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Platinum(II)-Catalyzed Cyclizations Forming Quaternary Carbon Centers, Using Enesulfonamides, Enecarbamates, or Enamides as Nucleophiles

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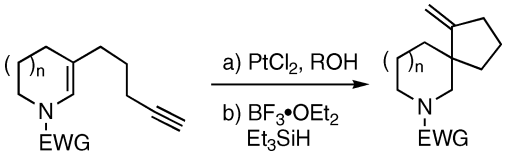
ABSTRACT



Cyclic enesulfonamides, enecarbamates, or enamides tethered to an alkyne cyclize readily with use of platinum(II) chloride. This reaction generates quaternary-substituted carbon centers within simple spiro-fused or more complex tri- and tetracyclic heterocyclic ring systems. The yields for this process range from 50% to 83%.

Additions of carbon-based nucleophiles to activated C−C π systems are of fundamental importance in synthetic organic chemistry. Classically, this process is facilitated by the use of electron-deficient acceptors (enones, ynones, enoates, etc.). Recent intense study has examined the activation of C−C π-systems toward nucleophilic attack with use of catalytic amounts of metal salts.[1] Important examples of this reactivity paradigm forming C−C bonds include the addition of β-dicarbonyl compounds (Conia-ene),[2] enol silyl ethers,[3] allylsilanes or allylstannanes,[4] and functionalized indoles[5] to alkynes or alkenes activated by electrophilic metal salts. In each of these cases, quite reactive π-nucleophiles are used.

In the context of developing reactions suitable for the synthesis of ring skeletons related to structurally complex alkaloids, our group has been studying the use of enecarbamate and enesulfonamide (*N*-carbamoyl or *N*-sulfonyl enamines) functional groups as pronucleophiles in metal-catalyzed reactions.[6] *The use of these enamine derivatives as π-nucleophiles in the metal-catalyzed formation of*

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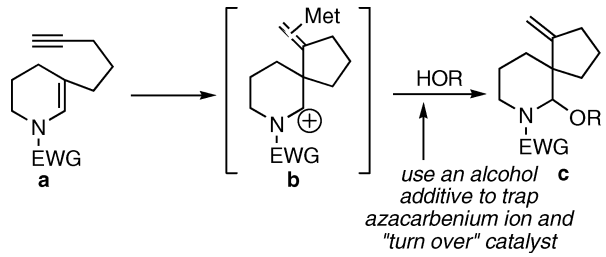
quaternary-substituted carbon atoms represents an important, yet unexplored, challenge. In considering a 3-substituted piperidene derivative of general structure **a** (Scheme 1), it

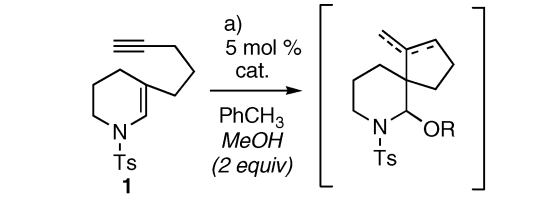
Scheme 1



was envisioned that addition of an electrophilic metal species would activate the alkyne toward nucleophilic attack to give intermediate **b**. In this instance, an additive would be necessary to (a) intercept the putative intermediary azacarbenium ion and (b) provide a means by which to protonate the organometallic intermediate and "turn over" the catalytic metal species.[7] It was reasoned that an alcohol could serve both roles. The products thus formed would be hemiaminals of general structure **c**. Presumably, compounds such as **c** could be further processed synthetically as required. This speculative reaction, as written, would form a heteroatom-containing spirocyclic ring system through the construction of a quaternary substituted carbon atom.[8] A singular example recently published by the Toste group using a silyl enol ether-based substrate prompts us to disclose our results.[3] This report describes our successful investigations using enesulfonamides and structurally related compounds in metal-catalyzed reactions forming quaternary carbon centers.

Our investigation began by subjecting enesulfonamide **1** to a set of electrophilic metal salts (Scheme 2). In initial experiments the desired cyclization took place, but we found the characterization of diastereomeric hemiacetal products (cf. **c**, Scheme 1) awkward. A one-pot cyclization−reduction sequence was developed to resolve that problem. In these experiments, **1** was treated with a metal salt (5 mol %) and 2 equiv of methanol in toluene (0.1 M). With the starting material consumed, the reaction mixture was cooled to room temperature and 1.2 equiv of triethylsilane followed by 1.0 equiv of $BF_3{\cdot}OEt_2$ was added.[9] This second step removed the hemiaminal functionality, making characterization of the reaction products simpler. Of the metal salts surveyed, the

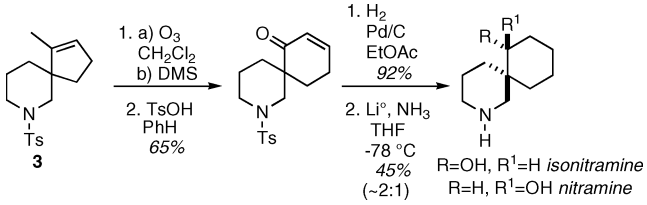
Scheme 2. Evaluation of Metal Salts for Cyclization



conditions	yield	ratio (**2**:**3**)
$PtCl_2$	*80%*	1:0
$PtCl_2$+AgOTf	*80%*	0:1
AgOTf	*37%*	1:2
PPh_3AuCl, AgOTf	*92%*	1:4

use of platinum chloride as a catalyst resulted in the formation of **2** as a single isomer in 80% yield.[10] Interestingly, a 1:1 mixture of platinum chloride and silver triflate enabled the complete formation of (or complete isomerization to) compound **3** in 80% yield.[11] Other silver salts were less effective.[12] The selective migration process proved advantageous as compound **3** could be converted in a few steps to a mixture of nitramine and isonitramine (Scheme 3).[13] A

Scheme 3. Conversion of **3** to Isonitramine and Nitramine



concerted effort to optimize reaction yields or diastereoselectivities in this synthesis was not undertaken. Finally, the use of a cationic gold catalyst in the cyclization of **1** was briefly examined. This catalyst is very active, allowing the reaction typically run at 50−80 °C to be performed at room temperature in high yield (92%). Unfortunately, both isomers **2** and **3** were obtained. Consequently, the conditions with platinum chloride became our standard.

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(9) Yamazaki, H.; Horikawa, H.; Nishitani, T.; Iwasaki, T. *Chem. Pharm. Bull.* **1990**, *38*, 2024−2026.

(10) No reaction was observed when compound **1** was treated with either hydrochloric acid or trifluoroacetic acid.

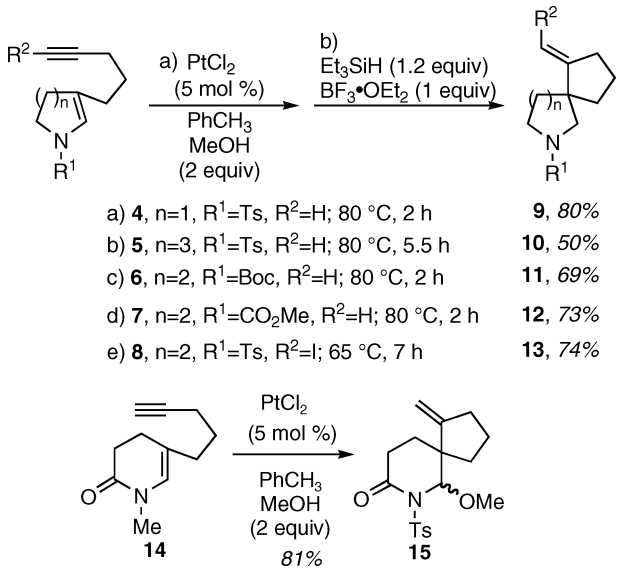
(11) For previous use of mixtures of platinum salts with silver trifluorosulfonate, see: (a) Ghosh, A. K.; Matsuda, H. *Org. Lett.* **1999**, *1*, 2157−2159. (b) Pignat, K.; Vallotto, J.; Pinna, F.; Strukul, G. *Organometallics* **2000**, *19*, 5160−5167. (c) Jia, B.; Lu, W.; Oyamada, J.; Kitamura, T.; Matsuda, K.; Irie, M.; Fujiwara, Y. *J. Am. Chem. Soc.* **2000**, *122*, 7252−7263. (d) Jia, C.; Piao, D.; Oyamada, J.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Science* **2000**, *287*, 1992−1995. (e) Fürstner, A.; Voigtländer, D.; Schrader, W.; Giebel, D.; Reetz, M. T. *Org. Lett.* **2001**, *3*, 417−420. (f) Oyamada, J.; Kitamura, T. *Tetrahedron* **2006**, *62*, 6918−6925.

(12) Either $AgPF_6$ or $AgSbF_6$ with platinum salts resulted in mixtures.

(13) (a) Alonso, E. R.; Tehrani, K. A.; Boelens, M.; De Kimpe, N. *Synlett* **2005**, 1726−1730. (b) Deyine, A.; Poirier, J.-M.; Duhamel, L.; Duhamel, P. *Tetrahedron Lett.* **2005**, *46*, 2491−2493.

With the standard conditions established, a survey of reaction scope was undertaken (Scheme 4). Both five- and

Scheme 4. Evaluation of Heterocycle Scope

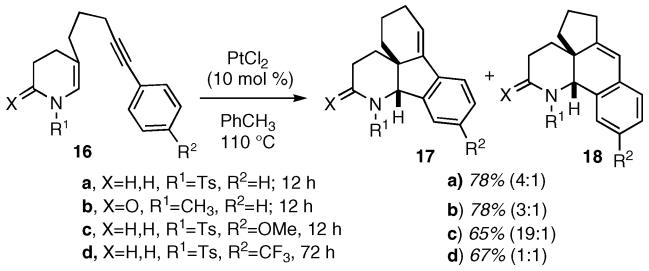


seven-membered heterocyclic substrates **4** and **5** participate in the reaction, although the yield for the conversion of **5** is moderate (entries a and b). As the *p*-toluenesulfonyl protecting group can be difficult to remove, alternative functional groups such as carbamates and amides were examined. *tert*-Butyl and methyl carbamoyl enamines **6** and **7** cyclize effectively in 69% and 73% yields, respectively (entries c and d). Interestingly, the cyclization of **7** provided a 12.5:1 mixture of exocyclic alkene **12** and its structural isomer (similar to **3**). The reaction also proceeded smoothly with use of alkynyl iodide **8**, providing the synthetically useful vinyl iodide **13** in 74% yield. The alkene stereochemistry of **13** was established by using X-ray crystallography. Enamide **14** also can be used in the platinum-catalyzed cyclization reaction to give aminals **15** in 81% yield. Compounds **15** decomposed upon treatment with triethylsilane and $BF_3{\cdot}OEt_2$.

Interestingly, in examining substituent effects on the alkyne, we found that capture of the intermediary azacarbenium ion could be achieved using an internal nucleophile in a Friedel-Crafts/Pictet-Spengler-type process (Scheme 5).[14] Treatment of **16a**, a compound having a 1-phenyl substituent on the alkyne, with 10 mol % of $PtCl_2$ gave a 4:1 mixture of tetracycles **17a** and **18a** in 78% yield. These structures were determined with X-ray crystallography. As the *p*-toluenesulfonyl protecting group was expected to have steric properties that should influence the regioselectivity of this cyclization reaction, the cyclization of **16b** was attempted. Somewhat surprisingly, **16b** gave a negligibly different product distribution. Modification of the electronic properties of the arene substituent proved to be more significant.

(14) Another example of Friedel-Crafts trapping of an intermediate in metal catalysis: Nieto-Oberhuber, C.; Lopez, S.; Echavarren, A. M. *J. Am. Chem Soc.* **2005**, *127*, 6178−6179.

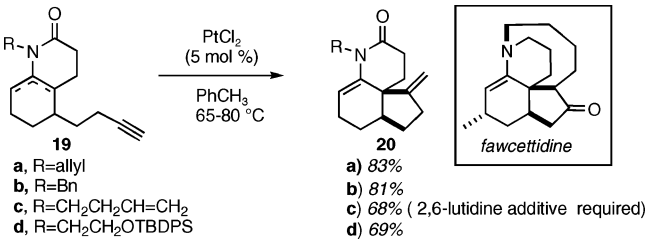
Scheme 5. Arylalkynes Generate Tetracycles



Cyclization of compound **16c** having an electron-donating methoxy function on the arene ring gave a 65% yield of **17c** and **18c** in 19:1 ratio. Replacing this donating group with an electron-withdrawing function as with CF_3 (in **16d**) did shift the reaction toward a "5-exo" mode of initial cyclization, although not to a great extent (67%, 1:1 mixture of **17d**:**18d**).

Pleased by the efficient formation of quaternary carbon atoms using this method, we recognized that this methodology could provide an effective entry to alkaloid ring systems structurally related to fawcettidine.[15] Enamides **19a**−**d** were synthesized by condensing an appropriate amine with a δ-ketoester precursor. The enamides were typically formed as ∼3:1 mixtures of alkene isomers favoring the tetrasubstituted enamide. The ratio of inseparable alkene isomers could not be manipulated further. In the event, subjecting **19a** to 5 mol % of platinum chloride provided the desired tricyclic ring system embedded within fawcettidine in 83% yield (Scheme 6). In this case methanol is not required as

Scheme 6. Fawcettidine Model Studies



the azacarbenium ion generated from **19a** can undergo proton loss. Other substrates structurally related to **19a** cyclized efficiently with these conditions. Common protecting groups such as benzyl and *tert*-butyldiphenylsilyloxy are compatible with these reaction conditions. A noteworthy point is the requirement for the addition of 10−20 mol % of 2,6-lutidine and 2 equiv of methanol to the reaction of **19c** (R = $CH_2CH_2CH{=}CH_2$). In the absence of these additional reagents, significant amounts of byproducts that we suspect

(15) (a) Ishii, H.; Yasui, B.; Harayama, T.; Inubushi, Y. *Tetrahedron Lett.* **1966**, *7*, 6215−6219. (b) Inubushi, Y.; Ishii, H.; Harayama, T.; Burnell, R. H.; Ayer, W. A.; Altenkirk, B. *Tetrahedron Lett.* **1967**, *8*, 1069−1072. (c) Burnell, R. H. *J. Chem. Soc.* **1959**, 3091−3093.

arise from aza-Cope−aza-Prins sequences[16] of the intermediary azacarbenium ion were observed. With the addition of these reagents to the reaction of **19c**, a 68% yield of **20c** was obtained.

In summary, platinum chloride is a useful catalyst for the formation of quaternary carbon centers embedded within simple spiro-fused and more complex tri- and tetracyclic heterocyclic systems.[17] In each of these examples, enamines derivatized with an electron-withdrawing group serve as the π nucleophile. The products obtained from these processes should serve as useful intermediates in either the construction of alkaloid natural products or, potentially, compounds having "natural product-like structure" of interest to the pharmaceutical industry. Further applications and explorations of this methodology are underway in our laboratory.

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

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(16) (a) Padwa, A.; Heidelbaugh, T. M.; Kuethe, J. T.; McClure, M. S.; Wang, Q. *J. Org. Chem.* **2002**, *67*, 5928−5937. (b) Overman, L. E. *Acc. Chem. Res.* **1992**, *25*, 352−359.

(17) **Representative procedure for cyclization reaction**: To a flask charged with 61 mg of **1** (0.20 mmol) and 2.7 mg of $PtCl_2$ (0.01 mmol) was added 2 mL of toluene followed by 17 μL of methanol (0.42 mmol) and the reaction was stirred for 3 h at 80 °C before being cooled to rt. To the resulting brown reaction mixture was added 49 μL of triethylsilane (0.31 mmol) followed by 26 μL of boron trifluoride diethyletherate (0.21 mmol) and stirring was continued at rt for 30 min. The resulting black reaction mixture was diluted with 5 mL of diethyl ether, filtered through a pipet of silica gel, and concentrated by rotary evaporation in vacuo to afford a crude brown oil. Purification of the crude material by column chromatography on silica gel (8:1 hexanes:ethyl acetate) afforded 49 mg (80 %) of **2** as a colorless film.