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Activation of *sp*³ C-H Bonds with Cobalt(I): Catalytic Synthesis of Enamines

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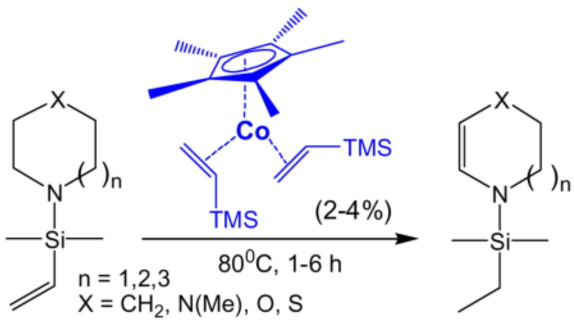
Abstract



C-H bond activation has been extensively studied with (Cp*)M(L)$_n$ (M = Ir, Rh), but cobalt, the third member of this triad, has not previously been shown to activate sp^3C-H bonds. Further, practical functionalization of the metal alkyl products of oxidative addition has not been fully explored. Towards these ends, we have developed catalytic dehydrogenation of alkyl amines with a Co(I) catalyst. Amine substrates are protected with vinyl silanes, followed by catalytic transfer hydrogenation to yield a broad range of stable protected enamines and 1,2-diheteroatom substituted alkenes, including several unprecedented heterocycles. (Cp*)Co(VTMS)$_2$ catalyzes transfer hydrogenation under surprisingly mild conditions with high chemo-, regio-, and diastereo-selectivity, while tolerating additional functionality.

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 sp^2 aromatic and aldehydic C-H bonds[5], has been notably absent from reports of sp^3 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 sp^3 C-H bonds by [(Cp*)Co(VTMS)$_2$] (**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**) -

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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, 6h, 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 hours at 140°C for conversion (Table 1, entry 1). In contrast, cobalt catalyst **1** afforded **4** in < 1h 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 di-substituted olefins **6** and **8** respectively, as the only observable products with no isomerization to the thermodynamically more stable tri-substituted 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].

One hallmark of late-metal catalysts is their compatability 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 7- and 8-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 minutes 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 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 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 *intra*-molecular hydrogen transfer selectivity. Further investigations into the scope of this transformation, mechanistic studies, and applications to synthesis are currently underway in this laboratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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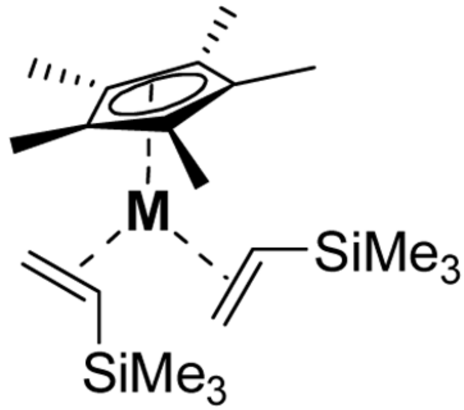
References

1. Janowicz AH, Bergman RG. J Am Chem Soc 1982;104:352.
2. Jones WD, Feher FJ. J Am Chem Soc 1982;104:4240.
3. Arndtsen BA, Bergman RG, Mobley TA, Peterson TH. Acc Chem Res 1995;28:154. (b) Jones WD, Feher FJ. Acc Chem Res 1989;22:91. (c) Halpern J. Inorg Chim Acta 1985;100:41.
4. Wilson RM, Thalji RK, Bergman RG, Ellman JA. Org Lett 2006;8:1745. [PubMed: 16597156]and references therein (b) Godula K, Sames D. Science 2006;312:67. [PubMed: 16601184] (c) Cho J-Y, Tse MK, Holmes D, Maleczka RE Jr, Smith MR III. Science 2002;295:305. [PubMed: 11719693] (d) Chen H, Schlecht S, Semple TC, Hartwig JF. Science 2000;287:1995. [PubMed: 10720320]
5. Lenges CP, Brookhart M, Grant BE. J Organometallic Chem 1997;528:199. (b) Lenges CP, Brookhart M. J Am Chem Soc 1997;119:3165. (c) Lenges CP, White PS, Brookhart M. J Am Chem Soc 1998;120:6965. (d) Wadepohl H, Borchert T, Pritzkow H. J Chem Soc, Chem Comm 1995:1447.
6. Bengali AA, Bergman RG, Moore CB. J Am Chem Soc 1995;117:3879.
7. Siegbahn PEM. J Am Chem Soc 1996;118:1487. (b) Poli R, Smith KM. Eur J Inorg Chem 1999:877.
8. Campos KR. Chem Soc Rev 2007;36:1069. [PubMed: 17576475]and references therein
9. Burk MJ, Crabtree RH. J Am Chem Soc 1987;109:8025. (b) Liu F, Pak EB, Singh B, Jensen CM, Goldman AS. J Am Chem Soc 1999;121:4086.
10. Lenges CP, White PS, Brookhart M. J Am Chem Soc 1999;121:4835.

11. Diaz-Requejo, MMar; DiSalvo, D.; Brookhart, M. J Am Chem Soc 2003;125:2038. [PubMed: 12590518]
12. RappoportZThe Chemistry of Enamines (Parts 1 & 2)WileyNew York1994 For a review of metal-mediated syntheses, see: (b) Dehli JR, Legros J, Bolm C. Chem Comm 2005:973. [PubMed: 15719090]
13. Zhang X, Fried A, Knapp S, Goldman AS. Chem Comm 2003:2060. [PubMed: 12934911]
14. Beeken P, Fowler FW. J Org Chem 1980;45:1336. (b) Wenkert E, Dave KG, Haglid F, Lewis RG, Oishi T, Stevens RV, Terashima M. J Org Chem 1968;33:747. [PubMed: 5636614] (c) Cook NC, Lyons JE. J Am Chem Soc 1966;88:3396.
15. Cook, AG., editor. Enamines: Synthesis, Structure, and Reactions. 2. Marcel Dekker; New York: 1988. p. 460
16. Evans DA, Bryan CA, Sims CL. J Am Chem Soc 1972;94:2891. (b) Evans DA. J Am Chem Soc 1970;92:7593. (c) Wenkert E. Acc Chem Res 1968;1:78. (d) Dake GR, Fenster MDB, Hurley PB, Patrick BO. J Org Chem 2004;69:5668. [PubMed: 15307738]
17. Takemiya A, Hartwig JF. J Am Chem Soc 2006;128:6042. [PubMed: 16669666]For exceptions, see: (b) Larivée A, Charette AB. Org Lett 2006;8:3955. [PubMed: 16928047] (c) Hegedus LS, McKearin JM. J Am Chem Soc 1982;104:2444.
18. Cook, AG., editor. Enamines: Synthesis, Structure, and Reactions. 2. Marcel Dekker; New York: 1988. p. 442
19. Novak BM, Cafmeyer JT. J Am Chem Soc 2001;123:11083. [PubMed: 11686722]
20. Gu XQ, Chen W, Morales-Morales D, Jensen CM. J Mol Cat A 2002;189:119–124.
21. Diaz-Requejo, MMar; DiSalvo, D.; Brookhart, M. J Am Chem Soc 2003;125:2038. [PubMed: 12590518]
22. Lenges CP, Brookhart M, Grant BE. J Organometallic Chem 1997;528:199.



M = Co (1), Rh (2)

Figure 1.
Isostructural Late Metal Catalysts for Transfer Hydrogenation

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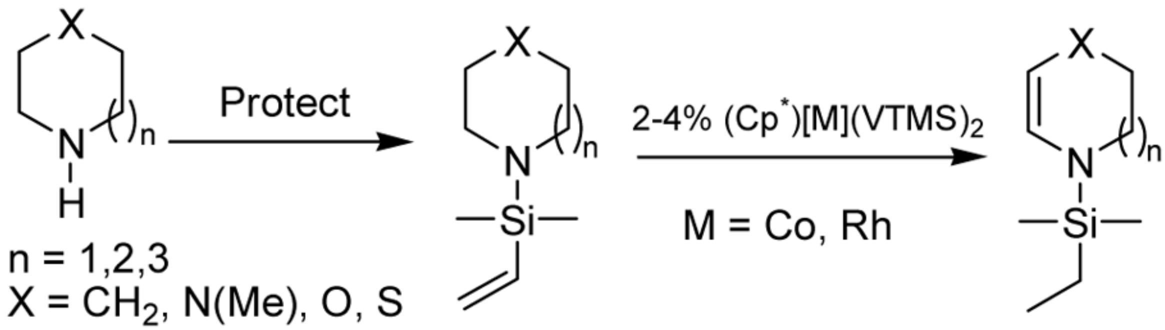
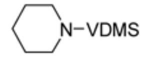
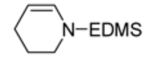
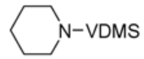
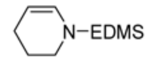
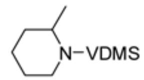
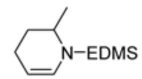
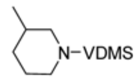
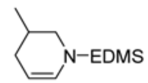
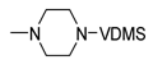
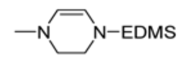
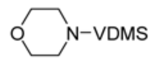
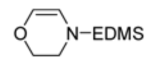
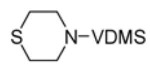
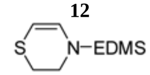
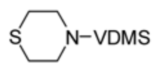
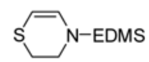
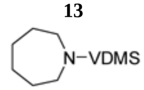
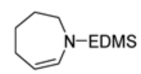
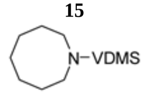
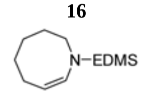
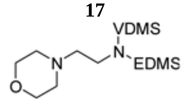
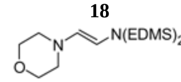


Scheme 1.

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 C_6D_{12}, 80°C, 1h.

[b]By ^{1}H NMR spectroscopy

[c]0.25 mmol substrate, 0.01 mmol **2** (4%), 0.5 mL C_6D_{12}, 140°C. VDMS = Vinyl(DiMethyl)Silyl. EDMS = Ethyl(DiMethyl)Silyl.