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Ligand-Based Carbon–Nitrogen Bond Forming Reactions of Metal Dinitrosyl Complexes with Alkenes and Their Application to C–H Bond Functionalization

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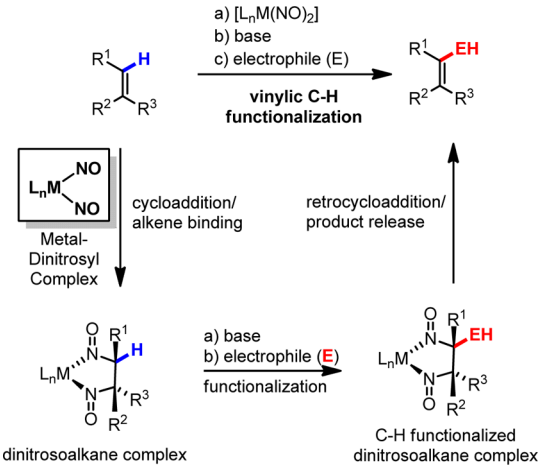
CONSPECTUS



Over the past few decades, researchers have made substantial progress in the development of transition metal complexes that activate and functionalize C–H bonds. For the most part, chemists have focused on aliphatic and aromatic C–H bonds and have put less effort into complexes that activate and functionalize vinylic C–H bonds. Our groups have recently developed a novel method to functionalize vinylic C–H bonds that takes advantage of the unique *ligand-based reactivity* of a rare class of metal dinitrosyl complexes. In this Account, we compare and discuss the chemistry of cobalt and ruthenium dinitrosyl complexes, emphasizing alkene binding, C–H functionalization, and catalysis.

Initially discovered in the early 1970s by Brunner and studied more extensively in the 1980s by the Bergman group, the cyclopentadienylcobalt dinitrosyl complex $CpCo(NO)_2$ reacts reversibly with alkenes to give, in many cases, stable and isolable cobalt dinitrosoalkane complexes. More recently, we found that treatment with strong bases, such as lithium hexamethyldisilazide, Verkade's base, and phosphazene bases, deprotonates these complexes and renders them nucleophilic at the carbon α to the nitroso group. This conjugate anion of metal dinitrosoalkanes can participate in conjugate addition to Michael acceptors to form new carbon–carbon bonds. These functionalized cobalt complexes can further react through alkene exchange to furnish the overall vinylic C–H functionalized organic product. This stepwise sequence of alkene binding, functionalization, and retrocycloaddition represents an overall vinylic C–H functionalization reaction of simple alkenes and does not require directing groups. We have also developed an asymmetric variant of this reaction sequence and have used this method to synthesize C_1- and C_2-symmetric diene ligands with high enantioinduction. Building upon these stepwise reactions, we eventually developed a simple one-pot procedure that uses stoichiometric amounts of a cobalt dinitrosoalkane complex for both inter- and intramolecular C–H functionalization. We can achieve catalysis in one-pot intramolecular reactions with a limited range of substrates.

Our groups have also reported an analogous ruthenium dinitrosyl complex. In analogy to the cobalt complex, this ruthenium complex reacts with alkenes in the presence of neutral bidentate ligands, such as TMEDA, to give octahedral dinitrosoalkane complexes. Intramolecular functionalization or cyclization of numerous ruthenium dinitrosoalkane complexes proceeds under mild reaction conditions to give the functionalized organic products in excellent yields. However, despite extensive efforts, so far we have not been able to carry out intermolecular reactions of these complexes with a variety of electrophiles or C–H functionalization reactions.

Although additional work is necessary to further boost the catalytic capabilities of both cobalt and ruthenium dinitrosyl complexes for vinylic C–H functionalization of simple alkenes, we believe this ligand-based vinylic C–H functionalization reaction has provided chemists with a useful set of tools for organic synthesis.

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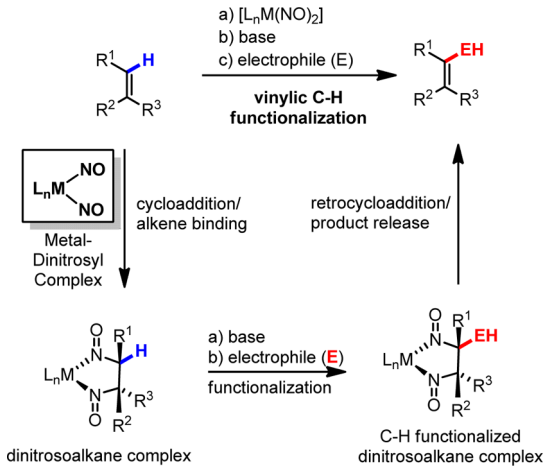
Introduction

In recent years, the field of transition metal-catalyzed C–H bond activation has undergone intensive development.[1−10] The ability to selectively activate and functionalize inert C–H bonds has provided powerful new methods for the synthesis of complex molecules.[11−14] Of paramount importance to this synthetic revolution has been the work of a number of groups to elucidate the intimate mechanisms of catalysts capable of C–H activation and functionalization.[15−23]

Despite the fast growth of this field, the activation of vinylic C–H bonds to generate metal–vinyl complexes directly from the corresponding alkene is underexplored.

In 1995, the Trost and Murai groups independently reported the ruthenium catalyzed alkylation of enones and enals via a directed vinylic C–H bond activation.[24,25] More recently, the vinylic C–H activation of alkenes conjugated with imine and ketoxime directing groups catalyzed by Rh(I) has been reported by the Bergman and Ellman groups[26−30] and the Cheng group.[31] Nevertheless, methods to activate sp^2 C–H bonds of alkenes in the absence of a directing group are sparse,[32−34] possible due to the high concentration of olefin present, especially under catalytic conditions, which favors π-coordination of the olefin over oxidative addition of the C–H bond.

SCHEME 1. Metal Dinitrosyl-Mediated Direct Vinylic C–H Bond Functionalization



In 2009, in a joint study, our groups documented a novel approach for the direct activation and functionalization of vinylic C–H bonds using the ligand-based reactivity of a metal dinitrosyl complex.[35−38] The reaction proceeds via reversible alkene binding to the nitrosyl ligands of the complex to form a metal dinitrosoalkane complex in which the sp^3 C–H bonds proximal to the metal nitroso moiety are acidified (Scheme 1). Under basic conditions, one of these C–H bonds may be deprotonated, and the resulting carbanion may act as a nucleophile toward Michael acceptors (and other electrophiles). The net reaction is a direct vinylic C–H functionalization of alkenes in the absence of a directing group.

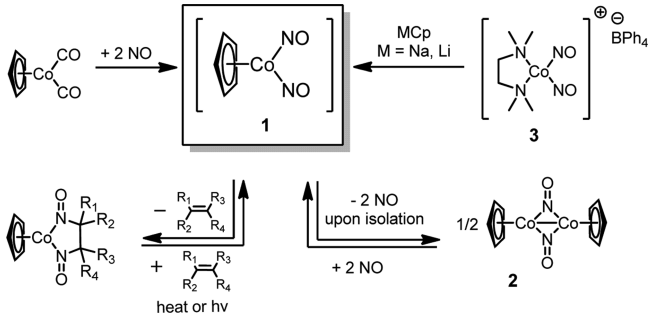
In this Account, we present a comprehensive comparison and discussion of the chemistry of cobalt and ruthenium dinitrosyl complexes and their suitability for the C–H functionalization of alkenes.

Metal Dinitrosyl Complexes

Cobalt Dinitrosyls. Initially reported in the early 1970s,[39−41] the cyclopentadienylcobalt dinitrosyl complex [$CpCo(NO)_2$] (**1**) is a reactive intermediate that has been studied by *in situ* spectroscopic techniques[42−44] and computational chemistry.[45] As depicted in Scheme 2, four different synthetic methods have been developed for the generation of [$CpCo(NO)_2$] (**1**). These include (i) the reaction of $CpCo(CO)_2$ with nitric oxide (NO) gas,[39−41] (ii) the reversible reaction of the cobalt dimer **2** with NO,[42−44] (iii) the salt metathesis of [(κ^2-TMEDA)$Co(NO)_2$][BPh_4] (**3**) with group 1 cyclopentadienyl salts,[46] and (iv) the thermal or UV-light promoted retrocycloaddition of alkenes from cobalt dinitrosoalkane complexes.

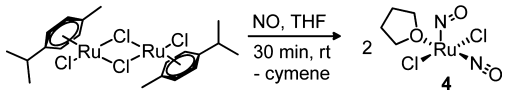
Although it has been detected spectroscopically, attempts to isolate the reactive cobalt dinitrosyl complex by tuning both the electronic and steric properties of the Cp ligand have to date proved unsuccessful.[39−41,45,46] In the absence of a suitable alkene trap, [$CpCo(NO)_2$] decomposes to a complex mixture including **2**. In related studies, we have shown that replacing the cyclopentadienyl ligand with the tris(pyrazolyl)borate, Tp*, allowed the isolation of the mononitrosyl complex [Tp*CoNO].[45,46] In line with expectations furnished by the Cp system, this paramagnetic species gave an intermediate believed to be $Tp^*Co(NO)_2$ upon exposure to an atmosphere of NO. Although attempts to isolate the cobalt dinitrosyl again failed, $Tp^*Co(NO)_2$ could be trapped with strained alkenes such as norbornadiene to yield the corresponding metal dinitrosoalkane complexes.

SCHEME 2. Synthetic Entry Points to [$CpCo(NO)_2$]



Ruthenium Dinitrosyl. In 2011, we reported the synthesis of the ruthenium dinitrosyl complex **4** from the reaction of NO and dichloro-(*p*-cymene)ruthenium(II) dimer in 88% yield (Scheme 3).[47] Unlike **1**, ruthenium complex **4** is an isolable compound. A single-crystal X-ray diffraction study demonstrated that **4** is a five-coordinate complex possessing a linear nitrosyl ligand in the basal plane of square-based pyramidal geometry and a bent nitrosyl occupying the apical position. Hence complex **4** may be described as a neutral, 16-electron complex with a vacant coordination site opposite the apical nitrosyl. A related ruthenium complex, $[RuCl(NO)_2(PPh_3)_2]PF_6$, bearing both a linear and bent NO ligand, was reported by Eisenberg and co-workers in 1970.[48–50]

SCHEME 3. Synthesis of Ruthenium Dinitrosyl Complex **4**

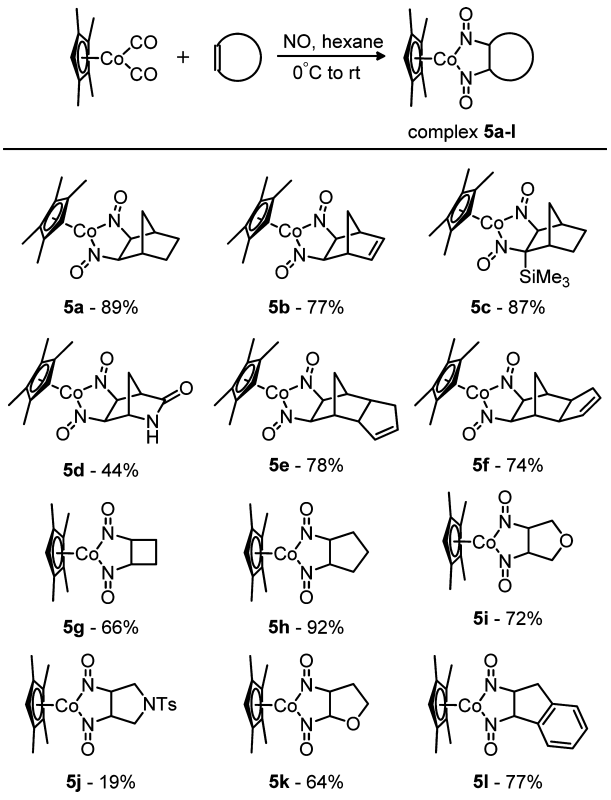


Alkene Binding and Exchange Reactions of Metal Dinitrosyl Complexes

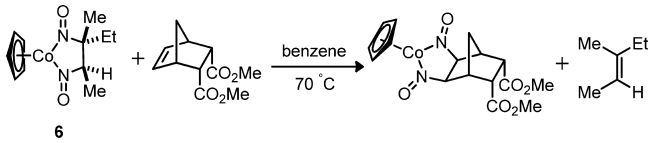
Reactions of Alkenes with $[Cp_2Co(NO)_2]$ (1). A variety of alkenes have been shown to bind to cobalt complex **1**, forming the corresponding cobalt dinitrosoalkane complexes (Scheme 4).[35–44] The binding event represents a rare example of a reaction of a metal dinitrosyl complex with an alkene to directly form two new carbon–nitrogen bonds. In general, electron-rich and strained alkenes bind to **1** much more readily than electron-poor and unstrained alkenes. Under the conditions we have examined, other unsaturated functional groups, such as alkynes, allenes, carbonyls, and α,β-unsaturated enones and ynones, do not react with **1** to form isolable dinitrosoalkane complexes.

Mechanistic studies demonstrated that alkene binding to **1** is reversible and stereospecific (Scheme 5), allowing olefin exchange of one cobalt dinitrosoalkane complex with an external alkene to form a different complex under either thermal or photochemical conditions.[42–44]

SCHEME 4. Synthesis of Cobalt Dinitrosoalkane Complexes from Simple Alkenes

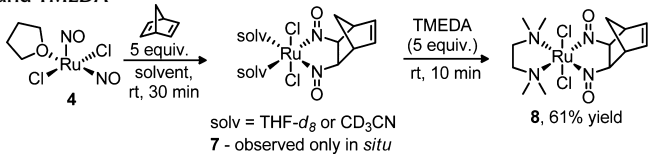


SCHEME 5. Reversible and Stereospecific Alkene Binding to Cobalt Complex **1**

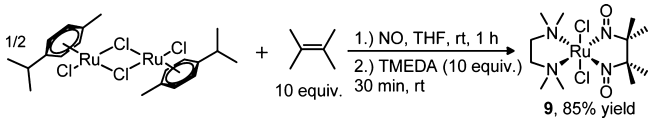


Reactions of Alkenes with $[RuCl_2(NO)_2THF]$ (4). Ruthenium complex **4** has been shown to bind alkenes in a fashion similar to that of complex **1**. When **4** and 5 equiv of norbornadiene were combined in either CD_3CN or THF-d_8, a putative bis solvent coordinated ruthenium dinitrosoalkane complex **7** was observed by NMR spectroscopy but could not be isolated (Scheme 6). Addition of a bidentate ligand, such as TMEDA, to the reaction mixture containing **7** led to the formation of the octahedral complex **8**, which was purified and isolated by silica-gel chromatography in 61% yield.[47] Furthermore, ruthenium dinitrosoalkane complexes **8** and **9** can also be synthesized directly from commercially available $[(\eta^6\text{-cymene})RuCl(\mu\text{-}Cl)]_2$ in the presence of an alkene, TMEDA, and NO in one pot (Scheme 7).[51]

SCHEME 6. Alkene Binding Reaction of Complex **4**, Norbornadiene, and TMEDA

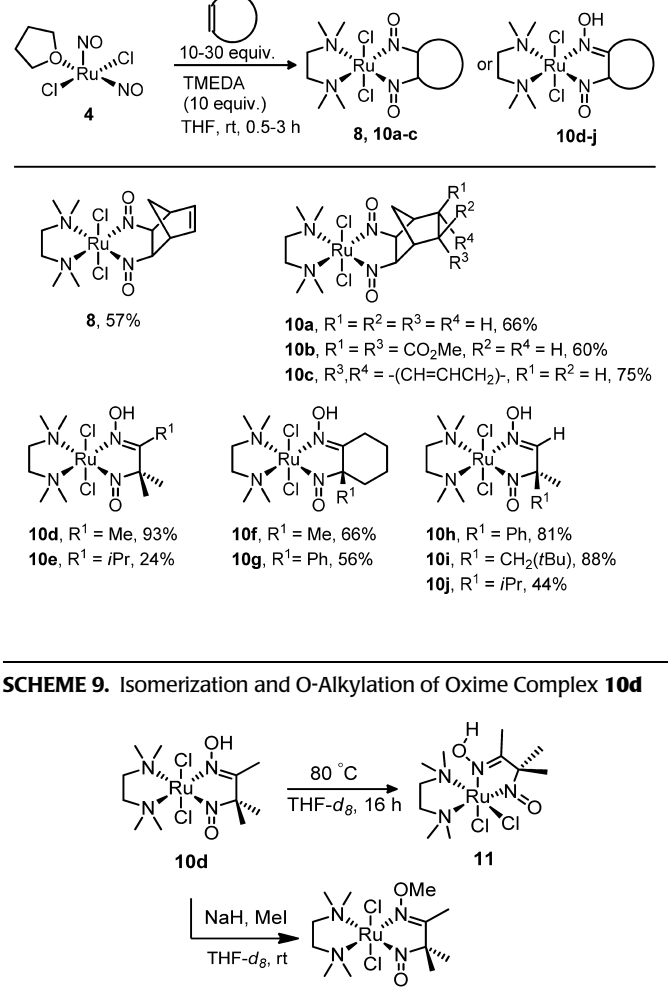


SCHEME 7. One-Pot Synthesis of Ruthenium Dinitrosoalkane Complex **9**



The scope of the reaction between **4** and simple alkenes has been surveyed and reported.[47] Under unoptimized reaction conditions, 10–30 equiv of alkene and 10–20 equiv of TMEDA were required to obtain the octahedral complexes in good yields (Scheme 8). Reactions of nonstrained alkenes containing at least one vinylic C–H bond, including 1,1-disubstituted and 1,1,2-trisubstituted alkenes, resulted in the isolation of mono-oxime ruthenium complexes such as **10d–j** upon work-up. Attempts to convert **10d** to the dinitroso complex thermally, with and without tertiary amine bases, gave the isomerized *cis*-isomer **11** as the major product. Methylation of **10d** gave the O-alkylated complex **12** as the major product, and no dinitroso complex was observed; prolonged heating (6 days at 80 °C) only led to decomposition of **12** (Scheme 9).

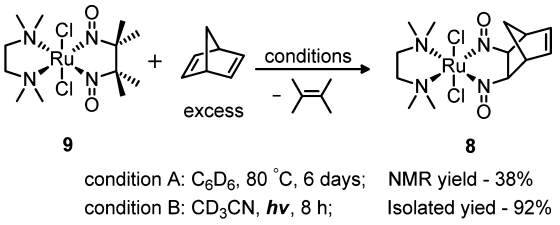
SCHEME 8. Scope of Binding Reaction between **4** and Simple Alkenes



SCHEME 9. Isomerization and O-Alkylation of Oxime Complex **10d**

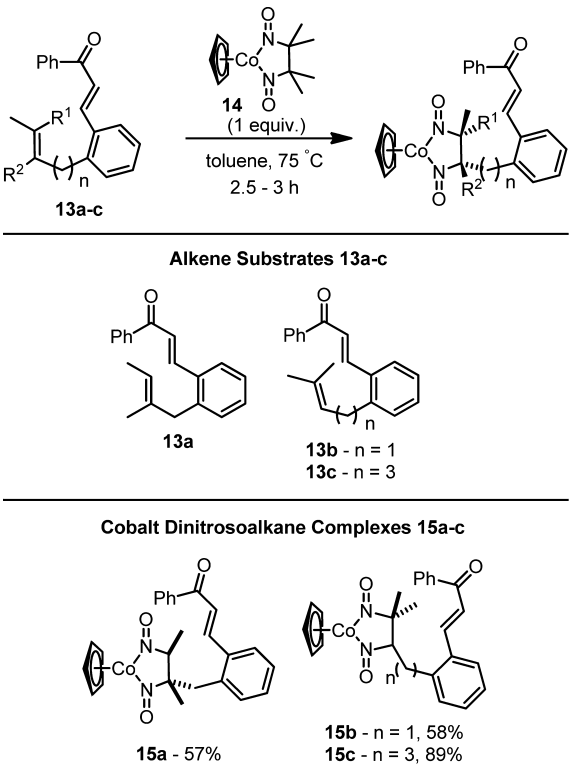
In contrast to the cobalt system, alkene exchange between norbornadiene and ruthenium complex **9** did not proceed cleanly under thermal conditions, and only proceeded photochemically (Scheme 10). The scope of this reaction is currently limited to norbornadiene and norbornene. Furthermore, the retention of stereochemistry upon alkene exchange seen with the analogous cobalt complexes has not been proven in the ruthenium system.

SCHEME 10. Alkene Exchange Reactions between Complex **9** and Norbornene



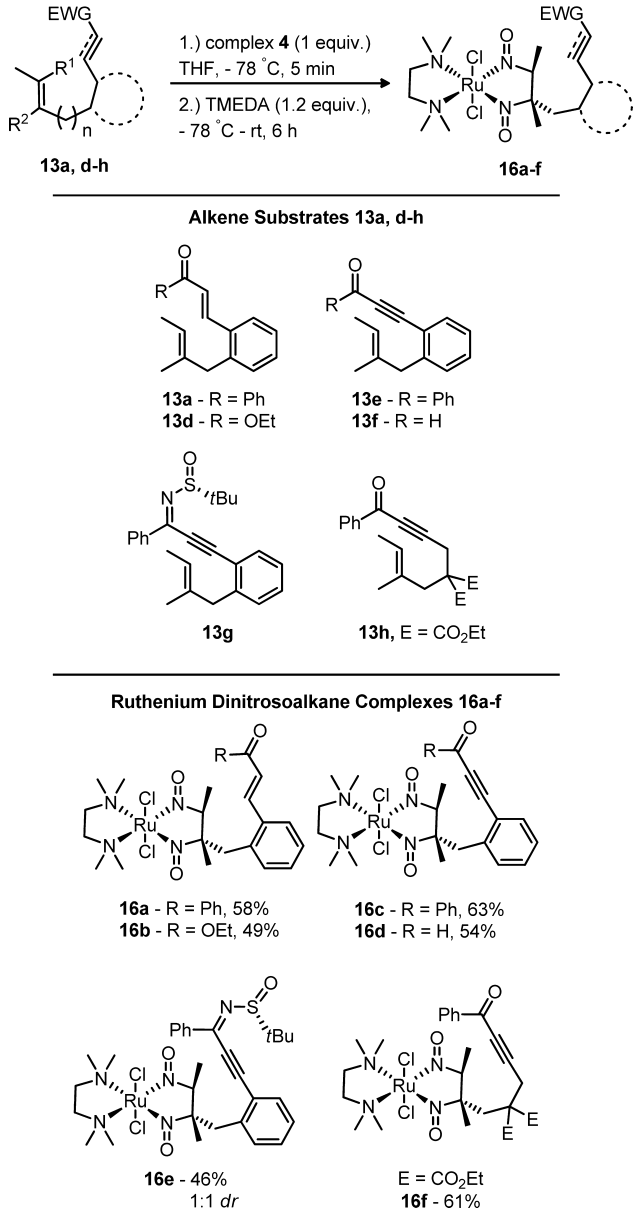
Selective Alkene Binding of Complex Substrates. In both the cobalt and ruthenium systems, selective binding of electron-rich alkenes in the presence of Michael acceptors has been achieved. Cobalt dinitrosoalkane complexes **15a–c** were synthesized by the alkene exchange method with complex **14** and the corresponding alkenes (**13a–c**) (Scheme 11).[38,51] Although 10 equiv of **13a–c** was generally required to obtain good yields, the mild reaction conditions allowed for recovery of the unreacted organic substrates.

SCHEME 11. Selective Alkene Binding of Complex Substrates with Cobalt Dinitrosyl Complex



Ruthenium complex **4** also selectively binds electron-rich alkenes in the presence of other conjugated π-systems, and substrates **13a** and **13d**–**h** reacted with **4** to give the corresponding dinitrosoalkane complexes **16a**–**f** (Scheme 12).[51] In order to prevent isomerization of the dinitrosoalkane complexes to the oxime isomers, a modified procedure was developed where the reaction was initially carried out at −78 °C with only slight excess of TMEDA, and the reaction mixture was allowed to slowly warm to room temperature over 14 h. This protocol allowed for the isolation of dinitrosoalkane complexes **16a**–**f**, and purification was achieved by silica gel chromatography to give the desired products in moderate to good yields. The order of addition proved vital for a successful reaction outcome; hence when TMEDA and complex **4** were first mixed for 1 h at room temperature, followed by addition of norbornadiene or tetramethylethylene, no desired complex was formed and only decomposition of **4** was observed. Screening of a variety of bidendate ligands for "delayed" alkene binding under these experimental conditions gave either no cycloaddition or only trace amounts of the desired complex.

SCHEME 12. Selective Alkene Binding of Complex Substrates with Ruthenium Dinitrosyl Complex



The Mechanism(s) of Alkene Binding to Metal–Dinitrosyl Complexes

A Concerted [3 + 2] Addition Mechanism for Alkene Binding? In simple terms, nitrosyl ligands may be described by conformations either possessing a linear (three-electron) or bent (one-electron) mode upon coordination to transition metals. If the five-coordinate intermediates $[CpCo(NO)_2]$ or $[Tp^*Co(NO)_2]$ possessed linear nitrosyl ligands, they could be described as 20-electron complexes (Figure 1), while the one-linear, one-bent nitrosyl and both-bent nitrosyl isomers are described as 18- and 16-electron complexes, respectively.

The ligand-based reaction between metal dinitrosyl complexes and alkenes resembles that between osmium tetroxide and alkenes. The substrates interact with the ligands but not the metal center to form two covalent carbon–heteroatom bonds. In 1986, Hoffmann and co-workers reported a comparative study of the reactions of **1** and OsO_4 with alkenes. Using extended Hückel computational methods, Hoffmann rationalized the reaction of cobalt complex **1** with alkenes in terms of a symmetry-allowed, concerted [3 + 2] cycloaddition of the metal fragment with the alkene, in which both 16- and 18-electron conformations of complex **1** (Figure 1) possess a HOMO and LUMO of the correct orbital symmetry to overlap with the LUMO and HOMO of ethylene, respectively.[52]

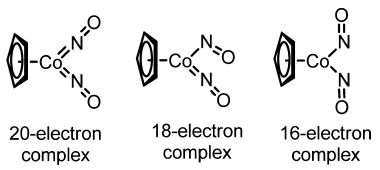


FIGURE 1. Possible isomers of $[CpCo(NO)_2]$.

Is Alkene Binding Ligand-Accelerated? Several thermodynamically stable four-coordinate cobalt dinitrosyl complexes, such as complex **3**, have been synthesized, but

these complexes have yet to be shown to bind alkenes.[46] In contrast, five-coordinate analogues, such as complex **1**, react readily with alkenes at and below room temperature. In the ruthenium system, alkene binding to the five-coordinate complex **4** in hydrocarbon or chlorinated solvents is not observed. However, in the presence of exogenous ligands, alkene binding is observed to give the six-coordinate dinitrosoalkane complexes.

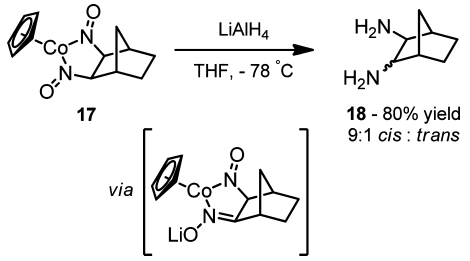
A Comparison of Alkene Binding Reactions with Cobalt and Ruthenium Dinitrosyl Complexes. It has been found experimentally that electron-rich and strained alkenes bind complex **1** readily to give stable cobalt dinitrosoalkane complexes. Complexes of styrene, cyclohexenes, and mono- and disubstituted alkenes have only been generated *in situ*, and attempts at isolation under ambient conditions failed. In contrast, these substrates bind with **4** to give the mono-oxime ruthenium complexes (Scheme 8). These complexes do not isomerize back to the dinitrosoalkane complexes or alkylate at the carbon atom, suggesting that they are thermodynamically stable (Scheme 9).

We propose that the difference in reactivity of the two systems is due to the coupling of the alkene binding and tautomerization steps. The binding of alkenes to both **1** and **4** results in rehybridization of the sp^2-carbon of the alkene to sp^3-carbon centers. In the case of strained alkenes, this rehybridization process is accompanied by the loss of ring strain, which accounts for the high selectivity of complex **1** binding to norbornene over styrene. The instability of cobalt complexes of unstrained alkenes may then be rationalized in terms of the equilibrium between the products and reactants lying further toward the side of the reactants than with strained alkenes. In the ruthenium system, facile tautomerization stabilizes the alkene bound products and prevents alkene decoordination. Although the pK_a's of the α-nitroso C−H bond in the cobalt and ruthenium dinitrosoalkane complexes have not been measured, strong bases, such as LiHMDS and Verkade's base, are required for deprotonation of cobalt complexes, while neutral amines are sufficient bases for deprotonation of ruthenium complexes (*vide infra*).

Synthesis of 1,2-Diamines by Reduction of Cobalt Dinitrosoalkane Complexes

Metal hydride ($LiAlH_4$) reduction of the cobalt dinitrosoalkane complexes, such as **17**, has also been demonstrated to afford the desired 1,2-diamine product **18** in 80% yield (Scheme 13).[42−44] Interestingly, a mixture of *cis* and *trans* isomers of **18** was obtained with the *cis*-exo diamine as the major diastereomer. The product distribution suggested epimerization at the carbon adjacent to the nitroso ligand during the reduction, which was hypothesized to proceed through a nitroso-oxime tautomerization catalyzed by deprotonation of the C−H bond by $LiAlH_4$.

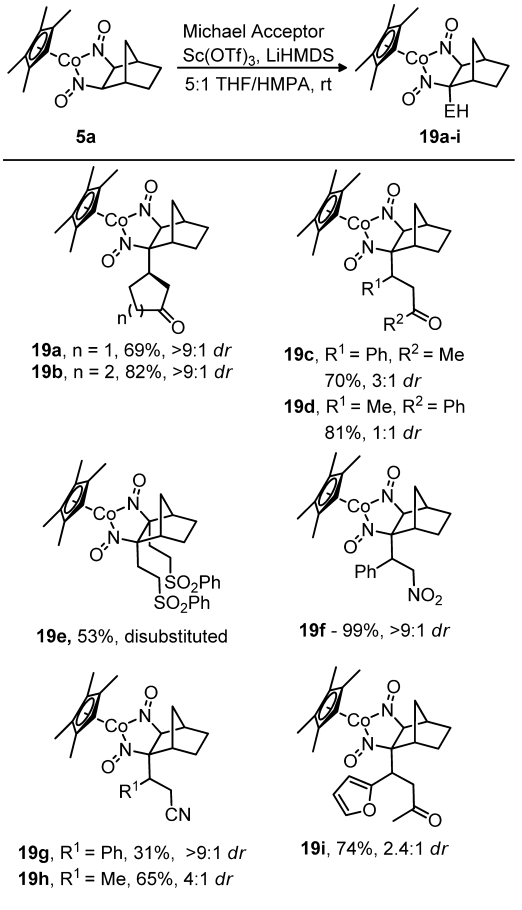
SCHEME 13. Reduction of Cobalt Dinitrosoalkane Complex **17**



Metal−Dinitrosyl Mediated Vinylic C−H Functionalization

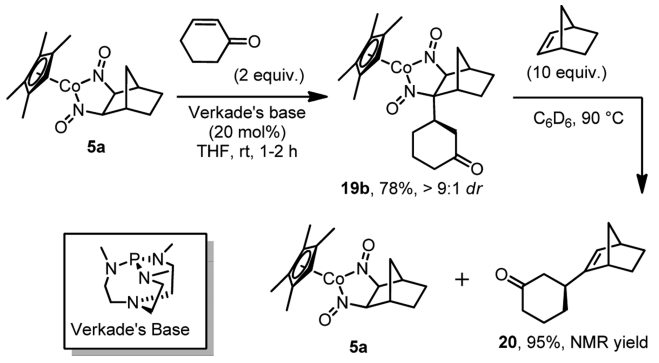
Stepwise C−H Functionalization of Alkenes Mediated by 1 and 4. Intermolecular C−H functionalization of a variety of cobalt dinitrosoalkane complexes with Michael acceptors has been achieved.[35] While in our initial report,

SCHEME 14. Cobalt−Dinitrosyl Mediated Intermolecular C−H Functionalization



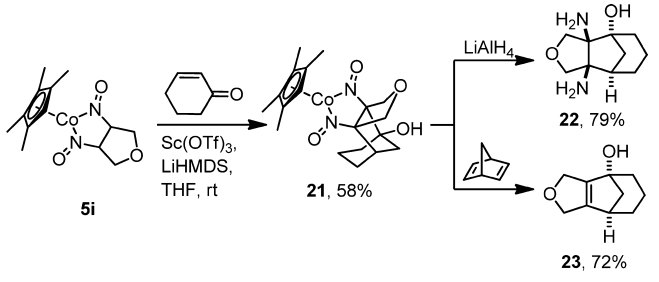
2 equiv of base and 1 equiv of Lewis acid were needed to obtain the functionalized complexes in good yields (Scheme 14), we have recently found that Verkade's base can catalyze the reaction between **5a** and cyclohexenone to give **19b** in 78% yield. Subsequent alkene exchange reactions were used to liberate the C−H functionalized products. For example, complex **19b** reacted with norbornene to give cobalt complex **5a** and the desired organic product **20** (Scheme 15).

SCHEME 15. Intermolecular C−H Functionalization of Complex **5a** Catalyzed by Verkade's Base and Alkene Exchange of Functionalized Complex **19b**



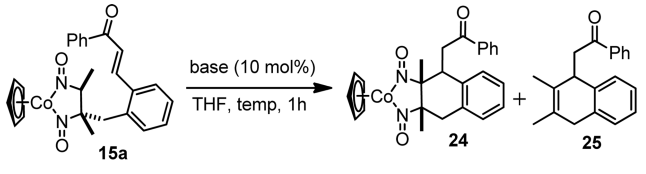
Cobalt dinitrosoalkane complexes can also participate in a [3 + 2] annulation reaction with enones.[36] Hence, complex **5i** reacted with cyclohexenone in the presence of $Sc(OTf)_3$ and LiHMDS to give complex **21** in 58% yield (Scheme 16). Complex **21** could be reduced with $LiAlH_4$ to give the bicyclic diamine **22** in 79%. Lastly, alkene exchange between **21** and norbornadiene furnished the bicyclic product **23** in 72% yield. Molecules containing this bicyclic moiety have also been synthesized by other processes, although in low yields with long reaction sequences.[53,54]

SCHEME 16. Cobalt-Mediated [3 + 2] Annulation Reaction of Alkene with Cyclohexenone

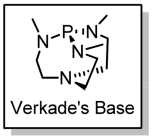


Inspired by the discovery of this double C−H functionalization reaction, we hypothesized that an intramolecular C−H functionalization could also be achieved.[38,51] Indeed, complex **15a** underwent a 6-*exo*-trig cyclization in the presence of catalytic amount of base at room temperature (Scheme 17). Unexpectedly, both cyclized complex **24** and the desired organic product **25** were present following work-up of the reaction mixture (entry 2). While repeating the cyclization of **15a** at −78 °C had no effect on this product distribution (entry 1), heating of **15a** with base gave the organic product **25** in much improved yields (entry 3 and 4). We believe that the labile cyclohexene moiety of compound **25** facilitates its retrocycloaddition from the $[CpCo(NO)_2]$ fragment.

SCHEME 17. Temperature Effect on the Cyclization of Complex **15a**

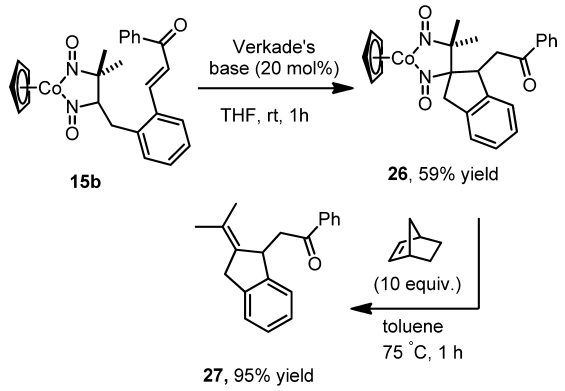


entry	base	temp (°C)	yield of **24**	yield of **25**
1	Verkade's	- 78	25%	26%
2	Verkade's	25	25%	25%
3	Verkade's	75	0%	80%
4	*t*BuOK	75	0%	81%



In contrast, the *5-exo-trig* cyclization of **15b** in the presence of Verkade's base (20 mol %) gave only complex **26** in 59% yield, and subsequent alkene exchange with norbornene gave the desired organic product **27** in 95% yield (Scheme 18).

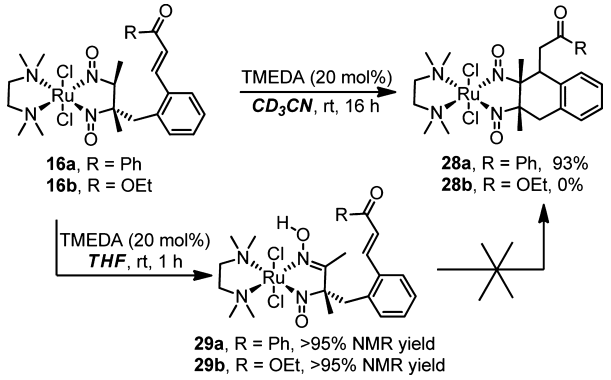
SCHEME 18. 5-*exo-trig* Cyclization of Cobalt Complex **15b**



The scope of this intramolecular vinylic C−H functionalization has been expanded to ruthenium dinitroso complexes in our laboratories.[51] A much milder base could be employed and treatment of **16a** with 20 mol % of TMEDA in CD_3CN at room temperature gave complex **28a** in 93% yield (Scheme 19). When the reaction was performed in THF,

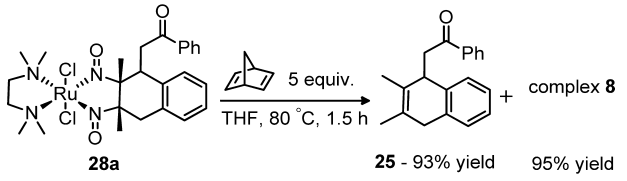
however, quantitative conversion to the oxime complex **29a** was observed and **28a** was not detected. Further heating of **29a** with and without the addition of strong bases, such as NaH, Verkade's base, or P_1-*t*Bu phosphazene, led to only decomposition. Similarly, treatment of complex **16b** with TMEDA in either THF or acetonitrile gave only the analogous oxime complex **29b** as observed by NMR spectroscopy.

SCHEME 19. Ruthenium-Mediated Intramolecular Addition of Alkene to Enone Group



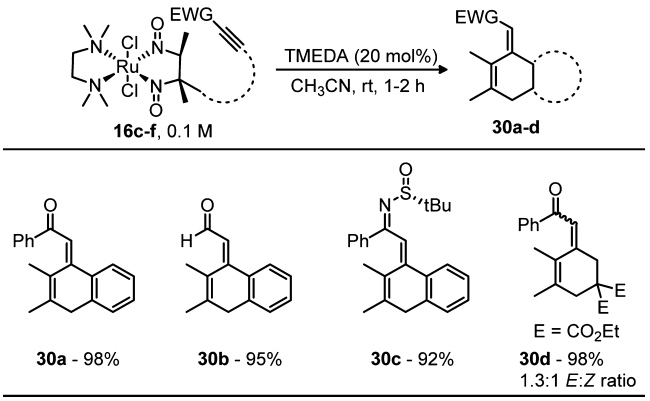
Thermal alkene exchange of **28a** with 5 equiv of norbornadiene at 80 °C for 1 h gave **25** and **8** in 93% and 95% isolated yields, respectively (Scheme 20). This observation provides another demonstration of the lability of the metal dinitrosyl fragment in dinitrosoalkane complexes of cyclohexene and its derivatives. This stepwise sequence of substrate binding, cyclization and retrocycloaddition represents the first example of a ruthenium dinitrosyl mediated intramolecular vinylic C–H functionalization.

SCHEME 20. Thermal Alkene Exchange of Complex **28a** with Norbornadiene



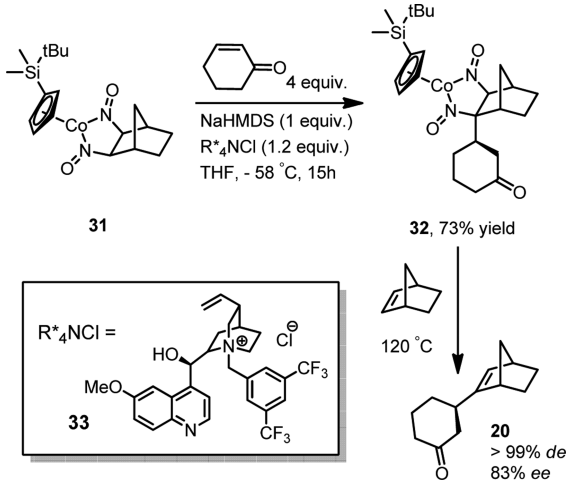
Cyclization of ynone containing ruthenium complexes **16c**–**f** also proceeded in the presence of TMEDA in acetonitrile (Scheme 21).[51] In contrast to **16a**, complexes **16c**–**f** cyclized to give only the corresponding organic products **30a**–**d**, and no organometallic products were observed under these conditions. Following isolation, compound **30d** was obtained as a mixture of *E* and *Z* isomers; however, over 5 days at room temperature in CD_2Cl_2, it isomerized to exclusively the *Z* isomer.

SCHEME 21. Ruthenium-Mediated Intramolecular Addition of Alkenes to Ynone Groups



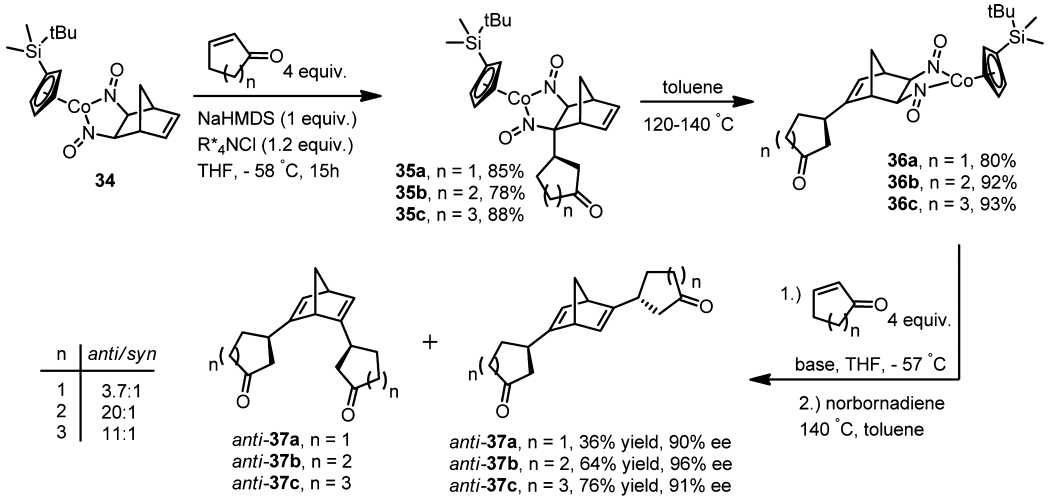
Enantioselective C–H Functionalization of Strained Alkenes with a Cobalt Complex. The enantioselective intermolecular C–H functionalization of alkenes with enones could also be achieved with a stoichiometric amount of a chiral base.[37] Hence, when **31** was treated with a premixed solution containing NaHDMS and cinchona alkaloid salt **33** at −58 °C in THF, alkylation followed by alkene exchange proceeded to give **20** in good yield with excellent diastereoselectivity (99% de) and enantioselectivity (83% ee) (Scheme 22). The order of reagent addition proved critical for an enantioselective reaction since NaHMDS is capable of promoting a racemic background reaction.

SCHEME 22. Enantioselective Synthesis of **20**



This methodology was applied to the synthesis of C_2- and C_1-symmetric dienes, which have been shown to be effective ligands for asymmetric organic transformations mediated by transition metals,[55] via two sequential enantioselective C–H activation/Michael addition events (Scheme 23).[37] Following the first alkylation of **34**, complexes **35a**–**c**

SCHEME 23. Asymmetric Synthesis of C_2- and C_1-Dienes



can undergo a thermally promoted isomerization of the cobalt dinitroso fragment to produce complexes **36a**–**c**. Following a second iteration of the sequence of C–H functionalization and alkene exchange, C_2-symmetric chiral dienes **37a**–**c** were obtained in moderate to good yields over the two steps with high enantiomeric excess (90–96% ee).

We believe that this selective C–H functionalization reaction sequence benefits from double stereodifferentiation where desymmetrization of the nucleophile controls enantioselectivity while the approach of the electrophile controls diastereoselectivity, as illustrated in Figure 2. As a result, the two orthogonal stereoselection events provide near perfect control during the formation of the two pairs of noncontiguous stereocenters. The *anti*-regioisomer was obtained as the major product.

The enantioselective cyclization of cobalt complex **15b** was also achieved in the presence of the chiral base mixture, and alkene exchange gave **27** in 57% ee (Scheme 24). When the enantio-enriched complex **26** was treated with the chiral base mixture for extended reaction times at higher temperatures, however, **27** was isolated in a low 3% ee. This control experiment suggests that the C–C bond forming step may be reversible, with racemization of the product occurring at longer reaction times. While attempts to trap the intermediate enolate to prevent the racemization process have not been successful, the cobalt–dinitrosyl mediated vinylic C–H functionalization has been shown to proceed enantioselectively in the presence of a chiral base mixture in both inter- and intramolecular fashions.

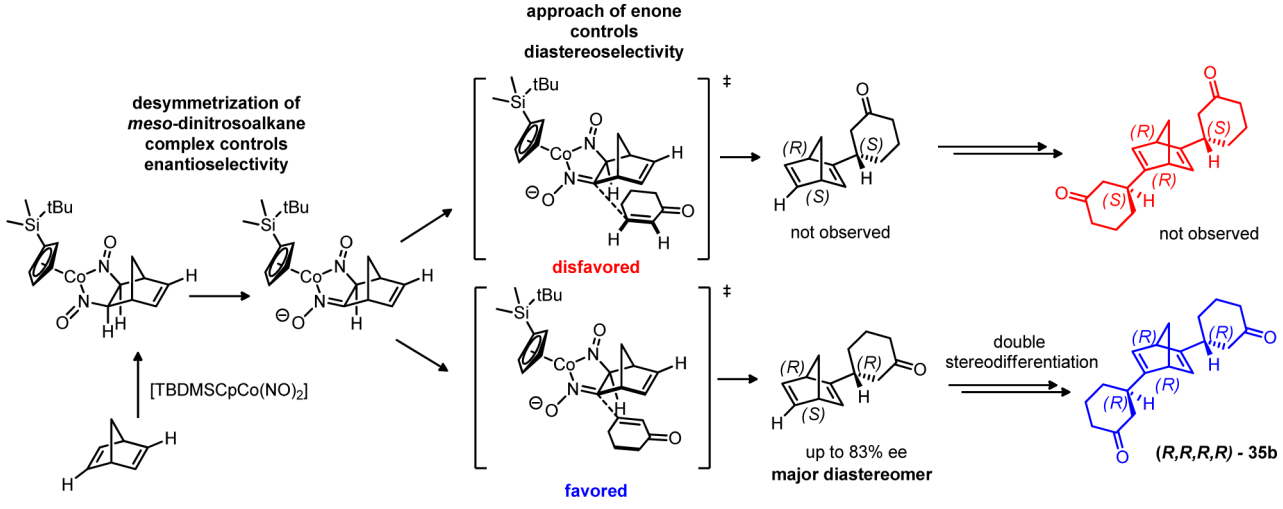
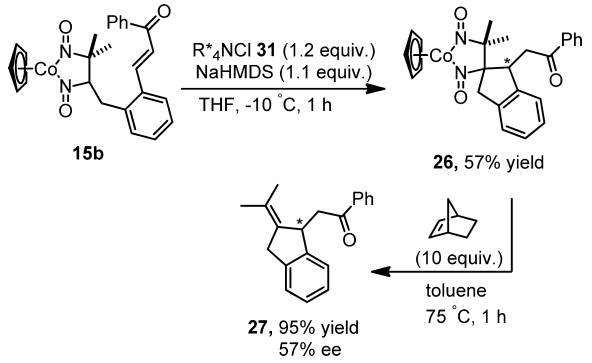


FIGURE 2. Proposed origin of enantioselectivity.

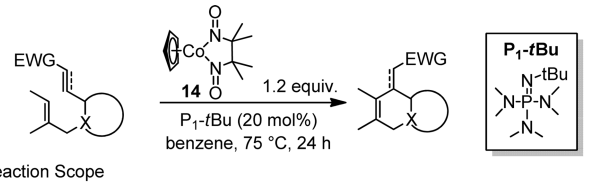
SCHEME 24. Enantioselective Cyclization of Complex **15b**



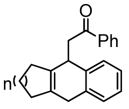
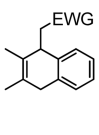
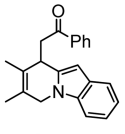
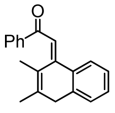
One-Pot C–H Functionalization of Alkenes. A one-pot procedure for the cobalt–dinitrosyl mediated vinylic C–H functionalization was also achieved.[38] As shown in Scheme 25, substrate **13a** cyclized in the presence of a stoichiometric amount of cobalt complex **14** and a catalytic amount of P_1-*t*Bu to give **25** in 85% yield. A relatively high concentration (0.33 M) of substrate was required for this one-pot procedure since the initial alkene binding step proceeded more efficiently under these conditions. The scope of this reaction proved to be general and tolerant of a variety of Michael acceptors. Intermolecular C–H functionalization of norbornene with cyclic enones also proceeded in the presence of a stoichiometric amount of **14** and 10 mol % of P_1-*t*Bu in a one-pot fashion (Scheme 26). In this case, attempts to replace P_1-*t*Bu with other strong and neutral bases, such as Verkade's base and P_2-Et phosphazene, gave lower yields of the desired products due to Baylis–Hillman-type dimerization of the electrophiles.

We also attempted to carry out a one-step intramolecular C–H functionalization reaction with the ruthenium complex **4**. As shown in Scheme 27, when **13a** and **4** were mixed in the presence of TMEDA at 75 °C for 48 h, **25** was obtained in 17% yield. Similarly, ynone substrate **13e** reacted with **4** in the presence of TMEDA to give **30a** in 15% isolated yield at room temperature. Despite extensive screening of reaction parameters, we have yet to find optimized conditions for ruthenium complex **4** mediated one-pot vinylic C–H functionalization in high yields. In addition, attempts to effect the intermolecular functionalization of C–H bonds with ruthenium nitroso intermediates have yet to give promising results.

SCHEME 25. Cobalt Complex **14** Mediated Intramolecular One-Pot C–H Functionalization

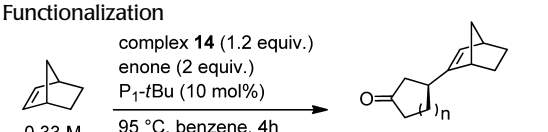


Reaction Scope

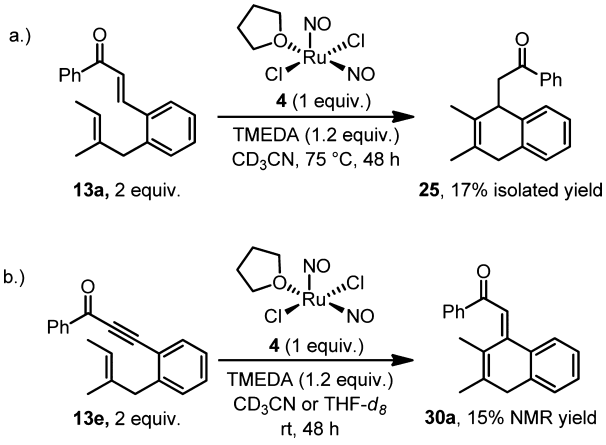
products[a]	yield[b]	products[a]	yield[b]
EWG = 	**25** - 85%		n = 1, **38f** - 91%[d] n = 2, **38g** - 19%
	**38a** - 75%[c]		
	**38b** - 83%[c] (61%)[a]		**38h** - 77%
	**38c** - 83% 3:1 *dr*		
	**38d** - 68%		**30a** - 78%[d] (46%)[a]
	**38e** - 74%[d]		

[a]Reaction conditions: 1.2 equiv of **14**, P_1-*t*Bu (20 mol %), 75 °C, 24 h, benzene (0.33 M). [b]Yields were determined by ^{1}H NMR spectroscopy with trimethoxybenzene as an internal standard. [c]P_1-*t*Bu (100 mol %), second equiv of **14** added after 12 h of heating, followed by additional heating for 24 h. [d]Isolated yields.

SCHEME 26. Cobalt Complex **14** Mediated Intermolecular One-Pot C–H Functionalization



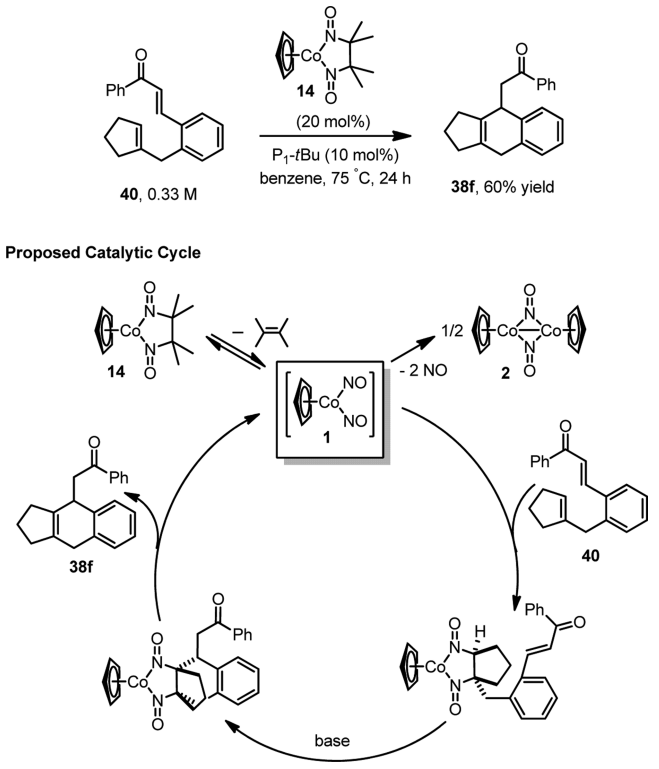
SCHEME 27. Ruthenium-Mediated One-Pot Intramolecular C–H Functionalization



Catalytic C–H Functionalization of Alkenes with Complexes 1 and 4. Although the stepwise chemistry of both cobalt and ruthenium dinitrosyl systems has been developed and investigated thoroughly, catalytic variants remain challenging. Nevertheless, catalysis has been demonstrated with the cobalt complex **14** in the cyclization and C–H functionalization of substrate **40** (Scheme 28).[38] Despite considerable effort, we have yet to find general experimental

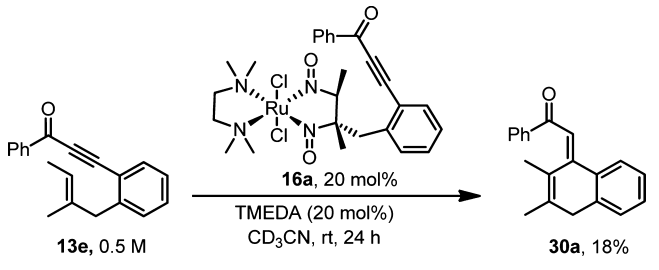
conditions for expanding the scope of this reaction. When tetramethylethylene was used as an additive in either catalytic or stoichiometric amounts or as a solvent, no improved catalytic turnover was obtained. As an attempt to prevent buildup of cobalt dimer **2**, when the reaction was carried out under an atmosphere of nitric oxide, decomposition of the organic substrate was observed and no catalytic enhancement was achieved. We believe that the instability of complex **1** in the presence of strong bases at high temperature, as well as its propensity to lose NO ligand and dimerize to form complex **2**, have thus far limited catalysis.

SCHEME 28. Cobalt–Dinitrosyl Catalyzed C–H Functionalization



Catalytic reactions of complex **4** with the enone or the ynone substrates gave low yields of the desired products. For example, the reaction between substrate **13e** and 20 mol % of complex **16a** (substrate-bound, ruthenium dinitrosoalkane complex of **13e**) and a catalytic amount of TMEDA yielded only 18% of **30a** (Scheme 29).

SCHEME 29. Attempted Catalytic C–H Functionalization with Ruthenium Complex **16a**



Conclusions

Over the past few years, our laboratories have developed a novel method for the functionalization of nonactivated vinylic C–H bonds using metal–dinitrosyl complexes. The reaction proceeds via reversible alkene binding to the metal dinitrosyl to give a dinitrosoalkane complexes, followed by *in situ* deprotonation of the formal vinyl C–H bond to generate a carbanion that participates in the C–C bond forming reaction with a variety of Michael acceptors. Along with the chemistry of the cobalt–dinitrosyl system, the ruthenium–dinitrosyl mediated reaction represents a rare class of ligand-based reactivity that allows for the stepwise, chemoselective generation of carbon nucleophiles directly from vinyl C–H bonds. While catalysis with $[(TMEDA)RuCl_2(NO)_2]$ remains elusive, the reaction has been rendered catalytic with $[CpCo(NO)_2]$. The catalytic reaction scope remains highly limited and requires improvement. If a reactive metal–dinitrosyl fragment could be discovered that effected *catalytic,* vinylic C–H activation with a broader substrate scope, it would not only represent a significant breakthrough in ligand-based catalysis of transition metal complexes but also in the field of C–H functionalization.

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BIOGRAPHICAL INFORMATION

Chen Zhao was born and raised in Tianjin, China, and then moved to upstate New York, USA. He obtained his B.S. from the University of California, San Diego, working with Professor Charles Perrin. In 2009, he began his graduate studies in the groups of Professors F. Dean Toste and Robert G. Bergman at the University of California, Berkeley. Currently, he is working in collaboration with the Raymond group on supramolecular chemistry.

Mark R. Crimmin is a Lecturer and Royal Society University Research Fellow at Imperial College London. He was born in Sussex, England, and took undergraduate studies at Imperial College. Following a Master's degree at the University of Bristol and Ph.D. at Imperial College, he trained as a research associate under the supervision of Professors R. G. Bergman and F. D. Toste at UC Berkeley. His current research focuses on the activation

and functionalization of chemically inert carbon−oxygen, carbon−fluorine, and carbon−hydrogen bonds using early transition metal and main group catalysts.

F. Dean Toste was born in Terceira, Azores, Portugal, but soon moved to Toronto, Canada. He obtained a B.Sc. and M.Sc. from the University of Toronto and his Ph.D. from Stanford University in 2000 from Professor Barry M. Trost. Following postdoctoral research at the California Institute of Technology in the laboratory of Professor Robert H. Grubbs, he joined the faculty at the University of California, Berkeley, in 2002. His research interests are in catalysis, in particular homogeneous catalysis, and its application to chemical synthesis.

Robert G. Bergman is Gerald E. K. Branch Distinguished Professor at the University of California, Berkeley. He was born in Chicago and educated at Carleton College and the University of Wisconsin, Madison. After postdoctoral studies at Columbia University, he joined the faculty at the California Institute of Technology in 1967 and moved with his research group to the University of California, Berkeley, in 1978. Bergman's early work focused on the synthesis of highly strained and conjugated organic molecules and the study of organic reaction mechanisms, and broadened to include organotransition metal chemistry in the mid-1970's. He is best known for the discovery of the ene−diyne-to-1,4-benzenediyl rearrangement and his work on carbon−hydrogen bond activation. He has also published collaborative work in biofuels development and supramolecular chemistry.

FOOTNOTES

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