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Synthesis of 2-Anilinotropones via Palladium-Catalyzed Amination of 2-Triflatotropone

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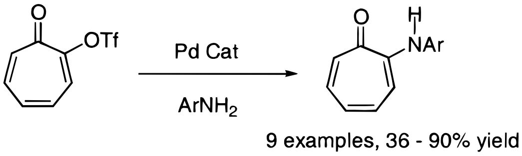
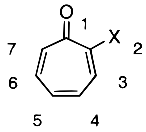
ABSTRACT

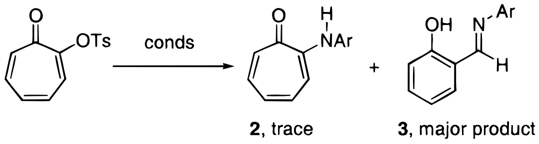


A series of 2-anilinotropones were synthesized via the palladium-catalyzed cross coupling of 2-triflatotropone and a wide variety of anilines, sterically hindered as well as electron-poor ones.

The chemistry of tropone derivatives has been a rich field of research for half a century due to inherent interest in their homoaromatic character and their presence in a number of biologically active natural compounds such as colchicine.[1] In particular, extensive investigations into the nucleophilic substitution chemistry of tropone derivatives have revealed complex reactivity patterns. For instance, tropones with a leaving group X in the 2-position, **1**, may produce compounds arising from attack at the 1-, 2-, 3-, 6-, or 7-position or admixtures thereof.[2] The site of attack is often difficult to predict and is dependent on the nature of the leaving group X, the nucleophile, and the nature and position of other substituents on the tropone ring. While this diversity of chemistry is interesting from a mechanistic perspective, utilizing the nucleophilic substitution of tropone derivatives in a synthetic sequence is an uncertain endeavor.



As part of a program focusing on the development of new ligands for transition metal chemistry, we attempted to synthesize a series of 2-anilinotropones **2** via nucleophilic substitution of the corresponding 2-tosyloxytropone. However, we were only able to obtain a trace of the desired product, **2**, using sterically hindered 2,6-diisopropylaniline (eq 1). Instead we isolated predominantly the benzenoid rearrangement product, **3**,[3] derived from attack of the aniline at the 3-position.[4] On the basis of the work of Buchwald[5]



2, trace   **3**, major product   (1)

Ar = 2,6-(iPr)$_2$C$_6$H$_3$

conds: neat 2,6-diisopropylaniline, 150 °C, 12 h

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[1] Pietra, F. *Chem. Rev.* **1973**, *73*, 293.

[2] (a) Ito, S.; Tsunetsugu, J.; Kanno, T.; Sugiyama, H.; Takeshita, H. *Tetrahedron Lett.* **1965**, 3659. (b) Biggi, G.; Cima, F. D.; Pietra, F. *J. Am. Chem. Soc.* **1973**, *95*, 7101. (c) Biggi, G.; de Hoog, A. J.; Cima, F. D.; Pietra, F. *J. Am. Chem. Soc.* **1973**, *95*, 7108.

[3] Chang, S.; Jones, L., II; Wang, C.; Henling, L. M.; Grubbs, R. H. *Organometallics* **1998**, *17*, 3460.

[4] Mukai, T. *Bull. Chem. Soc. Jpn.* **1959**, *32*, 272.

[5] (a) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (b) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125.

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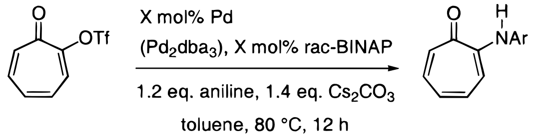
and Hartwig[6] on the palladium-catalyzed cross coupling of amines with aryl halides and triflates, we considered the possibility of a palladium-catalyzed cross coupling of the aniline and a 2-halo- or triflatotropone. While the synthetic utility of transition metal-catalyzed cross couplings employing halo- and triflatotropones to form carbon−carbon bonds has been demonstrated in recent years[7] no reports of related carbon−heteroatom bond formation have yet appeared.[8] We considered this approach an appealing alternative to the lack of control often associated with the nucleophilic substitution reactions of tropones and report its successful implementation herein.

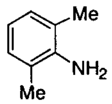
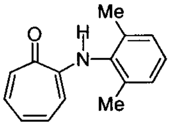
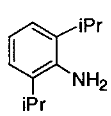
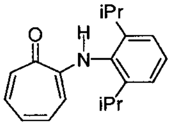
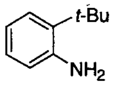
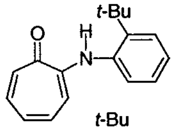
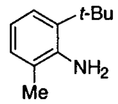
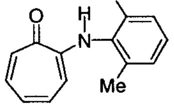
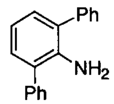
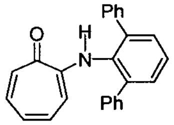
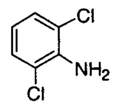
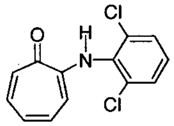
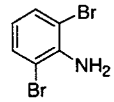
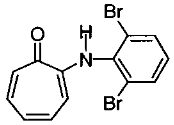
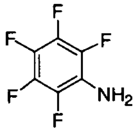
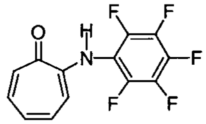
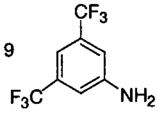
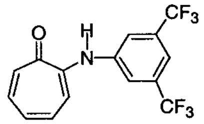
It was found that 2-triflatotropone[7g] could be cleanly coupled with a variety of anilines under conditions similar to those employed with aryl triflates (eq 2).[9−11] This method



(2)

is applicable to the synthesis of sterically hindered derivatives substituted in the 2,6-position of the aniline as indicated in entries 1 and 2 of Table 1. To test the limitations of this methodology with respect to steric influences, the coupling of a series of increasingly hindered anilines was investigated. While 2-*tert*-butylaniline (entry 3) could be utilized without incident, attempts to effect cross couplings with the more hindered 2-*tert*-butyl-6-methylaniline and 2,6-diphenylaniline (entries 4 and 5) led to product formation in noticeably decreased yield. These anilines seem to represent the upper limit with regard to steric hindrance as attempts to couple 2,4,6-tri-*tert*-butylaniline failed with this catalyst system. The ability to employ 2,6-dihaloanilines (entries 6 and 7) represents a particularly impressive result as these anilines are both sterically hindered and electron deficient, making them particularly poor candidates as nucleophiles. Additionally, the presence of halogens on the aniline, which could lead to potential cross coupling side products, was not a significant problem. It is interesting to note that the reaction involving 2,6-dibromoaniline is the only one which proceeds in substantially higher yield (69% vs 32%) when 5 rather than 1 mol % of catalyst is employed. Finally, extremely

Table 1. Synthesis of 2-Anilinotropones

	aniline	anilinotropone	x mol% Pd	yield (%)[a]
1			1	90
2			1	86
3			1	88
4			1	36
5			1	37
6			1	75
7			5 1	69 32
8			1	84
9			1	89

(a) All compounds characterized by ^{1}H and ^{13}C NMR spectroscopy and elemental analysis.

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(6) (a) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046. (b) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852.

(7) Heck coupling: (a) Horino, H.; Inoue, N.; Asao, T. *Tetrahedron Lett.* **1981**, *22*, 741. (b) Horino, H.; Inoue, N.; Asao, T. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 183. Suzuki coupling: (c) Nair, V.; Powell, D. W.; Suri, S. C. *Synth. Commun.* **1987**, *17*, 1897. (d) Suri, S. C.; Nair, V. *Synthesis* **1990**, 695. Stille coupling: (e) Banwell, M. G.; Collis, M. P.; Crisp, G. T.; Lambert, J. N.; Reum, M. E.; Scoble, J. A. *J. Chem. Soc., Chem. Commun.* **1989**, 616. (f) Banwell, M. G.; Cameron, J. M.; Collis, M. P.; Crisp, G. T.; Gable, R. W.; Hamel, E.; Lambert, J. N.; Mackay, M. F.; Reum, M. E.; Scoble, J. A. *Aust. J. Chem.* **1991**, *44*, 705. Carbonylative coupling: (g) Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1988**, *110*, 1557. Aryl zinc coupling: (h) Keenan, R. M.; Kruse, L. I. *Synth. Commun.* **1989**, *19*, 793. (i) Iyoda, M.; Sato, K.; Oda, M. *Tetrahedron Lett.* **1987**, *28*, 625.

(8) One example involving the use of a catalytic amount of $Cu(OAc)_2$ to promote phenolic substitution with 3-bromotropolone (yield increased from 49% uncatalyzed to 90%) has been reported. Takase, K. *Bull. Chem. Soc. Jpn.* **1964**, *37*, 1288.

(9) Åhman, J.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6363.

(10) Control reactions were conducted involving the cross coupling conditions in the absence of palladium. For 2-tosyloxytropone, only the rearranged product **3** was observed. For 2-triflatotropone, only unreacted aniline could be isolated at the end of the reaction.

(11) **Representative Procedure.** A Schlenk tube, flame-dried in vacuo, was placed under an Ar atmosphere on a vacuum line. The tube was charged with $Pd_2(dba)_3$ (5 mg, 0.005 mmol), rac-BINAP (7 mg, 0.01 mmol), Cs_2CO_3 (456 mg, 1.4 mmol), and 2-triflatotropone (254 mg, 1.0 mmol). Toluene (2 mL) was added followed by 2,6-dimethylaniline (148 μL, 1.2 mmol). The Schlenk tube was sealed and heated to 80 °C for 12 h. The reaction mixture was allowed to cool to room temperature, filtered through a pad of silica gel with the aid of ether (100 mL), and concentrated to afford the crude product. Purification via flash column chromatography on silica gel (eluants 3:2 hexane:ether) afforded 200 mg (89% yield) of an orange solid. Mp: 76−78 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.40 (bs, 1 H); 7.32 (m, 2 H); 7.18 (m, 3 H); 7.08 (t, J = 10.5 Hz, 1 H); 6.73 (m, 1 H); 6.22 (d, J = 10.5 Hz, 1 H); 2.15 (s, 6 H).

electron-poor anilines (entries 8 and 9) were also successfully coupled using this protocol.

In summary, a variety of 2-anilinotropones, which are inaccessible using traditional nucleophilic displacement approaches, can be readily synthesized via the palladium-catalyzed amination of 2-triflatotropone. The methodology shows a tolerance for anilines possessing a high degree of steric encumbrance and for highly electron deficient, poorly nucleophilic anilines. This work highlights the potential power of transition metal-catalyzed carbon−heteroatom bond formation for regioselective tropone synthesis, and this general approach should find application with respect to more highly substituted tropones and other nucleophiles.

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Supporting Information Available: The preparation and characterization of all compounds in Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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