Palladium-Catalysed Cascades Triggered by Dehydrogenation of Secondary or Tertiary Amines: Access to Bridged- and Fused-Ring Heterocycles

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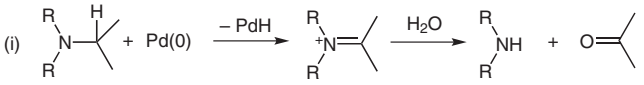
Abstract: Palladium-catalysed cascades triggered by dehydrogenation of secondary or tertiary amines and trapping the intermediate imines with cycloadditions and Mannich reactions result in a range of bridged- and fused-ring heterocyclic motifs in moderate to good yields.

Key words: cascade reaction, hydrogen transfer, Mannich reaction, dipolar cycloaddition

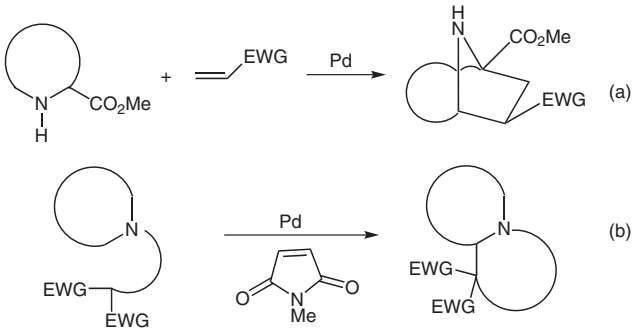
To increase the molecular complexity of a simple organic substrate using efficient (high atom economy), selective, high-yielding, and environmentally benign methods is one of the contemporary challenges for synthetic organic chemists.[1] Carbon–carbon bond formation is a pivotal method for achieving this goal. We have been involved in generating azomethine ylides and azomethine imines via catalytic dehydrogenation methods utilizing either palladium black, ruthenium black, or Wilkinson's catalyst.[2,3] Recently Beller et al. have reported dehydrogenation of primary amines using Shvo's catalyst[4] whilst Blacker et al. have reported dehydrogenation of secondary amines utilizing an Ir(III) catalyst.[5] Palladium catalysts have long been known to dealkylate tertiary amines via an intermediate iminium species followed by hydrolysis (Scheme 1).[6]



Scheme 1

In this communication we report two novel catalytic cascade combinations (i) palladium-catalysed cascade dehydrogenation of cyclic secondary α-amino acid esters → azomethine ylides → 1,3-dipolar cycloaddition generating bridged-ring heterocycles with formation of two new bonds, and 3/4 stereocentres [Scheme 2 (a)] (ii) palladium-catalysed cascade dehydrogenation of tertiary amines → iminium ion → intramolecular Mannich reaction → fused ring heterocycle [Scheme 2 (b)].

In Scheme 2 (b) *N*-methylmaleimide (NMM) is also used to regenerate the active palladium catalyst by acting as a recipient for the hydrogen removed from the tertiary amine in the dehydrogenation process.



Scheme 2

For our initial studies, we selected cyclic secondary α-amino acid esters **1** and **2** as precursors (Figure 1). Thus **1** (1 mmol) reacted with NMM (2 mmol) in boiling toluene in the presence of 10 mol% Pd black over 13 hours to afford the bridged ring compound **5** in 82% yield (Scheme 3). The initial regioselective dehydrogenation of **1** leads to the formation of cyclic imine **3** followed by 1,2-prototropy to the azomethine ylide **4**. Trapping of **4** with NMM via an *endo* transition state (with respect to the NH bridge) then affords **5**. In the NMR spectrum of **5** the bridgehead hydrogen H_a appears as a singlet at $\delta = 4.75$ ppm indicating that H_a and H_b are orthogonal. In an analogous fashion, **2** afforded **6** (Figure 2) in 68% yield. We and others have reported a related cycloaddition process on the preformed cyclic imines.[7]

Figure 1

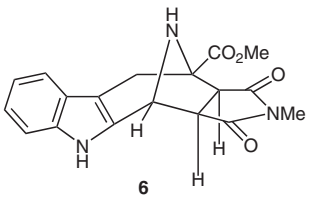


Figure 2

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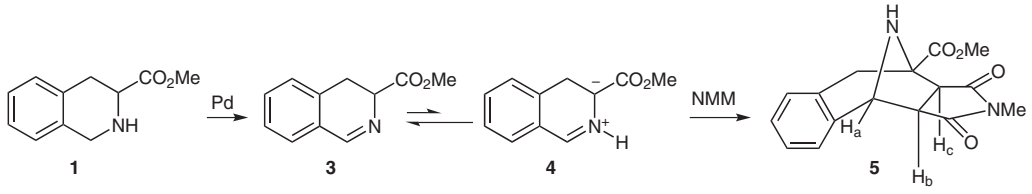


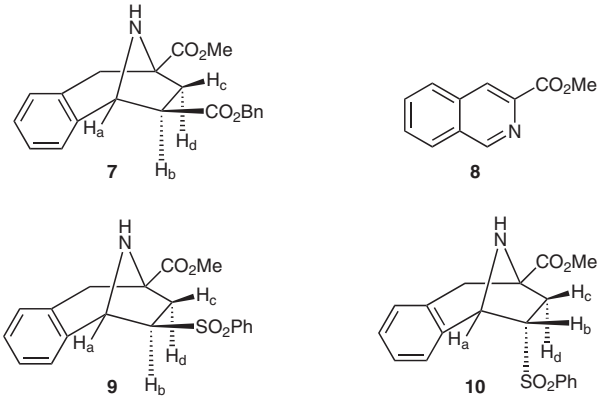
1 3 4 5

Scheme 3

We briefly studied the stereo- and regioselectivity of the 1,3-dipolar cycloaddition reactions using benzyl acrylate and phenyl vinyl sulfone as dipolarophiles. Thus secondary amine **1** (1 mmol) reacted regio- and stereospecifically with benzyl acrylate (2 mmol) in the presence of 10 mol% Pd black in boiling toluene for 15 hours to afford **7** (50%) together with a small amount of **8** (10%, Figure 3). The stereochemistry of **7** was assigned on the basis of ^{1}H NMR data. In particular the bridgehead hydrogen H_a appears as a singlet at δ = 4.57 ppm. In contrast **1** (1 mmol) reacted regioselectively with phenyl vinyl sulfone (2 mmol) in the presence of 10 mol% Pd black in boiling toluene over 20 hours to afford a 1:2.5 mixture of **9** and **10** (40%) together with **8** (30%). The stereochemistries of **9** and **10** were assigned from their ^{1}H NMR spectra. The bridgehead hydrogen H_a of **9** appears as a singlet at δ = 4.74 ppm indicating it is an *endo* cycloadduct with respect to the NH bridge. The signal for proton H_a of **10** appears as a doublet at δ = 3.95 ppm with a coupling constant of 6.2 Hz which confirms both the regio-and stereochemistry of the cycloadduct. In contrast to the previous observations, **10** is the major product. This stereoselectivity may reflect equilibrium between **9** and **10** over the longer reaction time.

In the reactions with less active dipolarophiles than NMM, the aromatized product **8** is also formed. That is, when the cycloaddition step is slow, aromatization of the imine begins to compete. The trend of increasing amounts of **8** reflects the observed reactivity rate of the dipolarophiles: NMM > benzyl acrylate > phenyl vinyl sulfone. The latter order has been established in our extensive work on cycloaddition reactions of azomethine ylides.[8]

Next we extended the dehydrogenation methodology to intramolecular Mannich reactions. The tertiary amine **12** (1 mmol) with a tethered malonate was synthesized by reductive amination of tetrahydroisoquinoline and aldehyde **11** (Figure 4). When **12** (1 mol equiv) reacted with 10 mol% Pd black in the presence of NMM (1 mol equiv) in DMF at 120 °C, it afforded the tricyclic amine **15** in 60% yield (Scheme 4). In an analogous fashion, **16** afforded **17**



7 8 9 10

Figure 3

in 40% yield. When **18** (1 mol equiv) was allowed to react in the presence of Pd black (DMF, 120 °C) and NMM (2 mol equiv), the reaction furnished the cycloadduct **22** in 45% yield (Scheme 5). Note that **22** can be regarded as an *endo* cycloadduct of the 1,3-dipole **20** or an *exo*-Diels–Alder cycloadduct of the isoindole **21**. The absence of any **23** indicates that conversion of **19** into **21** is significantly faster than the Mannich cyclisation **19** → **23**. In the NMR spectrum of **22** the bridgehead hydrogen H_a appears as a singlet at δ = 4.48 ppm indicating that H_a and H_b are orthogonal.

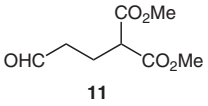


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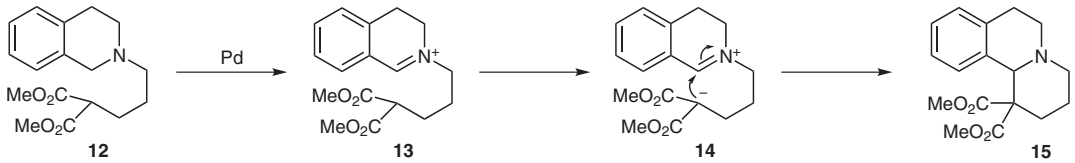
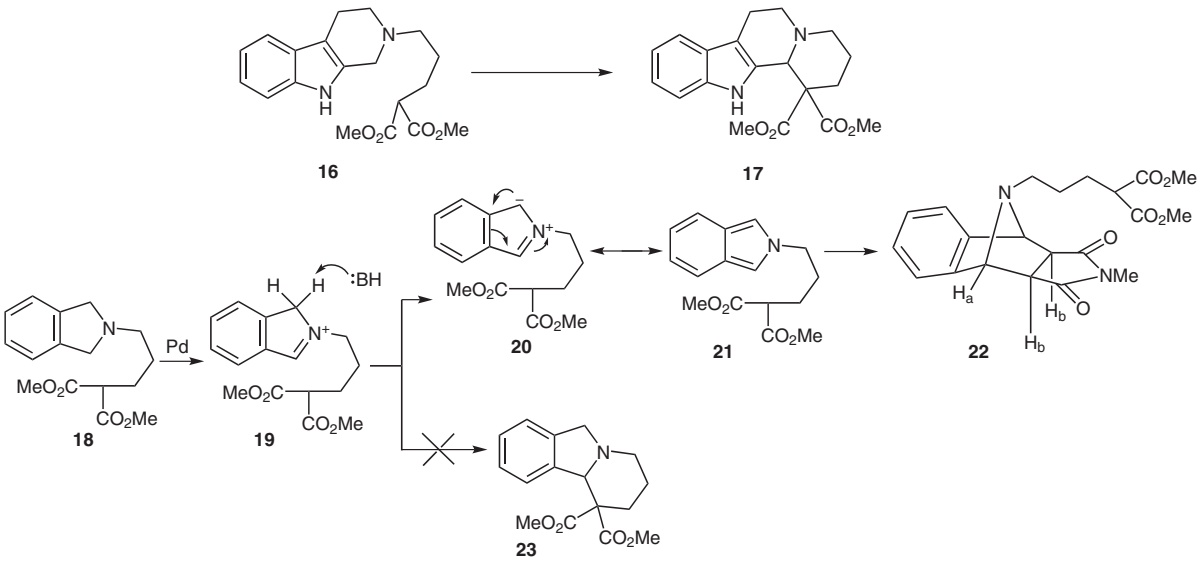
Figure 4

In conclusion we have developed two novel cascade combinations triggered by initial Pd-catalysed dehydrogenation. Overall these cascades result in the formation of 1–2 new bonds, 1–4 new stereocentres, and one new ring. A typical experimental protocol is appended.[9]



12 13 14 15

Scheme 4



Scheme 5

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(9) **1,2-Benzo-4,7-imino-4-methoxycarbonyl-*exo*-6-benzyloxycarbonylcyclohept-1-ene (7)**
Methyl 1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**1**, 0.1 g, 0.5 mmol), benzyl acrylate (0.17 g, 1.0 mmol), and Pd black (0.0055 g, 0.05 mmol) were mixed in toluene (15 mL) and heated at 110 °C for 15 h. After removal of the solvent the residue was purified by column chromatography eluting with Et_2O–PE (1:1, v/v) to afford **7** (0.091 g, 50%) as a colourless semisolid and **8** (10%). Anal. Calcd (%) for $C_{21}H_{21}NO_4$: C, 71.79; H, 5.98; N, 3.99. Found: C, 71.70; H, 6.20; N, 4.05. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.15–7.07 (m, 4 H, ArH), 5.12 (s, 2 H, CH_2Ph), 4.57 (s, 1 H, H_a), 3.79 (s, 3 H, CO_2Me), 3.26 (d, 1 H, *J* = 16.60 Hz, ArC*H*H), 3.14 (dd, 1 H, *J* = 8.85, 2.60 Hz H_b), 3.02 (d, 1 H, *J* = 16.60 Hz, ArCH*H*), 2.47 (dd, 1 H, *J* = 13.75, 2.60 Hz, H_c), 2.22 (dd, 1 H, *J* = 13.75, 8.85 Hz, H_d). MS: *m/z* (%) = 351 (0.2) [M^+], 292 (3), 260 (0.4), 189 (100), 157 (18).