Communication

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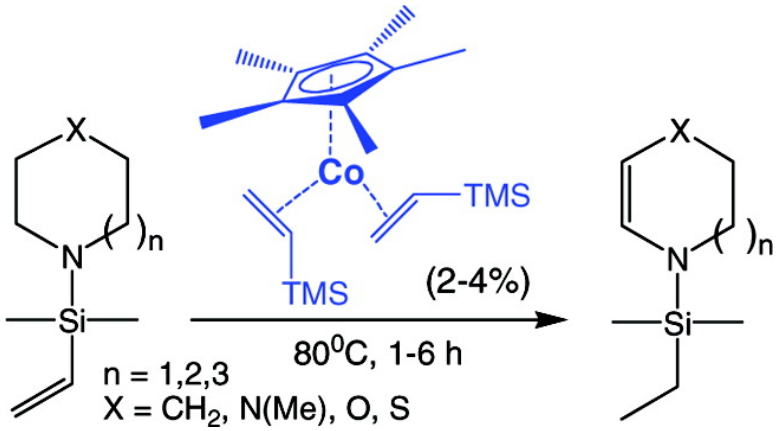

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Activation of sp³ C−H Bonds with Cobalt(I): Catalytic Synthesis of Enamines

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Twenty-five years after the seminal reports by Bergman[1] and Jones[2] on oxidative addition of C−H bonds to (Cp*)M(L) complexes of iridium and rhodium, respectively, extensive progress has been made in mechanistic understanding[3] and functionalization for applications in synthesis.[4] Cobalt, the analogous metal from the first transition series, while known to activate sp² aromatic and aldehydic C−H bonds,[5] has been notably absent from reports of sp³ C−H activation. In fact, experimental[6] and computational[7] studies have indicated that C−H bonds should not oxidatively add to the 16-electron Co(I) center as they do to Ir and Rh. This communication describes for the first time the facile and highly selective activation and functionalization of sp³ C−H bonds by [(Cp*)Co(VTMS)$_2$] (**1**, Figure 1) (VTMS = vinyltrimethyl silane), allowing synthesis of unique heterocycles.Direct functionalization of C−H bonds α to nitrogen is a particularly attractive transformation, but catalytic examples are still somewhat rare.[8] One strategy for functionalization of C−H oxidative addition products is the net dehydrogenation of organic substrates,[9] transforming C−H bonds into carbon−carbon bonds. In this area, our group has developed methodology for the synthesis of silyl enol ethers[10] and 1,2-diheteroatom alkenes[11] via [(Cp*)Rh(VTMS)$_2$] (**2**)-catalyzed intramolecular transfer dehydrogenation. Enamines[12] are versatile reactive intermediates for organic synthesis, so we explored the application of this strategy to their formation (Scheme 1).

Goldman[13] has reported synthesis of enamines from 3° alkyl amines via Ir-catalyzed *inter*molecular hydrogen transfer. Our *intra*molecular approach to hydrogen transfer is complementary and applicable to (protected) 2° amines. The silicon protecting group serves additionally as hydrogen acceptor and directing group. This strategy affords protected endocyclic enamines which are difficult to access via conventional methodology.

Substrate and catalyst screening was efficiently conducted in screw-cap NMR tubes with C_6D_{12} for convenient monitoring of reaction progress. Preparative scale reactions were then performed in Kontes flasks in pentane solvent (5 mmol substrate, 2% Co catalyst loading, 6 h, 80 °C) with isolated yields of metal-free products up to 90% (see Supporting Information for details).

Initially, we explored conversion of piperidine **3** into protected tetrahydropyridine **4**, an attractive target both as a mimic of biological hydrogen transfer agents and as a synthetic intermediate.[14] Unprotected endocyclic "enamines" of 2° amines generally react as, and are isolated as, the imine tautomer,[15] so (protected) enamines should be valuable synthons. Gratifyingly, rhodium catalyst **2** produced the desired enamine **4**, albeit requiring 6 h at 140 °C for conversion (Table 1, entry 1). In contrast, cobalt catalyst **1** afforded **4** in <1 h at 80 °C (Table 1, entry 2). Encouraged by this rapid conversion under mild conditions, we investigated the scope of this Co-catalyzed transfer dehydrogenation.

Subjection of 2- and 3-substituted piperidines (entries 3 and 4) to cobalt-mediated transfer catalysis led to disubstituted olefins **6** and **8**, respectively, as the only observable products with no isomerization to the thermodynamically more stable trisubstituted olefins even at long reaction times. Endocyclic enamines have been employed in natural products synthesis[16] but typically as the more substituted isomers available by previous methodology.[17]

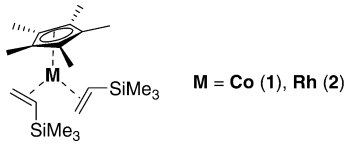
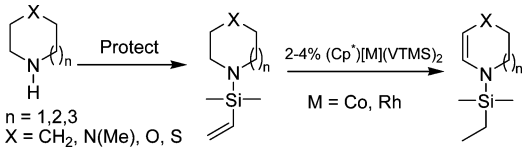


Figure 1. Isostructural late-metal catalysts for transfer hydrogenation.

Scheme 1



One hallmark of late-metal catalysts is their compatibility with Lewis basic functionality. Nitrogen- and oxygen-containing functional groups are well-tolerated by **1**, allowing synthesis of dehydrogenated piperazine and morpholine derivatives (entries 5 and 6, respectively). Sulfur apparently poisons the active cobalt species; only 13% conversion of **13** was observed with **1**, corresponding to a TON of <4. Rhodium catalyst **2** proved effective for this substrate, yielding clean transfer product **14**.

Unsaturated azacycles with ring size greater than 6 are rare,[18] yet **15** and **17** were transformed into seven- and eight-membered N-protected enamines by this methodology. In the former case (entry 9), starting material was consumed surprisingly rapidly (ca. 10 min), but additional species were observed at early reaction times which slowly isomerized to enamine **16**. Intriguingly, these products vary in the position of the double bond (allylic and homoallylic amines), indicating oxidative addition of truly "unactivated" C−H bonds to the metal center (see Supporting Information for details).

Next, we further probed the regioselectivity of this transformation with catalyst **1**. Substrate **19** contains two sites potentially amenable to dehydrogenation: the methylene groups of the diamine or those of the morpholine ring. After 30 min at 80 °C, only **20** was observed, with no isomerization over several hours. This result establishes that this process is (1) applicable to linear as well as cyclic amines (primary enamines are notoriously difficult to prepare,[19] so protected variants are expected to have synthetic utility); (2) regioselective; final products observed are consistent with activation of the C−H bond α to the protected nitrogen; (3) diastereoselective; whereas the *Z* geometry is thermodynamically favored for 1,2-diheteroatom-substituted olefins, only the *E* isomer was observed; (4) consistent with *intra*-, not *inter*molecular hydrogen transfer, as the morpholine moiety was not dehydrogenated.

Cobalt catalyst **1** was ineffective for transfer hydrogenation of the substrate analogous to **19** containing a free N−H (lacking the

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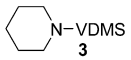
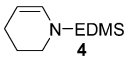
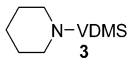
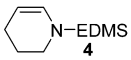
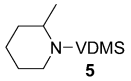
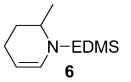
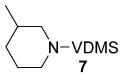
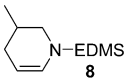
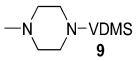
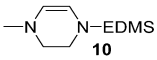
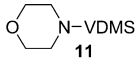
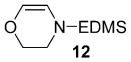
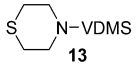
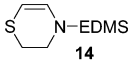
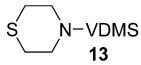
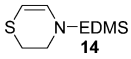
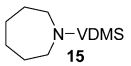
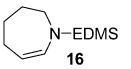
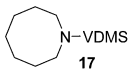
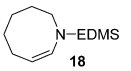
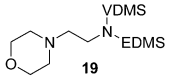
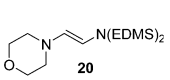
Table 1. Scope of Enamine Synthesis with **1** and **2**

	Substrate	Transfer Product	Cat[a]	t (h)	Yield[b] (%)
1	 **3**	 **4**	**2**[c]	6	>90
2	 **3**	 **4**	**1**		>99
3	 **5**	 **6**	**1**		>99
4	 **7**	 **8**	**1**	2	>95
5	 **9**	 **10**	**1**		>95
6	 **11**	 **12**	**1**		>99
7	 **13**	 **14**	**1**		13
8	 **13**	 **14**	**2**[c]	1	>90
9	 **15**	 **16**	**1**	6d	>90
10	 **17**	 **18**	**1**		>95
11	 **19**	 **20**	**1**		>95

[a] Unless noted otherwise, 0.25 mmol substrate, 0.01 mmol **1** (4%), 0.5 mL of C_6D_{12}, 80 °C, 1 h. [b] By ^{1}H NMR spectroscopy. [c] With 0.25 mmol substrate, 0.01 mmol **2** (4%), 0.5 mL of C_6D_{12}, 140 °C. VDMS = vinyl(dimethyl)silyl. EDMS = ethyl(dimethyl)silyl.

EDMS protecting group), indicating distinct chemoselectivity compared to Ir catalysts which produce imines from secondary amines.[20]

These observations are consistent with a mechanism analogous to that for dehydrogenation of protected alcohols with **1.**[21] As such, it involves formation of the 16 e$^-$ intermediate [(Cp*)Co(mono-olefin)] and oxidative addition of an sp^3 C−H bond (generally α to the heteroatom) to the cobalt(I) center. Migratory insertion of the vinyl silane into the cobalt hydride followed by *β*-hydride elimination (from the 3-position of the amine) and reductive elimination yields the observed enamine products. The more rapid turnover of the Co system relative to the Rh system must stem in part from the lower barrier to dissociation of a vinyl group from the (Cp*)Co(bis-olefin) resting state.[22]

In conclusion, we have demonstrated a convenient synthetic route to enamines based on cobalt-catalyzed hydrogen transfer of protected amines. This conversion is consistent with cobalt(I) sp^3 C−H bond activation, reactivity which was previously held to be the exclusive domain of the heavier group 9 metals. Catalyst **1** exhibits not only high reactivity under milder conditions than the other members of its triad but also impressive chemo-, regio-, diastereo-, and intramolecular hydrogen transfer selectivity. Further investigations into the scope of this transformation, mechanistic studies, and applications to synthesis are currently underway in this laboratory.

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Supporting Information Available: Experimental procedures and characterization of complexes **3**−**21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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