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Intramolecular Heck reactions of aryl chlorides with alkynes

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ABSTRACT

We have developed a reaction that affords the selective preparation of hexahydro-2*H*-pyrido[2,1-*a*]isoquinoline dienes, allenes, or alkenes via an intramolecular Heck cyclization of an aryl chloride with an alkyne. Tricyclic isoquinoline core structures of this nature are difficult to access by alternative methods. The unsaturated product formed can be partially controlled by choice of ligand and reaction solvent.

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1. Introduction

In the course of a lead optimization project, we wanted to prepare isoquinolines **1** and thought that the most straightforward route to this tricyclic system would be via an intramolecular Heck[1] reaction between an aryl chloride and an alkyne (Scheme 1). Heck substrates **2** would be readily available from a three-component, gold-catalyzed Mannich[2] reaction between readily accessible piperidines **3**, aldehydes, and alkynes.

The intramolecular Heck reaction in particular has been used extensively to access complex molecular frameworks and natural products with bioactive properties.[3] Challenging Heck reactions of this nature have traditionally been accomplished with iodides and bromides, as an oxidative addition of palladium occurs more readily with these substrates.[4] The use of aryl chlorides as Heck substrates is highly desirable, as aryl chlorides are more cost effective and readily available compared to alternative reagents. With significant advances made in catalysis by Fu,[5] Buchwald,[6] and others,[7] aryl chlorides are now widely used in Heck reactions. However, no Heck-based methods have been reported for the synthesis of isoquinolines **1** and very few methods exist in general for the construction of this tricyclic core.

Despite the known challenges, we set out to explore the intramolecular Heck strategy. Herein, we report a successful methodology to prepare hexahydro-2*H*-pyrido[2,1-*a*]isoquinolines **1** via an intramolecular Heck of aryl chlorides with alkynes. We note in this Letter that product formation for this particular Heck sequence depends upon the choice of phosphine ligand[8] and reaction solvent.

2. Initial results and discussion

We chose alkyne substrates **4** as a starting point for the exploration of the Heck reaction, because they could be readily prepared in one step from aryl piperidines **3**, readily accessed from commercially available reagents, via an efficient $AuBr_3$-catalyzed Mannich reaction carried out in H_2O (Scheme 2). After successfully preparing a number of alkyne substrates **4**, initial attempts at the intramolecular Heck were run using standard conditions for aryl chloride couplings from the literature. Conditions were explored at high temperatures on the bench and also with heating under microwave irradiation.[9] We quickly determined that the most effective protocol for this methodology was carried out at 140 °C in the microwave for 30 min. Having established a successful protocol for the intramolecular Heck of aryl chlorides and alkynes to form isoquinolines **5** and **6**, we next screened a number of ligands, bases, and solvents for further optimization. A number of trends emerged from our initial experiments. We noticed that conversion to the desired isoquinoline core was achieved using the following three catalytic systems: (1) palladium (II) acetate in the presence of 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (X-Phos), (2) palladium (II) acetate in the presence of diadamantyl-*n*-butylphosphine (AD_2BuP), and (3) bis(tri-*tert*-butylphosphine)palladium ($Pd(t\text{-}Bu_3P)_2$). While the Heck reaction could be carried out successfully in a number of solvents, we found that yields were optimal when the reaction was run in EtOAc.

To our surprise, we found that using solubilizing bases in place of Cs_2CO_3 for the Heck reaction, such as Cy_2NMe with $Pd_2(dba)_3$ as reported by Fu[10] failed to afford the desired tricyclic product. In fact, using Cy_2NMe with other catalytic systems, such as $Pd(OAc)_2/AD_2BuP$, a combination that consistently yields the desired product with Cs_2CO_3, also failed to give **5** or **6** (Scheme 2).

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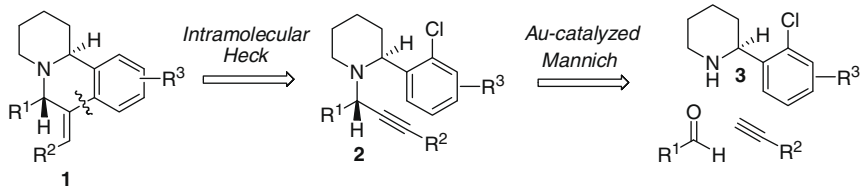
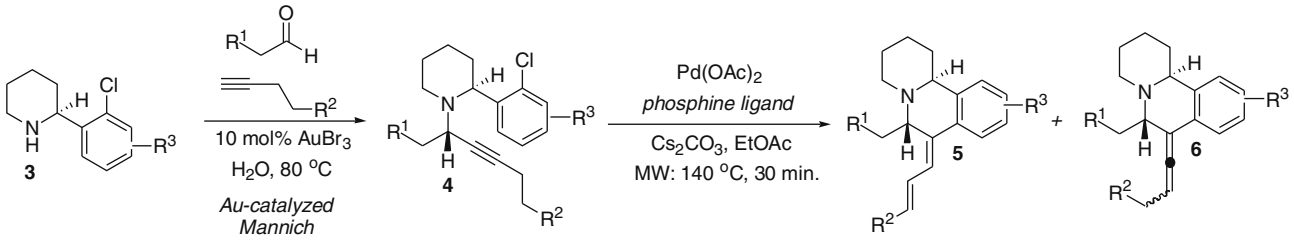


Scheme 1. Retrosynthesis of isoquinolines **1**.



Scheme 2. Intramolecular Heck cyclization of aryl chlorides with alkynes.

3. Aryl substitution

During the course of our reaction optimization with alkyne substrates **7**, prepared in high yield using the Au-catalyzed Mannich reaction with piperidine substrates **3**, isovaleraldehyde, and 5-methyl-1-hexyne, we discovered that both diene **8** and allene **9** (mixture of diastereomers) were formed in the product mixture (Table 1).[11,12] The product that was isolated as the major product depended upon the choice of phosphine ligand and solvent. Generally, we observed that using X-Phos invariably gave allenic products, while using the Pd(t-Bu_3P)$_2$ system afforded 1,3 dienes, and AD_2BuP gave allene predominantly with the exception of diene when R = CF_3. This observation suggests that the electronic nature of the aryl substituent plays an important role in influencing product formation.

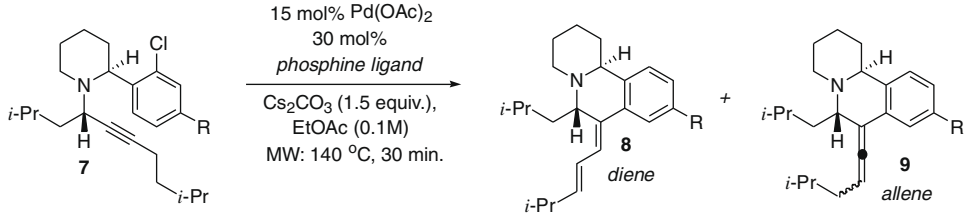
4. Alkyne substitution

What was particularly noteworthy was how varying the size and sterics of the acetylene alkyl substituent influences allene versus diene formation. Excellent yields were obtained for the Heck reaction of alkyne **10** and alkyne **13** where R = CF_3 using our standard microwave conditions in the presence of both AD_2BuP and X-Phos ligand systems (Tables 2 and 3). It is interesting to note that the Heck reaction of alkyne **10** in the presence of AD_2BuP gives a 2:1 mixture favoring diene **11** to allene **12**, while the Heck reaction under the same conditions in the presence of X-Phos affords a 4:1 mixture favoring allene **12** to diene **11**. To our surprise, low yields were obtained for all aryl chloride substrates where R^1 = H (Table 3, entries 3 and 4), presumably because electron-deficient systems are more activated toward the initial oxidative addition. Because formation of diene **14** was favored to allene **15** in all Heck reactions attempted for alkyne substrates **13**, it may be inferred that the structural configuration of the allene for the bulkier more crowded alkyne substituents is less energetically favorable.

5. Reaction in protic solvents

While screening a number of solvents during our Heck optimization of aryl chloride **16**, we discovered that when the reaction is carried out in the presence of a protic solvent, such as EtOH or *i*-

Table 1
Aryl substrate scope for the intramolecular Heck



Entry	R	Ligand	Major product	Yield (%)
1	CF_3	X-Phos	Allene **9**	78
2	CF_3	AD_2BuP	Diene **8**	76
3	CF_3	Pd(t-Bu_3P)$_2$	Diene **8**	56
4	H	X-Phos	Allene **9**	73
5	H	AD_2BuP	Allene **9**	81
6	H	Pd(t-Bu_3P)$_2$	Diene **8**	24[a]
7	OCH_3	X-Phos	Allene **9**	36
8	OCH_3	AD_2BuP	Allene **9**	18
9	OCH_3	Pd(t-Bu_3P)$_2$	Diene **8**	13

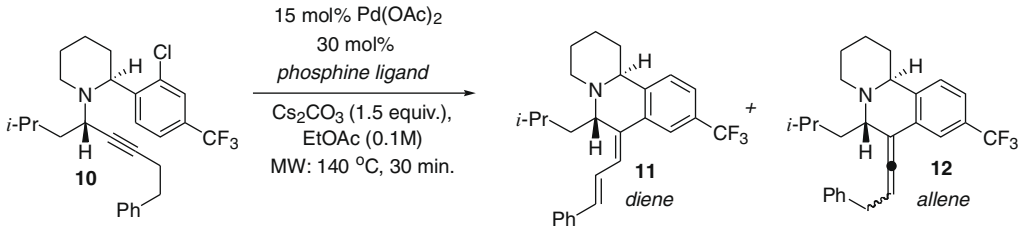
[a] 3:2 diene/allene product mixture.

PrOH, the major product formed via a reductive intramolecular Heck was alkene **17** (Table 4). We initially chose to run the reductive Heck in EtOH, because of its high microwave absorbing properties, but found that alkene yields were generally poor in the presence of EtOH under a number of conditions and substrates. We were pleased to find that the reductive Heck of alkyne substrates **16a** and **16d** affords alkene products **17a** and **17d**, respectively, in higher yield in the presence of *i*-PrOH when using AD_2BuP (Table 4, entries 4 and 5).[13,14] We were also pleased to find that the reductive Heck was successful using either X-Phos or AD_2BuP with a variety of alkyne substrates (**16b** and **16c**) in the presence of a protic solvent (Table 4, entries 2 and 3).

6. A more simplified isoquinoline system

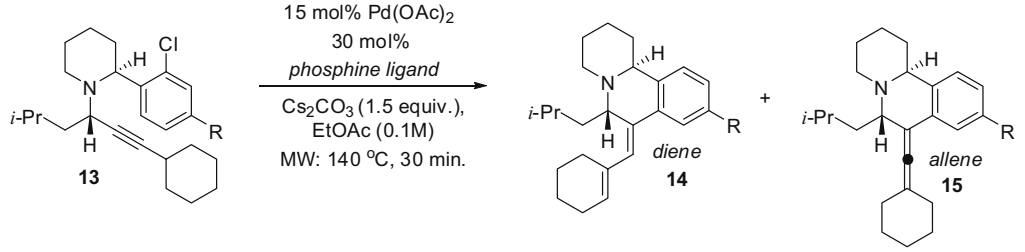
We also investigated the intramolecular Heck reaction of alkyne **18** to form a more simplified isoquinoline system (Table 5). Using our standard microwave conditions in the presence of either phosphine ligand AD_2BuP (entry 1) or X-Phos (entry 2) gave a 2:1 mixture of allene **20**:diene **19** favoring allene in high yield (99%), while employing

Table 2
Intramolecular Heck of substrate **10**



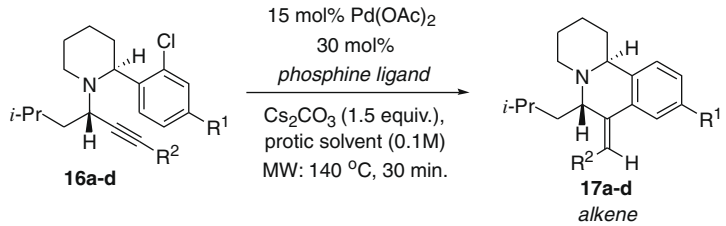
Entry	Ligand	Major product	Product ratio	Yield (%)
1	AD_2BuP	Diene **11**	2:1 diene/allene	62
2	X-Phos	Allene **12**	4:1 allene/diene	79

Table 3
Intramolecular Heck of substrates **13**



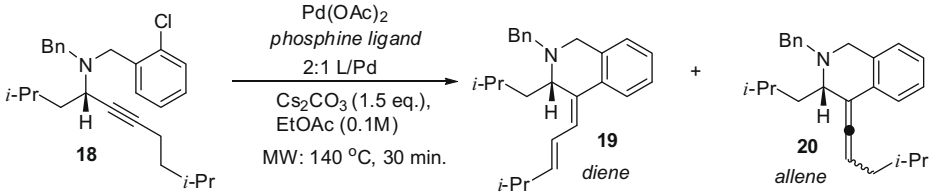
Entry	R	Ligand	Major product	Product ratio	Yield (%)
1	CF_3	X-Phos	Diene **14**	3:1 diene/allene	88
2	CF_3	AD_2BuP	Diene **14**	5:1 diene/allene	82
3	H	AD_2BuP	Diene **14**	—	36
4	H	X-Phos	Diene **14**	—	26

Table 4
Reductive Heck observed with substrates **16** in protic solvent



Entry	Substrate	R^1	R^2	Ligand	Solvent	Product	Yield%
1	**16a**	CF_3	$(CH_2)_2$*i*-Pr	X-Phos	EtOH	**17a**	19
2	**16b**	CF_3	Cy	AD_2BuP	EtOH	**17b**	10
3	**16c**	CF_3	$(CH_2)_2$Ph	X-Phos	EtOH	**17c**	29
4	**16a**	CF_3	$(CH_2)_2$*i*-Pr	AD_2BuP	IPA	**17a**	70
5	**16d**	H	$(CH_2)_2$*i*-Pr	AD_2BuP	IPA	**17d**	80

Table 5
Intramolecular Heck to form a more simplified isoquinoline system

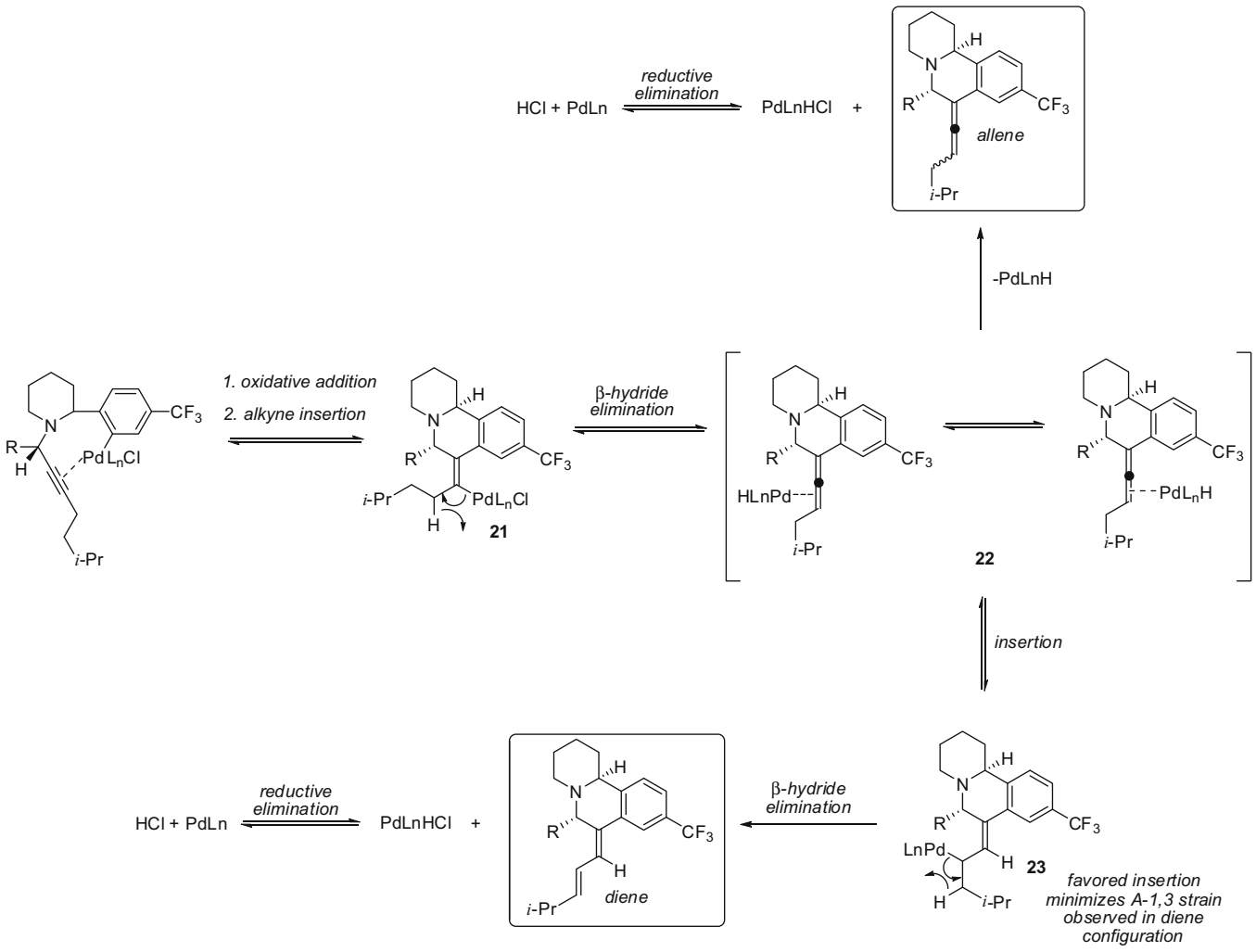


Entry	Ligand	Product ratio	Yield (%)
1	AD_2BuP	2:1 allene/diene	99
2	X-Phos	2:1 allene/diene	72
3	$Pd(t\text{-}Bu_3P)_2$	Diene (predominantly)	37

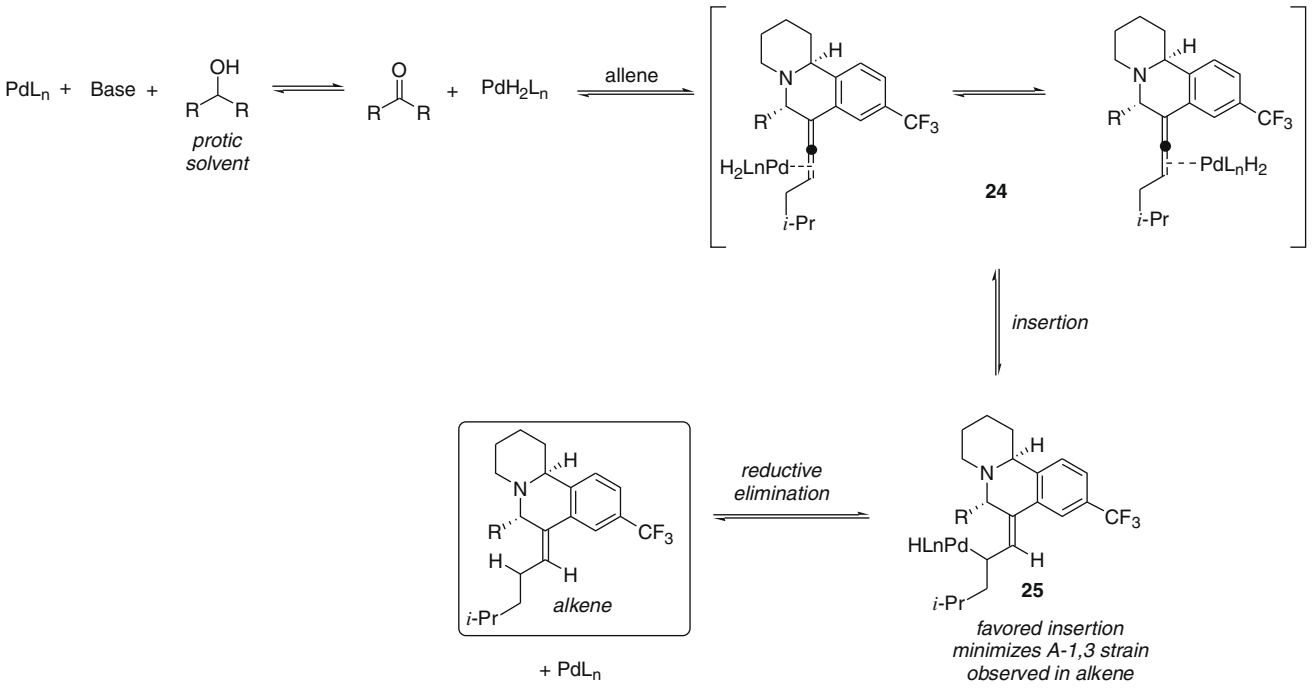
our microwave conditions with Fu's $Pd(t\text{-}Bu_3P)_2$ system afforded predominantly diene **19**, albeit in lower yield (Table 5, entry 3).[15]

7. Proposed mechanisms

We have proposed plausible mechanisms to account for the formation of both allene and diene products observed in (Scheme 3).[16] We propose that the formation of the allene occurs via an initial oxidative addition and an insertion of the resulting palladium species into the alkyne to form intermediate **21**. A β-hydride elimination leads to intermediate **22**, which can give allene directly or result in a subsequent insertion to form intermediate **23**. A second β-hydride elimination then leads to the observed diene product. The insertion step could occur from either face of the allene, but the preferred insertion leading to intermediate **23** avoids A-(1,3) strain between the aryl ring attached to the quinoline system and large alkyl substituent. The configuration of the isolated diene was confirmed by NOESY experiments.



Scheme 3. Proposed mechanisms for allene and diene formation.



Scheme 4. Proposed mechanism for the reductive Heck.

We have also proposed a plausible mechanism for the reductive Heck that accounts for alkene formation in the presence of a protic solvent (Scheme 4). Formation of the alkene could proceed via a three-step sequence: coordination of a dihydro palladium species (formed in a protic solvent with base) to the resulting allene initially formed (Scheme 3) to give intermediate **24**, followed by Pd-H insertion to give intermediate **25**, which undergoes a reductive elimination to form the observed alkene. The insertion step leading to intermediate **25** would again occur to minimize A-(1,3) strain between the aryl ring attached to the isoquinoline system and large alkyl substituent.

8. Conclusions

In summary, we have discovered an intramolecular Heck cyclization for the preparation of hexahydro-2*H*-pyrido[2,1-*a*]isoquinolines. Product formation may partially be controlled by the choice of phosphine ligand and solvent. In addition, we have applied these Heck conditions to form a more simplified isoquinoline system and are currently working to expand the scope and generality of this reaction to gain a better understanding of the mechanisms that influence product formation.

Acknowledgments

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11. Experimental procedure for the formation of allene **9** (Table 1, entry 1): A mixture of 2-(2-chloro-4-trifluoromethyl-phenyl)-1-(1-isobutyl-6-methyl-hept-2-ynyl)-piperidine (122 mg, 0.28 mmol), Pd(OAc)$_2$ (9.6 mg, 0.043 mmol), X-Phos (41 mg, 0.085 mmol), and Cs_2CO_3 (139 mg, 0.43 mmol) in ethyl acetate (2.8 mL) was irradiated in the Biotage Initiator microwave at 140 °C for 30 minutes. The reaction mixture was filtered over Celite and the solvent removed from the filtrate in vacuo. The crude residue was purified by flash chromatography (0–15% EtOAc/hexane) to afford 87 mg (78%) of allene **9** (mixture if diastereomers) as an oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.35 (d, *J* = 8.2 Hz, 1H), 7.29 (d, *J* = 8.1 Hz,1H), 5.46 (t, *J* = 7.4 Hz, 1H), 3.87 (d, *J* = 6.3 Hz, 1H), 3.50 (dd, *J* = 9.5, 4.6 Hz, 1H), 2.80–2.56 (m, 2H), 2.20–2.10 (m, 2H), 2.12–1.97 (m, 2H), 1.91–1.80 (m, 1H), 1.80–1.42 (m, 3H), 1.38–1.23 (m, 2H), 1.04 (d, *J* = 6.8 Hz, 2H), 0.94 (d, *J* = 6.9 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.86 (d, *J* = 5.1 Hz, 3H), 0.79 (d, *J* = 6.2 Hz, 3H); MS (ESI+): calcd [M+H]$^+$ 392, obs. 392.
12. *Experimental procedure for the formation of diene* **8** (Table 1, entry 2): A mixture of 2-(2-chloro-4-trifluoromethyl-phenyl)-1-(1-isobutyl-6-methyl-hept-2-ynyl)-piperidine (116 mg, 0.27 mmol), Pd(OAc)$_2$ (9.2 mg, 0.041 mmol), AD_2BuP (29 mg, 0.082 mmol), and Cs_2CO_3 (133 mg, 0.41 mmol) in ethyl acetate (2.7 mL) was irradiated in the Biotage Initiator microwave at 140 °C for 30 minutes. The reaction mixture was filtered over Celite and the solvent removed from the filtrate in vacuo. The crude residue was purified by flash chromatography (0–15% EtOAc/hexane) to afford 81 mg (76%) of diene **8** as an oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.39 (d, *J* = 7.9 Hz, 1H), 7.28 (d, *J* = 8.2 Hz, 1H), 6.61 (d, *J* = 10.9 Hz, 1H), 6.33 (dd, *J* = 14.5, 11.6 Hz, 1H), 5.91 (dd, *J* = 15.0, 6.5 Hz, 1H), 3.87 (d, *J* = 9.7 Hz, 1H), 3.69 (d, *J* = 5.1 Hz, 1H), 2.82–2.71 (m, 1H), 2.70–2.61 (m, 1H), 2.41 (qt, *J* = 13.0, 6.6 Hz, 1H), 2.16 (d, *J* = 12.0 Hz, 1H), 1.81–1.68 (m, 1H), 1.67–1.61 (m, 2H), 1.60–1.51 (m, 1H), 1.52–1.34 (m, 3H), 1.08–1.00 (m, 1H), 1.04 (d, *J* = 6.8 Hz, 6H), 0.96 (d, *J* = 5.9 Hz, 3H), 0.79 (d, *J* = 6.3 Hz, 3H); MS (ESI+): calcd [M+H]$^+$ 392, obs. 392.
13. *Experimental procedure for formation of alkene* **17a** (Table 4, entry 4): A mixture of alkyne **16a** (95 mg, 0.22 mmol), Pd(OAc)$_2$ (7.5 mg, 0.033 mmol), AD_2BuP (24 mg, 0.066 mmol), and Cs_2CO_3 (108 mg, 0.33 mmol) in 2-propanol (2.2 mL) was irradiated in the Biotage Initiator microwave at 140 °C for 30 minutes. The reaction mixture was filtered over Celite and the solvent removed from the

filtrate in vacuo. The crude residue was purified by flash chromatography (0–15% EtOAc/hexane) to afford 61 mg (70%) of alkene **17a** as an oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.38 (d, J = 8.1 Hz, 1H), 7.27 (d, J = 8.3 Hz, 1H), 5.99 (t, J = 7.2 Hz, 1H), 3.73 (dd, J = 9.9, 3.3 Hz, 1H), 3.70 (d, J = 7.4 Hz, 1H), 2.77–2.65 (m, 1H), 2.66–2.60 (m, 1H), 2.31–2.21 (m, 1H), 2.20–2.10 (m, 2H), 2.07–2.01 (m, 2H), 1.72–1.57 (m, 2H), 1.54–1.36 (m, 2H), 1.36–1.26 (m, 2H), 1.10–1.01 (m, 1H), 0.99 (dd, J = 13.2, 6.6 Hz, 2H), 0.94 (d, J = 6.0 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H), 0.87–0.83 (m, 3H), 0.80 (d, J = 6.3 Hz, 3H); MS (ESI+): calcd $[M+H]^+$ 394, obs. 394.

14. *Experimental procedure for formation of alkene* **17d** (Table 4, entry 5): A mixture of alkyne **16d** (143 mg, 0.40 mmol), $Pd(OAc)_2$ (13.3 mg, 0.059 mmol), AD_2BuP (43 mg, 0.12 mmol), and Cs_2CO_3 (194 mg, 0.59 mmol) in 2-propanol (3.9 mL) was irradiated in the Biotage Initiator microwave at 140 °C for 30 min. The reaction mixture was filtered over Celite and the solvent removed from the filtrate in vacuo. The crude residue was purified by flash chromatography (0–15% EtOAc/hexane) to afford 103 mg (80%) of alkene **19** as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (dd, J = 5.7, 2.2 Hz, 1H), 7.24–7.16 (m, 3H), 5.99 (t, J = 7.2 Hz, 1H), 3.78 (dd, J = 9.9, 3.3 Hz, 1H), 3.74 (dd, J = 8.5, 2.4 Hz, 1H), 2.83–2.74 (m, 1H), 2.74–2.63 (m, 1H), 2.33 (ddt, J = 13.1, 10.3, 6.5 Hz, 1H), 2.20 (dddd, J = 13.2, 9.5, 7.3, 5.6 Hz, 2H), 1.74–1.63 (m, 4H), 1.61–1.53 (m, 2H), 1.52–1.44 (m, 2H), 1.39 (ddd, J = 24.7, 10.9, 5.7 Hz, 2H), 1.22–1.14 (m, 1H), 1.00 (d, J = 6.2 Hz, 3H), 0.97 (d, J = 6.6 Hz, 6H), 0.86 (d, J = 6.3 Hz, 3H); MS (ESI+): calcd $[M+H]^+$ 326, obs. 327.
15. *Experimental procedure for formation of allene* **20**/diene **19** mixture (Table 5, entry 1): A mixture of benzyl-(2-chloro-benzyl)-(1-isobutyl-6-methyl-hept-2-ynyl)-amine (111 mg, 0.28 mmol), $Pd(OAc)_2$ (9.4 mg, 0.042 mmol), AD_2BuP (30 mg, 0.084 mmol), and Cs_2CO_3 (137 mg, 0.42 mmol) in ethyl acetate (3.0 mL) was irradiated in the Biotage Initiator microwave at 140 °C for 30 min. The reaction mixture was filtered over Celite and the solvent removed from the filtrate in vacuo. The crude residue was purified by flash chromatography (0–30% EtOAc/hexane) to afford 100 mg (99%) of a 2:1 allene/diene (**20/19**) mixture as an oil. Allene: (1:1 mixture of diastereomers) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.16 (m, 9H), 5.61 (t, J = 7.4 Hz, 1H), 5.50 (t, J = 7.2 Hz, 1H), 4.12 (t, J = 17.2 Hz, 1H), 3.79–3.60 (m, 4H), 2.17–2.03 (m, 2H), 2.03–1.88 (m, 1H), 1.88–1.77 (m, 1H), 1.77–1.64 (m, 1H), 1.52–1.42 (m, 1H), 1.41–1.28 (m, 1H), 1.10–1.00 (m, 6H), 1.00–0.92 (m, 6H); MS (ESI+): calcd $[M+H]^+$ 360, obs. 360. Diene: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.16 (m, 9H), 6.78 (d, J = 11.0 Hz, 1H), 6.15 (dd, J = 15.0, 11.0 Hz, 1H), 5.91 (dd, J = 15.0, 6.5 Hz, 1H), 4.12 (t, J = 17.2 Hz, 1H), 3.79–3.60 (m, 4H), 2.17–2.03 (m, 2H), 2.03–1.88 (m, 1H), 1.88–1.77 (m, 1H), 1.77–1.64 (m, 1H), 1.52–1.42 (m, 1H), 1.41–1.28 (m, 1H), 1.10–1.00 (m, 6H), 1.00–0.92 (m, 6H); MS (ESI+): calcd $[M+H]^+$ 360, obs. 360.
16. Chang, H. M.; Cheng, C. H. *J. Org. Chem.* **2000**, *65*, 1767–1773.