Stereoselective Nickel-Catalyzed [2+2+2] Cycloaddition of Enynes and Arynes

David A. Candito, Mark Lautens*

Department of Chemistry, University of Toronto, 80 St. George Street, Toronto, Ontario M5S 3H6, Canada
E-mail: mlautens@chem.utoronto.ca

Received 30 May 2011

Abstract: Examples of stereoselective reactions of aryne intermediates are rare in the literature. A stereoselective nickel-catalyzed [2+2+2] cycloaddition of 1,6-enynes with aryne intermediates is reported. Excellent stereoselectivities were observed when a substituent is adjacent to the olefin moiety resulting in *trans*-stereochemistry in the products. This reaction is capable of generating much complexity from simple and readily available starting materials. Furthermore, the products possess a synthetic handle which poises them for further modifications.

Key words: nickel-catalyzed, arynes, diastereoselective, 1,6-enynes, [2+2+2] cycloaddition

The coordination and stabilization of aryne intermediates by transition metals has been known for some time and their complexes with titanium and zirconium have been utilized in synthesis as stoichiometric reagents.[1]

With the advent of mild conditions for the formation of arynes there has been an increase in the number of reports in which aryne intermediates are participants in catalytic manifolds.[2] The most common transition metals utilized in these cases have been nickel and palladium.

We have had a longstanding interest in the chemistry of arynes, particularly stereoselective reactions using arynes. We have previously reported the diastereoselective aryne Diels–Alder reactions of cyclic and acyclic dienes where excellent selectivities could be obtained by utilizing a chiral auxiliary based upon camphorsultam.[3] In general, reports of the use of arynes in stereoselective reactions have been sparse. We became interested in the idea of a stereoselective metal-catalyzed process involving arynes as this would provide the potential for asymmetric catalysis. We outline our efforts towards the development of a stereoselective [2+2+2] cycloaddition of an enyne with an aryne intermediate to generate interesting tricyclic scaffolds.

The metal-catalyzed [2+2+2] cycloaddition of aryne intermediates has received considerable attention.[4] In a noteworthy contribution from Sato and co-workers it was reported that when the [2+2+2] cycloaddition of a 1,6-diene and an aryne was attempted, none of the desired cycloadducts was formed; instead products arising from the reaction of two aryne units and one olefin were observed.[4c] We elected to investigate the analogous cyclization of a 1,6-enyne substrate. We were aware of the success of 1,6-enynes in other metal-catalyzed cycloisomerizations such as Pauson–Khand-type reactions, where predictable diastereoselectivity has been displayed and enantioselective variants have been reported. We hypothesized that the reaction course would proceed similarly to other cycloisomerizations of enynes making this reaction an ideal candidate for the development of a stereoselective reaction with an aryne because the stereochemistry of the products would be set prior to reaction with the aryne intermediate.

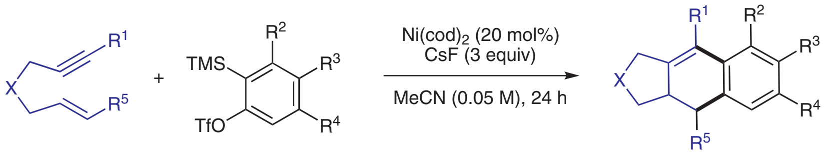
We began by investigating the reaction of enyne **1a** with aryne precursor **2a** (Table 1, entry 1). Optimization studies revealed that the amount of enyne relative to the aryne precursor was a critical parameter. An excess of enyne was necessary in order to achieve higher yields. Alternatively, an excess of the aryne precursor could be utilized, however, the yields were reduced due to competing side reactions. It was also found that the use of various phosphine and NHC-based ligands slowed the desired reaction leading to reduced yields. Common byproducts in these cases arose from dimerization and trimerization of the aryne intermediate. Thus, 'ligand-free conditions' were found to be optimal. A rather high catalyst loading was found to be necessary in order to strike a balance between the rate of aryne generation and the rate of catalytic turnover, otherwise side reactions of the aryne with itself and with the enyne begin to compete with the desired pathway. In an attempt to lower the concentration of the aryne intermediate in solution, slow addition of the aryne was attempted, and the use of more nonpolar co-solvents such as THF were employed, however, these changes did not provide any improvements.

With optimal conditions in hand, a substrate study was undertaken. Malonate-derived enynes reacted well under the optimized conditions (Table 1, entries 1 and 2). Steric bulk present on the olefin or alkyne slows the reaction leading to poor conversions and none of the desired cycloadducts (Table 1, entries 5 and 6).

The reaction of enyne **1c** with a nitrogen heteroatom proceeded in excellent yield to provide **3c**. This encouraging result prompted us to reduce the catalyst loading to 10 mol%, however, a dramatic decrease in yield was observed (Table 1, entry 4). We then went on to investigate the reactivity of different aryne precursors. Many silyl triflate precursors are now commercially available or can be prepared in a straightforward manner. Unfortunately, the aryne precursors which were investigated provide inferior results relative to **2a**.

SYNLETT 2011, No. 14, pp 1987–1992
Advanced online publication: 10.08.2011
DOI: 10.1055/s-0030-1261171; Art ID: S04911ST

Table 1 Scope of Nickel-Catalyzed [2+2+2] Cycloaddition[a]



1 2 3

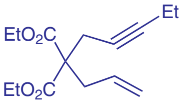
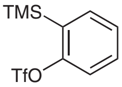
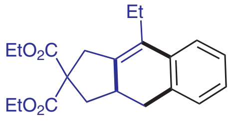
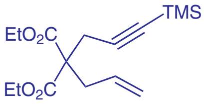
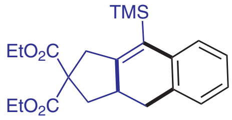
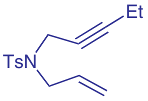
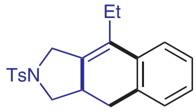
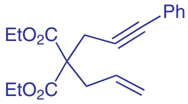
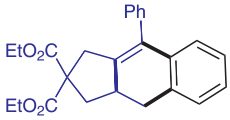
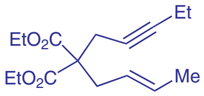
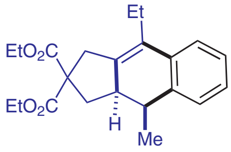
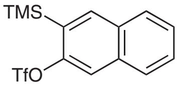
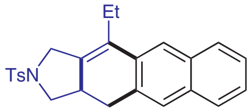
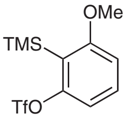
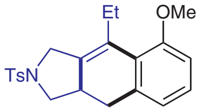
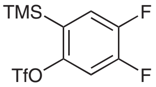
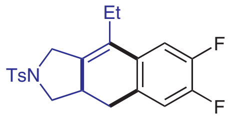
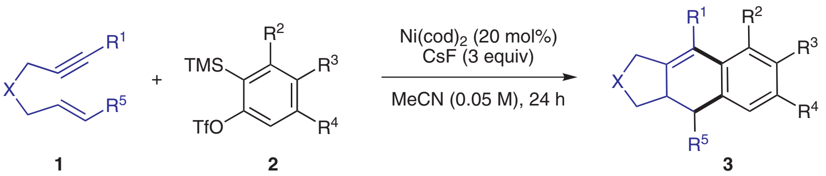
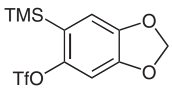
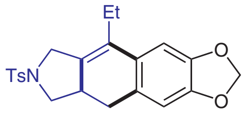
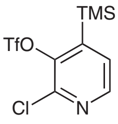
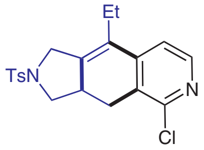
Entry	Enyne	Precursor	Product	Yield (%)[b]
1	 **1a**	 **2a**	 **3a**	73
2	 **1b**	**2a**	 **3b**	50
3	 **1c**	**2a**	 **3c**	89
4	**1c**	**2a**	**3c**	47[c]
5	 **1d**	**2a**	 **3d**	–[d]
6	 **1e**	**2a**	 **3e**	–[d,e]
7	**1c**	 **2b**	 **3f**	38
8	**1c**	 **2c**	 **3g**	39[f] (1.5:1)
9	**1c**	 **2d**	 **3h**	36

Table 1 Scope of Nickel-Catalyzed [2+2+2] Cycloaddition[a] (continued)



Entry	Enyne	Precursor	Product	Yield (%)[b]
10	**1c**	 **2e**	 **3i**	63
11	**1c**	 **2f**	 **3j**	–[d]

---

[a] Silyl triflate (1 equiv, 0.1 mmol), enyne (2 equiv), $Ni(cod)_2$ (20 mol%), CsF (3 equiv), MeCN (0.05 M), 60 °C, 24 h.

[b] Isolated yields.

[c] $Ni(cod)_2$ (10 mol%).

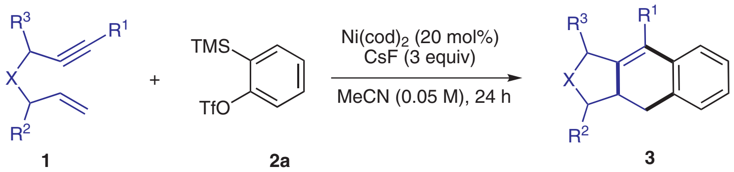
[d] Cycloadduct not detected.

[e] Silyl triflate (2 equiv), enyne (1 equiv, 0.1 mmol).

[f] Combined yield, measured by NMR of the crude reaction mixture, major isomer shown.

In the cases of **2b**, **2d**, and **2e** the aryne intermediates are symmetrical and the substituents are located at distances which should not dramatically affect the nature of the in-plane aryne triple bond, thus one would predict similar behavior as **2a**. It is known that substituents on arynes have an effect on their stability and lifetime and these subtle changes may be responsible for the discrepency in behavior.[5] In the case of aryne precursor **2c** poor regioselectivity was observed which did not improve upon lowering the temperature to room temperature. In this case there was a slight preference for the methoxy group to be on the same side as the ethyl group. The reaction of silyl triflate **2f** did not proceed as desired instead complete consumption of the aryne precursor was observed without the formation of the cycloadduct.

Table 2 Stereoselective Nickel-Catalyzed [2+2+2] Cycloaddition[a]



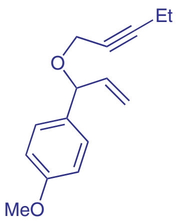
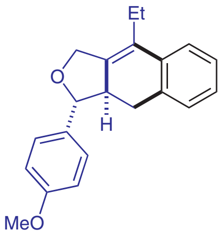
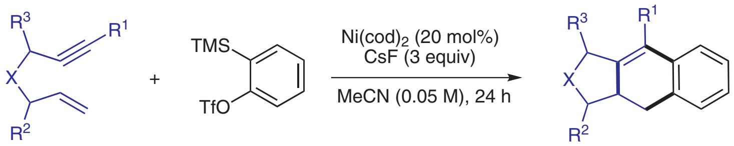
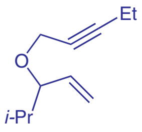
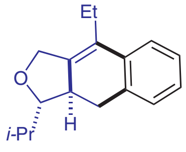
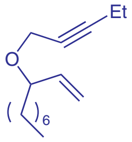
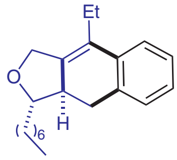
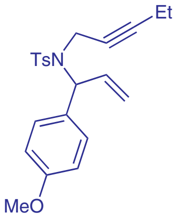
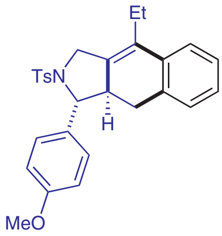
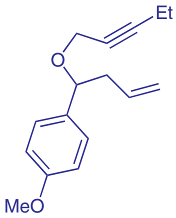
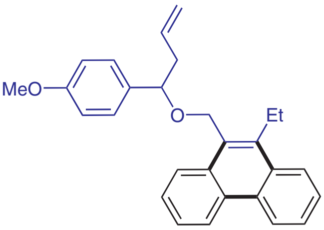
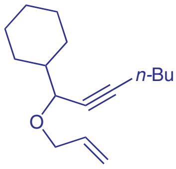
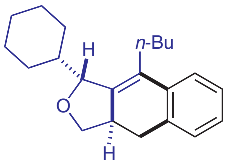
Entry	Enyne	Product	Yield (%)[b]	dr[c]
1	 **1f**	 **3k**	58	>20:1

Table 2 Stereoselective Nickel-Catalyzed [2+2+2] Cycloaddition[a] (continued)



1 2a 3

Entry	Enyne	Product	Yield (%)[b]	dr[c]
2	 **1g**	 **3l**	61	>20:1
3	 **1h**	 **3m**	35	>20:1
4	 **1i**	 **3n**	37[d]	>20:1
5	 **1j**	 **3o**	52[e,f]	–
6	 **1k**	 **3p**	100[d]	3:1

[a] Silyl triflate (2 equiv), enyne (1 equiv, 0.1 mmol), $Ni(cod)_2$ (20 mol%), CsF (3 equiv), MeCN (0.05 M), r.t., 24 h.

[b] Isolated yields.

[c] Combined yield, ratio taken by crude NMR, major isomer shown.

[d] Silyl triflate (1 equiv, 0.1 mmol), enyne (2 equiv), 60 °C, 24 h.

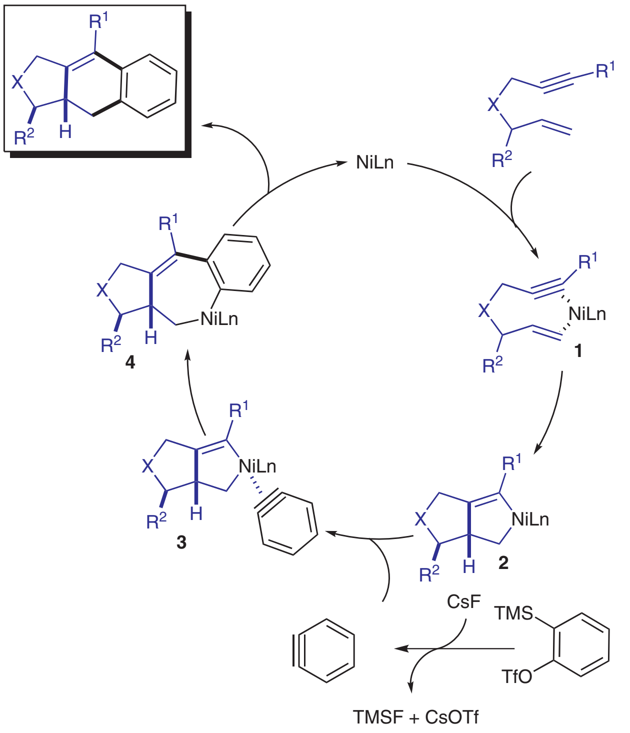
[e] Silyl triflate (1 equiv, 0.1 mmol), enyne (2 equiv), r.t., 24 h.

[f] Cycloadduct not detected.

We then wanted to address whether substrate control could be exerted (Table 2) and found that when a substituent is present near the olefin excellent diastereoselectivities could be obtained. The stereochemistry was determined to be *trans* for substrate **3n** using ROESY 2D NMR and **3k**–**m** were assigned by analogy. This stereochemistry is in line with that reported for the Pauson–Khand-type reaction of 1,6-enynes.[6]

In the case of enyne **1j** we wanted to evaluate the effect of the distance of the stereocenter from olefin, however, it was found that cyclization to form the desired adduct did not take place, rather, cyclization took place with two aryne units and the alkyne. This maybe due to a slower oxidative cyclization of the enyne due to the greater entropic barrier, vide infra. In the case of enyne **1k**, cyclization proceeded in excellent yield but poor stereoselectivity was observed (Table 2, entry 6).

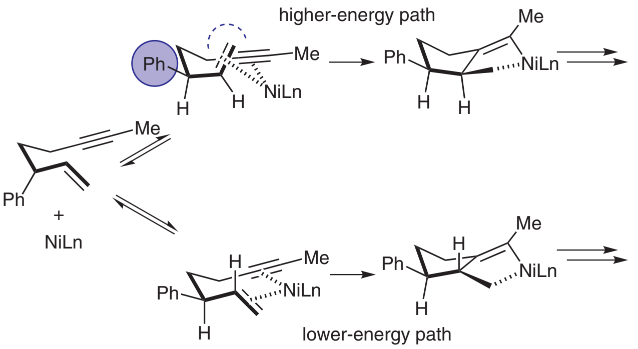
In order to explain the formation of the observed products we propose a mechanism involving initial coordination of the enyne to give a nickel(0) complex such as **1** then oxidative cyclization can take place to give metallacycle **2**. At this point coordination of the aryne intermediate and insertion into one of the carbon–metal bonds can take place generating **4** which reductively eliminates to provide the final product (Scheme 1).



Scheme 1 Proposed mechanism

The stereochemistry is set at the stage of intermediate **2**. This *trans* stereochemistry is common in the metal-catalyzed cycloisomerization of 1,6-enynes and can be rationalized by the model illustrated in Scheme 2.[6] Complexation yields two diastereomeric complexes which can go on to cyclize in an irreversible step. The transition state leading to the *trans* product minimizes 1,3-allylic strain making the *trans* product favored.

In conclusion we have demonstrated the feasibility of the metal-catalyzed [2+2+2] reaction of an enyne with an aryne intermediate and have shown that excellent stereoselectivities can be obtained. It is noteworthy that complex polycyclic scaffolds can be accessed from simple and readily available starting materials. Furthermore, the products posses an olefin which can be a useful synthetic handle for further transformations. Future work will focus on improving this useful reaction and exploring other strategies for stereoselective synthesis using arynes.



Scheme 2 Stereochemical model

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

We thank NSERC (Canada), Merck-Frosst (IRC), and the University of Toronto for support of these studies. D. A. C. would like to thank Dr. Robert Webster for providing inspiration for this study.

References

(1) (a) Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701. (b) Sanz, R. *Org. Prep. Proced. Int.* **2008**, *40*, 215. (c) Dyke, A. M.; Hester, A. J.; Lloyd-Jones, G. C. *Synthesis* **2006**, 4093. (d) Bennett, M. A.; Schwemlein, H. P. *Angew. Chem. Int. Ed.* **1989**, *28*, 1296.

(2) (a) Recent reports of metal-catalyzed reactions involving arynes: Morishita, T.; Yoshida, H.; Ohshita, J. *Chem. Commun.* **2010**, *46*, 640. (b) Huang, X.; Sha, F.; Tong, J. *Adv. Synth. Catal.* **2010**, *352*, 379. (c) Cant, A. A.; Roberts, L.; Greaney, M. F. *Chem. Commun.* **2010**, *46*, 8671. (d) Li, R.-J.; Pi, S.-F.; Liang, Y.; Wang, Z.-Q.; Song, R.-J.; Chen, G.-X.; Li, J.-H. *Chem. Commun.* **2010**, *46*, 8183. (e) Pi, S.-F.; Yang, X.-H.; Huang, X.-C.; Liang, Y.; Yang, G.-N.; Zhang, X.-H.; Li, J.-H. *J. Org. Chem.* **2010**, *75*, 3484. (f) Jeganmohan, M.; Bhuvaneswari, S.; Cheng, C.-H. *Angew. Chem. Int. Ed.* **2009**, *48*, 391. (g) Yoshida, H.; Morishita, T.; Nakata, H.; Ohshita, J. *Org. Lett.* **2009**, *11*, 373. (h) Gerfaud, T.; Neuville, L.; Zhu, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 572. (i) Liu, Y.-L.; Liang, Y.; Pi, S.-F.; Huang, X.-C.; Li, J.-H. *J. Org. Chem.* **2009**, *74*, 3199. (j) Pi, S.-F.; Tang, B.-X.; Li, J.-H.; Liu, Y.-L.; Liang, Y. *Org. Lett.* **2009**, *11*, 2309. (k) Worlikar, S. A.; Larock, R. C. *Org. Lett.* **2009**, *11*, 2413.

(3) (a) Dockendorff, C.; Sahli, S.; Olsen, M.; Milhau, L.; Lautens, M. *J. Am. Chem. Soc.* **2005**, *127*, 15028. (b) Webster, R.; Lautens, M. *Org. Lett.* **2009**, *11*, 4688.

(4) (a) Iwayama, T.; Sato, Y. *Heterocycles* **2010**, *80*, 917. (b) Qiu, Z.; Xie, Z. *Angew. Chem. Int. Ed.* **2009**, *48*, 5729. (c) Saito, N.; Shiotani, K.; Kinbara, A.; Sato, Y. *Chem. Commun.* **2009**, 4284. (d) Hsieh, J.-C.; Cheng, C.-H. *Chem. Commun.* **2008**, 2992. (e) Sato, Y.; Tamura, T.; Kinbara, A.; Mori, M. *Adv. Synth. Catal.* **2007**, *349*, 647. (f) Quintana,

I.; Boersma, A. J.; Pena, D.; Perez, D.; Guitian, E. *Org. Lett.* **2006**, *8*, 3347. (g) Pena, D.; Perez, D.; Guitian, E.; Castedo, L. *Eur. J. Org. Chem.* **2003**, 1238. (h) Pena, D.; Perez, D.; Guitian, E.; Castedo, L. *J. Org. Chem.* **2000**, *65*, 6944.

(5) Gaviña, F.; Luis, S.; Costro, A. *Tetrahedron* **1986**, *42*, 155.

(6) (a) Evans, P. A.; Robinsom, J. E. *J. Am. Chem. Soc.* **2001**, *123*, 4609. (b) Wang, H.; Sawyer, J. R.; Evans, P. A.; Baik, M.-H. *Angew. Chem. Int. Ed.* **2008**, *47*, 342.