

Tropene Derivatives by Sequential Intermolecular and Transannular, Intramolecular Palladium-Catalyzed Hydroamination of Cycloheptatriene

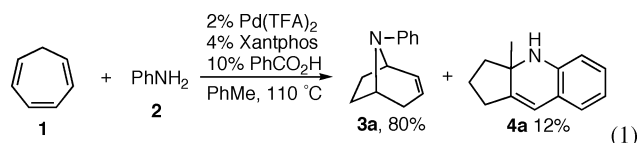
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We report a metal-catalyzed dual hydroamination to produce the common biologically active azabicyclic tropene ring system.^{1,2} This reaction formally combines an intermolecular hydroamination of a triene with a subsequent intramolecular transannular hydroamination of a diene. Most routes to tropenes involve additions of amines to activated trienes³ or multiple steps,^{4–8} but the metal-catalyzed hydroamination forms a precursor to functionalized tropanes and related alkaloids,⁹ such as cocaine derivatives,¹ in one step by linking two common, commercially available reagents. This new addition sequence extends the scope of metal-catalyzed hydroaminations and demonstrates that transannular hydroaminations can form the bridged polycyclic cores that are common in alkaloids.

Studies to develop conditions (see Supporting Information) for consecutive hydroaminations of cycloheptatriene with aniline (eq 1) showed that the tropene product **3a** formed in the highest yields with a combination of Xantphos and Pd(TFA)₂ (TFA = trifluoroacetate) as catalyst and benzoic acid as cocatalyst. In the presence of the combination of 4 mol % of Xantphos (9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene), 2 mol % of Pd(TFA)₂ and 10 mol % PhCO₂H, product **3a** was isolated in 80% yield after 2 h at 110 °C. In addition to tropene **3a**, the quinoline derivative **4a** was isolated in 12% yield.¹⁰ In many cases, the addition occurred in nearly equivalent yields in the absence of benzoic acid, although some substrate combinations did require the presence of added acid (vide infra). The structures of one of the tropene and one of the quinoline derivatives were confirmed by X-ray diffraction.¹¹



Reactions conducted with catalysts generated from DPEphos (bis-(2-(diphenylphosphino)phenyl) ether), which has a smaller bite angle than Xantphos, and DPFphos (4,6-bis(diphenylphosphino)-dibenzofuran), which has a larger bite angle than Xantphos,¹² occurred in lower yields than those conducted with catalysts generated from Xantphos (Table S11). Moreover, reactions conducted with the monodentate ligands Ph₃P and tBu₃P occurred in low yields. The reactions catalyzed by complexes generated from DPPF (1,1'-bis(diphenylphosphino)ferrocene) formed much larger amounts of the quinoline side product. No hydroamination reaction occurred at 110 °C in the absence of palladium or ligand or both. Reactions conducted with the Xantphos–palladium catalyst and a strong acid cocatalyst such as TFA and TfOH¹³ formed the tropene in lower yields than did reactions conducted with the weaker benzoic acid or with no acid.

Table 1 summarizes the scope of the reactions of primary aromatic amines with cycloheptatriene. The reactions were typically run at 110 °C with 0.5–1 M amine and 3–4 equiv of triene. The reactions of the triene with electron-poor or electron-rich arylamines formed the tropene product in good to excellent yields (entries 1–8 in Table 1). Reactions of electron-rich arylamines occurred faster

Table 1. Pd-Catalyzed Hydroamination of Cycloheptatriene with Aryl and Heteroaryl Amines^a

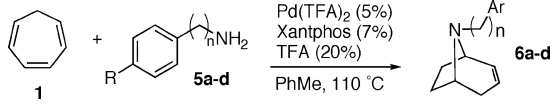
entry	product 3 (%) ^b	product 4 (%) ^b	entry	product 3 (%)	product 4 (%)
1	 3b : 5 h, 64%	 4b : 25%	6	 3g : 1 h, 80%	 4g : 15%
2	 3c : 15 h, 66%	 4c : 24%	7	 3h : 72 h, 61%	 4h : trace
3	 3d : 5 h, 56% E = CO ₂ Et	 4d : 32%	8	 3i : 1.5 h, 90%	 4i : ND
4	 3e : 15 h, 42%	 4e : 38%	9	 3j : 3 h, 58%	 4j : 14%
5	 3f : 1.5 h, 73%	 4f : 9%	10 ^c	 3k : 24 h, 41%	 4k : 18%

^a Reaction conditions: triene (2.0–4.0 mmol, 4 equiv), aniline (0.5–1.0 mmol), Pd(TFA)₂ (2%), Xantphos (4%), PhCO₂H (10%), and toluene (0.5–1.0 mL). ^b Isolated yields based on amine. ^c 5% Pd(TFA)₂, 7% Xantphos, and 10% trifluoroacetic acid was used.

than reactions of electron-poor arylamines and gave the bicyclic products in slightly higher yields (entries 5 and 6). Reactions conducted with di- or trisubstituted arylamines formed smaller amounts of the quinoline side product, presumably due to steric hindrance toward reaction at the ortho position of the aryl ring (entries 7 and 8).

Heteroaryl amines also formed the tropene product. The reaction of 3-aminoquinoline with cycloheptatriene under the standard conditions gave the addition product in 58% yield (entry 9). A dihydroquinoline derivative of **4** was formed as side product in this case. The reaction of 3-aminopyridine with the conjugated triene did not occur under the conditions that led to addition of the arylamines, but the addition did occur in the presence of 5% Pd(TFA)₂, 7% Xantphos, and 10% of the stronger acid TFA to form the corresponding hydroamination products in substantial yields (entry 10).

Additions of benzylamine and β -phenethylamine to cycloheptatriene also occurred. These reactions occurred in good yield at 110 °C in the presence of higher quantities of catalyst and trifluoroacetic acid and were faster with a lower ratio of ligand to metal (5 mol % of Pd(TFA)₂, 7 mol % of Xantphos). Under these conditions, the reaction of benzylamine (**5a**) with cycloheptatriene generated exclusively the nitrogen-bridged heterocycle **6a** in 68%

Table 2. Pd-Catalyzed Hydroamination of Triene with Primary Alkyl Amines^a


entry	R	n	time (h)	yield: 6 ^b (%)
1	H	1	40	6a 68
2	MeO	1	48	6b 70
3	CF ₃	1	48	6c 62 ^c
4	H	2	48	6d 72

^a Reaction conditions: triene (2.0 mmol), amine (0.5 mmol), and toluene (0.5 mL). ^b Isolated yield based on amine. ^c Yield by ¹H NMR spectroscopy with an internal standard.

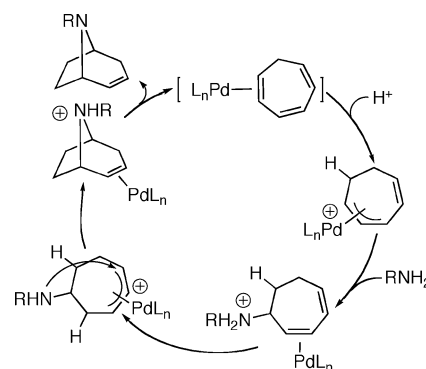
isolated yield (entry 1 in Table 2). Thus far, analogous reactions of purely aliphatic amines have not occurred.

Table 2 summarizes the results of the dual hydroamination of cycloheptatriene with benzylic amines and with β -phenethylamine. As did the reactions of arylamines, the reactions of more electron-rich benzylic amines occurred in higher yields than reactions of less electron-rich benzylic amines. The reaction of β -phenethylamine with cycloheptatriene occurred in high yield without formation of a major side product (entry 4).

Preliminary mechanistic experiments showed that H/D exchange between the amine and triene occurs faster than the addition process. Specifically, the reaction of aniline-*d*₂ with 4 equiv of cycloheptatriene led to the incorporation of deuterium equally on all carbons of the tropene product, except those of the *N*-aryl group. This global incorporation of deuterium resulted from an H/D exchange of D₂-NPh with the starting cycloheptatriene prior to the addition reaction. Unreacted cycloheptatriene consisted of the isotopomers 61% *d*₀, 43% *d*₁, 13% *d*₂, and 1% *d*₃.

Preliminary mechanistic experiments also showed that the addition process is reversible only under stringent conditions and that the side product is not formed directly from the tropene. We considered that the addition could be reversible because hydroamination has a small driving force, the reactant is highly conjugated, and the product may have some ring strain. However, heating the *p*-tolyl-substituted tropene **3g** (entry 6 in Table 1) with an equal molar amount of 4-*tert*-butylaniline (**2l**) in the presence of 2 mol % of Pd(TFA)₂, 4 mol % of Xantphos, and 10 mol % of benzoic acid for 1.5 h at 110 °C left 90% of the starting **3g** unreacted. This time is longer than the 1 h time required to form **3g** in high yield. After 66 h, the tropene did partially exchange with the arylamine, and the corresponding *p*-*t*Bu-substituted *N*-aryl tropene was formed in 24% yield. Thus, the thermodynamics for the addition process are favorable enough that the cleavage of **3** is slow. In addition, heating of the *N*-aryl tropene **3a** with the catalyst components without amine left 87% of **3a** unreacted after 1.5 h. Thus, the tropene is not a direct precursor to the isomeric quinoline side product.

Scheme 1 shows a possible pathway for the sequential hydroamination. Most likely, a Xantphos–palladium(0) species, acid, and triene combine to form an η^3 -pentadienyl complex that would undergo nucleophilic attack by the amine to generate a palladium complex containing an amino-substituted diene. This reaction could occur by initial formation of a palladium hydride or by protonation of a Pd(0) complex of the triene as noted in recent work on the hydroamination of vinylarenes.¹⁴ Intramolecular, transannular hydroamination would then form the protonated form of the coordinated tropene. Dissociation of the product and proton transfer to the combination of palladium and triene would then regenerate the pentadienyl intermediate. If so, then the initial step of the cycle to form the aminodiene would be turnover-limiting or endothermic

Scheme 1

and reversible because no free aminodiene was detected during the reaction.¹⁵ Alternatively, the reaction could occur by a combination of attack of amine on Pd(II) complexes of the triene and other polyene intermediates, along with protonation of the resulting polyenyl complexes, as suggested by a reviewer.

In summary, we show that palladium-catalyzed hydroamination of a cyclic triene generates products that result, at least formally, from a consecutive intermolecular hydroamination and transannular intramolecular hydroamination to form a bridged bicyclic system. A photochemical, lithium-mediated reaction reported by Trost as part of the synthesis of morphine¹⁶ and a reaction of a nonconjugated aminodiene to form a fused bicyclic system reported by Marks¹⁷ are the most closely related examples of hydroaminations to form bicyclic systems. Studies toward enantioselective versions of this process will be part of future studies.

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Supporting Information Available: Reaction procedures, characterization of reaction products, and summary of the effect of varying reaction conditions. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- (a) Carroll, F. I.; Lewin, A. H.; Boja, J. W.; Kuharf, M. J. *J. Med. Chem.* **1992**, *35*, 969. (b) Carroll, F. I.; Blough, B. E.; Nie, Z.; Kuharf, M. J.; Howell, L. L.; Navarro, H. A. *J. Med. Chem.* **2005**, *48*, 2767.
- Salmon, R.; Smith, S. C.; Brightwell, C. I. PCT Application WO99/38865, 1999.
- (a) Grundmann, C.; Ottman, G. *Liebigs Ann. Chem.* **1957**, *605*, 24. (b) Kline, R. H.; Wright, J.; Fox, K. M.; Eldeffrawi, M. E. *J. Med. Chem.* **1990**, *33*, 2024. (c) Okano, K.; Ito, O. Jpn. Patent 2001213881, 2001.
- (a) Takaya, H.; Makino, S.; Hayakawa, Y.; Noyori, R. *J. Am. Chem. Soc.* **1977**, *99*, 1765. (b) Hayakawa, Y.; Baba, Y.; Makino, S.; Noyori, R. *J. Am. Chem. Soc.* **1978**, *100*, 1786. (c) Paparin, J.-L.; Crévisy, C.; Toupet, L.; Grée, R. *Eur. J. Org. Chem.* **2000**, 3909.
- For dipolar cycloadditions, see ref 6.
- (a) Takahashi, T.; Fujii, A.; Sugita, J.; Hagi, T.; Kitano, K.; Arai, Y.; Koizumi, T. *Tetrahedron: Asymmetry* **1991**, *2*, 1379. (b) Pham, V. C.; Charlton, J. L. *J. Org. Chem.* **1995**, *60*, 8051. (c) Rumbo, A.; Mourino, A.; Castedo, L.; Mascarenas, J. L. *J. Org. Chem.* **1996**, *61*, 6114. (d) Kozikowski, A. P.; Araldi, G. L.; Ball, R. G. *J. Org. Chem.* **1997**, *62*, 1095.
- For rhodium(II)-mediated reactions of vinylcarbenoids with pyrroles see ref 8.
- Davies, H. M. L.; Matasi, J. J.; Hodges, L. M.; J. S. Huby, N.; Thornley, C.; Kong, N.; Houser, J. H. *J. Org. Chem.* **1997**, *62*, 1095.
- Lin, R.; Castells, J.; Rapoport, H. *J. Org. Chem.* **1998**, *63*, 4069.
- We have not been able to rationalize the formation of this side product.
- See Supporting Information
- (a) Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Goubitz, K.; Fraanje, J. *Organometallics* **1995**, *14*, 3081. (b) Kamer, P. C. J.; van Leeuwen, P. W. N.; Reek, J. N. H. *Acc. Chem. Res.* **2001**, *34*, 895.
- (a) Löber, O.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 4366. (b) Pawlas, J.; Nakao, Y.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 3669.
- Johns, A. M.; Utsunomiya, M.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, ASAP.
- For comparison, the intermolecular hydroamination of dienes with the same catalyst occurs at or near room temperature (ref 14).
- Trost, B. M.; Tang, W. P. *J. Am. Chem. Soc.* **2002**, *124*, 14542.
- Ryu, J.-S.; Marks, T. J.; McDonald, F. E. *J. Org. Chem.* **2004**, *69*, 1038. JA061349A