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Divergent Pd-Catalyzed and Radical Cyclizations of Nucleophilic Cyclic Enamines Derived from Functionalized Amine and Aldehyde Fragments

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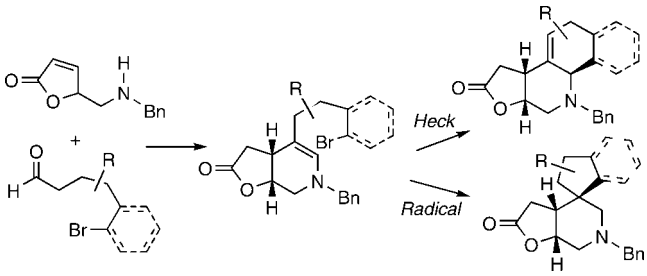
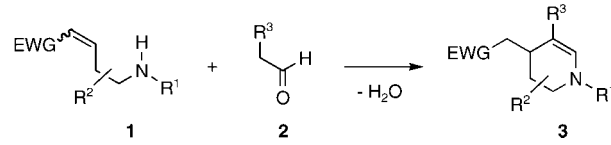


Tetrahydropyridines carrying pendant halide functionality at the enamine β-carbon have been prepared by condensation between appropriately functionalized aldehydes and a vinylogous Mannich adduct. Those enamines display divergent behavior in radical and Heck reactions. Thus, radical addition takes place in a 5-*exo*-trig fashion whereas Heck couplings follow a 6-*endo*-trig pathway. The resulting polycyclic products are obtained with high regio- and stereoselectivity.

The condensation between vinylogous Mannich adducts **1** and aldehydes **2** leads to cyclic enamines **3** (Scheme 1), and this reaction has found recent use in the preparation of polysubstituted piperidine derivatives via hydrogenation reactions as well as nucleophilic addition- and reductive-type couplings.[1]

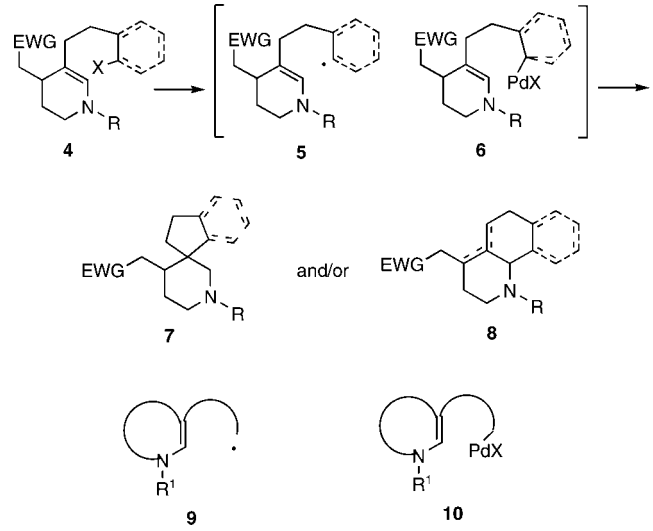
Appropriately substituted tetrahydropyridines **4** could in principle be envisaged as precursors of polycyclic systems **7** and/or **8** via intramolecular radical-[2] or Heck-type[3] additions

SCHEME 1. Formation of Tetrahydropyridines from Amines and Aldehydes



1 **2** **3**

SCHEME 2. Strategy to Polycyclic Building Blocks 7 and 8



4 **5** **6** **7** **8** **9** **10**

to the enamine double bond through intermediates **5** and **6**, respectively (Scheme 2). Compounds with general structures **7** and **8** are interesting as functionalized building blocks because their respective azaspirocyclic and tricyclic benzo[*h*]quinoline basic skeletons are found in a number of biologically active products.[4] A condensation/cyclization approach to these compounds (Schemes 1 and 2) would be attractive because of its simplicity, conciseness, and flexibility to introduce precursors for various types of *C*-radicals and Pd-complexes through simple aldehydes **2**. Furthermore, because R, R^1, and R^3 are necessarily alkyl groups in **3** and **4**, these cyclizations would involve nucleophilic cyclic enamine intermediates of the general types represented by **9** and **10**, which have seldom been reported except for indole-type enamines.[5,6] Moreover, in the case of radicals **9**, the cyclizations are poorly regioselective[5b] unless additional activation is provided at the enamine α-position.[5a]

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(4) See: (a) Khan, F. A.; Dash, J. *J. Org. Chem.* **2003**, *68*, 4556–4559. (b) McManus, A. H.; Fleming, M. J.; Lautens, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 433–436. (c) Harrison, T. J.; Patrick, B. O.; Dake, G. R. *Org. Lett.* **2007**, *9*, 367–370, and references cited therein.

(5) Radical reactions of type **9** with indole derivatives: (a) Yang, C. C.; Chang, H. T.; Fang, J. M. *J. Org. Chem.* **1993**, *58*, 3100−3105. (b) Flanagan, S. R.; Harrowven, D. C.; Bradley, M. *Tetrahedron Lett.* **2003**, *44*, 1795−1798 and references cited therein. For reactions involving *N*-sulfonyl- or *N*-methoxycarbonyl enamines, see:(c) Ahman, J.; Somfai, P. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1079–82. (d) Parsons, P. J.; Penkett, C. S.; Cramp, M. C.; West, R. I.; Warrington, J.; Saraiva, M. C. *Synlett* **1995**, *Sp. Iss.*, 507–509. (e) Parsons, P. J.; Penkett, C. S.; Cramp, M. C.; West, R. I.; Warren, E. S. *Tetrahedron* **1996**, *52*, 647–60.

(6) Heck reaction of type **10** with indole derivatives: (a) Joucla, L.; Putey, A.; Joseph, B. *Tetrahedron Lett.* **2005**, *46*, 8177–8179. (b) Avila-Zarraga, J. G.; Lujan-Montelongo, A.; Covarrubias-Zuniga, A.; Romero-Ortega, M. *Tetrahedron Lett.* **2006**, *47*, 7987–7989.

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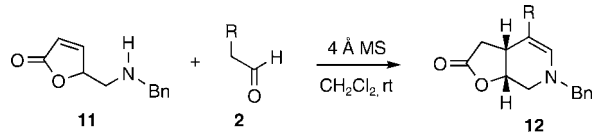
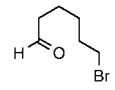
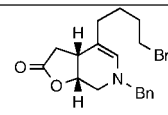
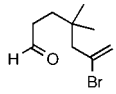
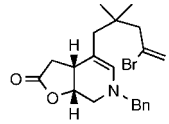
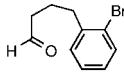
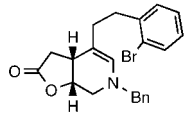
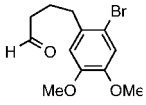
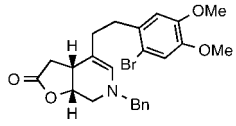
TABLE 1. Preparation of Tetrahydropyridines 12



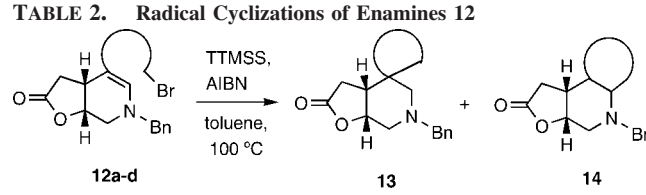
	Aldehyde **2**		Enamine **12**		Yield (%)
1		**2a**		**12a**	68
2		**2b**		**12b**	49
3		**2c**		**12c**	72
4		**2d**		**12d**	78

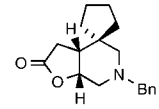
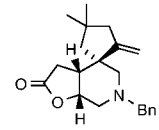
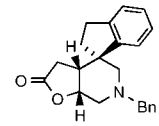
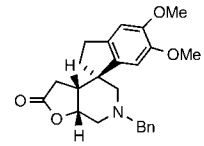
Therefore, the possibility of using tetrahydropyridines of type **4** appeared to be worth exploring since this would provide an opportunity to further examine the radical and Pd-catalyzed chemistry of the enamine functional group. In this paper we report an expeditious and divergent approach to building blocks of general types **7** and **8** through a common tetrahydropyridine **4** utilizing highly regio- and stereoselective 5-*exo*-trig radical additions and 6-*endo*-trig Heck couplings, respectively.[7]

Amine **11**[1b,8] and aldehydes **2a**−**d** were selected as precursors of representative substrates for radical and Pd-catalyzed reactions. The choice of amine **11** as a convenient starting material was dictated by its ready availability in multigram quantities.[1b] Aldehydes **2a**−**c** were known compounds,[9] while the preparation of **2d** followed the procedure reported for **2c**.[9c] Tetrahydropyridines **12a**−**d** were then prepared by condensation between **11** and **2a**−**d** in CH_2Cl_2 at room temperature with the yields indicated in Table 1. Enamines **12** were conveniently purified by column chromatography and could be stored for several days without appreciable degradation, with the exception of **12a**, which underwent self-decomposition on standing at room temperature and had to be used soon after purification. This is not completely surprising since **12a** holds at the same time a nucleophilic enamine and an alkylating agent. In any case, it is remarkable that reaction conditions are mild enough to allow the preparation of this type of compound.

Treatment of tetrahydropyridines **12** under typical radical cyclization conditions with $(TMS)_3SiH$/AIBN in toluene at 100 °C resulted in the formation of spirocycles **13** in good yields (Table 2). Products derived from alkyl (entry 1), vinyl (entry 2), or aryl (entries 3 and 4) radicals are all effectively obtained in a highly regio- and stereoselective fashion, with the alternative regioisomers **14** and/or stereoisomers being formed in only minor amounts. In the reaction of **12b** a furoquinoline derivative of type **14** was clearly identified by comparison of diagnostic ^{13}C NMR signals with those of the spiro derivative **13b**. Thus, a CH_2 unit and the characteristic spirocyclic quaternary carbon of **13b** were replaced by two CH carbons in the corresponding regioisomer. As expected, the major stereoisomer in these reactions was formed by radical addition to the less congested face of the enamine double bond, i.e., *anti* to the fused lactone moiety. This was determined for **13b**−**d** by the observation of NOE's between the lactone bridgehead protons and either one vinylic hydrogen (in the case of **13b**) or the aromatic *o*-H proximal to the spirocyclic quaternary carbon (in the case of **13c** and **13d**).

TABLE 2. Radical Cyclizations of Enamines 12



	12	Major Product		Yield (%)	**13/14**
1	**12a**		**13a**	65	-
2	**12b**		**13b**	78	7.3:1
3	**12c**		**13c**	60	14:1[a]
4	**12d**		**13d**	50	14:1[a]

[a] Ratio of **13** to an undetermined mixture of isomers.

The cyclizations depicted in Table 2 represent an unusual type involving the addition of a nucleophilic *C*-radical to an electron-rich enamine double bond. This polarity mismatch has been shown to retard the rate of addition of nucleophilic *C*-radicals to enamines,[10] and as a result, intermolecular reactions have mainly employed electrophilic radicals containing

(7) Related 6-*endo*-trig radical and 6-*exo*-trig Pd-catalyzed reactions have been reported for enamide-type systems with the cyclizing chain attached to the enamide α-carbon. Radical: (a) Ripa, L.; Hallberg, A. *J. Org. Chem.* **1998**, *63*, 84–91. Pd-catalyzed: (b) Ripa, L.; Hallberg, A. *J. Org. Chem.* **1996**, *61*, 7147–7155. (c) Ripa, L.; Hallberg, A. *J. Org. Chem.* **1997**, *62*, 595–602. (d) Lindstrom, S.; Ripa, L.; Hallberg, A. *Org. Lett.* **2000**, *2*, 2291–2293.

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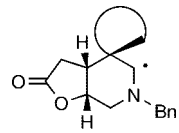
(10) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 753–764.

(11) (a) Renaud, P.; Schubert, S. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 433–434. (b) Renaud, P.; Schubert, S. *Synlett* **1990**, 624–626. (c) Russell, G. A.; Wang, K. *J. Org. Chem.* **1991**, *56*, 3475–3479. (d) Curran, D. P.; Thoma, G. *J. Am. Chem. Soc.* **1992**, *114*, 4436–4437. (e) Renaud, P.; Björup, P.; Carrupt, P. A.; Schenk, K.; Schubert, S. *Synlett* **1992**, 211–213. (f) Schubert, S.; Renaud, P.; Carrupt, P. A.; Schenk, K. *Helv. Chim. Acta* **1993**, *76*, 2473–2489. (g) Chuang, C.-P.; Wu, Y.-L. *Tetrahedron* **2004**, *60*, 1841–1847. (h) Tsai, A.-I.; Chuang, C.-P. *Tetrahedron* **2006**, *62*, 2235–2239.

electron-withdrawing groups,[11] while the corresponding intramolecular reactions[5,12] have been mostly limited to indole derivatives[5,12e] and to enamines with additional activation provided by aryl groups.[12b–d] Alternatively, the less nucleophilic, as well as more stable and easier to handle, enamide-type systems have been widely employed in a variety of synthetic applications.[2] In fact, the reactions reported here appear to be the first examples of 5-*exo*-trig radical cyclizations of systems of type **9** (R = alkyl) not involving indole derivatives.

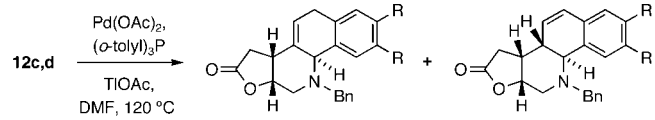
The regiochemistry of these radical cyclizations follows the trends observed with typical hex-5-enyl radicals, which are known to cyclize with high 5-*exo*-trig selectivity.[13,14] In addition, in this particular case, the observed 5-*exo*-trig mode of addition is also consistent with the tendency displayed by intermolecular radical additions to unconstrained enamines, where the regiochemistry appears to be governed by the preservation of conjugation. As a result, addition takes place at the enamine β-carbon with formation of a relatively stable α-aminoalkyl radical.[11] However, 5-*exo* to 6-*endo* cyclization ratios have also been found to be very dependent on the extent of steric congestion around the alkene terminus. For example, for simple model systems, the ratio 5-*exo*/6-*endo* goes from nearly 50:1 in the unsubstituted hex-5-enyl radical to approximately 1:2 in the 5-methylhex-5-enyl case.[13,14] Therefore, in the cyclizations of sterically encumbered enamines **12** the driving force provided by the formation of an α-aminoradical **15** is remarkable, particularly in the more substituted cases of **12b**−**d**.



15

The reactivity of enamines **12c**,**d** under typical Heck conditions was examined next. Ample precedent existed on the use of enamides, formamidines, enaminones, enaminoesters, dehydroaminoesters, pyrroles, and indoles, which have all been extensively utilized in intramolecular Heck reactions.[3,6,15] However, reports on the alternative use of simple enamines are very scarce and, in any case, restricted to 5-*endo* additions at the enamine β-position.[15c,16] After some experimentation, conditions which led efficiently to intramolecular arylation products were found (Scheme 3). The major products **16** displayed an alkene moiety exocyclic to the piperidine ring, and were accompanied by minor amounts of double bond isomerization products **17**. The use of TlOAc as additive was found to be important to minimize this isomerization,[7b,c,17] as shown by the increased amount of **17c** (**16c/17c** = 1.4:1, 52%) obtained when TlOAc was replaced by KOAc under otherwise similar conditions. Additionally, a significantly higher efficiency was noticed

SCHEME 3. Heck Reactions of Tetrahydropyridines 12



c R = H **16c** (52%) **17c** (5%)
d R = OMe **16d** (76%) **17d** (4%)

in the reaction of electron-rich-substituted phenyl derivative **12d**, and this could also be related to the use of that halide-scavenger additive.[17] Thus, in the presence of Tl(I) a cationic pathway is presumably involved[17] and, in that case, addition of the electron-rich aryl group to the more electron-deficient α-carbon is expected to be particularly favorable.[18] Formation of both **16** and **17** took place with very high stereoselectivity since no other stereoisomers were found. The stereochemistry of **16** and **17** was unambiguously established by NOE experiments and is consistent with a reaction course involving carbopalladation from the less hindered face of the enamine double bond, followed by β-H elimination with the exocyclic methylene unit.

In conclusion, starting from readily available aldehydes **2** and amine **11**, the tactical combination of a condensation step and either a radical- or Heck-type ring-closure provides a rapid build-up of molecular complexity in a regiodivergent and very stereoselective manner. The different regiochemistries displayed by the radical and Pd-catalyzed reactions make the two methods complementary, a feature also recognized in earlier work.[7] Additionally, the presence of a lactone ring in **13** and **16** is particularly convenient as it offers further possibilities for structural diversification.[1b] It is noted, however, that simpler tetrahydropyridines **3** (EWG = CO_2Et) are similarly available from acyclic α,β-unsaturated esters.[1a] All of these combined features contribute to make the methodology appealing for the preparation of structurally diverse families of polycylic nitrogen heterocycles.

Experimental Section

General Procedure for the Preparation of Tetrahydropyridines 12. In a typical experiment, to a solution of amine **11**[1b,8] (0.402 g, 1.98 mmol) and the appropriate aldehyde **2** in CH_2Cl_2 (24 mL) was added powdered 4 Å molecular sieves (4.0 g), and the resulting suspension was stirred at room temperature for 14 h. The mixture was filtered over Celite and the solid was washed with CH_2Cl_2 (3 × 15 mL). Evaporation of the combined filtrates afforded an oil that was purified by flash chromatography (silica gel saturated with Et_3N) under the conditions indicated in the Supporting Information for the individual cases.

General Procedure for Radical Cyclizations of Tetrahydropyridines 12: Preparation of Azaspirocycles 13. In a typical experiment, a solution of **12** (1.0 mmol), AIBN (0.164 g, 0.30 mmol), and $(TMS)_3SiH$ (616 μL, 2.0 mmol) in toluene (10 mL) was heated at 100 °C (oil bath temperature) for 16 h under Ar. After cooling, the mixture was either diluted with EtOAc (15 mL) and extracted with 1 M HCl (4 × 20 mL) (in the case of **12a** and **12b**) or, alternatively, evaporated to dryness, then the resulting residue was redissolved in EtOAc (20 mL) and extracted with 1 M HCl (3 × 15 mL) (in the case of **12c** and **12d**). In either case, the acidic extracts were basified with saturated $NaHCO_3$ to pH 8, the solution was extracted with CH_2Cl_2 (3 × 25 mL), and the organic extracts were washed with brine (10 mL) and dried (Na_2SO_4). The residue after evaporation was purified by flash chromatography (silica gel saturated with Et_3N) under the conditions indicated in the Supporting Information for the individual cases.

(12) (a) Glover, S. A.; Warkentin, J. *J. Org. Chem.* **1993**, *58*, 2115–2121. (b) Cladingboel, D. E.; Parson, P. J. *J. Chem. Soc., Chem. Commun.* **1990**, 1543–1544. (c) Ozlu, Y.; Cladingboel, D. E.; Parsons, P. J. *Synlett* **1993**, 357–358. (d) Oezlue, Y.; Cladingboel, D. E.; Parsons, P. J. *Tetrahedron* **1994**, *50*, 2183–2206. (e) Tanino, H.; Fukuishi, K.; Ushiyama, M.; Okada, K. *Tetrahedron* **2004**, *60*, 3273–3282.

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(15) Recent examples: (a) Sorensen, U. S.; Pombo-Villar, E. *Helv. Chim. Acta* **2004**, *87*, 82–89. (b) Wu, X.; Nilsson, P.; Larhed, M. *J. Org. Chem.* **2005**, *70*, 346–349. (c) Lachance, N.; April, M.; Joly, M.-A. *Synthesis* **2005**, 2571–2577. (d) Michael, J. P.; de Koning, C. B.; Mudzunga, T. T.; Petersen, R. L. *Synlett* **2006**, 3284–3288.

(16) Ackermann, L.; Althammer, A. *Synlett* **2006**, 3125–3129.

(17) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2–7.

General Procedure for Heck Cyclizations of Tetrahydropyridines 12: Preparation of Tetracycles 16 and 17. In a typical experiment, a solution of **12** (0.50 mmol), $Pd(OAc)_2$ (5.61 mg, 0.025 mmol), *o*-tolylphosphine (0.015 g, 0.050 mmol), and thalium acetate (0.145 g, 0.55 mmol) in DMF (6.0 mL) was stirred at 120 °C (oil bath temperature) for 3.5−6 h under Ar. After cooling, the solvent was evaporated and the remaining solid was purified by flash chromatography (silica gel saturated with Et_3N) under the conditions indicated in the Supporting Information for the individual cases.

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Supporting Information Available: Characterization data, stereochemical elucidation details, and copies of ^1H NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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