ORGANIC
LETTERS

2004
Vol. 6, No. 26
5023−5026

Pt(II) or Ag(I) Salt Catalyzed Cycloisomerizations and Tandem Cycloadditions Forming Functionalized Azacyclic Arrays

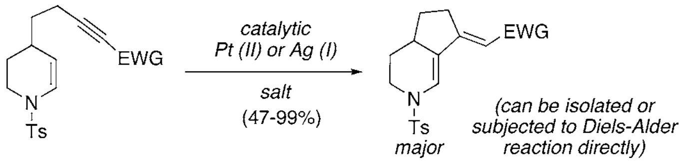
Tyler J. Harrison and Gregory R. Dake*

Department of Chemistry, 2036 Main Mall, University of British Columbia,
Vancouver, B.C., Canada, V6T 1Z1

gdake@chem.ubc.ca

Received November 9, 2004

ABSTRACT



Cyclic ene-*N*-*p*-toluenesulfonamides tethered to an electron-deficient alkyne undergo cycloisomerizations readily under the influence of catalytic Pt(II) salts ($PtCl_2$ or $[dppbPt\mu\text{-}OH]_2(BF_4)_2$) or AgOTf. Yields for this process range from 47% to 99%. The resulting functionalized 2-azahydrindans can be reacted further using the Diels–Alder reaction. Tandem cycloisomerization–cycloaddition reactions in one pot generate highly functionalized 1-azadecalin ring systems in a highly stereocontrolled manner.

Their combination of structural complexity and biological potency make alkaloids inspiring targets for the synthetic organic chemistry community.[1] As representative examples, each of the alkaloids in Figure 1 contains heterocyclic arrays that have served as the basis of a number of studies.[2]

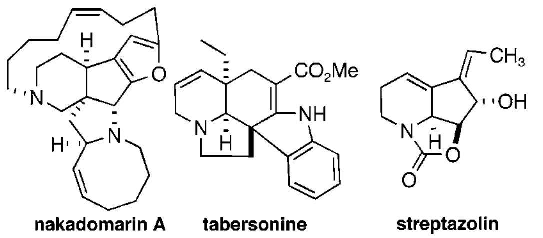


Figure 1. Representative target alkaloids.

In the context of developing new methods for the construction of complex ring systems containing a nitrogen atom suitable for alkaloid synthesis, we considered the following transformation (eq 1). Although enamides (*N*-acyl enamines), enecarbamates (*N*-carbamoyl enamines), and enesulfonamides (*N*-arylsulfonyl enamines) possess latent nucleophilic character,[3] this property has not been examined extensively, especially within the context of transition-metal catalyzed processes.[4] The skeletal reorganization of carbon frameworks catalyzed by the coordination of platinum(II) or other salts to carbon−carbon π-systems has been a renewed subject of interest among many researchers.[5] We postulated that an *N*-carbamoyl or *N*-sulfonyl enamine may possess sufficient reactivity to capture a transient electrophilic species generated

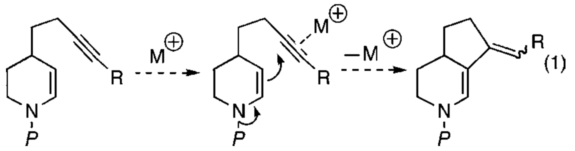
---

[1] (a) Michael, J. P. *Nat. Prod. Rep.* **2003**, *20*, 458−475. (b) Michael, J. P. *Nat. Prod. Rep.* **2003**, *20*, 476−493.

[2] Representative synthetic studies. Nakadomarin A: (a) Ono, K.; Nakagawa, M.; Nishida, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 2020−2023. (b) Magnus, P.; Fielding, M. R.; Wells, C.; Lynch, V. *Tetrahedron Lett.* **2002**, *43*, 947−950. (c) Fürstner, A.; Guth, O.; Duffels, A.; Seidel, G.; Liebl, M.; Gabor, B.; Mynott, R. *Chem: A Eur. J.* **2001**, *7*, 4811−4820. Tabersonine: (d) Kozmin, S. A.; Iwama, T.; Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 4628−4641. (e) Kobayashi, S.; Peng, G.; Fukuyama, T. *Tetrahedron Lett.* **1999**, *40*, 1519−1522. (f) Kuehne, M. E.; Bandarage, U. K.; Hammach, A.; Li, Y. L.; Wang, T. S. *J. Org. Chem.* **1998**, *63*, 2172−2183. Streptazolin: (g) Trost, B. M.; Chung, C. K.; Pinkerton, A. B. *Angew. Chem., Int. Ed.* **2004**, *43*, 4327−4329. (h) Huang, S. L.; Comins, D. L. *Chem. Commun.* **2000**, 569−570. (i) Yamada, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **1996**, *118*, 1054−1059. (j) Kozikowski, A. P.; Park, P. *J. Org. Chem.* **1990**, *55*, 4668−4682. (k) Flann, C. J.; Overman, L. E. *J. Am. Chem. Soc.* **1987**, *109*, 6115−6118.

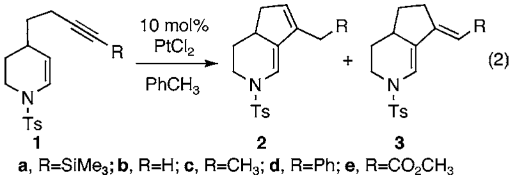
10.1021/ol047696b CCC: $27.50 © 2004 American Chemical Society
Published on Web 12/01/2004

by metal catalysis. If feasible, this process would produce azabicyclic systems that possess functional group arrays suitable for further manipulation. We have uncovered just such a reactivity profile using either platinum(II) or silver(I) salts. This report documents the results of our initial investigations.



Our preliminary experiments were somewhat promising (eq 2 and Table 1). Alkynes **1a**−**e**[6] were subjected to a standard set of conditions (10 mol % of platinum(II) chloride) in toluene at 80 °C for the designated time. The trimethylsilyl-substituted alkene **1a** failed to react (entry 1), and the terminal alkyne **1b** (or its corresponding products) decomposed under the reaction conditions. Only a 20% yield of **2b** could be recovered from its reaction mixture (entry 2). Despite these drawbacks, we were excited to observe the formation of **2c** in 58% isolated yield when the internal alkyne **1c** was subjected to these reaction conditions. The isolation, purification, and characterization of **2b** and **2c** was difficult as these materials readily decomposed. Alkynes that contain conjugating substituents such as in **1d** and **1e** were tested in an effort to alleviate this problem. The products proved to be more stable, but the reaction of **1d** was complicated by the formation of isomeric dienes **2d** and **3d** (entry 4) in 52% combined yield. Gratifyingly, the reaction of alkynoate **1e** generated one isomeric diene, **3e**, in 69% yield. Not only did the ester functionality make the alkyne more reactive, the reaction product **3e** was substantially more stable.

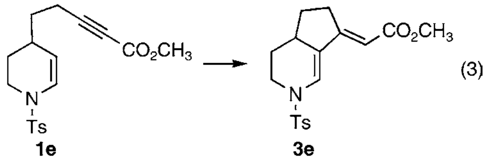
Table 1. Test Reactions of **1a**−**e** with PtCl$_2$



entry	substrate	T (°C)	time (h)	% yield[a]	ratio **2/3**[b]
1	**1a**	80	15	NR	n/a
2	**1b**	50	3	20	1:0
3	**1c**	80	2	58	1:0
4	**1d**	80	4.5	52	1:1
5	**1e**	80	0.75	69	0:1

[a] Isolated yields; NR = no reaction. [b] Ratios established by ^{1}H NMR spectroscopy of the product mixture; n/a = not applicable.

With the feasibility of this proposed process established, alkynoate **1e** was subjected to a wide variety of conditions in order to improve this process in terms of yield, rate and catalyst loading. Importantly, no reaction products were observed in the absence of metal catalysts or using BF$_3$•OEt$_2$ (1 equiv) as a Lewis acid. After a number of metal precatalyst systems were examined, two alternative methods stood out (eq 3).[7]



[dppbPtOH]$_2$(BF$_4$)$_2$ (**4**) (6 mol%)	CH$_2$Cl$_2$, 40 °C, 15 min	*86%*
AgOTf (1 mol%)	CH$_2$Cl$_2$, 40 °C, 1.5 h	*75%*

The complex [(dppb)Pt(μ-OH)]$_2$(BF$_4$)$_2$[8] (**4**) proved to be effective in the conversion of **1e** to **3e**. In addition, as silver salts are used in the literature preparation of **4**, we decided to examine the capability of silver(I) salts in promoting this reaction. Happily, in our first attempt, the cycloisomerization of **1e** using 1 mol % of silver trifluoromethanesulfonate in CH$_2$Cl$_2$ efficiently produced **3e** in 75% yield. The yield of the silver(I)-catalyzed process could be improved to 99% through minor modification of the experimental conditions (see Figure 2).

With these lead results, a series of substrates were subjected to these precatalyst systems (Figure 2). A number of

---

(3) (a) Shono, T.; Matsumura, Y.; Tsubata, K.; Sugihara, S.; Yamane, T.; Kanazawa, T.; Aoki, T. *J. Am. Chem. Soc.* **1982**, *104*, 6697−6703. (b) Eberson, L.; Malmberg, M.; Nyberg, K. *Acta Chem. Scand.* **1984**, *38*, 391−396. (c) Angle, S. R.; Frutos, R. P. *J. Chem. Soc., Chem. Commun.* **1993**, 171−173. (d) de Faria, A. R.; Salvador, E. L.; Correia, C. R. D. *J. Org. Chem.* **2002**, *67*, 3651−3661. (e) Adam, W.; Bosio, S. G.; Turro, N. J.; Wolff, B. T. *J. Org. Chem.* **2004**, *69*, 1704−1715. (f) Cossey, K. N.; Funk, R. L. *J. Am. Chem. Soc.* **2004**, *126*, 12216−12217.

(4) (a) Matsubara, R.; Nakamura, Y.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 1679−1681. (b) Matsubara, R.; Nakamura, Y.; Kobayashi, S. *Angew. Chem, Int. Ed.* **2004**, *43*, 3258−3260. (c) Matsubara, R.; Vital, P.; Nakamura, Y.; Kiyohara, H.; Kobayashi, S. *Tetrahedron* **2004**, *60*, 9769−9784. (d) For a palladium-catalyzed cycloisomerization of an alkynyl *N*-acyl enamine that does not act as a latent nucleophile, see: Trost, B. M.; Pedregal, C. *J. Am. Chem. Soc.* **1992**, *114*, 7292−7294.

(5) For examples, see: (a) Chatani, N.; Furukawa, N.; Sakurai, H.; Murai, S. *Organometallics* **1996**, *15*, 901−903. (b) Chatani, N.; Inoue, H.; Ikeda, T.; Murai, S. *J. Org. Chem.* **2000**, *65*, 4913−4918. (c) Méndez, M.; Muñoz, M. P.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2001**, *123*, 10511−10520. (d) Fürstner, A.; Stelzer, F., Szillat, H. *J. Am. Chem. Soc.* **2001**, *123*, 11863−11869. (e) Oi, S.; Tsukamoto, I.; Miyano, S.; Inoue, Y. *Organometallics* **2001**, *20*, 3704−3709. (f) Madine, J. W.; Wang, X.; Widenhoefer, R. A. *Org. Lett.* **2001**, *3*, 385−388. (g) Kisanga, P.; Goj, L. A.; Widenhoefer, R. A. *J. Org. Chem.* **2001**, *66*, 635−637. (h) Fernández-Rivas, C.; Méndez, M.; Nieto-Oberhuber, C.; Echavarren, A. M. *J. Org. Chem.* **2002**, *62*, 5197−5201. (i) Martín-Matute, B.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2003**, *125*, 5757−5766. (j) Liu, C.; Han, X.; Wang, X.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2004**, *126*, 3700−3701. (k) Cadran, N.; Cariou, K.; Hervé, G.; Aubert, C.; Fensterbank, L.; Malacria, M.; Marco-Contelles, J. *J. Am. Chem. Soc.* **2004**, *126*, 3408−3409. (l) Mamane, V.; Gress, T.; Krause, H. Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 8654−8655. For reviews, see: (m) Méndez, M.; Mamane, V.; Fürstner, A. *Chemtracts−Org. Chem.* **2003**, *16*, 397−425. (n) Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Chem.−Eur. J.* **2003**, *9*, 2627−2635.

(6) The substrates used in this study are readily available in five to seven steps from *N*-*p*-toluenesulfonyl-2-piperidone, as adapted from the method of Shono: Shono, T.; Terauchi, J.; Ohki, Y.; Matsumura, Y. *Tetrahedron Lett.* **1990**, *31*, 6385−6286.

(7) Other precatalysts that were investigated include HBF$_4$, PdCl$_2$, Pd$_2$(dba)$_3$, (COD)PtCl$_2$, (dppb)PtCl$_2$, K$_2$PtCl$_4$, K$_2$PtCl$_6$, (phen)PtCl$_2$, [(phen)-Ptμ-OH]$_2$(BF$_4$)$_2$, and RuCl$_3$.

(8) (a) Li, J. J.; Li, W.; Sharp, P. R. *Inorg. Chem.* **1996**, *35*, 604−613. (b) Gavagnin, R.; Cataldo, M.; Pinna, F.; Strukul, G. *Organometallics* **1998**, *17*, 661−667.

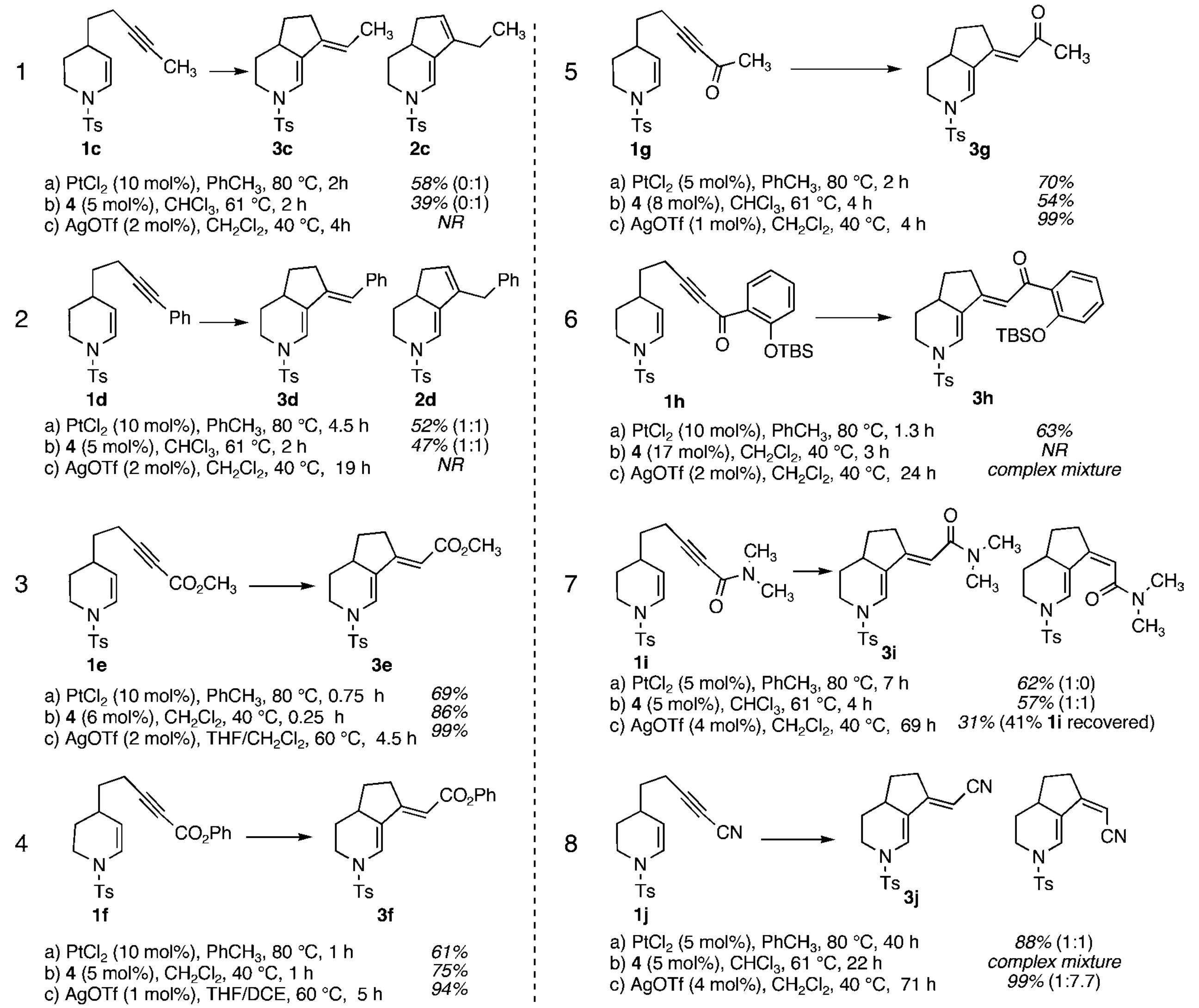
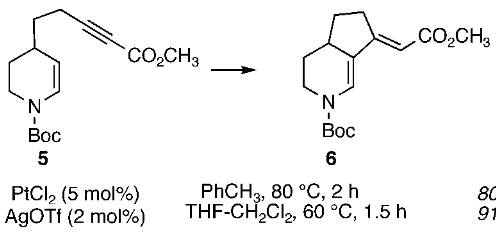


Figure 2. Cycloisomerization experiments.

points deserve comment. Unless specifically indicated, the reactions were quite clean and the designated time was required to consume the starting material. Cyclizations of **1c** and **1d** catalyzed by AgOTf were unsuccessful, even when heated to 120 °C (entries 1c and 2c). Electron-withdrawing groups such as ketones, esters, amides, and nitriles were sufficient to both activate the alkyne and stabilize the reaction products. With ynoates or ynones, reactions catalyzed by AgOTf typically proceed with much lower catalyst loading and can result in substantially higher yields compared to the reactions catalyzed by platinum(II) salts (entries 3−5). Reactions were found to be faster, but not as clean, in chlorinated solvents (CH_2Cl_2, $CHCl_3$, $ClCH_2CH_2Cl$). A mixture of THF and a chlorinated solvent proved to be optimal in terms of rate and efficiency. Although dimethyl amide **1i** cyclized smoothly with $PtCl_2$ or **4**, catalysis using AgOTf proved to be quite sluggish. Even after 69 h, the process using AgOTf gave only a 31% yield of **3i** with 44% of **1i** remaining (entry 7). The cycloisomerization of nitrile **1j** using $PtCl_2$ or AgOTf proceeded in high yield, but in those cases produced **3j** as a mixture of alkene isomers (entries 8a and 8c).

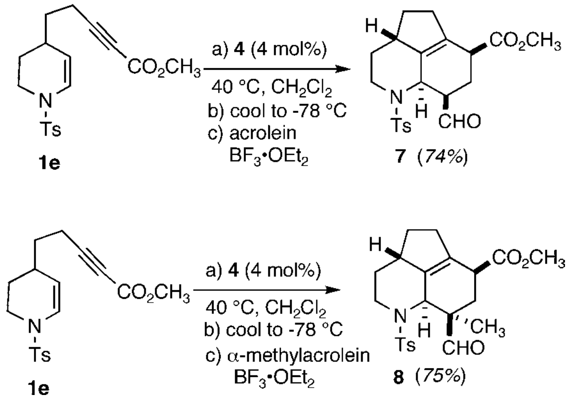
As the robust *p*-toluenesulfonyl protecting group can sometimes be difficult to remove, enecarbamate **5** was subjected to cycloisomerization conditions (eq 4). These reactions proved to be quite efficient, providing diene **6** in 80% and 91% yield using $PtCl_2$ or AgOTf catalysis, respectively.



(4)

The products of these cycloisomerization processes are obvious candidates for further manipulation using the Diels−Alder reaction. Diene **3e** undergoes smooth low-temperature

Scheme 1. Tandem Cycloisomerization−Cycloaddition Reactions



(−78 °C) Diels−Alder reactions with acrolein and α-methylacrolein.[9] In fact, because of the relative mildness of both the catalyzed cycloisomerization reaction and the cycloaddition process, these reactions may be sequentially carried out in one reaction vessel (Scheme 1).[10] As examples, the consecutive reactions of **1e** with **4** at 40 °C, followed by cooling of the reaction mixture to −78 °C, and addition of the dienophile (acrolein or α-methylacrolein) with catalytic amounts of $BF_3 \cdot Et_2O$ produce cycloadducts **7** and **8** in a highly diastereoselective manner in 74% and 75% yields, respectively. The structural constitution of **7** was confirmed by single-crystal X-ray crystallography. This one-pot, two-step process can also be carried out using silver(I) catalysis in the cycloisomerization step [(a) 1 mol % AgOTf in CH_2Cl_2, (b) α-methylacrolein; 93% of **8**].

In summary, the ability of enesulfonamides to cyclize onto electron-deficient alkynes under the influence of platinum(II) or silver(I) salt precatalysts has been demonstrated. The functionalized azahydrindan ring systems in the reaction products are well suited for further reactions, especially within a tandem cyclization−cycloaddition manifold. Further studies, including detailed investigations into the mechanism of these metal-catalyzed processes, an evaluation of the scope of this process, and applications in total synthesis, are currently underway in our laboratories.

Acknowledgment. We thank the University of British Columbia, the Natural Science and Engineering Research Council (NSERC) of Canada, the Canada Foundation for Innovation (CFI), Merck-Frosst, and Glaxo SmithKline for the financial support of our programs. T.J.H. thanks NSERC for PGS A and PGS B graduate fellowships.

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.

OL047696B

---

[9] These experiments are presented in the Supporting Information.

[10] For some reviews of "tandem" or "domino" reactions, see: (a) Neushutz, K.; Velker, J.; Neier, R. *Synthesis* **1998**, 227−255. (b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115−136.