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Pt(IV)-catalyzed cyclization of arene–alkyne substrates via C–H bond functionalization

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Abstract—We herein report that $PtCl_4$ has proven to be a hydroarylation catalyst with an efficiency and substrate scope superior to previously known methods. This catalyst demonstrated consistent performance with arene–yne substrates of diverse structural features, including propargyl ethers, propargylamines, and alkynoate esters, providing good to excellent yields of the 6-*endo* products (chromenes, dihydroquinolines, and coumarins). In contrast, Pt(II), Pd(II), and Ga(III) salts were shown to be sensitive to the substitution on the alkyne moiety. $PtCl_4$ is compatible with both terminal and disubstituted alkynes, as well as with various functionalities on the arene ring, including methyl, methoxyl, hydroxyl, protected amine, and halide.

1. Introduction

C–H bond functionalization represents a chemical process of broad synthetic potential owing to two major factors: first, the ubiquity of C–H bonds in organic compounds and second, a direct transformation of C–H bonds reduces the number of reactive groups required for a coupling processes. These seemingly simple points lead to consequences of significant importance to both the strategy and practice of organic synthesis. On a formal level, constraints imposed by current methodologies would be loosened and new disconnection strategies for the assembly of organic compounds may be considered. Such formal analyses influence our choice of chemical and synthetic problems to undertake.

From the onset of our program, natural products have provided a complex structural context for our reaction development program (Fig. 1). For instance, the key step in the synthesis of rhazinilam involved activation of a sp^3 C–H bond (ethyl group) in the presence of several reactive groups.[1] Similarly, the core of teleocidin B4 was assembled via two tandem C–H activation/C–C bond formation reactions, transforming *ortho-t*-butylaniline to a complex fragment containing two quaternary centers.[2] These investigations led to the development of catalytic C–H activation processes, including hydroxylation of free amino acids in water (Fig. 1),[3] and directed arylation of alkyl groups (not shown).[4]

In addition to alkane C–H bonds, we began to investigate functionalization of a broad range of C–H bonds, including those of arene substrates. Arenes, in comparison to alkanes, are generally more reactive due to accessibility of various reactivity modes and mechanisms, intimately linked with unsaturated arene rings. For instance, a formal process of C–H bond functionalization may proceed via an electrophilic substitution mechanism.[5] As part of our initial goals in this area, we have focused our attention on the direct arylation of hetero-arenes[6] and intramolecular hydroarylation processes (Fig. 1).[7] The latter reaction comprises the subject of this account.

1.1. Hydroarylation

Intramolecular hydroarylation, a formal addition of arene C–H bonds across multiple bonds in an intramolecular manner, provides a direct route to valuable organic compounds such as annulated arene heterocycles and carbocycles. In contrast to the Heck reaction, a hydroarylation approach not only eliminates the requirement for a halogen (or triflate) substituent, but also allows for multiple mechanistic possibilities, which in turn may lead to different regio-isomeric products (Fig. 2). These alternative mechanistic routes include arene metallation-Heck type addition,[8] multiple bond activation-electrophilic substitution,[9] and metal-catalyzed Claisen rearrangement (Fig. 3).[10,11]

2. Results and discussion

2.1. Systematic screening study: lead identification

We focused our initial efforts in this area on the cyclization

Keywords: C–H fuctionalization; C–H activation; platinum(IV); hydroarylation; alkynes; chromenes; benzopyrans.
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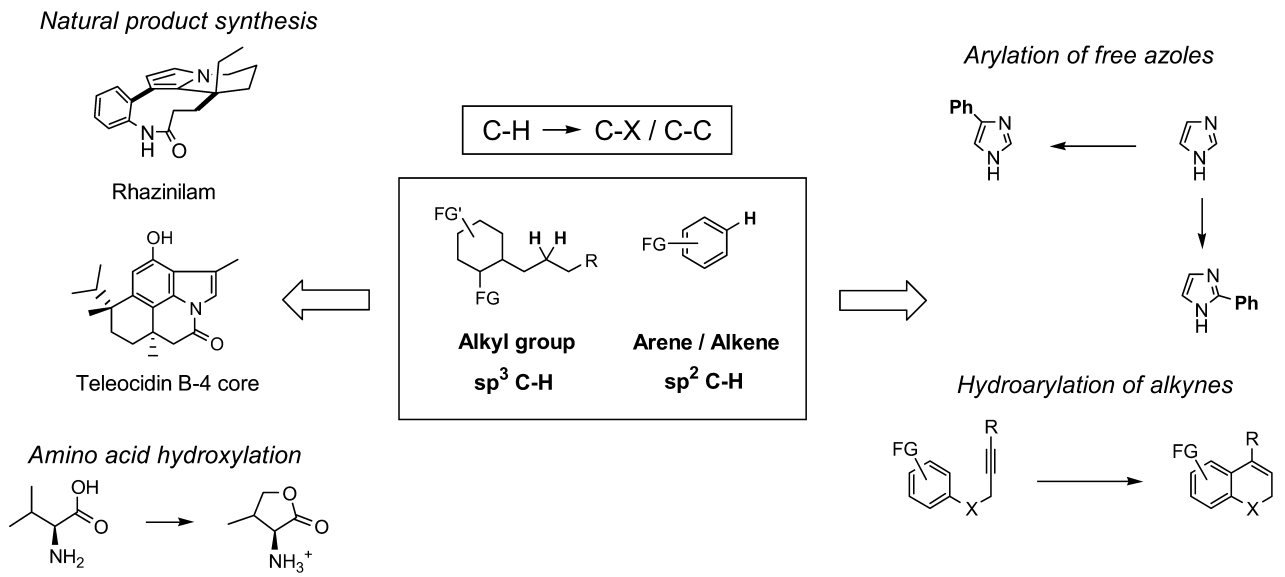


Figure 1. C–H bond functionalization in complex organic substrates. Overview of Sames group synthetic program.

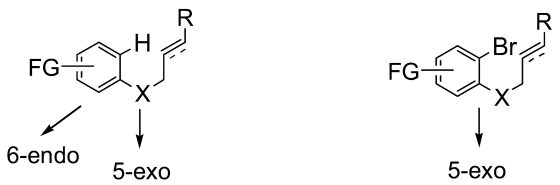


Figure 2. Hydroarylation vs. the Heck reaction.

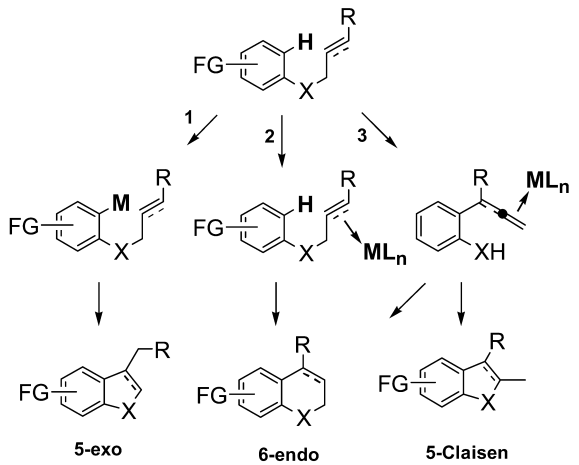
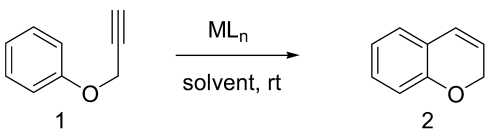


Figure 3. Intramolecular hydroarylation of alkynes and alkenes offers alternative mechanistic possibilities.

of alkyne substrates, specifically propargylic aryl ethers. Propargyl ether **1**, the parent member of this class, was selected as the first substrate for screening of a broad spectrum of metal salts and complexes. We assured that reagents and catalysts, reported previously to either promote reactivity of alkenes and alkynes toward nucleophiles or facilitate metallation of arenes, were included in the screen. The experiments were conducted in parallel in a reaction block and analyzed by automated HPLC. Thirty metal salts and complexes were evaluated under approximately 80 reaction conditions in total (Table 1). Such a matrix rapidly unveiled the incompetence of many known methods for alkyne activation, as low or no yields of **2** were observed (<6%, Table 1) in nearly all experiments. A notable exception was the method based on the use of $Pd(OAc)_2$, NaOAc, and formic acid which has previously been developed for the synthesis of coumarins via coupling of alkynoate esters and electron rich phenols.[11a] In our screen, this protocol showed a promising yield of 18%, however, upon closer examination it showed limited substrate scope and low isolated yields.

A related method for the preparation of coumarins via intramolecular cyclization of aryl alkynoate esters has recently been disclosed by Fujiwara, utilizing a catalytic amount of $Pd(OAc)_2$ in TFA–CH_2Cl_2.[12] Surprisingly, product **2** was not formed under these conditions. The use of $Pd(CH_3CN)_2Cl_2$, recently reported to catalyze the intramolecular reaction between unactivated alkenes and 1,3-diketones, also failed to promote the cyclization (Table 1).[13]

Table 1. Selected data from a systematic screening



Catalyst	Solvent	Yield of **2** (**1**)	Reference
$AgBF_4$	$CHCl_3$	0 (96)	10
$AuCl_3$	Toluene	6 (82)	15
$GaCl_3$	Toluene	3 (103)	16
$Pd(OAc)_2$/NaOAc	HCO_2H	18 (25)	11
$Pd(OAc)_2$	TFA	0 (0)	12
$Pd(CH_3CN)_2Cl_2$	CH_3CN	0 (56)	13
$PtCl_2$	Toluene	3 (74)	9
$PtCl_4$	CH_2Cl_2	32 (7)	18
	Toluene	19 (30)	
	THF	18 (36)	

Conditions: 5 mol% catalyst, substrate **1** (0.2 M), rt, 12 h. The yield was determined by HPLC in the presence of an internal standard. 30 metal salts/complexes were examined under 80 experimental conditions in total.

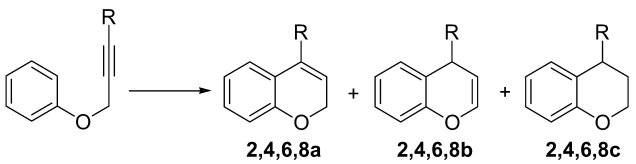
Historically, silver and mercuric salts have been known to mediate the cyclization of propargylic aryl ethers, but only by employing a stoichiometric quantity of the heavy metal.[14] Under the catalytic conditions of our screening, $AgBF_4$ gave no yield of chromene **2** (Table 1). In more recent disclosures, $AuCl_3$, $GaCl_3$ and $PtCl_2$ have been reported to promote the coupling of alkynes with arenes and heteroarenes. Specifically, $AuCl_3$ has been shown to catalyze intramolecular reactions of alkynes and furans to provide substituted phenols,[15] while $GaCl_3$[16] and $PtCl_2$[17] have hitherto been the most efficient catalysts for intramolecular electrophilic hydroarylation of terminal alkynes. Again, all three salts proved ineffective in the cyclization of **1** as only low yields of **2** were observed (<6%, Table 1).

We were delighted to uncover an exciting lead, which unambiguously stood out in the array of experiments owing to the highest yield of the product. Remarkably, $PtCl_4$ in CH_2Cl_2 furnished chromene **2** in 32% HPLC yield (other solvents also yielded promising results, Table 1). In contrast, $PtCl_2$ showed no or very low activity under the same conditions (<3%). This result prompted us to investigate both the efficiency and scope of Pt(IV)-catalyzed hydroarylation reactions, and to compare $PtCl_4$ with $PtCl_2$.[18]

2.2. Second generation screening: alkyne substitution

With the establishment of an exciting lead we were prepared to determine the efficacy of the cyclization protocol with regard to alkyne substitution. Thus, terminal alkyne **1**, methyl derivative **3**, phenyl derivative **5**, and alkynoate ester **7** were prepared and subsequently examined (Table 2). Consistent with the results described above, $PtCl_4$ was the only catalyst that afforded acceptable isolated yields of product **2** from terminal alkyne **1** (55%). In the case of methyl substrate **3**, the desired product **4a** was isolated in 66% isolated yield using dichloroethane as solvent, and interestingly increased to 92% yield in dioxane. In contrast, $PtCl_2$ produced only 25% yield of **4a**, and $Pd(OAc)_2$ according to the Fujiwara[12] protocol provided none of the chromene.

Table 2. Catalytic cyclization of propargyl ether substrates



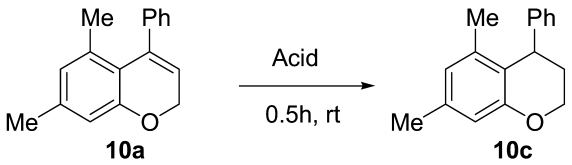
Substrate	$PtCl_4$[a] a/b/c (SM)	$PtCl_2$[b] a/b/c (SM)	$Pd(OAc)_2$[c] a/b/c (SM)
1, R=H	55:0:0 (0)[d]	6:0:0 (23)[e]	9:0:0 (40)
3, R=Me	92:0:0 (0)[f]	25:0:0 (61)[e]	0:0:10 (41)
5, R=Ph	57:28:0 (0)	51:0:0 (30)	0:0:67 (0)
7, R=CO_2Me	54:0:0 (0)	<1:0:0 (85)	59:0:0 (0)[g]

[a] Conditions: 5 mol% $PtCl_4$, $(CH_2)_2Cl_2$, 70°C, 24 h.
[b] 5 mol% $PtCl_2$, toluene, 80°C, 24 h.
[c] 1 mol% $Pd(OAc)_2$, TFA, rt, 1 h.
[d] 3 mol% $PtCl_4$, $(CH_2)_2Cl_2$, rt, 24 h.
[e] Reaction conducted at rt.
[f] In dioxane at rt, 2 h. 66% yield was obtained in $(CH_2)_2Cl_2$.
[g] Reaction conducted at 50°C. Isolated yields (%) are given in the table.

The phenyl substrate **5** turned out to be particularly interesting. In this case, $PtCl_4$ and $PtCl_2$ were equally effective in providing 50% yield of desired compound **6a**, while $Pd(OAc)_2$ in TFA generated saturated benzopyran **6c** as the only isolated product in 67% yield. In the case of ester **7**, the greater electrophilicity of Pt(IV) vs. Pt(II) became apparent as $PtCl_4$ yielded 54% of desired chromene **8a**, while only a trace of this product was detected in the presence of $PtCl_2$. The highly electrophilic conditions of $Pd(OAc)_2$ in TFA at 50°C proved marginally superior to $PtCl_4$, furnishing **8a** in 59% yield.

Intrigued by the fact that the Fujiwara method produced the saturated benzopyran **6c** in 67% yield we discovered that the chromene **6a** was reduced under the reaction conditions. Furthermore, we found that **6a** is reduced by TFA itself. In addition we found that this reaction occurs with substrate **10a**, and occurs in other acids as well (Table 3). The futility of the Fujiwara method can be realized by the fact that the desired chromene products are not stable under the strong acidic conditions, which are necessary for the cyclization to proceed ($Pd(OAc)_2$ in CH_2Cl_2 or AcOH results in no reaction).[19]

Table 3. Acid promoted reduction of chromene substrate

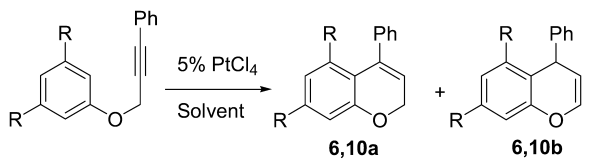


Entry	Acid	Yield **10c** (%)	**10a** (%)
1	TFA	80	0
2	MsOH	28	21
3	TfOH	22	17
4	AcOH	Trace	92
5	HCl/Et_2O	Trace	96

Yields determined by the mass recovery of the purified reaction mixture and the ratio was determined by ^{1}H NMR of the mixtutre.

A striking advantage of this $PtCl_4$ catalyzed cyclization is that a variety of organic solvents can be used, including polar coordinating solvents (dioxane, THF, EtOAc). Two interesting solvent effects arose during the optimization period: (1) the overall cyclization yield and rate of reaction was found to be generally higher/faster in dioxane vs. dichloroethane, and (2) the amount of undesired 4-H chromene isomer was typically higher in dioxane (Table 4).

Table 4. Dioxane vs. dichloroethane



Substrate	Solvent	Temperature, time	Yield (%) A/B
5, R=H	Dioxane	rt, 5 h	57:28
5, R=H	$ClCH_2CH_2Cl$	70°C, 24 h	50:5
9, R=Me	Dioxane	rt, 3 h	66:11
9, R=Me	$ClCH_2CH_2Cl$	70°C, 5 h	49:3

Isolated yields given in table.

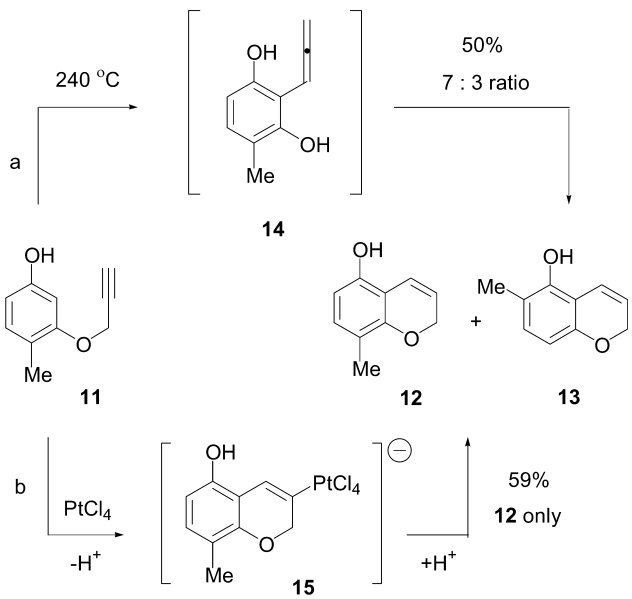
The cyclization of phenyl alkyne substrates **5** and **9** was achieved at ambient temperature in dioxane, but elevated temperatures were required to achieve cyclization in dichloroethane (Table 4). In addition, the overall cyclization yield was significantly higher (>25%) in dioxane for both substrates. Unfortunately, the undesired 4-H isomers **6b**, and **10b** were also formed to a greater extent in dioxane. In order to determine if the products were equilibrating under the reaction conditions the 2-H chromenes **6a** and **10a** were subjected to the cyclization protocol and were not found to isomerize to their 4-H counterparts.

Noteworthy is the fact that the catalyst exhibits increased solubility in dioxane over dichlororethane. This may suggest that the higher reactivity of $PtCl_4$ (in comparison to $PtCl_2$ and other metal salts) may be related not only to the higher oxidation state of the platinum metal, but also to the solubility of the catalyst.[20]

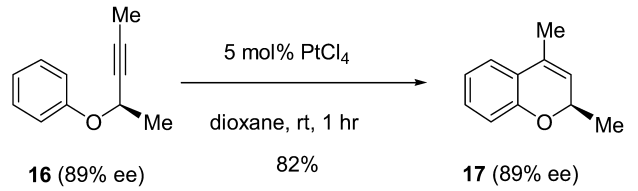
2.3. Electrophilic hydroarylation vs. Claisen rearrangement

In the next stage of this project, we posed an important mechanistic question as to whether the cyclization proceeded via the electrophilic substitution mechanism or via the Claisen rearrangement manifold. In order to address this issue, we constructed a substrate probe **11**, which in the event of Claisen rearrangement ought to lead to two isomeric products **12** and **13** (Scheme 1). This was confirmed by submitting phenol **11** to the harsh conditions of thermal rearrangement (240°C),[21] and indeed, two products **12** and **13** were formed in a 7:3 ratio. In contrast, substrate **11** in the presence of 2 mol% of $PtCl_4$ in dioxane at ambient temperature afforded **12** in 59% yield, whereas isomer **13** was not detected in the crude reaction mixture.

Closely linked to these mechanistic considerations was the important question of whether a stereogenic center in chiral propargyl ethers would be compromised during the cyclization. We were delighted to find that chiral propargyl ether **16** afforded chromene **17** in 82% yield while no racemization was observed (Scheme 2). This finding significantly expands the scope of this hydroarylation methodology.[22]



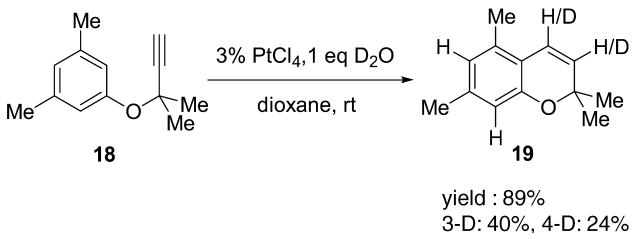
Scheme 1. *Conditions*: (a) 240°C, diethyleneglycol; (b) 2 mol% $PtCl_4$, dioxane, rt.



Scheme 2.

2.4. Electrophilic hydroarylation vs. arene metallation

Since reactions were compatible with a small amount of water (0.5%), we were able to address the third mechanistic possibility, namely arene metallation followed by Heck reaction (path 1, Fig. 3). The cyclization of the geminal dimethyl substrate **18** in the presence of 1 equiv. of D_2O (Scheme 3) revealed that the deuterium atoms were incorporated in product **19** at the 3 and 4 positions as judged by ^1H NMR.[23] These results suggest three important mechanistic points: (1) the intermediacy of a vinyl platinum species, (2) the proton on the arene is released into the solvent along the reaction path, and (3) reversible metallation of the arene ring does not occur.



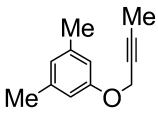
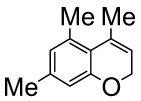
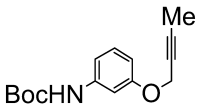
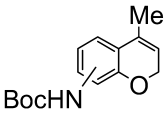
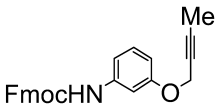
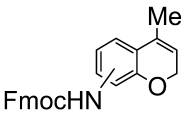
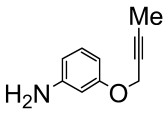
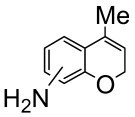
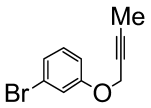
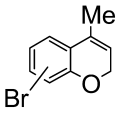
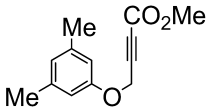
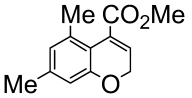
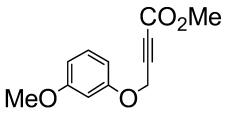
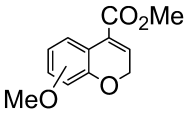
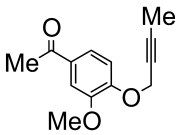
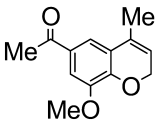
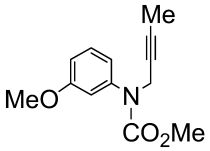
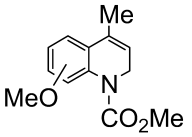
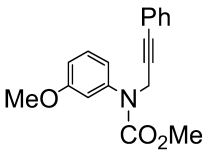
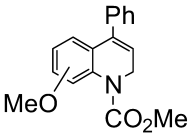
Scheme 3.

Our results support a mechanistic picture whereby coordination of $PtCl_4$ activates the alkyne for interception by the benzene ring (electrophilic hydroarylation, path 2, Fig. 3) followed by some type of protonation event. However, we cannot rule out the possibility that coordination of the alkyne directs the metal to the arene nucleus (ortho-metallation), and then proceeds through a Heck-type addition. The latter seems unlikely as only 6-*endo* products were formed for 1,5 arene–eyne substrates[24] and the products would have to result from a *trans* carbo-platination event.[25]

2.5. Substrate scope: arene substitution

The utility of $Pt(IV)Cl_4$ for the cyclization of propargyl-aryl ethers is demonstrated in Tables 5 and 6. This method demonstrated good compatibility with various functional groups, including alkyl groups, free phenols (Scheme 1), protected amines, halides and carbonyls. It was found that, electron releasing groups generally increased the reactivity of these substrates and as such higher yields of the corresponding products are usually obtained. For example, substrate **20** bearing two methyl groups on the benzene

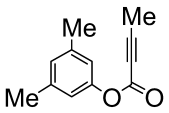
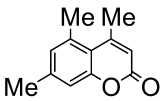
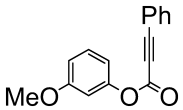
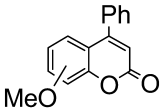
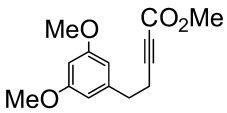
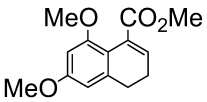
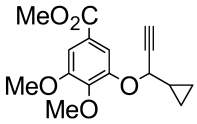
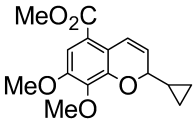
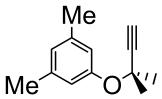
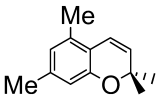
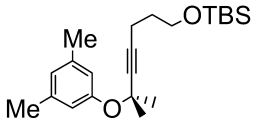
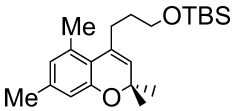
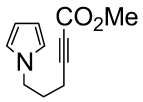
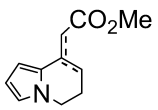
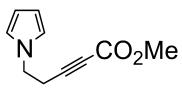
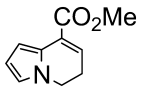
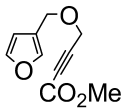
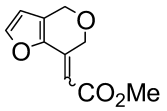
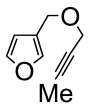
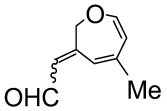
Table 5. Catalytic cyclization of arene–eyne substrates

Substrate		Conditions	Product		Yield (%)[a]
20		1% $PtCl_4$, dioxane, rt, 1 h	**21**		86 (9)
22		2% $PtCl_4$, $ClCH_2CH_2Cl$, rt, 6 h	**23a/23b**		67, *p*-/*o*-=9:1
24		3% $PtCl_4$, dioxane, rt, 1 h	**25a/25b**		74, *p*-/*o*-=76:24
26		5% $PtCl_4$, $ClCH_2CH_2Cl$, rt, 48 h	**27a/27b**		34
28		5% $PtCl_4$, $ClCH_2CH_2Cl$, rt, 1.5 h	**29a/29b**		66, *p*-/*o*-=88:12
30		5% $PtCl_4$, $ClCH_2CH_2Cl$, 70°C, 5.5 h	**31**		78
32		5% $PtCl_4$, $ClCH_2CH_2Cl$, 70°C, 5 h	**33a/33b**		68, *p*-/*o*-=4.5:1
34		2% $PtCl_4$, dioxane, rt, 3 h	**35**		92, *p*-/*o*-=5.5:1
36		5% $PtCl_4$, $ClCH_2CH_2Cl$, 70°C, 2 h	**37a/37b**		82, *p*-/*o*-=78:22
38		5% $PtCl_4$, $ClCH_2CH_2Cl$, 70°C, 1 h	**39a/39b**		63, *p*-/*o*-=75:25

[a] Yields refer to those of pure isolated products. Yield in parenthesis corresponds to the yield of 4*H*-chromene isomer.

nucleus was converted to the chromene **21** in 86% isolated yield in the presence of only 1 mol% of $PtCl_4$ (Table 5). Both the Boc- and Fmoc-protected anilines **22** and **24** were converted to the corresponding chromenes **23a/23b** and **25a/25b** in 67 and 74% yield, respectively. Conversion was also observed with free aniline **26**; however, the yield dropped to 34% and higher temperature and longer reaction time was required. Substrates, containing an electron-withdrawing bromine substituent **28** or ketone functionality **34** were also tolerated. In the case of the ketone substrate, cyclization was achieved in 88% yield with only 2 mol% $PtCl_4$ in less than 3 h. Substitution in the 2-position was tolerated as demonstrated by the conversion of the geminal dimethyl substrates **48**, **50**, and the 2-cyclopropyl substrate **46**, to their corresponding chromenes (Table 6). In addition to propargyl ethers, propargyl amines **36**, **38** were also good substrates furnishing the corresponding dihydroquinolines **37** and **39** in good yields. Furthermore, coumarin **41**, **43a/43b** and dihydronapthalene **45** products were successfully produced from their corresponding acyclic precursors under the action of $PtCl_4$. The pyrrole substrate **52** smoothly cyclized to dihydro-indolizines **53a/53b** via a 6-*exo* mode,

Table 6. Catlaytic cyclization of arene–eyne substrates

Substrate		Conditions	Product		Yield (%)[a]
40		5% $PtCl_4$, $ClCH_2CH_2Cl$, 70°C, 24 h	**41**		72
42		5% $PtCl_4$, $ClCH_2CH_2Cl$, 70°C, 24 h	**43a/43b**		50
44		5% $PtCl_4$, $ClCH_2CH_2Cl$, 70°C, 24 h	**45**		50
46		15% $PtCl_4$, dioxane, rt, 12 h	**47**		55
48		1% $PtCl_4$, dioxane, rt, 1 h	**49**		90
50		3% $PtCl_4$, dioxane, rt, 3 h	**51**		85
52		5% $PtCl_4$, $ClCH_2CH_2Cl$, 70°C, 10 h	**53a/53b**		72 *exo*/*endo*=63:37
54		5% $PtCl_4$, $ClCH_2CH_2Cl$, 70°C, 38 h	**55**		24
56		5% $PtCl_4$, $ClCH_2CH_2Cl$, 70°C, 36 h	**57a/57b**		57 *E*/*Z*=1:1
58		5% $PtCl_4$, $ClCH_2CH_2Cl$, 70°C, 13 h	**59a/59b**		14 *E*/*Z*=1:14

[a] Yields refer to those of pure isolated products.

in 72% yield, while pyrrole **54** with a shorter carbon tether cyclizes via the 6-*endo* mode in 24% yield and required longer reaction time. The furyl-ether **56** expectedly yielded the *exo*-cyclization product in 57% yield. Albeit in low yield, the formation of the 7-membered oxacyle **59a/59b** from furyl-ether **58** stands out as a particularly interesting case. We believe this product was formed via several tandem rearrangements starting with a 7-*endo* cyclization.[26]

It appears that the presence of at least one electron donating substituent on the benzene ring was required for the cyclization to proceed. For example, 4-phenyl-1-butyne was resistant to cyclization in the presence of either $PtCl_2$ or $PtCl_4$, providing only recovered starting material at ambient temperature, with slight decomposition occurring at elevated temperatures.

3. Conclusion

In summary, we have developed a mild and neutral method for hydroarylation of arene–yne substrates with promising efficiency and scope. $PtCl_4$ demonstrated consistent performance with arene–yne substrates of diverse structural features, including propargyl ethers, propargyl amines, and alkynoate esters, providing good to excellent yields of the 6-*endo* products. In contrast, Pt(II) and Pd(II) salts were shown to be sensitive to the substitution on the alkyne moiety. $PtCl_4$ was compatible with both terminal and disubstituted alkynes, as well as with various functionalities on the arene ring, including carbonyl, methyl, methoxyl, hydroxyl, protected amine, halide, and carbonyl. At least one electron-donating group on the arene ring was required for the reaction to proceed.

Some trends have emerged from the current study regarding the comparison of $PtCl_4$ with $PtCl_2$.[7] For instance, the activity of $PtCl_2$ and $PtCl_4$ was comparable toward substrates containing arene rings with two or more electron-donating substituents. These findings are consistent with those shown for the cycloisomerization of enynes.[18] In the case of enynes, $PtCl_2$ was sufficiently electrophilic for the activation of the alkyne toward an intramolecular attack by an alkene. Electron-rich arenes compare to alkenes in terms of nucleophilicity and reactivity,[27] and thus $PtCl_2$ should be sufficient for facile hydroarylation reaction of these substrates. However, in the case of arenes of lower electron density or electron-poor alkynes, $PtCl_2$ does not exert sufficient activation of the alkyne group and therefore the more electrophilic $PtCl_4$ is required. The greater reactivity and scope of $PtCl_4$ may stem not only from the higher oxidation state of the platinum metal, but also from the greater solubility of $PtCl_4$ in organic solvents. Faster rates of $PtCl_4$-catalyzed cyclization reactions in dioxane in comparison to dichloromethane may also be ascribed to better solubility of the catalyst in the former solvent.

From a practical standpoint this $PtCl_4$ cyclization method is user friendly. Reactions can be carried out in air and rigorous exclusion of moisture is unnecessary since reactions are typically compatible with a small amount of water (0.5%). Electrophilic hydroarylation constitutes an attractive class of transformations, which in contrast to the Heck reaction, do not require a halide (or triflate) at the site of the C–C coupling on the arene ring. Furthermore, 6-*endo* products are formed exclusively. It appears that $PtCl_4$ possesses a special blend of reactivity and selectivity, as demonstrated by the selective activation of a triple bond toward one class of nucleophiles, namely the arenes.[28]

4. Experimental

4.1. General

Nuclear Magnetic Resonance spectra were recorded on Bruker 300 or 400 Fourier transform NMR spectrometers. Spectra were recorded in $CDCl_3$ solutions referenced to TMS or the solvent residual peak. IR spectra were taken as neat for liquids on NaCl plates, and as KBR pellet for solids using a Perkin–Elmer 1600 FTIR spectrometer. High Resolution Mass Spectra were obtained on a JOEL JMS_HX110 HF mass spectrometer. Flash chromatography was performed on SILICYCLE silica gel (230–400 mesh).

4.2. Procedure for catalytic cyclization of arene alkyne substrates with $PtCl_4$

A solution of substrate (0.2 M) and $PtCl_4$ (1–5%) were stirred in air until the substrate was completely consumed. Reactions were monitored by TLC. After completion, the solvent was evaporated and the products purified by filtration through silica gel.

4.2.1. (4-Methyl-2*H*-chromen-7-yl)-carbamic acid 9*H*-fluoren-9-ylmethyl ester (25a). A white solid (mp 119–121°C (dec.)) (SiO_2, hexane/EtOAc=1:5). IR 3297, 1697, 1590, 1527, 1223, 740 cm^{-1}; ^1H NMR δ 1.97 (q, J=1.7 Hz, 3H), 4.25 (t, J=6.6 Hz, 1H), 4.51 (d, J=6.6 Hz, 2H), 4.71 (sextet, J=1.7 Hz, 2H), 5.47 (tq, J=1.7, 3.5 Hz, 1H), 6.65 (br s, 1H), 6.85 (br s, 1H), 6.91 (d, J=7.5 Hz, 1H), 7.03 (d, J=8.2 Hz, 1H), 7.31 (t, J=7.5 Hz, 2H), 7.40 (t, J=7.4 Hz, 2H), 7.59 (d, J=7.4 Hz, 2H), 7.76 (d, J=7.5 Hz, 2H); ^{13}C NMR δ 17.8, 47.1, 65.6, 66.8, 106.2, 111.1, 116.9, 120.0, 124.0, 124.9, 127.1, 127.7, 129.8, 138.21, 141.3, 143.7, 153.1, 154.8 (One carbon is missing due to overlapping). HRFABMS m/z 383.1511 $(M)^+$, calcd for $C_{25}H_{21}NO_3$ 383.1521.

4.2.2. (4-Methyl-2*H*-chromen-5-yl)-carbamic acid 9*H*-fluoren-9-ylmethyl ester (25b). A white solid (mp 188–190°C) (SiO_2, hexane/EtOAc=5:1). IR 3267, 1697, 1604, 1525, 1450, 1220, 738 cm^{-1}; ^1H NMR δ 2.05 (br s, 3H), 4.22 (br s, 1H), 4.45 (dq, J=1.4, 4.4 Hz, 2H), 4.52 (d, J=5.7 Hz, 2H), 5.67 (tq, J=1.4, 4.4 Hz, 1H), 6.38 (br s, 1H), 6.76 (d, J=8.0 Hz, 1H), 7.00 (br s, 1H), 7.11 (t, J=8.0 Hz, 1H), 7.28 (t, J=7.0 Hz, 2H), 7.37 (t, J=7.4 Hz, 2H), 7.56 (m, 2H), 7.74 (d, J=7.5 Hz, 2H); ^{13}C NMR δ 20.0, 47.4, 64.4, 67.0, 112.5, 113.8, 118.5, 119.9, 121.18, 124.8, 126.9, 127.6, 128.6, 130.1, 133.0, 141.2, 143.5, 153.9, 155.8. HRFABMS m/z 383.1511 $(M)^+$, calcd for $C_{25}H_{21}NO_3$ 383.1521.

4.2.3. 7-Methoxy-2*H*-chromene-4-carboxylic acid methyl ester (33a). A clear oil (SiO_2, hexane/EtOAC=7:1). IR 2955, 2840, 1732, 1617, 1506, 1257, 1028 cm^{-1}; ^1H NMR δ 3.78 (s, 3H), 3.84 (s, 3H), 4.80 (d, J=4.2 Hz), 6.43 (d, J=2.6 Hz), 6.52 (dd, J=2.6, 8.7 Hz), 6.74 (t, J=4.2 Hz, 1H), 7.84 (d, J=8.7 Hz); ^{13}C NMR δ 51.9, 55.3, 64.8, 101.9, 107.4, 112.7, 127.0, 127.3, 128.7, 155.5, 160.9, 165.4. HRFABMS m/z 219.0659 $(M-H)^+$, calcd for $C_{12}H_{11}O_4$ 219.0657.

4.2.4. 5-Methoxy-2*H*-chromene-4-carboxylic acid methyl ester (33b). A clear oil (SiO_2, hexane/EtOAC=7:1). IR 2952, 2843, 1738, 1606, 1476, 1271, 1249, 1092 cm^{-1}; ^1H NMR δ 3.80 (s, 3H), 3.81 (s, 3H), 4.63 (d, J=6.24 Hz, 1H), 6.52–6.59 (m, 2H), 7.16 (t, J=8.3 Hz, 1H); ^{13}C NMR δ 51.7, 56.1, 64.2, 104.9, 109.4, 110.8, 124.7, 128.8, 130.3, 155.5, 155.7, 168.6. HRFABMS m/z 219.0650 $(M-H)^+$, calcd for $C_{12}H_{11}O_4$ 219.0657

4.2.5. 1-(8-Methoxy-4-methyl-2*H*-chromen-6-yl)-ethanone (35). A white solid (SiO_2, hexane/EtOAC=4:1). IR 1673, 1581, 1288, 1216 cm^{-1}; ^1H NMR δ 2.04–2.05 (m, 3H), 2.54, (s, 3H), 3.89 (s, 3H), 4.89–4.90 (m, 2H), 5.58–5.62 (m, 1H), 7.39–7.42 (m, 2H); ^{13}C NMR δ 18.4, 26.3, 56.2, 66.3, 111.2, 117.2, 118.4, 123.5, 129.2, 129.7, 147.4, 147.5, 196.2. APCI m/z 219.0817 $(M+H)^+$, calcd for $C_{13}H_{15}O_3$ 219.1021.

4.2.6. 7-Methoxy-4-phenyl-2*H*-quinoline-1-carboxylic acid methyl ester and 5-methoxy-4-phenyl-2*H*-quinoline-1-carboxylic acid methyl ester (39a, 39b). The mixture of *p*- and *o*-isomers was obtained as a yellow solid (SiO_2, hexane/EtOAC=1:6). IR 1711, 1611, 1441, 1225, 1050 cm^{-1}; *p*-isomer ^1H NMR δ 3.81 (s, 3H), 3.82 (s, 3H), 4.44 (d, J=4.6 Hz, 2H), 5.87 (t, J=4.6 Hz, 1H), 6.59 (dd, J=2.6, 8.7 Hz, 1H), 6.96 (d, J=8.7 Hz, 1H), 7.23–7.36 (m, 6H). *o*-isomer ^1H NMR δ 3.39 (s, 3H), 3.77 (s, 3H), 4.29 (d, J=5.1 Hz, 2H), 6.04 (t, J=5.1 Hz, 1H), 6.66 (dd, J=1.0,

8.2 Hz, 1H), 7.19–7.36 (m, 7H). ^{13}C NMR mixture of *p*- and *o*-isomers: δ 42.7, 43.3, 53.1, 53.1, 55.4, 55.5, 108.3, 109.6, 109.8, 116.6, 120.1, 122.2, 124.2, 126.3, 126.7, 127.3, 127.5, 128.0, 128.1, 128.4, 137.4, 138.1, 138.4, 138.7, 139.3, 141.1, 153.9, 154.2, 155.8, 158.7 (two carbons are missing due to overlapping). HRFABMS *m/z* 295.1202 $(M)^+$, calcd for $C_{18}H_{17}NO_3$ 295.1208.

4.2.7. 6,8-Dimethoxy-3,4-dihydro-naphthalene-1-carboxylic acid methyl ester (45). A clear oil (SiO_2, hexane/EtOAC=3:1). IR 1734, 1604, 1210, 1153 cm^{-1}; ^{1}H NMR δ 2.22–2.28 (m, 3H), 2.66 (t, 2H; J_{av}=7.6 Hz), 3.73 (s, 3H), 3.77 (s, 3H), 3.80 (s, 3H), 6.35 (d, *J*=2.3 Hz, 1H), 6.38 (d, *J*=2.0 Hz, 1H), 6.48 (t, *J*=5.0 Hz, 1H); ^{13}C NMR δ 22.7, 28.9, 51.7, 55.3, 55.9, 97.1, 105.2, 114.3, 130.9, 131.6, 139.7, 156.1, 160.3, 170.4. HRFABMS *m/z* 248.0852 $(M)^+$, calcd for $C_{17}H_{12}O_2$ 248.1049.

4.2.8. 2,2,5,7-Tetramethyl-2*H*-chromene (49). A clear oil (SiO_2, hexane/CH_2Cl_2=3:1). IR 1614, 1312 cm^{-1}; ^{1}H NMR δ 1.40 (s, 6H), 2.23 (s, 3H), 2.25 (s, 3H), 5.58 (d, *J*=10 Hz), 6.46–6.52 (m, 3H); ^{13}C NMR δ 18.3, 21.3, 27.8, 75.2, 114.8, 117.1, 119.3, 123.2, 129.4, 133.6, 138.6, 152.9. HRFABMS *m/z* 188.1215 $(M)^+$, calcd for $C_{13}H_{16}O$ 188.1201.

4.2.9. *tert*-Butyldimethyl-[3-(2,2,5,7-tetramethyl-2*H*-chromen-4-yl)propoxy]silane (51). A clear oil (SiO_2, hexane/CH_2Cl_2=3:1). IR 2857, 1612, 1472, 1103 cm^{-1}; ^{1}H NMR δ 0.04 (s, 3H), 0.90 (s, 9H), 1.34 (s, 6H), 1.61 (m, 2H), 2.23 (s, 3H), 2.43 (s, 3H), 2.59 (t, J_{av}=7.7 Hz, 2H), 3.61 (t, *J*=6.2 Hz, 2H), 5.47 (s, 1H), 6.52 (s, 1H), 6.56 (s, 1H); ^{13}C NMR δ −5.1, 18.5, 21.2, 23.1, 26.1, 26.9, 31.5, 32.3, 62.4, 74.3, 115.7, 119.7, 125.5, 128.7, 133.6, 133.8, 137.9, 155.4. APCI *m/z* 361.1644 $(M+H)^+$, calcd for $C_{22}H_{37}O_2Si$ 361.2563.

4.2.10. (5,6-Dihydroindolizin-8-yl)acetic acid methyl ester and (5,6-dihydroindolizine-8-carboxylic acid methyl ester (53a, 53b). The mixture of *exo*- and *endo*-isomers was obtained as a yellow oil (SiO_2, hexane/EtOAc=8:1). IR 3103, 1741, 1700, 1605, 1482, 1340, 1157, 1081, 857, 727 cm^{-1}; *exo*-isomer ^{1}H NMR δ 2.01 (quintet, *J*=6.1 Hz, 2H), 3.18 (td, *J*=1.9, 6.3 Hz, 2H), 3.69 (s, 3H), 3.97 (t, *J*=5.9 Hz, 2H), 6.13 (t, *J*=1.8 Hz, 1H), 6.17 (dd, *J*=2.5, 4.0 Hz, 1H), 6.63 (dd, *J*=1.5, 4.0 Hz, 1H), 6.72 (dd, *J*=1.6, 2.2 Hz, 1H); ^{13}C NMR δ 23.3, 25.3, 45.50, 50.8, 106.3, 107.4, 109.4, 123.5, 129.0, 146.6, 167.59. *endo*-isomer: ^{1}H NMR δ 2.50 (td, *J*=4.6, 7.2 Hz, 2H), 3.30 (d, *J*=1.0 Hz, 2H), 3.67 (s, 3H), 3.92 (t, *J*=7.2 Hz, 2H), 5.58 (t, *J*=4.5 Hz, 1H), 6.09 (m, 2H), 6.57 (t, *J*=2.0 Hz, 1H); ^{13}C NMR δ 24.6, 38.4, 43.5, 52.1, 104.5, 107.6, 118.0, 121.2, 125.1, 129.7, 171.5. HRFABMS *m/z* 193.1098 $(M)^+$, calcd for $C_{11}H_{15}NO_2$ 193.1103.

4.2.11. 5,6-Dihydro-indolizine-8-carboxylic acid methyl ester (55). A yellow oil (SiO_2, hexane/EtOAC=10:1). IR 3101, 1718, 1608, 1436, 1270, 1165, 1060, 800, 717 cm^{-1}; ^{1}H NMR 2.62 (td, *J*=5.0, 7.1 Hz, 2H), 3.82 (s, 3H), 3.94 (t, *J*=7.1 Hz, 2H), 6.15 (dd, *J*=2.8, 3.5 Hz, 1H), 6.61 (dd, *J*=1.6, 2.5 Hz, 1H), 6.64 (dd, *J*=1.5, 3.6 Hz, 1H), 6.78 (t, *J*=5.0 Hz, 1H); ^{13}C NMR δ 24.9, 42.9, 51.8, 108.1, 108.7, 121.5, 125.3, 125.4, 128.9, 165.1. HRFABMS *m/z* 177.0779 $(M)^+$, calcd for $C_{10}H_{11}NO_2$ 177.0790.

4.2.12. (5-Methyl-oxepin-3-ylidene)acetaldehyde (59a/59b). The title compound was obtained as pale yellow oil as mixture of *E* and *Z* isomers. IR 2920, 1724, 1668, 1628, 1446, 1117, 1033 cm^{-1}; *E*-isomer ^{1}H NMR δ 2.02 (d, *J*=0.7 Hz, 3H), 4.58 (s, 2H), 5.10 (dd, *J*=1.3, 6.8 Hz, 1H), 5.53 (d, *J*=7.6 Hz, 1H), 6.62 (d, *J*=6.8 Hz, 1H), 7.06 (s, 1H), 10.17 (d, *J*=7.6 Hz, 1H); ^{13}C NMR δ 27.1, 75.6, 108.9, 121.6, 125.1, 141.6, 148.3, 152.2, 191.2. *Z*-isomer ^{1}H NMR δ 1.98 (d, *J*=0.8 Hz, 3H), 5.06 (s, 2H), 5.14 (dd, *J*=1.3, 6.7 Hz, 1H), 5.90 (d, *J*=7.8 Hz, 1H), 6.30 (s, 1H), 6.68 (d, *J*=6.7 Hz, 1H), 10.05 (d, *J*=7.8 Hz), ^{13}C NMR δ 26.9, 67.0, 110.0, 125.4, 129.4, 142.1, 149.6, 153.0, 190.0. APCI *m/z* 151.0759 $(M+H)^+$, calcd for $C_9H_{11}O_2$ 151.1857.

4.3. Preparation of 24

To a solution of **26**[7] (198 mg, 1.23 mmol) in aq. dioxane (3 mL) were added *i*-Pr_2NEt (258 μL, 1.47 mmol) and FmocCl (360 mg, 1.35 mmol) at 0°C. After being stirred at rt for 30 min, the reaction mixture was extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel by eluting EtOAc/hexane (1:4).

4.3.1. *O*-(2-Butynyl)-*N*-Fmoc-3-aminophenol (24). Isolated in 88% yield as a white solid, mp 143–146°C. IR 3312, 2230, 1732, 1707, 1610, 1541, 1448, 1222, 1025 cm^{-1}. ^{1}H NMR δ 1.84 (t, *J*=2.3 Hz, 3H), 4.25 (t, *J*=6.5 Hz, 1H), 4.52 (d, *J*=6.6 Hz, 2H), 4.61 (q, *J*=2.2 Hz, 2H), 6.67 (dd, *J*=2.0, 8.2 Hz, 1H), 6.73 (br s, 1H), 6.93 (d, *J*=7.5 Hz, 1H), 7.08 (br s, 1H), 7.18 (t, *J*=8.1 Hz, 1H), 7.31 (t, *J*=7.4 Hz, 2H), 7.40 (t, *J*=7.4 Hz, 2H), 7.60 (d, *J*=7.3 Hz, 2H), 7.76 (d, *J*=7.4 Hz, 2H);^{13}C NMR 3.7, 47.1, 56.4, 66.8, 73.9, 83.8, 105.5, 110.1, 111.6, 120.0, 124.9, 127.1, 127.7, 129.71, 138.9, 141.3, 143.7, 153.2, 158.5. HRFABMS *m/z* 383.1508 $(M)^+$, calcd for $C_{25}H_{21}NO_3$ 383.1521.

4.4. Preparation of 32

To a solution of 1-methoxy-3-prop-2-ynyloxy-benzene (440 mg, 2.71 mmol) in 5 mL of THF was added *n*-butyl lithium at −78°C. After 30 min $ClCO_2Me$ (230 μL, 3.00 mmol, 1.1 equiv.) was added. The reaction was allowed to warm to ambient temperature and stirred overnight. Volatiles were removed and the residue was purified by column chromatography by eluting with hexanes/EtOAc (6:1).

4.4.1. 4-(3-Methoxyphenoxy)but-2-ynoic acid methyl ester (32). Isolated in 93% yield as a pale yellow oil. IR 2240, 1716, 1608, 1255, 1206, 1157, 1065 cm^{-1}; ^{1}H NMR δ 3.79 (s, 3H), 3.81 (s, 3H), 4.80 (s, 2H), 6.51–6.60 (m, 3H), 7.21 (t, *J*=8.1 Hz, 1H); ^{13}C NMR δ 52.8, 54.9, 55.3, 82.1, 101.5, 106.7, 107.6, 130.0, 153.3, 158.5, 160.8. HRFABMS *m/z* 218.0932 $(M)^+$, calcd for $C_{13}H_{14}O_3$ 218.0943.

4.5. Preparation of 38

To a solution of (3-hydroxy-phenyl)-carbamic acid methyl

ester[7] (287.4 mg, 1.59 mmol), in DMF (4 mL) was added NaH (76.2 mg, 1.91 mmol), and 3-phenyl-2-propynl methanesulfonate (367.0 mg, 1.75 mmol) in 1 mL of DMF. After 2 h, water was added and the crude product was extracted with EtOAc (10 mL×3), washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel by eluting EtOAc/hexane (1:5).

4.5.1. *N*-(3-Phenyl-2-propynyl)-*N*-(methoxycarbonyl)-3-amino-1-methoxybenzene (38). Isolated in quantitative yield as a pale yellow oil. IR 2240, 1712, 1603, 1445, 1244, 1034 cm^{-1}; ^1H NMR δ 3.73 (s, 3H), 3.79 (s, 3H), 4.61 (s, 2H), 6.83 (ddd, J=0.9, 2.1, 7.8 Hz, 1H), 6.94–6.97 (m, 2H), 7.24–7.39 (m, 6H); ^{13}C NMR δ 41.0, 53.3, 55.3, 84.1, 84.9, 112.7, 119.2, 122.7, 128.2, 128.3, 129.6, 131.7, 142.5, 155.6, 159.9. HRFABMS m/z 295.1202 $(M)^+$, calcd for $C_{18}H_{17}NO_3$ 295.1208.

4.6. Preparation of entry 44

Compound **44** was prepared in the same manner as described above for the synthesis of **32**. But-3-ynyl-3,5-dimethoxy-benzene[29] (200 mg, 1.05 mmol), *n*-BuLi (600 μL, 1.6 M solution in hexanes, 1.10 mmol), and $ClCO_2Me$ (90 μL, 1.6 mmol). Purification by column chromatography by eluting with hexanes/EtOAc (6:1).

4.6.1. 5-(3,5-Dimethoxyphenyl)pent-2-ynoic acid methyl ester (44). Isolated in 85% yield as a pale yellow oil. IR 2238, 1717, 1597, 1436, 1257, 1206, 1069; ^1H NMR δ 2.61 (t, J=7.5 Hz, 2H), 2.83 (t, J_{av}=7.5 Hz, 2H), 3.76 (s, 3H), 3.81 (s, 6H), 6.34–6.39 (m, 3H); ^{13}C NMR δ20.7, 34.1, 52.5, 54.9, 55.3, 73.5, 88.7, 98.7, 106.4, 141.9, 160.9. HRFABMS m/z 248.1049 $(M)^+$, calcd for $C_{17}H_{12}O_2$ 248.1049.

4.7. Preparation of 46

Compound **46** was prepared in a two step sequence from 3-hydroxy-4,5-dimethoxy-benzoic acid methyl ester following the procedure of Wipf.[30]

4.7.1. 3-(1-Cyclopropylprop-2-ynyloxy)-4,5-dimethoxy-benzoic acid methyl ester (46). A pale yellow oil. IR 2836, 2117, 1719, 1588, 1502, 1422, 1344, 1226, 1110, 765 cm^{-1}; ^1H NMR δ 0.56–0.69 (m, 4H), 1.43–1.50 (m, 1H), 2.45 (d, J=2.0 Hz, 1H), 3.89 (s, 6H), 3.93 (s, 3H), 4.64 (dd, J=2.0, 6.7 Hz, 1H), 7.31 (d, J=1.8 Hz, 1H), 7.44 (d, J=1.8 Hz, 1H); ^{13}C NMR 2.1, 3.5, 15.0, 52.2, 56.2, 61.0, 73.0, 75.0, 79.7, 107.6, 111.8, 124.8, 150.5, 153.0. APCI m/z 291.0579 $(M+H)^+$, calcd for $C_{16}H_{19}O_5$ 291.1232.

4.8. Preparation of 50

To a solution **48** (195 mg, 1.04 mmol) in 1 mL of HMPA was added *n*-BuLi (680 μL, 1.6 M solution in hexanes, 1.09 mmol, 1.05 equiv.) at 0°C. After 30 min (3-bromo-propoxy)-*tert*-butyl-dimethyl-silane (262 mg, 1.04 mmol) was added. The reaction was allowed to warm to ambient temperature and stirred overnight. The reaction was quenched with water and extracted with pentane dried over $MgSO_4$ and concentrated in vacuo. The residue was purifed by colum chromatography by eluting with hexanes/CH_2Cl_2 (8:2).

4.8.1. *tert*-Butyl-[6-(3,5-dimethylphenoxy)-6-methyl-hept-4-ynyloxy]dimethylsilane (50). Isolated in 46% yield as a colorless oil. IR 2858, 2361, 1610, 1595, 1472, 1103 cm^{-1}; ^1H NMR 0.05 (s, 3H), 0.90 (s, 9H), 1.60 (s, 6H), 1.70 (quintet, J_{av}=6.5 Hz, 2H), 2.27–2.36 (m, 8H), 3.66 (t, J=6.1 Hz, 2H), 6.68 (s, 1H), 6.84 (s, 2H); ^{13}C NMR δ −5.4, 15.1, 18.3, 21.4, 25.9, 30.0, 31.6, 61.5, 72.5, 82.8, 85.6, 119.1, 124.2, 138.2, 155.7. APCI m/z 361.1588 $(M+H)^+$, calcd for $C_{22}H_{37}O_2Si$ 361.2563.

4.9. Preparation of 52

Compound **52** was prepared in the same manner as described above for the synthesis of **32**. 1-Pent-4-ynyl-1*H*-pyrrole[31] (291 mg, 2.19 mmol), *n*-BuLi (1.5 mL, 1.6 M solution in hexanes, 2.40 mmol), and $ClCO_2Me$ (204 μL, 2.61 mmol). Purification by column chromatography by eluting with hexanes/EtOAc (8:1).

4.9.1. 6-Pyrrol-1-yl-hex-2-ynoic acid methyl ester (52). Isolated in 77% yield as a clear oil. IR 3100, 2238, 1716, 1434, 1261, 1078, 728 cm^{-1}; ^1H NMR δ 2.00 (quintet, J=6.8 Hz, 2H), 2.26 (t, J=6.9 Hz, 2H), 3.77 (s, 3H), 4.00 (t, J=6.6 Hz, 2H), 6.14 (t, J=2.1 Hz, 2H), 6.65 (t, J=2.1 Hz, 2H); ^{13}C NMR δ 15.56, 29.07, 47.50, 52.46, 73.55, 87.65, 108.18, 120.35, 153.79. HRFABMS m/z 192.1022 $(M+H)^+$, calcd for $C_{11}H_{14}NO_2$ 192.1025.

4.10. Preparation of 54

Compound **54** was prepared in a three step sequence from 3-pyrrol-1-yl-propan-1-ol[32] using Dess–Martin oxidation[33] and the Corey–Fuchs[34] procedure.

4.10.1. 5-Pyrrol-1-ylpent-2-ynoic acid methyl ester (54). Isolated in 11% overal yield as a clear oil. IR 3103, 2237, 1716, 1654, 1560, 1258, 1070, 721 cm^{-1}; ^1H NMR δ 2.75 (t, J=5.3 Hz, 2H), 3.75 (s, 3H), 4.09 (t, J=5.3 Hz, 2H), 6.15 (t, J=1.6 Hz, 2H), 6.67 (t, J=1.6 Hz, 2H); ^{13}C NMR δ 22.4, 47.2, 52.7, 74.7, 85.2, 108.7, 120.3, 153.5. HREIMS m/z 177.0800 $(M)^+$, calcd for $C_{10}H_{11}NO_2$ 177.0790.

4.11. Preparation of 58

Compound **58** was prepared in the same manner described above for **38**. 3-Furylmethanol (1.5 mL, 17.2 mmol), NaH (759 mg, 19.0 mmol), and 1-bromo-2-butyne (1.7 mL, 19.0 mmol). Purification by column chromatography by eluting with hexanes/EtOAC (8:1).

4.11.1. 3-But-2-ynyloxymethylfuran (58). Isolated in 65% yield as a colorless oil. IR 3132, 2292, 2226, 1503, 1355, 1159, 1136, 1082, 1064, 874, 795, 602 cm^{-1}; ^1H NMR δ 1.85 (t, J=2.3 Hz, 3H), 4.08 (q, J=2.3 Hz, 2H), 4.43 (s, 2H), 6.41 (d, J=1.2 Hz, 1H), 7.37 (t, J=1.6 Hz, 1H), 7.41 (s, 1H). ^{13}C NMR δ 3.6, 57.3, 62.4, 74.9, 82.6, 110.4, 121.5, 141.0, 143.3. HREIMS m/z 151.0761 $(M+H)^+$, calcd for $C_9H_{11}O_2$ 151.0759.

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