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$PtCl_2$-Catalyzed Cycloisomerization of 1,8-Enynes: Synthesis of Tetrahydropyridine Species

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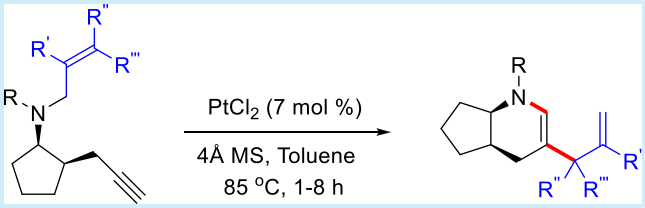
Supporting Information

ABSTRACT: The cycloisomerization of 1,8-enynes in the presence of platinum(II) chloride was developed to generate bicyclic nitrogen-containing heterocycle species via 6-*endo*-*dig* cyclization and [3,3]-sigmatropic rearrangement in acceptable to good yields. The related control experiments and preliminary mechanistic studies indicate a plausible mechanism involving 1,6-*endo*-*dig* aminoplatination of the alkyne and allylic [3,3]-sigmatropic rearrangement with total inversion of the allylic moiety.



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Chemical reactions proceeding with high atom economy are very attractive.[1−5] Such economy often depends on a catalytic mechanism,[6a−c] and alkynes are often used as substrates because of their resilience and chemoselectivities.[6d] For example, transition-metal-electrophilic activation of alkynes has recently supported an explosion of synthetic strategies[7] as well as asymmetric catalytic pathways.[8] Several transition-metal catalysts have been developed to activate alkynes, including complexes of Rh,[9] Au,[10] Ru,[11] Pd,[12] Ir,[13] Fe,[14] and In.[15] In these catalytic systems, Pt catalysts have attracted particular attention from the academic and industrial communities.[16] Platinum chemistry is expanding exponentially, so the number of Pt catalysts available to form simple and complex heterocycles is expected to continue its momentum.[17] One useful application of Pt catalysts is for cycloisomerization of 1,*n*-enynes,[18] which provides access to a wide variety of new chemical structures, primarily via 5-*endo*-*dig* cyclization.[19] Here, we described Pt-catalyzed cycloisomerization of 1,8-enynes involving 6-*endo*-*dig* cyclization to generate the tetrahydropyridine ring. It is noteworthy that piperidines are prevalent heterocyclic structural units in natural products and pharmaceutical substances.[20a−c]

We initially attempted cycloisomerization of 1,8-enynes using enyne **1a** as a model substrate in the presence of Au catalysts. The well-known catalysts Ph_3PAuCl, tris[(3,5-phenyl)phosphine]AuCl, and (tricyclohexylphosphine)AuCl failed to induce any reaction under different conditions (Table 1, entries 1−3). Although we obtained acceptable results with $AuCl_3$ (Table 1, entries 4−6), much more efficient catalysts were needed. Therefore, we next tried several Pt salts under various conditions (Table 1, entries 7−11). Cycloisomerization of **1a** proceeded optimally with $PtCl_2$ (10 mol %) at 85 °C in toluene, affording **2a** in 75% yield (entry 11). Under the same reaction conditions, other Pt salts gave the same product in lower yields (entries 7 and 9).

To optimize the reaction conditions, we tested solvents of different polarities while fixing the catalyst as $PtCl_2$ (10 mol %) and using only elevated temperatures. Low yields were obtained with diethyl ether (18%), hexane (31%), or ethyl acetate (39%) (Table 1, entries 12−14). Better yields were obtained with acetonitrile (54%) and 1,2-dichloroethane (61%) (entries 15 and 16), but these yields were still lower than that with toluene (entry 11). In an effort to further improve the yield with toluene, we increased the temperature to 110 °C; this reduced the reaction time to 4 h but decreased the yield to 60% (entry 17). After fixing the catalyst as $PtCl_2$, solvent as toluene, and temperature as 85 °C, we optimized the amount of catalyst required for a complete transformation within 6 h (Table 1). We were able to decrease catalyst loading to 7 mol % without sacrificing the yield (entries 18−20).

After optimization of the reaction conditions, we then explored the substrate scope of the reaction using substrates with various electronic and steric properties (Table 2, **1a−r**). Substitutions on the phenyl ring, allyl moiety, or alkyne affected reaction time and yields. Most substrates with a benzyl moiety reacted faster than other substrates (cf. **2a−p** with **2q−r**), especially when the phenyl ring contained an electron-donating group (e.g., methoxy). The position of the methoxy group also affected reaction time (cf. **2e** with **2i**, cf. **2h** with **2l**). The reaction tolerated various substitutions on the allyl moiety, including a 3,3-disubstituted allyl group. In fact, the substrate **1l** with a methoxy group in the *para* position as well as a 3,3-disubstituted allyl moiety gave the highest yield (87%)

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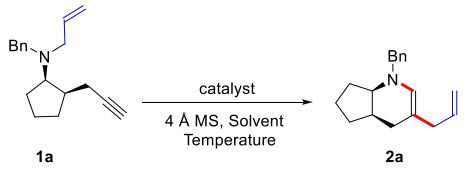
Table 1. Optimization of the Reaction Conditions[a]



1a 2a

entry	catalyst (mol %)	additive	solvent	T (°C)	yield[b] (%)
1	Ph_3PAuCl (10)	none	CH_2Cl_2	23	0
2	tris[F_5-phenyl)phosphine]AuCl (10)	$AgSbF_6$	CH_2Cl_2	23	0
3	(tricyclohexylphosphine) AuCl (10)	$AgSbF_6$	toluene	85	0
4	$AuCl_3$ (10)	none	CH_2Cl_2	23	0
5	$AuCl_3$ (10)	none	toluene	85	58
6	$AuCl_3$ (10)	$AgSbF_6$	toluene	85	64
7	$PtBr_2$ (10)	none	toluene	85	59
8	PtI_4 (10)	none	CH_2Cl_2	23	0
9	PtI_4	none	toluene	85	53
10	$PtCl_2$ (10)	none	CH_2Cl_2	23	0
11	$PtCl_2$ (10)	none	toluene	85	75
12	$PtCl_2$ (10)	none	diethyl ether	38	18
13	$PtCl_2$ (10)	none	hexane	60	31
14	$PtCl_2$ (10)	none	ethyl acetate	70	39
15	$PtCl_2$ (10)	none	CH_3CN	75	54
16	$PtCl_2$ (10)	none	DCE	80	61
17	$PtCl_2$ (10)	none	toluene	110[c]	60
18	$PtCl_2$ (1.5)	none	toluene	85	28
19	$PtCl_2$ (5)	none	toluene	85	52
20	$PtCl_2$ (7)	none	toluene	85	75

[a]Reaction condition: a solution of **1a** (0.2 mmol, 0.1 M) was added to a vessel containing catalyst, 4 Å MS, and additive (if applicable) at 23 °C and stirred at the mentioned temperature for 6 h. [b]Isolated yield. [c]4 h.

in 1 h. The product **2l** showed 1,3-transposition of the allyl moiety (Table 2), generating a quaternary carbon.

To demonstrate the chemoselectivity of 1,3-transposition, we carried out several derivatizations. Given the apparent preference between different allyl groups, we synthesized substrate **1r** in which the nitrogen contained two allylic substituents with quite different steric and electronic properties. Exposing this substrate to catalytic $PtCl_2$ furnished the allyl transfer products in good yield as a 46:54 mixture of regioisomers (Table 2, **2r**/**2r′**). Both allylic substituents are equally likely to undergo sigmatropic rearrangement, suggesting that the allylic group transfer is likely not rate-determining in the mechanism. Tests with various substrates showed that the methyl substituent on allylic group affected reaction time and yield (cf. **2a** with **2d**, cf. **2i** with **2l**, together with several open-chained enynes, see the Supporting Information). We further found that the reaction was highly sensitive to steric effects around the alkynyl group (see the Supporting Information).

In fact, replacing the hydrogen atom on the terminal alkyne with methyl or phenyl groups led to no detectable product formation, even after 8 h, and starting material was recovered in each individual case. A plausible reason for these behaviors will be presented in connection with a discussion of the reaction mechanism (vide infra). Next, we tried to expand the scope of this transformation by testing several open-chained enynes, but in all cases, these starting materials were recovered under our standard conditions (see the Supporting Information). Moreover, to demonstrate the usefulness of this synthetic protocol, the enamine function in the above tetrahydropyridines **2** were further allowed to react to generate new stereocenters. As shown in Scheme 1, derivatives **2a**,**b** and **2g** were able to react with *p*-benzoquinone in the presence of $SnCl_4$ (50 mol %), forming a tetracyclic structure **3a**,**b** and **3g** with four stereocenters, including one all-carbon quaternary stereocenter, in 49−57% yield with excellent diastereoselectivities (Scheme 1, > 99:1 dr) or to react with dimethyl acetylene dicarboxylate (DMAD) in the presence of $SnCl_4$ (20 mol %) to produce useful product **4a** in 68% yield.

To gain further insight into the reaction mechanism, deuterated substrate **1s** in the terminal alkynyl position was prepared and subjected to the standard reaction conditions. The deuterium atom was fully incorporated into the relevant position of compound **2s** (Scheme 2).

Based on these findings (connectivity, the scope, reaction limitations) and literature studies,[21] we then suggested a plausible reaction mechanism (Scheme 3) in which Pt-mediated cyclization leads to intermediate **A**. Subsequent *endo-dig* cyclization involving attack on the organoplatinum−π-alkyne complex leads to intermediate **B**, which undergoes intramolecular [3,3]-sigmatropic rearrangement to **C**. Decomplexation of **C** generates the final product and regenerates the active platinum intermediate. The proposed mechanism is in accordance with our observations. For example, an allylic moiety with an electron-donating group (methyl) could accelerate the reaction by stabilizing cationic intermediate **B** (Scheme 3), but transfer of the allylic group took place at a fast step in the mechanism pathway (**B** to **C**). There is therefore no selectivity, and both groups have an almost equal chance at transposition rearrangement (cf. Table 2, **2r**/**2r′** ratio). Furthermore, our mechanistic proposal is in accordance with the observation that internal alkynes did not lead to the desired

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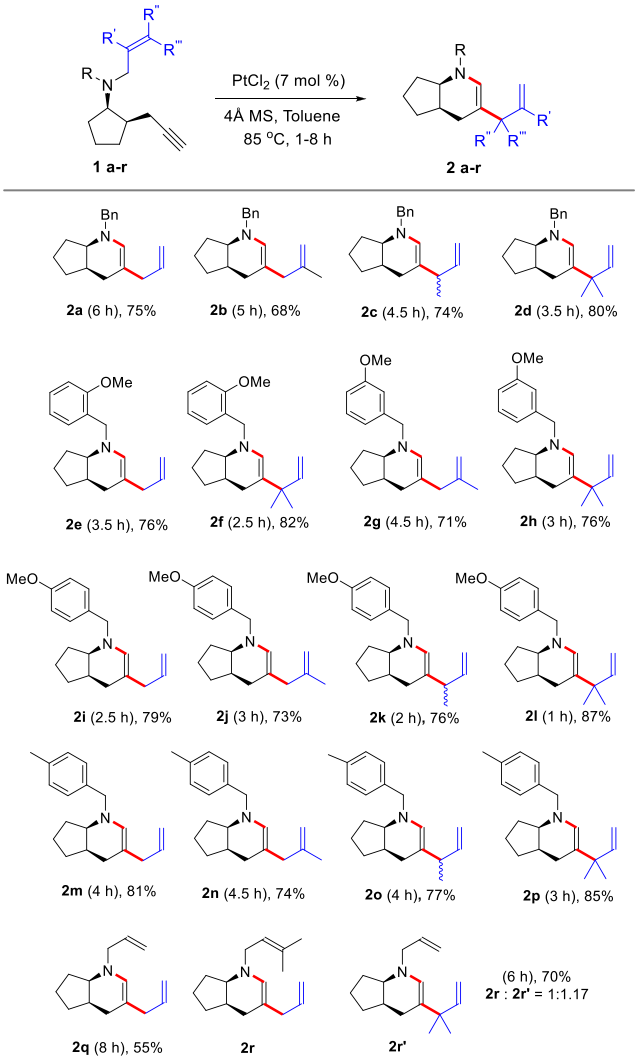
Table 2. Substrate Scope[a,b]

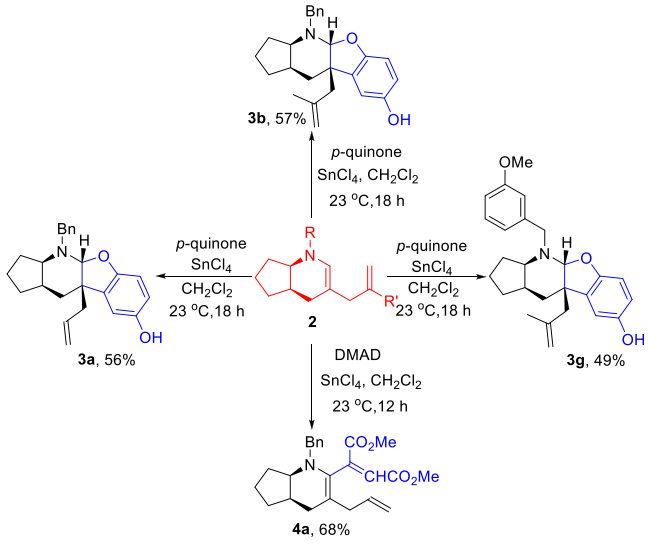


[a]Reaction conditions: a solution of **1a−r** (0.2 mmol, 0.1 M) was added to a vessel containing catalyst and 4 Å MS at 23 °C and stirred at 85 °C for 1−8 h. [b]Isolated yields.

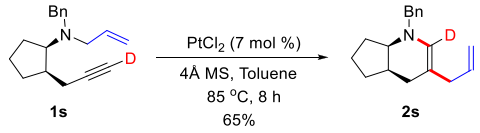
piperidine derivatives at all. We hypothesize that attack to the terminal position of alkyne by nitrogen is the rate-limiting step in the mechanism pathway (Scheme 3, formation of **B**) and the bulky group (bigger than hydrogen) can block this position.

In summary, we have shown that $PtCl_2$ is an efficient, user-friendly, adaptable catalyst for different structural isomerizations. We have developed protocols for Pt(II)-catalyzed 1,8-enyne cycloisomerization, C−N and C−C bond formation, and C−C bond migration, which we applied to the synthesis of bicyclic pyridine derivatives. A wide range of substrates undergo the cycloisomerization under optimized reaction conditions. Substrate scope and deuteration experiments indicate an intramolecular mechanism involving 1,6-*endo-dig* attack of the alkyne by nitrogen and allylic [3,3]-sigmatropic rearrangement, with total inversion of the allylic moiety.

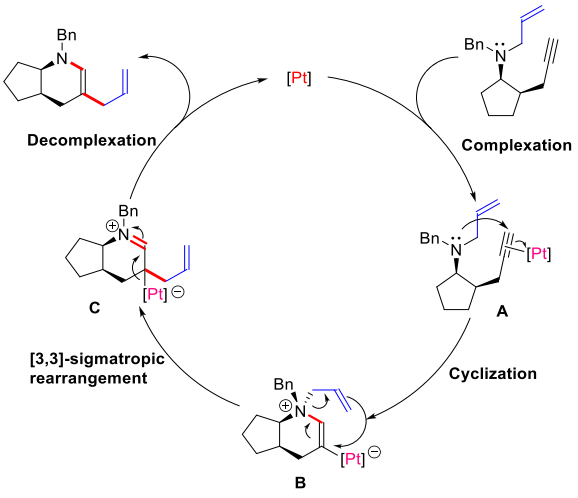
Scheme 1. Synthetic Application of Tetrahydropyridines



Scheme 2. Deuterium-Labeling Crossover Experiment



Scheme 3. Proposed Mechanism



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01250.

Experimental procedures and compound characterization (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Nguyen, T. B.; Retailleau, P. *Org. Lett.* **2017**, *19*, 3879−3882.
(2) Kolesnikov, P. N.; Usanov, D. L.; Muratov, K. M.; Chusov, D. *Org. Lett.* **2017**, *19*, 5657−5660.
(3) Li, H.; Zhong, Y. L.; Chen, C. Y.; Ferraro, A. E.; Wang, D. *Org. Lett.* **2015**, *17*, 3616−3619.
(4) Trost, B. M.; Maulide, N.; Livingston, R. C. *J. Am. Chem. Soc.* **2008**, *130*, 16502−16503.
(5) Trost, B. M.; Gholami, H. *J. Am. Chem. Soc.* **2018**, *140*, 11623−11626.
(6) (a) Tanabe, H.; Ichikawa, J. *Chem. Lett.* **2010**, *39*, 248−249. (b) Yang, S.; Shi, M. *Acc. Chem. Res.* **2018**, *51*, 1667−1680. (c) Afewerki, S.; Cordova, A. *Chem. Rev.* **2016**, *116*, 13512−13570. (d) *Modern Acetylene Chemistry*; Stang, P. J., Diederich, F., Eds.; VCH: Weinheim, 1995.
(7) (a) Zeng, M.; Herzon, S. B. *J. Org. Chem.* **2015**, *80*, 8604−8618. (b) Chi, Y.; Yan, H.; Zhang, W. X.; Xi, Z. *Org. Lett.* **2017**, *19*, 2694−2697. (c) Ren, H.; Du, G. F.; Zhu, B.; Yang, G. C.; Yao, L. S.; Guan, W.; Su, Z. M. *Organometallics* **2018**, *37*, 2594−2601. (d) Clark, R. J.; French, J. M.; Jecs, E.; Diver, S. T. *Org. Lett.* **2012**, *14*, 4178−4181.
(8) Cruz, F. A.; Dong, V. M. *J. Am. Chem. Soc.* **2017**, *139*, 1029−1032.
(9) (a) Dermenci, A.; Whittaker, R. E.; Gao, Y.; Cruz, F. A.; Yu, Z. X.; Dong, G. *Chem. Sci.* **2015**, *6*, 3201−3210. (b) Hyster, T. K.; Dalton, D. M.; Rovis, T. *Chem. Sci.* **2015**, *6*, 254−258. (c) Mo, J.; Wang, L.; Cui, X. *Org. Lett.* **2015**, *17*, 4960−4963.
(10) (a) Dorel, R.; Echavarren, A. M. *Chem. Rev.* **2015**, *115*, 9028−9072. (b) Li, T.; Yang, P. *J. Org. Chem.* **2018**, *83*, 14751−14757.
(11) (a) Chatani, N.; Morimoto, T.; Muto, T.; Murai, S. *J. Am. Chem. Soc.* **1994**, *116*, 6049−6050. (b) Rosca, D. A.; Radkowski, K.; Wolf, L. M.; Wagh, M.; Goddard, R.; Thiel, W.; Fürstner, A. *J. Am. Chem. Soc.* **2017**, *139*, 2443−2455.
(12) Trost, B. M.; Lumb, J. P.; Azzarelli, J. M. *J. Am. Chem. Soc.* **2011**, *133*, 740−743.
(13) Hirabayashi, T.; Sakaguchi, S.; Ishii, Y. *Adv. Synth. Catal.* **2005**, *347*, 872−876.
(14) Brenna, D.; Villa, M.; Gieshoff, T. N.; Fischer, F.; Hapke, M.; Wangelin, A. J. V. *Angew. Chem., Int. Ed.* **2017**, *56*, 8451−8454.
(15) Alonso-Marañón, L. A.; Martínez, M. M.; Sarandeses, L. A.; Bengoa, E. G.; Sestelo, J. P. *J. Org. Chem.* **2018**, *83*, 7970−7980.
(16) Kettler, P. B. *Org. Process Res. Dev.* **2003**, *7*, 342−354.
(17) (a) Xing, X.; Xu, C.; Chen, B.; Li, C.; Virgil, S. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **2018**, *140*, 17782−17789. (b) Sultana Poly, S.; Siddiki, S. M. A. H.; Touchy, A. S.; Ting, K. W.; Toyao, T.; Maeno, Z.; Kanda, Y.; Shimizu, K. I. *ACS Catal.* **2018**, *8*, 11330−11341. (c) Wain, A. J.; O'Connell, M. A.; Attard, G. A. *ACS Catal.* **2018**, *8*, 3561−3570. (d) Preger, Y.; Root, T. W.; Stahl, S. S. *ACS Omega* **2018**, *3*, 6091−6096.
(18) (a) Spina, R.; Colacino, E.; Gabriele, B.; Salerno, G.; Martinez, J.; Lamaty, F. *J. Org. Chem.* **2013**, *78*, 2698−2702. (b) Chen, Z.; Jia, X.; Huang, J.; Yuan, J. *J. Org. Chem.* **2014**, *79*, 10674−10681. (c) Shibata, T.; Uno, N.; Sasaki, T.; Kanyiva, K. S. *J. Org. Chem.* **2016**, *81*, 6266−6272.
(19) (a) Cariou, K.; Ronan, B.; Mignani, S.; Fensterbank, L.; Malacria, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1881−1884. (b) Fürstner, A.; Davies, P. W. *J. Am. Chem. Soc.* **2005**, *127*, 15024−15025. (c) Nakamura, I.; Mizushima, Y.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 15022−15023. (d) Tobisu, M.; Nakai, H.; Chatani, N. *J. Org. Chem.* **2009**, *74*, 5471−5475.
(20) (a) Rubiralta, M.; Giralt, E.; Diez, A. *Piperidine: Structure, Preparation, Reactivity, and Synthetic Applications of Piperidine and Its Derivatives*; Elsevier: Amsterdam, 1991. (b) Jain, R.; Chen, D.; White, R. J.; Patel, D. V.; Yuan, Z. *Curr. Med. Chem.* **2005**, *12*, 1607−1621. (c) Kubota, H.; Fujii, M.; Ikeda, K.; Takeuchi, M.; Shibanuma, T.; Isomura, Y. *Chem. Pharm. Bull.* **1998**, *46*, 351−354.
(21) (a) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271−2296. (b) Stathakis, C. I.; Gkizis, P. L.; Zografos, A. L. *Nat. Prod. Rep.* **2016**, *33*, 1093−1117.

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