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Enamides and Enesulfonamides as Nucleophiles: Formation of Complex Ring Systems through a Platinum(II)-Catalyzed Addition/Friedel−Crafts Pathway

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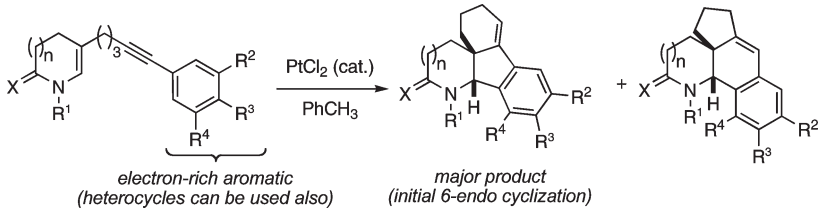

Cyclic enamine derivatives (enesulfonamides and enamides) tethered to an 1-arylalkynyl fragment undergo a platinum(II)-catalyzed tandem alkyne addition/Friedel−Crafts ring closure to form nitrogen-containing polycyclic structures. Regioselectivity in the initial addition of the enesulfonamide or enamide nucleophile to the platinum(II)−alkyne complex is important. Electron-rich arenes and heterocycles led to the formation of products resulting from an initial *6-endo* cyclization. Twenty-three examples of this process are presented.

Introduction

The complexity and diversity of nitrogen-containing ring systems within alkaloids make them inspiring targets for the synthetic organic chemistry community.[1] Alkaloids often have significant interest for chemical biology studies as well.[2] Indeed, the biological potency of nitrogen-containing molecules is a main interest of the pharmaceutical industry.[3] Consequently, the development of methods to generate ring systems that contain nitrogen for applications to either natural product synthesis or non-natural compound construction is a useful aim.[4]

As part of our research direction involved in this topic, we have been interested in developing metal-catalyzed reactions that utilize the π-nucleophilicity of enamine derivatives.[5] The enamine nitrogen in most instances is derivatized using an electron-withdrawing group such as an amide (forming an *N*-acylenamine or enamide), carbamate (*N*-carbamoylenamine or enecarbamate), or sulfonyl group (*N*-sulfonylenamine or enesulfonamide) to improve stability and enable isolation and purification (Figure 1).[6] These enamide, enecarbamate, or enesulfonamide functional groups have most been used most often as precursors to *electrophilic* reactive species such as *N*-acylazacarbenium ions.[7] The latent nucleophilic behavior

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(4) Some reviews dealing with heterocycle construction: (a) Dake, G. R. *Tetrahedron* **2006**, *62*, 3467–3492. (b) Padwa, A.; Bur, S. K. *Tetrahedron* **2007**, *63*, 5341–5378. (c) Naito, T. *Chem. Pharm. Bull.* **2008**, *56*, 1367–1383.

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(6) For a review of the chemistry of enamides and related derivatives: Carbery, D. R. *Org. Biomol. Chem.* **2008**, *6*, 3455–3460.

(7) (a) For examples, see: (a) Norton Matos, M.; Afonso, C. A. M.; Batey, R. A. *Tetrahedron* **2005**, *61*, 1221–1244. (b) Padwa, A.; Lee, H. I.; Rashatasakhon, P.; Rose, M. *J. Org. Chem.* **2004**, *69*, 8209–8218. (c) David, M.; Dhimane, H.; Vanucci-Bacque, C.; Lhommet, G. *Heterocycles* **2001**, *55*, 941–949. (d) Leroy, C.; Dupas, G.; Bourguigon, J.; Queguiner, G. *Tetrahedron* **1994**, *50*, 13135–13144. (e) Flynn, G. A.; Giroux, E. L.; Dage, R. C. *J. Am. Chem. Soc.* **1987**, *109*, 7914–7915. (f) Cassayre, J.; Quiclet-Sire, B.; Saunier, J.-P.; Zard, S. Z. *Tetrahedron Lett.* **1998**, *39*, 8995–8998. (g) Lee, J. Y.; Lee, Y. S.; Chung, B. Y.; Park, H. *Tetrahedron* **1997**, *53*, 2449–2458. (h) Shinohara, T.; Takeda, A.; Toda, J.; Sano, T. *Heterocycles* **1998**, *48*, 981–992. (i) Hurley, P. B.; Dake, G. R. *J. Org. Chem.* **2008**, *73*, 4131–4138. (j) Dake, G. R.; Fenster, M. D. B.; Hurley, P. B. *J. Org. Chem.* **2004**, *69*, 5668–5675. (k) Fenster, M. D. B.; Patrick, B. O.; Dake, G. R. *Org. Lett.* **2001**, *3*, 2109–2112.

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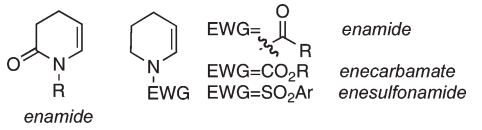
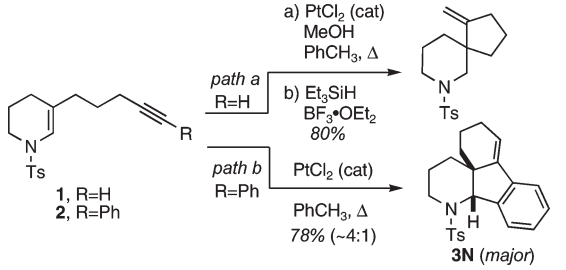


FIGURE 1. Enamine derivatives.

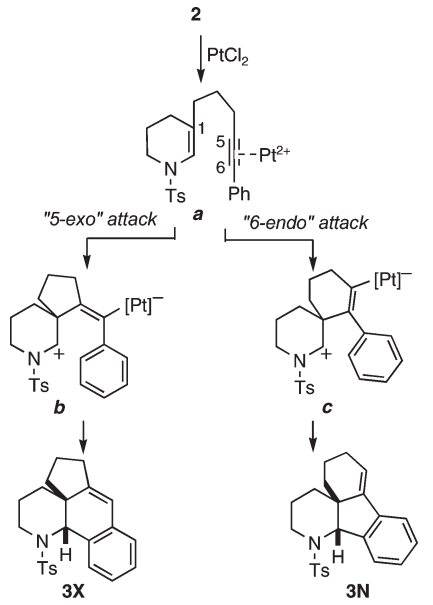
of these enamine derivatives also has been recognized and used, especially within the past decade.[8] The use of these compounds as π-nucleophiles within reactions activated by metal catalysis has been studied to a much lesser extent.[5,9−11]

We have been interested in developing reactions that utilize the latent nucleophilicity of these enamine derivatives within the context of "electrophilic" metal-catalyzed processes, specifically those that involve platinum(II), gold(I), or silver(I) salts.[12] An example of such a process is a spiroannulation forming quaternary carbon centers at the 3-position of enamine derivatives (Scheme 1, path a).[5b] Interestingly, modification of the substrate structure by the addition of a phenyl ring to the alkyne terminus led to an alternative reactivity profile. In this instance, both the latent nucleophilic and electrophilic character of the

SCHEME 1. Spiroannulations at the β-Carbon of Enesulfonamides



SCHEME 2. Formation of Regioisomeric Products



enesulfonamide was observed (Scheme 1, path b). Presumably, an interaction between the 1-aryl-substituted alkyne in **2** with the Pt(II) salt led to a tandem addition of the enesulfonamide to the (putative) metal−alkyne complex followed by a Friedel−Crafts/Pictet−Spengler-type ring closure to generate tetracycle **3N**[5b] as the major product within a roughly 4:1 mixture of constitutional isomers.

As indicated in the text above, two products were observed in the reaction of **2** with platinum(II) chloride. These compounds arose from differing regiochemical modes of addition of the enesulfonamide to the alkyne within **2** (Scheme 2). Formation of an intermediary platinum−alkyne π-complex ***a*** activates the alkyne for addition by the nucleophilic enesulfonamide. Addition of the nucleophile to the alkyne complex could occur in a *5-exo* fashion to form intermediate ***b***. Alternatively, addition could take place through a *6-endo* manifold to produce intermediate ***c***. Each of these intermediates could then undergo a Friedel−Crafts (Pictet−Spengler)-type ring

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(13) The suffixes "N" and "X" used in the numbering system in this paper are derived as follows: products that are formed through an initial *6-endo* addition of the enamine derivative to the alkyne complex are given the suffix "N", while products that derive from an initial *5-exo* cyclization are given the suffix "X".

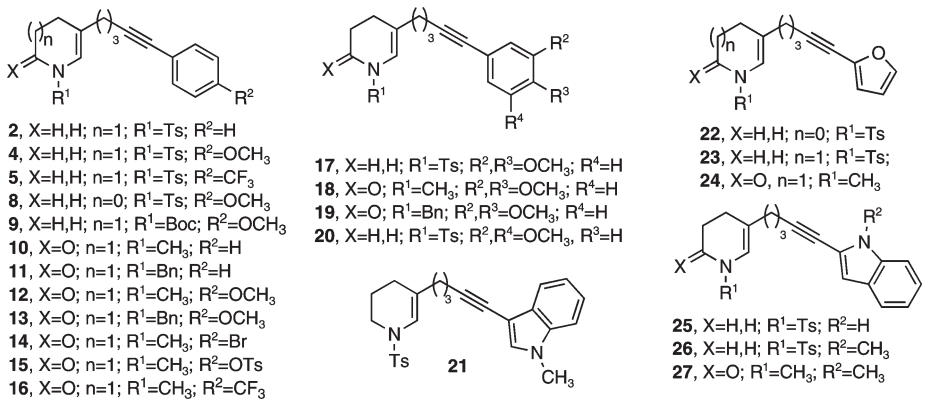
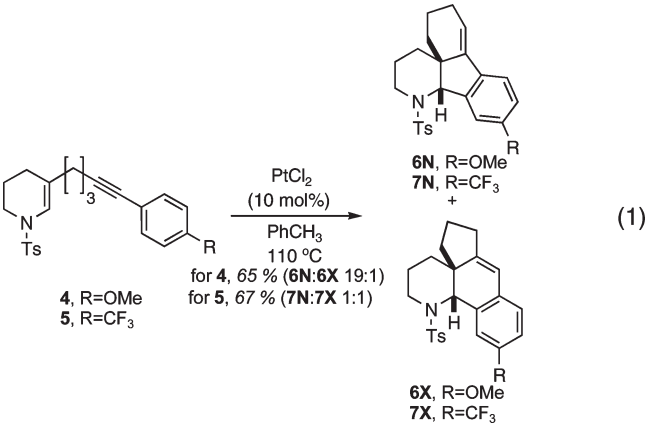


FIGURE 2. Substrates used in this study.

closure and proto-demetalation to generate the observed products **3X** or **3N**, respectively.[13,14]

On the basis of Scheme 2, it was reasonable to predict that manipulation of the electronic properties of the alkyne, and therefore the electronics of an intermediary alkyne−platinum π-complex, could affect the regioselectivity of this platinum(II)-catalyzed cyclization reaction. For example, an electron-donating substituent on the arene ring could add electron density through resonance to one of the carbons of the alkyne, rendering that alkyne carbon less electrophilic. To that end, it was demonstrated that substituents at the 4-position of the aryl ring attached to the alkyne could be modified in order to adjust the ratio of products in this process (eq 1). An electron-donating substituent (R = OMe) within **4** favored the formation of isomer **6N** in a 19:1 ratio. An electron-withdrawing substituent ($R = CF_3$) in **5** altered the ratio roughly 5-fold in the opposite direction relative to the standard (R = H) process, generating **7N** and **7X** as a 1:1 mixture of constitutional isomers.



(1)

The relatively high regioselectivity within the reaction of **4** with platinum(II) chloride encouraged us to more fully explore this transformation. Specifically, other electron-rich arene or heteroaromatic systems installed as the 1-alkynyl substituent were examined. It is important to note that during the course of these investigations, Zhai and co-workers used our reported platinum(II)-catalyzed cyclization as the basis to build a molecule that incorporated the tetracyclic ring system within nakadomarin. The cyclization substrate in that case featured a five-membered enecarbamate tethered via a sulfonamide linker to a 3-alkynylfuran.[15] Our studies of this platinum(II)-catalyzed cyclization chemistry are presented in this report.

Results and Discussion

Substrate Preparation. The structures of the substrates used in this study are shown in Figure 2. In our experience, six-membered enamine derivatives display a reasonable balance between synthetic accessibility, stability, and reactivity compared to those enamine derivatives within five- or seven-membered rings. As the most regioselective reaction in our previous study had an arene ring with a *p*-methoxy (electron-donating) group, we determined to largely study substrates having electron-rich arene or heterocyclic ring systems. A generalized synthesis of these substrates is shown in Scheme 3. The methods are patterned from those previously reported by our group.[5b] The key step in the substrate construction was a Sonogashira coupling process that was used to form the C−C bond between the alkyne and arene ring.[16] The full details of the synthesis of each substrate are presented in the Supporting Information.[17]

Cyclization Experiments. It is important to note that the products of these cyclization experiments are inseparable. The product ratios were determined by inspection of the ^{1}H NMR spectrum of unpurified reaction mixtures. The characteristic data for a typical NMR analysis are presented in Figure 3. In this example, the diagnostic signals for the product mixtures **3X**/**3N** and **6X**/**6N** are the signals due to alkenyl protons H_{N1} or H_{X1} and the benzylic protons H_{N2} or H_{X2}. The structures of **3X**/**3N** were established using X-ray crystallography.[18] The products resulting from an initial

(14) For other examples of "coinage-metal"-catalyzed reactions that are sequenced with a Friedel−Crafts reaction, see: (a) Nieto-Oberhuber, C.; López, S.; Echavarren, A. M. *J. Am. Chem. Soc.* **2005**, *127*, 6178–6179. (b) Nieto-Oberhuber, C.; Pérez-Galán, P.; Herrero-Gómez, E.; Lauterbach, T.; Rodríguez, C.; López, S.; Bour, C.; Rosellón, A.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2008**, *130*, 269–279. (c) Toullec, P. Y.; Genin, E.; Leseurre, L.; Genêt, J.-P.; Michelet, V. *Angew. Chem., Int. Ed.* **2006**, *45*, 7427–7430. (d) Toullec, P. Y.; Chao, C.-M.; Chen, Q.; Gladiali, S.; Genêt, J.-P.; Michelet, V. *Adv. Synth. Catal.* **2008**, *350*, 2401–2408. (e) Leseurre, L.; Chao, C.-M.; Seki, T.; Genin, E.; Toullec, P. Y.; Genêt, J.-P.; Michelet, V. *Tetrahedron* **2009**, *65*, 1911–1918. (f) Odabachian, Y.; Gagosz, F. *Adv. Synth. Catal.* **2009**, *351*, 379–386. (g) Gourdet, B.; Lam, H. W. *J. Am. Chem. Soc.* **2009**, *131*, 3802–3803. (h) For an early example, see: Snider, B. B.; Kwon, T. *J. Org. Chem.* **1992**, *57*, 2399–2410.

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(16) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874–922.

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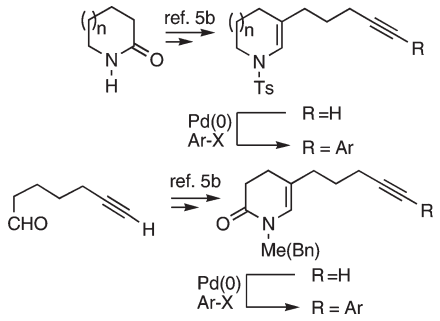
(18) Please see the Supporting Information for details regarding the X-ray structure. Compound sets **3N/3X** and **36N/36X** contain both isomers in the unit cell. Atoms within the minor isomer are displayed in the CIF.

SCHEME 3. Substrate Preparation



6-endo cyclization (e.g., **3N** and **6N**, in these examples) had a triplet between δ 5.50 and 6.00 with a characteristically small coupling constant ($J \approx 3.5$ Hz) in the ^{1}H NMR spectra. In the case of **3N** and **6N**, these signals are at δ 5.96 and δ 5.83, respectively. Those isomers resulting from an initial *5-exo* cyclization had alkenyl protons that resonated further downfield in the ^{1}H NMR spectrum. The signals are at δ 6.15 and δ 6.11 for **3X** and **6X**, respectively. The protons labeled H_{N2} also gave rise to useful signals for interpretation in the ^{1}H NMR spectrum. The signals from products of initial *6-endo* cyclization were consistently upfield compared to the signals from products of initial *5-exo* cyclization.

A set of substrates that had *para* substitution on the aryl ring were initially evaluated (eq 2 and Table 1). Unless otherwise noted, substrates were subjected to 10 mol % of the platinum catalyst in toluene at 110 °C. Less reactive substrates required heating at 130 °C to achieve reasonable cyclization rates (entries 18, 20, and 21). Results from the earlier study are included in Table 1 for completeness (entries 1−3). Two alternative catalyst systems were attempted for the cyclization of **4**. Running the reaction under a CO atmosphere[19] inhibited the reaction as a slow conversion only led to the isolation of a 38% yield of a 3:2 mixture of **4** and **6N**/**6X** (entry 4). Alternatively, catalysis using a cationic gold(I) system (PPh_3AuCl, $AgSbF_6$, 10 mol % each) resulted in a 30% yield of **6N** (entry 5). These and some later experiments (entries 12 and 13) established that Pt(II) systems were superior for this reaction. The enesulfonamide **8** within a five-membered ring cyclized effectively to generate largely the *"6-endo"* cyclization product **28N** in 62% yield (entry 6). Ene *tert*-butyl carbamate **9** was briefly studied. The best conditions for the reaction of **9** involved 20 mol % loading of platinum(II) chloride at 60 °C for 48 h to obtain 48% of **29N** (entry 7). Further reaction optimization for **9** was not successful. Happily, though, enamides **10**−**13** reacted effectively and generally followed the same regiochemical trend as the enesulfonamides. Substrates having phenyl-substituted alkynes cyclized to form products having a modest ratio favoring the *6-endo* product (entries 8, 9 and 10). We were interested to test whether the use of platinum(II) bromide as the catalyst would optimally alter the regioselectivity of the addition reaction.[20] Its use did not result in any useful trends; generally, the cyclizations were less regioselective for the *6-endo* cyclization isomer (entries 10, 17, and 21). Substrates having electron-donating *p*-methoxy groups typically reacted to favor the *6-endo* isomer in a synthetically useful ratio (entries 11, 16, and 17). Alternative catalyst systems were briefly examined in the cyclizations of **12**. Gold(I) systems ranged from inactive to overly destructive (entries 12−14). The addition of S-Phos to a platinum(II)-based catalyst system substantially decreased the reactivity (entry 15).[21] Lastly, electron-withdrawing substituents on the arene ring such as −Br, −OTs, or $-CF_3$ groups lowered the reactivity of the substrates and decreased the regioselectivity of the process (entries 18−21). The structure of the product of *5-exo* cyclization from the reaction of **16** under these conditions was supported using X-ray crystallography. As expected, the aryl bromide substituent within **14** was compatible with the reaction conditions involving Pt(II), highlighting the orthogonal nature between Pt(II)- and Pd(0)-based catalytic cycles (entry 18).

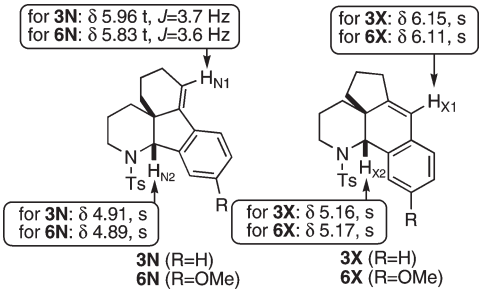


FIGURE 3. Diagnostic signals in sample ^{1}H NMR analysis of **3N**/**3X** and **6N**/**6X**.

The results from Table 1 indicated that the reaction proceeded most effectively with substrates that were appended to electron-rich aromatic rings. A set of substrates derived from veratrole (1,2-dimethoxybenzene) were consequently examined (Scheme 4). Enesulfonamide **17** reacted with platinum chloride to produce **37N**/**37X** in a 20:1 ratio, as established by NMR spectroscopy, in a 61% yield (entry 1). Although in principle two sites are available for the second step of this process involving electrophilic aromatic substitution, the more sterically hindered potential product was not observed. Generally, the reactions of enamides are higher yielding. The reaction of enamide **18** proceeded in 98% yield using platinum chloride as a 10:1 mixture of products (entry 2). Enamide **39N**, the product of the reaction of **19** with platinum(II), was also characterized using X-ray crystallography. As observed previously, the utilization of platinum bromide (10 mol %) to catalyze the reaction of **19** offered little practical advantage (entry 4).

Unlike **17**, enesulfonamide **20** contains a symmetrically substituted dimethoxylated arene ring attached to the alkyne. A comparison of the results of the reaction of **17** and **20** to

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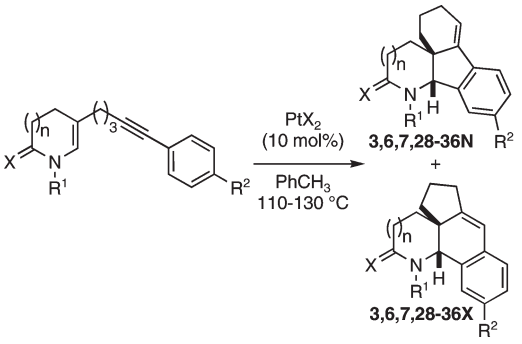
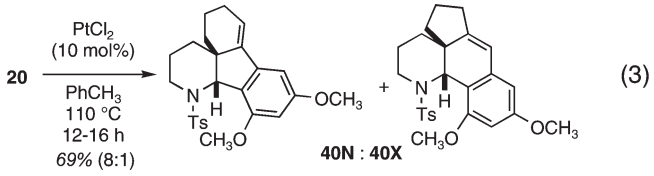
platinum(II) catalysis can be used to evaluate the relative importance of the para substituent on the regioselectivity of the addition of the enesulfonamide to the alkyne. The result in eq 3 (69%, 8:1) compared to that in Scheme 3 (61%, 20:1) suggests that the electron donation from the substituent para to the alkyne within the substrate is a significant contributor. Not too surprisingly, these results suggest that the electronic polarization of the alkyne is more important relative to the nucleophilicity of the arene ring in the subsequent Friedel−-Crafts reaction.



(2)



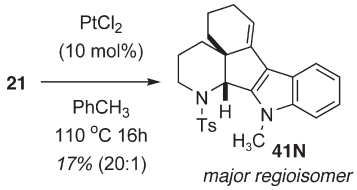
(3)

TABLE 1. Evaluation of Substrates Having Para-Substituted Arene Rings

entry	substrate	X	R^1	R^2	n	products	yield[a] (%)	ratio[b]
1	**2**	H, H	Ts	H	1	**3N:3X**	78	4:1
2	4	H, H	Ts	OCH_3	1	**6N:6X**	65	19:1
3	5	H, H	Ts	CF_3	1	**7N:7X**	67	1:1
4[c]	**4**	H, H	Ts	OCH_3	1	**6N:6X**	see text	nd
5[d]	**4**	H, H	Ts	OCH_3	1	**6N:6X**	30	>25:1
6	**8**	H, H	Ts	OCH_3	0	**28N:28X**	62	25:1
7[e]	**9**	H, H	Boc	OCH_3	1	**29N:29X**	48	>25:1
8	**10**	O	CH_3	H	1	**30N:30X**	98	10:1
9	**11**	O	Bn	H	1	**31N:31X**	77	4:1
10[f]	**11**	O	Bn	H	1	**31N:31X**	61	1.5:1
11	**12**	O	CH_3	OCH_3	1	**32N:32X**	79	7:1
12[g]	**12**	O	CH_3	OCH_3	1	**32N:32X**	NR	nd
13[h]	**12**	O	CH_3	OCH_3	1	**32N:32X**	41	3:1
14[i]	**12**	O	CH_3	OCH_3	1	**32N:32X**	dec	nd
15[j]	**12**	O	CH_3	OCH_3	1	**32N:32X**	11	nd
16	**13**	O	Bn	OCH_3	1	**33N:33X**	79	18:1
17[e]	**13**	O	Bn	OCH_3	1	**33N:33X**	88	9:1
18	**14**	O	CH_3	Br	1	**34N:34X**	66	2:1
19	**15**	O	CH_3	OTs	1	**35N:35X**	68	2:1
20	**16**	O	CH_3	CF_3	1	**36N:36X**	52	1:2
21[e]	**16**	O	CH_3	CF_3	1	**36N:36X**	46	1:1.6

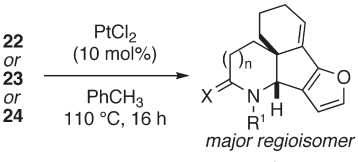
[a]Isolated yields. NR = no reaction; dec = decomposition. [b]Ratio was determined by inspection of ^{1}H NMR spectrum of product mixture. nd = not determined. [c]Reaction was carried out using $PtCl_2$ under a CO atmosphere. [d]Reaction was carried out using PPh_3AuCl (10 mol %) and $AgSbF_6$ (10 mol %) at 60 °C. [e]Reaction was carried out using $PtCl_2$ (20 mol %) at 60 °C for 48 h. [f]Reaction was carried out using $PtBr_2$ (10 mol %). [g]Reaction was carried out using AuCl, PPh_3, and $AgSbF_6$ (5 mol % each) at 60 °C. [h]Reaction was carried out using PPh_3AuCl and $AgSbF_6$ (5 mol % each) at 80 °C. [i]Reaction was carried out using S-PhosAuCl and $AgSbF_6$ (5 mol % each) at 60 °C. [j]Reaction was carried out using $PtCl_2$ (10 mol %) and S-Phos (15 mol %).

Heterocyclic Arenes. We were interested in incorporating heteroaromatic components within these platinum(II)-catalyzed cyclization processes to increase the structural complexity of the products. Unfortunately, these experiments revealed some limitations of scope for this metal-catalyzed process. As an example, compound **21** has its alkyne substituted with a *N*-methylindole substituent at the 3-position of the indole. Pentacycle **41N** is produced in low yield (17%) when **21** is heated with platinum(II) chloride in toluene. The majority of the reaction mixture is noncharacterizable decomposition.



(4)

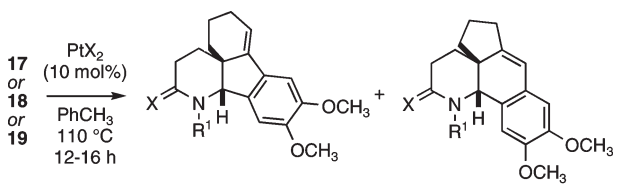
Compounds **22**−**24** each have a furan ring (attached at C-2 of the furan) appended to its alkyne. These cyclization reactions proceed in low to moderate yield (eq 5). As an example, enesulfonamide **22** reacts to produce tetracycle **42N** in 37% yield. Although, or perhaps because, the overall isolated yield is low, the minor regioisomer in these cyclizations was only detected to a very small extent or not at all. In contrast, enamide **24** reacted to generate tetracyclic products **44N**/**44X** in 51% yield as a 7:1 ratio of isomers.



(5)

1) for **22** **42N**:**42X** (X=H,H, n=0, R^1=Ts) *37%* (>25:1)
2) for **23** **43N**:**43X** (X=H,H, n=1, R^1=Ts) *32%* (20:1)
3) for **24** **44N**:**44X** (X=O, n=1, R^1=CH_3) *51%* (7:1)

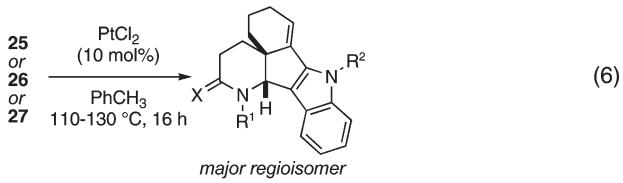
SCHEME 4. Cyclization of Veratrole Derivatives



1) for **17** (X=H,H, R^1=Ts) using $PtCl_2$: **37N**: **37X** *61%* (20:1)
2) for **18** (X=O, R^1=CH_3) using $PtCl_2$: **38N**: **38X** *98%* (10:1)
3) for **19** (X=O, R^1=Bn) using $PtCl_2$: **39N**: **39X** *78%* (20:1)
4) for **19** (X=O, R^1=Bn) using $PtBr_2$: **39N**: **39X** *79%* (14:1)

Replacement of the furan moiety with an indole fragment gave better results (eq 6). The treatment of enesulfonamide **25** with platinum(II) catalysis generated **45N**/**45X** as a 20:1 mixture of isomers in 36% yield. The low yield for this process was attributed to the unfunctionalized nitrogen on the indole ring since its *N*-methylated analogue **26** cyclized to form a similar ratio in 77% yield. Enamide **27** could be reacted in an analogous manner to produce **47N**/**47X** in 80% yield as a 20:1 mixture of isomers. The unusual ring skeleta of

46N and **47N** could have use as structural mimics of indole alkaloids.



(6)

1) for **25** **45N:45X** (X=H,H, R^1=Ts, R^2=H) *36%* (20:1)
2) for **26** **46N:46X** (X=H,H, R^1=Ts, R^2=CH_3) *77%* (20:1)
3) for **27** **47N:47X** (X=O, R^1=CH_3, R^2=CH_3) *80%* (20:1)

Concluding Remarks

These results demonstrate a potential utility for these platinum(II)-catalyzed addition−Friedel−Crafts processes to generate nitrogen-containing ring fragments with reasonable structural complexity. The understanding of the direction and magnitude of the regioselectivity of the derivatized enamine nucleophile to the metal complexed alkyne is critical as, in our hands at least, the products of these cyclizations are inseparable. The electronic properties of the 1-arylalkyne could be adjusted by modification of either the substituents on the arene ring or the arene ring itself. Substrates having electron-rich aromatic systems react in a predictable manner to produce useful ratios of the product isomer that results from an initial 6-endo cyclization. Some heteroaromatic systems (e.g., furans and unsubstituted indoles) do not appear to be compatible with the reaction conditions at this current stage of reaction development. Future work includes: (a) the modification of the metal catalyst in order to generate products with some level of enantiopurity, (b) a study in which the putative azacarbenium ion intermediate is reacted with different internal or external nucleophiles (e.g., heteroatoms or allylsilanes), and (c) the synthetic processing of these reaction products to generate compounds of interest in natural product synthesis or biological studies. Efforts toward these ends are ongoing in our laboratory.

Experimental Section

Tetracycles 28N and 28X. A solution of 0.025 g of enesulfonamide **8** (0.69 mmol) and 1.8 mg of platinum(II) chloride (0.0069 mmol) in 0.5 mL of toluene was stirred in a sealed tube at 110 °C for 16 h. The reaction mixture was cooled to rt and directly purified by column chromatography on triethylamine-washed silica gel (6:1 hexanes/ethyl acetate) to afford 0.017 g (62%) of a 25:1 mixture of **28N** and **28X** as a white crystalline solid. Mp: 162 °C dec. IR (film): 2937, 1343, 1162, 735 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, J = 8.2 Hz, 2H), 7.37−7.35 (m, 1H), 7.36 (d, J = 7.8 Hz, 2H), 7.25 (d, J = 8.6 Hz, 1H), 6.84 (dd, J = 8.6, 2.3 Hz, 1H), 5.83 (t, J = 3.5 Hz, 1H), 4.61 (s, 1H), 3.87 (s, 3H), 3.56−3.52 (m, 1H), 3.28−3.21 (m, 1H), 2.47 (s, 3H), 2.21−2.02 (m, 2H), 1.86−1.74 (m, 2H), 1.66−1.40 (m, 2H), 1.04 (m, 1H), 0.90 (m, 1H). Additional peaks associated with the minor isomer **28X**: δ 6.10 (s, 1H), 4.79 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) for the major isomer **28N**: δ 160.6, 144.5, 143.8, 141.2, 134.4, 131.5, 129.9, 128.1, 121.4, 117.0, 116.6, 110.2, 72.9, 55.8, 53.2, 49.0, 34.8, 29.0, 24.5, 21.8, 19.3. HRMS (EI): calcd for $C_{23}H_{25}O_3NS$ $(M)^+$ 395.1555, found 395.1552.

Tetracycles 6N and 6X. A solution of 40 mg of enesulfonamide **4** (0.098 mmol) and 2.7 mg of platinum(II) chloride (0.010 mmol) in 1 mL of toluene was stirred in a sealed tube at 110 °C for 12 h. The reaction mixture was cooled to rt and directly purified by column chromatography on triethylamine-washed silica gel (8:1 to 5:1 hexanes/ethyl acetate) to afford 26 mg (65%) of a 19:1 mixture of **6N** and **6X** as a colorless film which solidified into a white solid upon storage in the freezer. The solid was recrystallized from diethyl ether. Mp: 121−123 °C. IR (film): 2938, 1608, 1484, 1154 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, J = 8.3 Hz, 2H), 7.35 (d, J = 8.3 Hz, 2H), 7.25 (d, J = 8.3 Hz, 1H), 6.76 (dd, J = 8.3, 2.2 Hz, 1H), 6.60 (s, 1H), 5.83 (t, J = 3.6 Hz, 1H), 4.89 (s, 1H), 3.91 (d, J = 14.0 Hz, 1H), 3.71 (s, 3H), 2.91 (td, J = 12.6, 2.2 Hz, 1H), 2.44 (s, 3H), 2.17−2.10 (m, 2H), 1.79−1.53 (m, 4H), 1.50−1.16 (m, 4H). Additional peaks associated with the minor isomer **6X**: δ 6.90 (d, J = 8.3 Hz, 1H), 6.67 (dd, J = 8.3, 2.6 Hz, 1H), 6.55 (s, 1H), 6.11 (s, 1H), 5.17 (s, 1H), 3.61 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) for the major isomer **6N**: δ 159.9, 143.3, 143.0, 142.1, 138.9, 132.6, 129.6, 127.0, 121.7, 116.9, 114.8, 108.3, 66.2, 55.4, 44.5, 41.7, 29.1, 28.9, 24.5, 21.5, 20.8, 18.1. HRMS (ESI): calcd for $C_{24}H_{28}NO_3{}^{32}S$ $(M + H)^+$ 410.1790, found 410.1784.

Tetracycles 33N and 33X. A solution of 68 mg of enamide **13** (0.19 mmol) and 5.0 mg of platinum(II) chloride (0.019 mmol) in 0.5 mL of toluene was stirred in a sealed tube at 110 °C for 16 h. The reaction mixture was cooled to rt and directly purified by column chromatography on triethylamine-washed silica gel (5:1 to 1:1 hexanes:ethyl acetate) to afford 54 mg (79%) of an 18:1 mixture of **33N** and **33X** as a white foam. IR (film): 2938, 1642, 732, 648 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.32−7.25 (m, 6H), 6.77 (dd, J = 8.2, 2.0 Hz, 1H), 6.46 (d, J = 1.6 Hz, 1H), 5.78 (t, J = 3.7 Hz, 1H), 5.34 (d, J = 14.5 Hz, 1H), 4.50 (d, J = 14.5 Hz, 1H), 4.39 (s, 1H), 3.68 (s, 3H), 2.39−2.32 (m, 1H), 2.27−2.20 (m, 1H), 2.18−2.11 (m, 1H), 2.05−1.93 (m, 2H), 1.78−1.63 (m, 4H), 1.32−1.25 (m, 1H). Additional peaks associated with the minor isomer **33X**: δ 6.97 (d, J = 8.2 Hz, 1H), 6.16 (s, 1H), 5.95 (d, J = 14.1 Hz, 1H), 4.26 (s, 1H), 3.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) for the major isomer **33N**: δ 173.2, 161.1, 145.7, 144.5, 138.8, 133.7, 129.8, 129.7, 128.7, 122.0, 116.7, 115.8, 108.8, 70.5, 56.5, 52.0, 47.3, 34.4, 33.6, 32.1, 25.2, 19.0. HRMS (ESI): calcd for $C_{24}H_{25}NO_2Na$ $(M + Na)^+$ 382.1783, found 382.1771.

Tetracycles 38N and 38X. A solution of 34 mg of enamide **18** (0.11 mmol) and 2.8 mg of platinum(II) chloride (0.011 mmol) in 0.5 mL of toluene was stirred in a sealed tube at 110 °C for 16 h. The reaction mixture was cooled to rt and directly purified by column chromatography on triethylamine washed silica gel (1:1 hexanes/ethyl acetate) to afford 33 mg (98%) of a 10:1 mixture of **38N** and **38X** as an off-white solid. Mp: 132−134 °C. IR (neat): 2964, 1642, 731 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.87 (s, 1H), 6.76 (s, 1H), 5.82 (br s, 1H), 4.33 (s, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.33 (s, 3H), 2.37−2.22 (m, 3H), 2.14−2.03 (m, 2H), 1.90−1.83 (m, 2H), 1.77−1.71 (m, 2H), 1.62−1.52 (m, 1H). Additional peaks associated with the minor isomer **38X**: δ 6.60 (s, 2H), 6.15 (br s, 1H), 3.25 (s, 3H), 2.80 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) for the major isomer **38N**: δ 172.6, 150.7, 150.6, 144.8, 136.4, 133.2, 116.9, 107.2, 104.0, 73.8, 57.1, 57.0, 47.0, 37.9, 32.8, 31.3, 30.6, 25.2, 18.9. HRMS (ESI): calcd for $C_{19}H_{23}NO_3Na$ $(M + Na)^+$ 336.1576, found 336.1570.

Tetracycle 42N. A solution of 17 mg of enesulfonamide **22** (0.048 mmol) and 1.3 mg of platinum(II) chloride (0.0048 mmol) in 0.5 mL of toluene was stirred in a sealed tube at 110 °C for 16 h. The reaction mixture was cooled to rt and directly purified by column chromatography on triethylamine-washed silica gel (5:1 hexanes/ethyl acetate) to afford 6.4 mg (37%) of the title compound **42N** as a clear, colorless oil. IR (film): 2930, 1344, 1164 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 8.6 Hz, 2H), 7.32 (d, J = 2.0 Hz, 1H), 6.43 (d, J = 2.0 Hz, 1H), 5.63 (t, J = 3.7 Hz, 1H), 4.43 (s, 1H), 3.55−3.50 (m, 1H), 3.24 (q, J = 8.6 Hz, 1H), 2.46 (s, 3H), 2.27−2.18 (m, 1H), 2.13−2.03 (m, 1H), 2.00−1.96 (m, 2H), 1.74−1.64 (m, 1H), 1.37−1.21 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.9, 146.9, 143.7, 135.0, 133.1,

129.8, 129.3, 127.9, 114.4, 109.5, 77.4, 66.2, 58.1, 48.3, 35.5, 30.0, 23.8, 21.8, 18.8. HRMS (EI): calcd for $C_{20}H_{21}O_3NS$ $(M)^+$ 355.1242, found 355.1244.

Tetracycle 46N. A solution of 0.025 g of enesulfonamide **26** (0.058 mmol) and 1.5 mg of platinum(II) chloride (7.0 μmol) in 1.0 mL of toluene was stirred in a sealed tube at 130 °C for 16 h. The reaction mixture was cooled to rt and directly purified by column chromatography on triethylamine-washed silica gel (1:1 to 1:2 hexanes/dichloromethane to dichloromethane to 98:2 dichloromethane/ethyl ether) to afford 17 mg (78%) of the title compound **46N** as a colorless film. IR (film): 2934, 1458, 1331, 1166, 1150 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 7.5 Hz, 2H), 7.24 (d, J = 8.2 Hz, 1H), 7.18−7.13 (m, 2H), 6.98 (t, J = 7.2 Hz, 1H), 5.80 (t, J = 3.8 Hz, 1H), 5.14 (s, 1H), 3.96−3.88 (m, 1H), 3.78 (s, 3H), 3.04 (dd, J = 10.9, 2.7 Hz, 1H), 2.47 (s, 3H), 2.33−2.12 (m, 2H), 1.89−1.80 (m, 2H), 1.74−1.66 (m, 2H), 1.66−1.45 (m, 3H), 1.38−1.29 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.8, 143.0, 142.1, 139.3, 138.2, 129.8, 127.2, 124.1, 121.8, 119.9, 119.5, 117.8, 116.4, 109.4, 62.2, 49.3, 42.0, 31.3, 31.0, 29.8, 24.6, 21.7, 21.3, 18.0. HRMS (ESI): calcd for $C_{26}H_{29}N_2O_2{}^{32}S$ $(M + H)^+$ 433.1950, found 433.1960.

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Supporting Information Available: Experimental procedures and characterization data for all previously unreported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.