

Cross-Coupling of sp^3 C–H Bonds and Alkenes: Catalytic Cyclization of Alkene–Amide Substrates

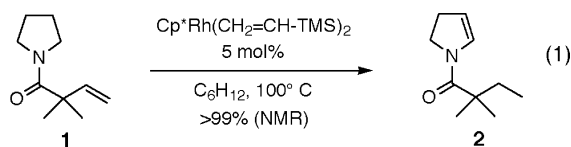
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As part of a program directed toward C–H bond functionalization in complex synthesis, we became interested in the direct cross-coupling of sp^3 C–H bonds and alkenes. Although many structural contexts may be envisioned, we chose to study the intramolecular coupling of alkenes and amides owing to its significant synthetic appeal (Figure 1). This overall transformation requires tandem sp^3 C–H activation (at the position adjacent to the amide nitrogen) and C–C bond formation. We herein present a lead in this direction as a new oxidative cyclization of alkene–amide substrates was accomplished under neutral and catalytic conditions.

There is only limited precedent for the direct and catalytic coupling of sp^3 C–H bonds and alkenes,¹ and to our knowledge no examples have been reported for amide substrates. To address this challenge, we commenced our studies with prototype substrate **1**, wherein the possibility of alkene migration was eliminated by the installation of an adjacent geminal dimethyl group. In this way, our attention was fully focused on achieving C–C bond formation via C–H bond activation. The magnitude of such a proposition may be appreciated in light of our first lead, namely the quantitative conversion of substrate **1** to enamide **2** catalyzed by $Cp^*Rh(CH_2=CH-TMS)_2$ (eq 1). This transformation, proceeding via intramolecular transfer hydrogenation, is analogous to the conversion of vinylalkoxysilanes to silylenol ethers reported by Brookhart.^{2,3} This result was very instructive as it demonstrated the feasibility of amide substrate activation but also highlighted the key challenge to be addressed: suppression of β -hydride elimination in favor of C–C bond formation.



A major step in this direction was made when we observed that $[Ir(coe)_2Cl]_2$ and tricyclohexylphosphine (PCy_3) afforded both 5-exo and 6-endo cyclization products **3** and **4**, albeit in low yields, as well as reduction product **5** (entry 1, Table 1). Substituting PCy_3 for the carbene ligand IPr [N,N' -bis-(2,6-diisopropylphenyl)-imidazolyl carbene] led to a significant increase in both efficiency and selectivity, favoring product **3** (41%) over **4** (4%) as determined by NMR (entry 2, Table 1). To suppress formation of compound **5**, norbornene (4 equiv) was added as a hydrogen acceptor. Indeed, the yields of products **3** (66%) and **4** (17% yield) were further increased at the expense of **5** (entry 3, Table 1). Thus, the optimized procedure afforded good yields of compounds **3** and **4**, products of 5-exo and 6-endo oxidative cyclization, respectively.

It is noteworthy that lowering the loading of iridium to 5 mol % did not significantly affect the yield of the major product (50% isolated yield of **3**).

Our initial thoughts regarding the nature of an active complex led us to consider complexes of type $(R_3P)_2Ir(X)H_2$, known to

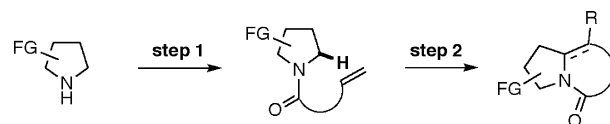


Figure 1. A two-step sequence for the assembly of pyrrolizidinones and indolizidinones.

Table 1. Catalytic Oxidative Cyclization, Lead Discovery

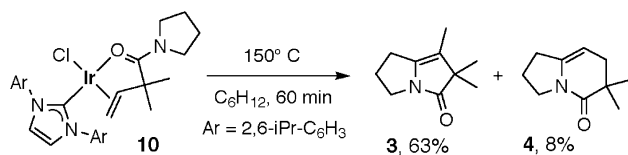
entry	complex	NMR yields ^a		
1	$[Ir(COE)_2Cl]_2 / PCy_3$ (2 eq)	26	11	25
2	$[Ir(COE)_2Cl]_2 / IPr$ (2 eq)	41	4	41
3	$[Ir(COE)_2Cl]_2 / IPr$ (2 eq) + 4 eq NBE	66	17	10
4	$(Cy_3P)_2Ir(Cl)H_2$, 6	9	0	20
5	$(Cy_3P)_2Ir(CF_3CO_2)H_2$, 7	0	0	24
6		trace	0	trace
7		0	0	0

^a Reported yields were determined by NMR using an internal standard (average of three runs). NBE, norbornene. Total loading of Ir catalyst was 10 mol %.

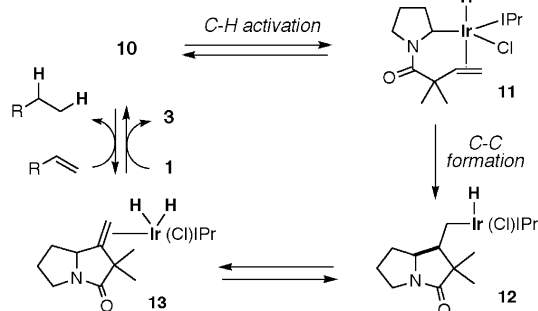
catalyze transfer dehydrogenation of alkanes.^{4,5} However, we found that the corresponding chloride complex **6** showed only marginal activity, providing product **3** in 9% yield, while trifluoroacetate **7^{ab}** was completely inactive (Table 1). Furthermore, bis-carbene complex **8** also proved inactive, clearly refuting our initial hypothesis. On a formal level, we concluded that the $[L_2Ir-X]$ fragment ($L = R_3P$ or IPr) did not support the C–H activation/C–C formation chemistry required for converting amide **1** to products. This conclusion was further supported by the fact that the Goldman's pincer complex **9** showed no activity at all in this context.⁶

Consequently, we proposed that the “active fragment” must be $[IPr-Ir-Cl]$, containing only one carbene ligand. To test this rationale, complex **10** was prepared in a pure form, and its reactivity was investigated in detail. Indeed, heating **10** in cyclohexane afforded products **3** and **4** in 63% and 8% yield, respectively (Scheme 1; IPr ligand underwent complete decomposition, and 19% of reduced compound **5** was also formed). This stoichiometric experiment suggested that complex **10**, formed in situ from $[Ir(coe)_2Cl]_2$, IPr ligand, and the substrate, may be a pivotal point in the catalytic cycle. This notion was further strengthened by

Scheme 1. Stoichiometric Reaction



Scheme 2. Proposed Catalytic Cycle



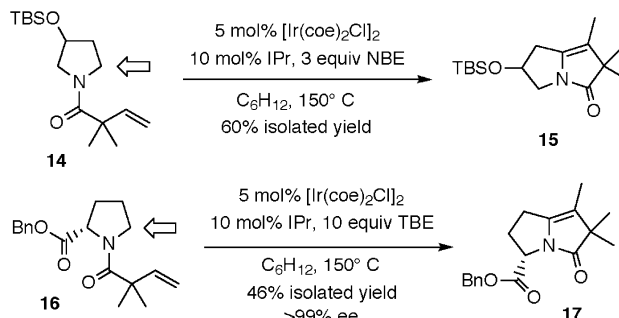
showing that complex **10** was a competent catalyst, providing nearly identical yields and kinetics in comparison to the system formed in situ (Supporting Information).

On the basis of these results, we proposed the following catalytic cycle (Scheme 2). First, complex **10** is assembled in situ by replacing cyclooctene ligands (coe) at the iridium metal by the carbene ligand and the substrate. The second step involves rearrangement of **10** and iridium insertion into a C–H bond adjacent to the amide nitrogen, providing an alkyl iridium hydride (cf. **11**).⁷ This is followed by the third key step, alkene insertion. Apparently, this particular ligand sphere [IPr–Ir–Cl] favors alkene insertion over β -hydride elimination, which represents the key advance allowing for formation of C–C bond.⁸ This observation stands in contrast to studies using the Brookhart catalyst {the source of [Cp*Rh]} wherein β -hydride elimination was fast (eq 1). In the fourth main step, intermediate **12** undergoes β -hydride elimination (reductive elimination would give the saturated product) to furnish an alkene complex (cf. **13**). To regenerate complex **10**, two hydrides would be removed by hydrogenation of either the substrate or the added hydrogen acceptor, followed by release of the product. Importantly, a metal complex capable of linking the C–H activation and alkene insertion in the context of amide substrates was found.

Last, we were delighted that the method developed herein also showed promising functional group compatibility. For example, substrate **14** containing a silyl ether underwent efficient cyclization at the less-hindered site to produce compound **15** as the major product with none of the regioisomeric material detected (Scheme 3). Furthermore, exposure of proline derivative **16** to the reaction conditions furnished pyrrolizidinone **17** as the major product (46%).⁹ Although other unidentified compounds were detected as minor products, this reaction was regioselective, and remarkably, the absolute stereochemistry was preserved!

In summary, we have developed a new oxidative cross-coupling of sp^3 C–H bonds and alkenes under neutral and catalytic conditions. From a mechanistic standpoint, the key advance was

Scheme 3



the ability to facilitate C–H activation and alkene insertion in tandem and in preference to β -hydride elimination. With respect to complex synthesis, the catalytic and neutral conditions of this method unlock new exciting opportunities as illustrated by the cyclization of proline derivative **16**. This reaction serves as an important prototype for further advancement in terms of substrate scope, mechanistic insight, and efficiency.

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Supporting Information Available: Experimental procedures, synthesis, and spectral data for compounds **2–8**, **10**, **14–17**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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