	toluene	100	48	81	17	0
17	NaOH	80	DMF	48	43	89	0	0
18	NaOH	80	toluene/DMF 1:1	48	57	70	0	0
19	NaOH	80	toluene/DMF 5:1	48	51	79	0	0
20	NaOH	80	toluene/DMF 10:1	48	59	87	trace	0
21	NaOH	80	toluene/DMF 20:1	48	50	95	3	0

[a] The reaction was carried out with 0.30 mmol of *N*-(2-methyl-3,4-nonadienyl)toluenesulfonamide **4k**, 0.45 mmol of iodobenzene **6a**, 1.20 mmol of base, and 5 mol % $[Pd(PPh_3)_4]$ in solution. [b] A mixture of isomers, unless otherwise stated. [c] Only the *trans*-*Z*-isomer was formed.

base to improve the yield (entries 18–21, Table 4). The product **10ka** was isolated in 50 % yield with 95 % *de* and **11ka** in 3 % yield with 89 % *de* under conditions C (5 mol % $[Pd(PPh_3)_4]$, 4 equiv NaOH, toluene/DMF 20:1, 80 °C) (entry 21, Table 4).

Subsequently, we studied the reaction of different 5-substituted 3,4-allenyl amides under conditions B or C (Table 5). The reaction afforded the related products in relatively low yields and high *de* under conditions B and higher yields and relatively low *de* under conditions C (Table 5). However, for R^1 = *i*Pr or *t*Bu, the reaction is more complicated. Interestingly for R^3 = Bz again only the four-membered compound **11za** was formed [compare Eq. (1) with entry 22 in Table 5]. The reaction of 6-phenyl-substituted amide **4u** afforded the carbopalladation–β-elimination product **12** in 38 % yield as the major product probably due to the presence of benzylic protons for the β-H elimination (Scheme 6).

When *N*-(2-methyl-3-butylocta-3,4-dienyl)-*p*-toluenesulfonamide (**13**)[17] was used under conditions B, the six-membered cyclic product **14** was isolated in 21 % yield [Eq. (2)].

Next we studied the scope for organic halides in this reactions with 3,4-allenyl amide **4l**. Iodobenzene worked better than bromobenzene (compare entry 1 of Table 6 with entries 3 and 4 of Table 5). Both electron-donating and electron-withdrawing aryl iodides could react with **4l** to afford the products in moderate yields and good *de* (entries 2–12, Table 6). Heteroaromatic halides such as 2-iodothiophene (entries 13 and 14, Table 6) or the alkenyl halides such as (*E*)-1-hexenyl iodide

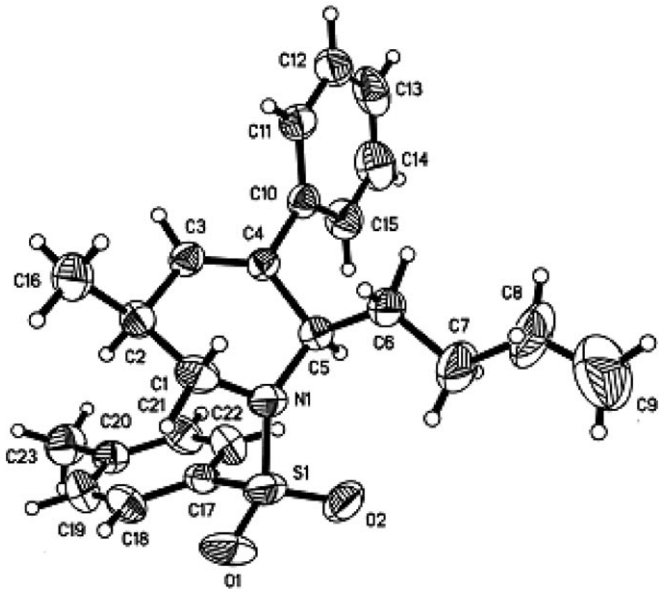


Figure 2. Molecular structure of **10ka**.

also smoothly reacted with **4l** (entries 15 and 16, Table 6). The results of [Pd(PPh$_3$)$_4$]-catalyzed reaction of *N*-(2-ethyl-3,4-octadienyl)toluenesulfonamide (**4q**) with 1,4-diiodobenzene **6r** afforded double cyclization product **15** (Scheme 7).

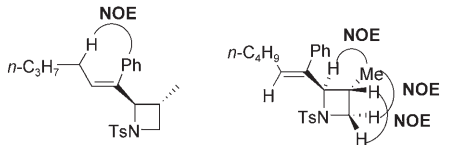
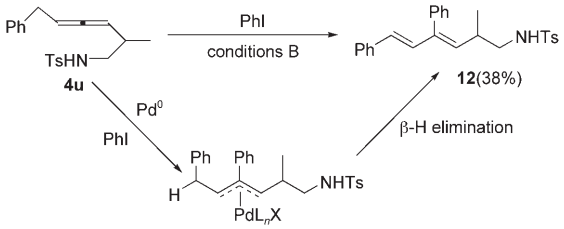


Figure 3.



Scheme 6.

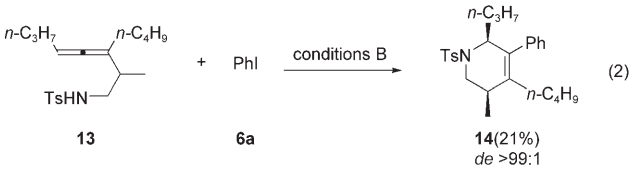
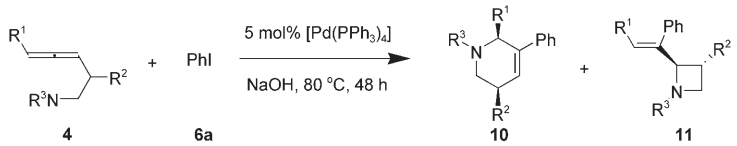


Table 5. Pd-Catalyzed coupling cyclization reaction of 5-monosubstituted-3,4-allenyl amides **4** with iodobenzene **6a**.[a]



Entry	R^1	R^2	R^3		Conditions[b]	Yield **10** [%]	*de* **10** [%]	Yield **11** [%]	*de* **11** [%]
1	n-C_4H_9	CH_3	Ts	**4k**	B	41 (**10ka**)	97	12 (**11ka**)	>99:1
2					C	50 (**10ka**)	95	3 (**11ka**)	>99:1
3	n-C_3H_7	CH_3	Ts	**4l**	B	42 (**10la**)	96	4 (**11la**)	>99:1
4					C	61 (**10la**)	86	3 (**11la**)	62
5	n-C_7H_{15}	CH_3	Ts	**4m**	B	35 (**10ma**)	95	9 (**11ma**)	>99:1
6					C	45 (**10ma**)	88	3 (**11ma**)	–[c]
7	CH_3	CH_3	Ts	**4n**	B	63 (**10na**)	86	trace	–
8	n-C_3H_7	C_2H_5	Ts	**4q**	B	36 (**10qa**)	90	13 (**11qa**)	>99:1
9					C	56 (**10qa**)	82	7 (**11qa**)	71
10	n-C_3H_7	n-C_3H_7	Ts	**4r**	B	37 (**10ra**)	89	17 (**11ra**)	>99:1
11					C	58 (**10ra**)	88	6 (**11ra**)	84
12	i-C_3H_7	C_2H_5	Ts	**4s**	B	7 (**10sa**)	>99:1	12 (**11sa**)	>99:1
13	i-C_3H_7	n-C_3H_7	Ts	**4t**	B	5(**10ta**)	>99:1	8 (**11ta**)	>99:1
14					C	7 (**10ta**)	>99:1	7 (**11ta**)	>99:1
15	n-C_7H_{15}	CH_3	Ms	**4v**	B	38 (**10va**)	>99:1	trace	–
16					C	39 (**10va**)	>99:1	trace	–
17	n-C_7H_{15}	CH_3	Ac	**4w**	B	15 (**10wa**)	>99:1	trace	–
18	n-C_7H_{15}	CH_3	Bn	**4x**	B	41 (**10xa**)	93	trace	–
19					C	49 (**10xa**)	>99:1	trace	–
20	n-C_7H_{15}	CH_3	Ns	**4y**	B	21 (**10ya**)	88	4 (**11ya**)	86
21					C	32 (**10ya**)	84	5 (**11ya**)	89
22	n-C_7H_{15}	CH_3	Bz	**4z**	B	trace	–	30 (**11za**)	>99:1

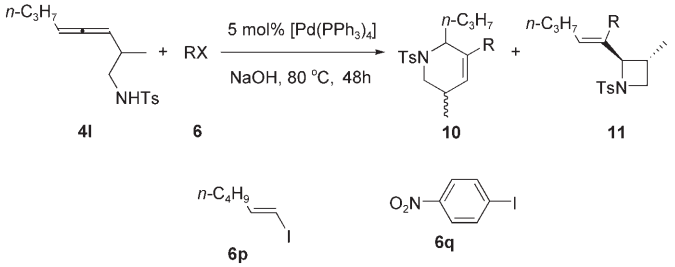
[a] The reaction was carried out with 0.30 mmol of 3,4-allenyl amides **4**, 0.45 mmol of iodobenzene **6a**, 1.20 mmol of NaOH, and 5 mol% [Pd(PPh$_3$)$_4$] in solvent (2 mL). [b] Conditions B: 5 mol% [Pd(PPh$_3$)$_4$], 4 equiv of NaOH, toluene, 80°C. Conditions C: 5 mol% [Pd(PPh$_3$)$_4$], 4 equiv of NaOH, toluene/DMF 20:1, 80°C. [c] A mixture of three isomers.

The stereochemistry of the major isomer of **15** was unambiguously determined by the single crystal X-ray diffraction study (Figure 4).[18]

Conclusion

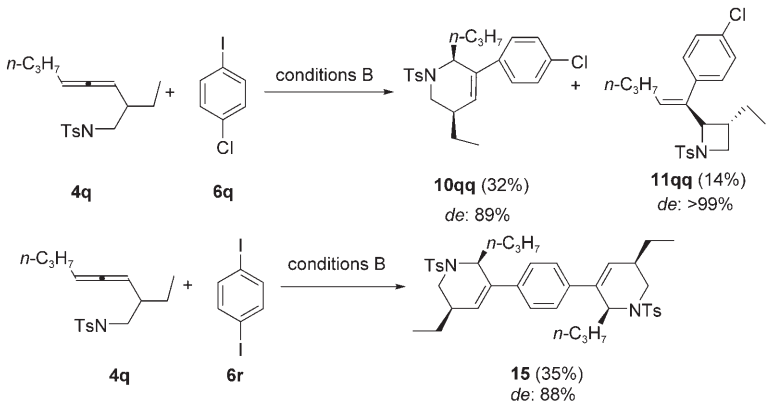
In summary, we have studied the Pd^0-catalyzed coupling–cyclization reaction of β-amino allenes with organic halides. The reaction of 3-substituted-3,4-allenyl amides afforded five-membered cyclic products while 5-substituted-3,4-allenyl toluenesulfonamides afforded a mixture of four- and six-membered products. The nature of the *N*-protecting group may also change the reaction pathway. The reaction may proceed via the carbopalladation forming π-allylic palladium intermediate or the nucleometallation–reductive elimination pathway.[1c] Further studies in this area are being conducted in our laboratory.

Table 6. Pd-Catalyzed coupling cyclization reaction of *N*-(2-methyl-3,4-octadienyl)toluenesulfonamide **4l** with organic halides **6**.[a]



Entry	RX	Conditions[b]	Yield **10** [%]	*de* **10** [%]	Yield **11** [%]	*de* **11** [%])
1	**6j**	B	12 (**10la**)	94	2 (**11la**)	>99:1
2	**6b**	B	40 (**10lb**)	92	5 (**11lb**)	94
3		C	55 (**10lb**)	85	4 (**11lb**)	64
4	**6f**	B	46 (**10lf**)	92	7 (**11lf**)	89
5		C	50 (**10lf**)	88	2 (**11lf**)	72
6	**6q**	B	14 (**10lq**)	>99:1	trace	–
7	**6i**	B	24 (**10li**)	85	trace	–
8		C	60 (**10li**)	73	trace	–
9	**6h**	B	28 (**10lh**)	88	trace	–
10		C	62 (**10lh**)	77	trace	–
11	**6g**	B	19 (**10lg**)	76	trace	–
12		C	31 (**10lg**)	61	trace	–
13	**6m**	B	37 (**10lm**)	89	5 (**11lg**)	>99:1
14		C	61 (**10lm**)	68	6 (**11lm**)	>99:1
15	**6p**	B	29 (**10lp**)	95	trace	–
16		C	53 (**10lp**)	90	trace	–

[a] The reaction was carried out with 0.30 mmol of *N*-(2-methyl-3,4-octadienyl)toluenesulfonamide **4l**, 0.45 mmol of organic halide **6**, 1.20 mmol of NaOH, and 5 mol% $[Pd(PPh_3)_4]$ in solvent (2.0 mL). [b] Conditions B: 5 mol% $[Pd(PPh_3)_4]$, 4 equiv of NaOH, toluene, 80°C. Conditions C: 5 mol% $[Pd(PPh_3)_4]$, 4 equiv of NaOH, toluene/DMF 20:1, 80°C.



Scheme 7.

Experimental Section

General methods: All the reactions were carried out under a nitrogen atmosphere with dry solvent under anhydrous conditions, unless otherwise indicated. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer with TMS as the internal standard. IR spectra were recorded on a Bruker Perkin–Elmer 983 spectrometer. MS spectra were recorded on a HP 5989A spectrometer. HRMS spectra were recorded on Finnigan MAT 8430 spectrometer. Flash-column chromatography was carried out on silica gel H (10–40 μ). Petroleum ether b.p. range 60–90°C. Yields refer to spectroscopically pure compounds, unless otherwise indicated.

3,4-Allenoates: Compounds **2a–v** were prepared from the oxy-Cope rearrangement reaction of the corresponding propargylic alcohols **1a–v**.[9]

Ethyl 2,3-dimethylpenta-3,4-dienoate (2c): Typical procedure I: A mixture of 2-butyn-1-ol (**1c**) (2.969 g, 42.4 mmol), triethyl orthopropionate (30 mL, 26.4 g, 150 mmol), and a catalytic amount of propanoic acid was heated at 140°C for 3 h. After being cooled to room temperature, flash chromatography on silica gel (petroleum ether/Et_2O 3:1) produced **2c** as a liquid (2.960 g, 64%). ^1H NMR (300 MHz, $CDCl_3$): δ = 4.70–4.60 (m, 2H), 4.12–4.02 (m, 2H), 2.91–2.82 (m, 1H), 1.65 (t, J=2.7 Hz, 3H), 1.26–1.07 (m, 6H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ=206.3, 174.0, 98.4, 75.8, 60.3, 42.9, 16.9, 15.4, 14.0; IR (neat): $\tilde{\nu}$ = 1960, 1735, 1453, 1181 cm^{-1}; MS: m/z (%): 155 (1.20) [M^++H], 139 (44.15) [M^+-CH_3], 111 (100); EI-HRMS: m/z: calcd for $C_9H_{14}O_2$: 154.09938; found 154.09978.

3,4-Allenols: Compounds **3a–v** were prepared via reduction of 3,4-allenates **2a–v** with $LiAlH_4$.

2-Methyl-3-(*n*-heptyl)penta-3,4-dienol (3d): Typical procedure II: A solution of 2-methyl-3-(*n*-heptyl)penta-3,4-dienoate (**2d**) (3.820 g, 16.0 mmol) in THF (30 mL) under cooling (ice bath) to a suspension of $LiAlH_4$ (0.734 g, 19.3 mmol) in THF (30 mL) was added dropwise. After addition, the mixture was allowed to warm up to room temperature. After the reaction was complete as monitored by TLC (petroleum ether/Et_2O 10:1), it was quenched with water, filtrated, washed with Et_2O for three times. Then the combined organic phase was washed with brine for three times and dried over anhydrous sodium sulfate. Evaporation and flash chromatography on silica gel (petroleum ether/Et_2O 5:1→1:1) produced **3d** as a liquid (1.909 g, 61%). ^1H NMR (300 MHz, $CDCl_3$): δ = 4.78–4.72 (m, 2H), 3.61–3.43 (m, 2H), 2.20–2.10 (m, 1H), 1.98–1.86 (m, 2H), 1.81 (brs, 1H), 1.57–1.18 (m, 10H), 1.03 (d, J=6.9 Hz, 3H), 0.87 (d, J=6.9 Hz, 3H); ^{13}C NMR (CD_3Cl, 75.4 MHz): δ=204.9, 105.5, 77.1, 66.2, 38.8, 31.8, 30.5, 29.3, 29.1, 27.6, 22.6, 16.1, 14.0; IR (neat): $\tilde{\nu}$ = 3346, 1953, 1458, 1378, 1032 cm^{-1}; MS: m/z (%): 196 (3.56) [M^+], 83 (100); elemental analysis calcd (%) for $C_{13}H_{24}O$: C 79.53, H 12.32; found: C 79.32, H 12.06; HRMS (EI): m/z: calcd for $C_{13}H_{24}O$: 196.18272; found 196.18175.

5-Butyl-4-methylocta-5,6-dien-3-ol (3w): 3-Butyl-2-methylpenta-3,4-dienol (**3a**) (1.766 g, 11.5 mmol) in CH_2Cl_2 (10 mL) was added to a solution of the Dess–Martin reagent (7.302 g, 17.2 mmol) in CH_2Cl_2 (25 mL). When the reaction was completed as monitored by TLC, the reaction was quenched with saturated aqueous solution of $Na_2S_2O_3$. Then the solution was washed subsequently with satd aq solution of $Na_2S_2O_3$ and satd

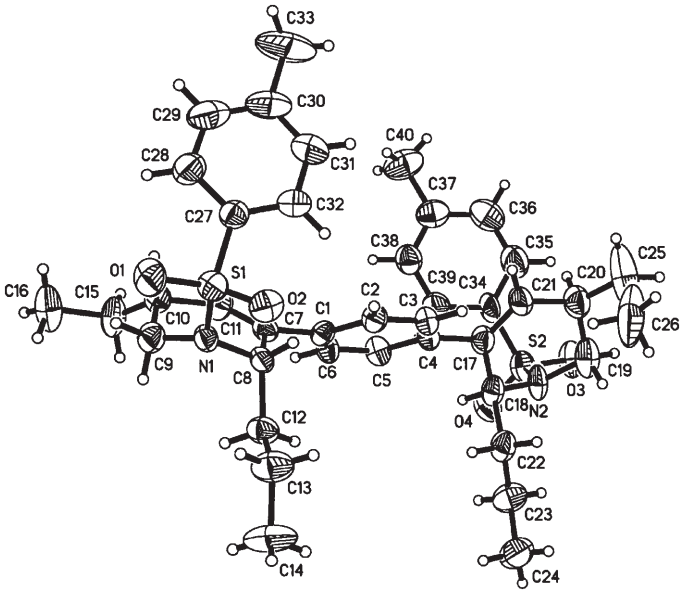


Figure 4. Molecular structure of the major stereoisomer of **15**.

aq solution of $NaHCO_3$. The combined organic extracts were dried over anhydrous magnesium sulfate. After filtration, the Grignard reagent, which was prepared via the reaction of EtBr (4.4 mL, 6.16 g, 56.5 mmol) with Mg turnings (1.38 g, 57.5 mmol) in THF (60 mL), was added dropwise to the solution at room temperature. The resulting solution was stirred under reflux. When the reaction was complete as monitored by TLC, it was quenched with water. The solution was brought to pH 3 by the addition of aqueous 1 N HCl and then extracted with Et_2O (3×50 mL). After evaporation, the filtrate was purified by flash chromatography on silica gel (petroleum ether/Et_2O 10:1→3:1) to afford **3w** as a liquid (1.252 g, 60%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.82–4.64 (m, 2H), 3.59–3.34 (m, 1H), 2.04–1.82 (m, 3H), 1.75 (brs, 1H), 1.52–1.26 (m, 6H), 0.99 (d, J=6.9 Hz, 3H), 0.94 (t, J=7.2 Hz, 3H), 0.88 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 205.6, 106.7, 77.2, 74.3, 40.9, 30.8, 29.7, 27.2, 22.4, 13.9, 12.6, 10.6; IR (neat): $\tilde{\nu}$ = 3390, 1956, 1463, 1150 cm^{-1}; MS: m/z (%): 182 (1.20) [M^+], 167 (39.99) [M^+-CH_3], 139 (35.59) [$M^+-C_3H_7$], 67 (100); EI-HRMS: m/z: calcd for $C_{12}H_{22}O$: 182.16706; found 182.16447.

3,4-Allenyl amides: Compounds **4a–z**, **5v**, **5w**, and **13** were prepared from the Mitsunobu amination of the related 3,4-allenols **3a–v**.

***N*-(2-Methyl-3-(*n*-heptyl)penta-3,4-dienyl)-*p*-toluenesulfonamide (4d)**: *Procedure III*: Diethyl azodicarboxylate (6.6 mL, 40% in toluene, 15.2 mmol) with cooling (ice bath) was added dropwise to a solution of 2-methylocta-2,3-dienol (**3d**) (1.690 g, 8.6 mmol), triphenylphosphine (4.060 g, 15.5 mmol), and phthalimide (1.313 g, 8.9 mmol) in anhydrous THF (40 mL). The resulting yellow solution was allowed to warm up to room temperature overnight. The solvent was removed in vacuo followed by the addition of ether. The resulting solid was filtered off. After evaporation, the filtrate was purified by flash chromatography on silica gel to afford the corresponding phthalimide (2.254 g).

A solution of the above phthalimide (2.250 g) and hydrazine hydrate (0.80 mL, 85% purity, 13.9 mmol) in dry MeOH (30 mL) was heated under reflux for 2 h resulting in the formation of a white precipitate. Then concentrated HCl (2.5 mL) was added with cooling (ice bath) and the precipitate was removed by filtration. The filtrate was brought to pH 13 by the addition of 1 N NaOH and extracted with Et_2O (3×50 mL). The combined extracts were dried over anhydrous magnesium sulfate. After evaporation, the crude product was used without further purification. To a solution of the above crude product and triethylamine (1.2 mL, 8.4 mmol) in dichloromethane (20 mL) was added tosyl chloride (1.541 g, 8.1 mmol) in one portion with cooling (ice bath). The mixture was allowed to warm up to room temperature overnight. After removal of the solvent, the mixture was submitted to flash chromatography on silica gel to produce **4d** as a liquid (1.801 g, 75%) (overall yield for three steps: 60%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.72 (d, J=8.1 Hz, 2H), 7.28 (d, J=8.1 Hz, 2H), 4.80–4.09 (m, 3H), 2.99–2.72 (m, 2H), 2.40 (s, 3H), 2.18–2.00 (m, 1H), 1.84–1.66 (m, 2H), 1.35–1.13 (m, 10H), 0.95 (d, J=6.6 Hz, 3H), 0.86 (t, J=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ=204.5, 143.2, 136.9, 129.6, 127.0, 105.5, 77.7, 47.0, 36.0, 31.7, 30.1, 29.2, 29.1, 27.4, 22.6, 21.4, 17.3, 14.0; IR (neat): $\tilde{\nu}$ = 3281, 1953, 1599, 1162 cm^{-1}; MS: m/z (%): 349 (0.75) [M^+], 194 (100); elemental analysis calcd for $C_{20}H_{31}NO_2S$ (%): C 68.72, H 8.94, N 4.01; found: C 68.89, H 8.87, N 3.85.

Pd^0-catalyzed coupling–cyclization reaction of 3,4-allenyl amides with organic halides: *Procedure IV*: A mixture of 3,4-allenyl amide **4** (0.3 mmol), organic halide **6** (0.45 mmol), K_2CO_3 (1.2 mmol), and [Pd(PPh_3)$_4$] (5 mol%) was stirred at 70°C in DMF (2 mL). When the reaction was completed as monitored by TLC (petroleum ether/Et_2O), the reaction mixture was diluted with Et_2O, washed with brine (3×10 mL), dried over Na_2SO_4, evaporated, and purified by flash chromatography on silica gel (petroleum ether/Et_2O 5:1) to afford the pure product.

5-Benzyl-3,4-dimethyl-1-(*p*-toluenesulfonyl)-2,3-dihydro-1*H*-pyrrole (7ca): The reaction of **4c** (0.086 g, 0.32 mmol) with iodobenzene **6a** (51 μL, 0.093 g, 0.46 mmol) afforded **7ca** (0.073 g, 66%), *trans*-**8ca** (0.009 g, 8.5%) and *cis*-**8ca** (0.003 g, 2.4%). **7ca**: solid; m.p. 100–101°C (*n*-hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47 (d, J=8.4 Hz, 2H), 7.29–7.07 (m, 7H), 3.83 (s, 2H), 3.90–3.77 (m, 1H), 3.11 (dd, J=6.9, 11.7 Hz, 1H), 2.33 (s, 3H), 2.31–2.24 (m, 1H), 1.56 (s, 3H), 0.63 (d, J=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ=143.2, 138.8, 134.6, 134.5, 129.3, 128.5, 128.3, 127.6, 127.3, 126.1, 56.4, 38.5, 31.9, 21.5, 18.1, 11.5; IR (neat): $\tilde{\nu}$ = 1598, 1453, 1342, 1167 cm^{-1}; MS: m/z (%): 341 (19.33) [M^+], 91 (100); elemental analysis calcd for $C_{20}H_{23}SNO_2$ (%): C 70.35, H 6.79, N 4.10; found: C 70.20, H 6.79, N 3.78.

3,4-Dimethyl-2-methylene-3-phenyl-1-(*p*-toluenesulfonyl)pyrrolidine (8ca): *trans*-**8ca**: liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.69 (d, J=8.7 Hz, 2H), 7.21 (d, J=8.7 Hz, 2H), 7.15–6.94 (m, 5H), 5.22 (d, J=1.5 Hz, 1H), 3.99 (d, J=1.5 Hz, 1H), 3.62 (dd, J=6.9, 9.9 Hz, 1H), 3.18 (dd, J=6.9, 9.3 Hz, 1H), 2.39 (s, 3H), 2.39–2.30 (m, 1H), 0.91 (s, 3H), 0.76 (d, J=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ=152.3, 144.7, 144.0, 129.7, 129.4, 128.0, 127.5, 126.9, 126.4, 92.0, 54.5, 53.7, 41.1, 21.6, 20.0, 12.3; IR (neat): $\tilde{\nu}$ = 1655, 1599, 1459, 1351, 1165 cm^{-1}; MS: m/z (%): 341 (2.01) [M^+], 131 (100); EI-HRMS: m/z: calcd for $C_{20}H_{23}SNO_2$: 341.14495; found 341.14258.

cis-**8ca**: liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.88 (d, J=8.4 Hz, 2H), 7.40 (d, J=8.4 Hz, 2H), 7.11–7.05 (m, 1H), 6.99–6.91 (m, 2H), 6.64–6.57 (m, 2H), 5.29 (d, J=1.8 Hz, 1H), 4.27 (d, J=1.8 Hz, 1H), 3.89 (dd, J=6.9, 9.6 Hz, 1H), 2.96 (dd, J=9.6, 11.1 Hz, 1H), 2.51 (s, 3H), 2.12–1.99 (m, 1H), 1.47 (s, 3H), 0.60 (d, J=6.9 Hz, 3H).

Pd^0-catalyzed coupling–cyclization reaction of 3,4-allenyl amides with organic halides under conditions B: *Procedure V*: A mixture of 3,4-allenyl amide **4** (0.3 mmol), aryl or vinyl halide **6** (0.45 mmol), NaOH (1.2 mmol), and [Pd(PPh_3)$_4$] (5 mol%) was stirred at 80°C in toluene (2 mL). When the reaction was complete as monitored by TLC (petroleum ether/Et_2O 5:1), the reaction mixture was diluted with Et_2O, washed with brine (3×10 mL), dried over Na_2SO_4, evaporated, and purified by flash chromatography on silica gel (petroleum ether/Et_2O 5:1) to afford the pure products.

***cis*-2-(*n*-Butyl)-5-methyl-3-phenyl-1-(*p*-toluenesulfonyl)-1,2,5,6-tetrahydropyridine (10ka)**: The reaction of **4k** (0.060 g, 0.20 mmol), iodobenzene **6a** (34 μL, 0.062 g, 0.30 mmol), NaOH (0.033 g, 0.83 mmol) and [Pd(PPh_3)$_4$] (0.013 g, 5 mol%) afforded **10ka** (0.031 g, 41%) and **11ka** (0.009 g, 12%). **10ka**: solid; m.p. 124–126°C (Et_2O); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.68 (d, J=8.4 Hz, 2H), 7.38–7.16 (m, 5H), 7.14 (d, J=8.1 Hz, 2H), 5.41 (s, 1H), 4.77 (t, J=2.1 Hz, 1H), 3.86 (dd, J=6.6, 14.7 Hz, 1H), 2.72 (dd, J=11.4, 14.7 Hz, 1H), 2.29 (s, 3H), 2.02–1.94 (m, 1H), 1.45–1.04 (m, 6H), 0.85 (d, J=6.9 Hz, 3H), 0.76 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ=143.0, 139.7, 139.2, 138.4, 129.4, 129.2, 128.6, 127.5, 126.9, 126.1, 55.1, 44.5, 32.9, 28.6, 27.8, 22.3, 21.5, 18.3, 14.0; IR (neat): $\tilde{\nu}$ = 1600, 1494, 1332, 1165, 1152 cm^{-1}; MS: m/z (%): 326 (100) [$M^+-C_4H_9$]; elemental analysis calcd (%) for $C_{23}H_{29}NO_2S$: C 72.02, H 7.62, N 3.65; found: C 72.12, H 7.74, N 3.48.

***trans*-3-Methyl-2-(1′-phenylhex-1′(*Z*)-enyl)-1-(*p*-toluenesulfonyl)azetidine (11ka)**: liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75 (d, J=8.4 Hz, 2H), 7.46–7.10 (m, 7H), 5.78 (t, J=7.5 Hz, 1H), 3.98 (d, J=7.2 Hz, 1H), 3.61 (t, J=8.1 Hz, 1H), 3.13 (t, J=7.8 Hz, 1H), 2.46 (s, 3H), 2.30–2.22 (m, 1H), 1.89–1.80 (m, 2H), 1.31–1.17 (m, 4H), 0.81 (t, J=7.2 Hz, 3H), 0.72 (d, J=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ=143.8, 138.5, 137.6, 132.5, 131.9, 129.6, 128.4, 128.0, 126.9, 75.7, 54.3, 31.7, 31.1, 29.7, 28.3, 22.2, 21.6, 17.6, 14.0; IR (neat): $\tilde{\nu}$ = 1347, 1162, 1090 cm^{-1}; MS: *m*/*z* (%): 384 (3.51) [M^++H], 326 (38.62) [M^+−C_4H_9], 91 (100); elemental analysis calcd (%) for $C_{23}H_{29}NO_2S$: C 72.02, H 7.62, N 3.65; found: C 71.63, H 7.63, N 3.52.

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[15] Crystal data for **10ka**: $C_{23}H_{29}NO_2S$, M_W=383.53, triclinic, space group $P\bar{1}$, $Mo_{K\alpha}$, final R indices [$I>2\sigma(I)$], $R1$=0.0509, $wR2$=0.0900, a=9.9649(7), b=14.2504(10), c=15.9793(11) Å, α=79.8620(10), β=83.890(2), γ=72.9800(10)°, V=2132.2(3) Å^3, T=293(2) K, Z=4, reflections collected/unique: 13129/9453 (R_{int}=0.0390), no observation [$I>2\sigma(I)$] 3877, parameters 585. CCDC-602380 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[18] Crystal data for **15**: $C_{40}H_{52}N_2O_4S_2$, M_s=688.96, triclinic, space group $P\bar{1}$, $Mo_{K\alpha}$, final R indices [$I>2\sigma(I)$], $R1$=0.0558, $wR2$=0.0751, a=10.3409(16), b=11.5838(18), c=16.899(3) Å, α=81.636(3), β=89.226(3), γ=81.647(3)°, V=1981.4(5) Å^3, T=293(2) K, Z=2, reflections collected/unique: 11715/8394 (R_{int}=0.0912), no observation [$I>2\sigma(I)$] 8394, parameters 455. CCDC-600503 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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