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Radical Cyclizations Terminated by Ir-Catalyzed Hydrogen Atom Transfer

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Abstract: A system for coupling catalytic radical cyclization and Ir-catalyzed hydrogen atom transfer (HAT) is described. It is essential that the HAT catalyst activates H_2 quickly and is not a hydrogenation catalyst. Vaska's complex was found to fulfill both purposes efficiently.

Radical cyclizations are highly useful for the synthesis of complex molecular architectures due to their high selectivity and compatibility with densely functionalized substrates.[1] For synthetic applications catalytic, sustainable methodology without stoichiometric amounts of toxic and expensive substances, especially hydrogen atom donors, is highly desirable. To this end, H_2O,[2] alcohols,[3] and H_2 are especially attractive.[4] A first example of a H_2-mediated, Cr-catalyzed radical cyclization was recently reported by Norton.[5] Unfortunately, the remarkable threefold task of the catalyst−H_2 activation, radical generation, and radical reduction via hydrogen atom transfer (HAT)—limits the substrate scope of the reaction.

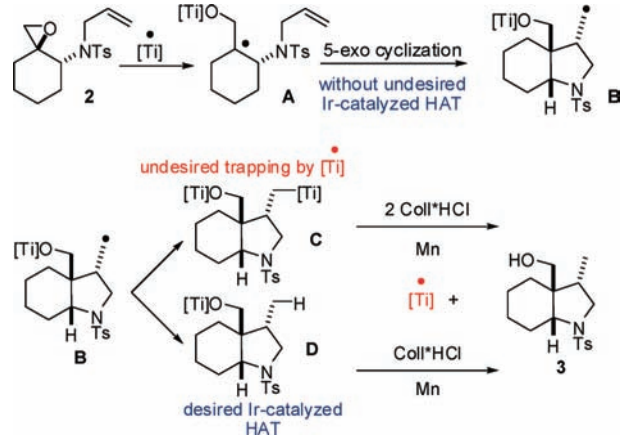
A conceptually different and unprecedented approach to such cyclizations is the coupling of catalytic cycles for radical generation and for hydrogen activation and HAT. In that manner, more general reactions become available. However, potential pitfalls for such methodology are numerous. Most notably, the kinetics of radical generation, cyclization, H_2 activation, and HAT have to be precisely adjusted to preclude undesired side reactions such as hydrogenation of radical acceptors or reduction of radical intermediates by a HAT before cyclization (Scheme 1).

We chose Vaska's complex, $IrCl(CO)(PPh_3)_2$ (**1**), as HAT catalyst to address these issues.[6] It forms a stable product of oxidative addition to H_2 without free coordination sites and hence displays low activity in the hydrogenation reactions of radical acceptors, especially alkynes. Since premature reduction of intermediate radicals must be avoided, the steric shielding of the hydrido ligands in $[IrH_2Cl(CO)(PPh_3)_2]$ seems favorable.

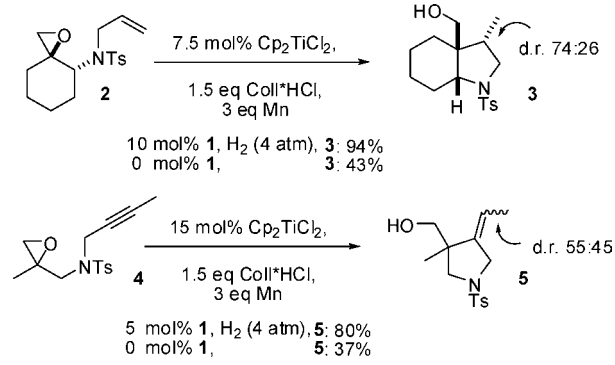
The use of **1** also imposes limitations for a catalytic system for radical generation. No H_2 activation or ligand exchange with **1** should occur. The cyclization must take place before undesired HAT to intermediate radicals. Finally, the radical-generating agent must not intercept the final radical before the catalytic HAT. Titanocene-catalyzed reductive epoxide opening[7] is an attractive method for these purposes. The titanocene complexes involved do not bind phosphines and CO and do not activate H_2.

The presence of the desired and undesired pathways can be readily distinguished experimentally. If **A** is intercepted by HAT, an undesired product will be formed. In the absence of **1** or in the case of an inefficient HAT, **B** will be trapped by Cp_2TiCl to give **C**. From **C**, liberation of **3** and regeneration of Cp_2TiCl_2 requires the protonation of the Ti−O and Ti−C bonds by at least 2 equiv of Coll·HCl. In the case of trapping of **B** by HAT, the formation

Scheme 1. Concept of the Catalytic Radical Cyclization of **2** Terminated by an Ir-Catalyzed HAT



Scheme 2. Study of the Competing Pathways of Trapping of Radicals Formed by 5-*exo* Cyclization for **2** and **4**



of **3** and regeneration of Cp_2TiCl_2 from **D** requires only the protonation of the Ti−O bond by 1 equiv of Coll·HCl. Subsequently, Cp_2TiCl is re-formed by reduction with Mn. Thus, the amount of Coll·HCl added to the reaction provides a simple experimental means for studying the efficiency of the Ir-catalyzed HAT. Scheme 2 summarizes the results of the catalytic cyclizations of **2** and **4** in the absence and in the presence of **1**.

In the absence of **1**, the yields of **3** and **5** are below 50%, even with 1.5 equiv of Coll·HCl.[8] The remainder consists of starting material. In the presence of **1** and H_2 (4 atm), the isolated yields increase by more than a factor of 2. This indicates an efficient coupling of catalytic radical cyclization and Ir-catalyzed HAT. No products of undesired HAT to radicals of type **A** were observed. Even when taking into account that both radical and HAT reagent are present in catalytic amounts, and therefore a bimolecular trapping is disfavored, this is still amazing, because reactions of radicals with M−H bonds are exothermic and can have rate constants much higher than those of 5-*exo* cyclizations.[9] As a reason

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for the chemoselectivity of the HAT, we suggest that the steric shielding of the hydrido ligands in $[IrH_2Cl(CO)(PPh_3)_2]$ by PPh_3 retards the trapping of radicals of type **A**. This could be especially relevant for the tertiary radicals employed here.

In the case of **4**, the situation is more complex. After the cyclization, a highly reactive vinyl radical is generated that is not trapped Cp_2TiCl. Instead, its high reactivity results either in a reduction by the Ir-catalyzed HAT or by a HAT from THF. In the latter case, a tetrahydrofuranyl radical is generated that can be either trapped by Cp_2TiCl or reduced by an Ir-catalyzed HAT. The 80% isolated yield of **5** obtained in the presence of **1** (37% without **1**) demonstrates that the coupling of the catalytic cycles is not affected by the nature of the final HAT step. The identical diastereoselectivity of the formation of **4** with or without **1** may suggest an initial HAT from THF. Hydrogenation catalysts, such as Wilkinson's catalyst, $RhCl(PPh_3)_3$,[10] are not useful, because hydrogenation, especially of alkynes, competes with the desired coupling of the catalytic cycles. Table 1 summarizes further examples of the synthesis of pyrrolidines.

Table 1. Radical Cyclizations Terminated by Ir-Catalyzed HAT (1.5 equiv of Coll·HCl, 3 equiv of Mn, 0.1 M THF, 4 atm H_2)

R = H : **6**
R = Ph : **8**
R = 4-Br-C_6H_4 : **10**
R = 4-MeO-C_6H_4 : **12**

R = H : **7**
R = Ph : **9**
R = 4-Br-C_6H_4 : **11**
R = 4-MeO-C_6H_4 : **13**

entry	substrate	conditions	product
1	**6**	15 mol % Cp_2TiCl_2, 5 mol % **1**	**7**, 72%
2	**6**	15 mol % Kagan's complex, 5 mol % **1**	**7**, 77%[a]
3	**8**	15 mol % Cp_2TiCl_2, 5 mol % **1**	**9**, 76%[b]
4	**10**	15 mol % Cp_2TiCl_2, 5 mol % **1**	**11**, 70%[c]
5	**12**	15 mol % Cp_2TiCl_2, 5 mol % **1**	**13**, 70%[d]

[a] er = 63:37. [b] dr = 96:4. [c] dr = 91:9. [d] dr = 89:11.

For all substrates investigated, satisfactory yields of the desired products could be obtained. Gratifyingly, the aryl-substituted olefins are formed in much higher selectivity [(*E*):(*Z*) = 89:11 to 96:4, see Supporting Information for details] than **5**. Presumably, this is due to enhanced steric interactions by aryl substitution. Kagan's complex,[11] bearing two bulky menthyl substituents at the cyclopentadienyl ligands, gave only a slightly higher yield (entry 2) than Cp_2TiCl_2. This indicates that interactions between the two metal complexes can be neglected and provides yet another hint that the two catalytic cycles operate independently.

Reactions leading to carbocyclic products can also proceed in high yields. Table 2 summarizes the development of efficient reaction conditions. For **1**, a catalyst loading of 5 mol % (entry 2) is sufficient, whereas a reduction to 1 mol % (entry 1) leads to unsatisfactory yields. For Cp_2TiCl_2, a catalyst loading of 15 mol % is adequate for high yields (entries 3 and 5).

In summary, we have devised a system of coupled catalytic cycles for sustainable radical cyclizations terminated by Ir-catalyzed HAT with H_2 as terminal reductant. It is essential that the HAT catalyst, Vaska's complex, is not a hydrogenation catalyst.

Table 2. Radical Cyclizations to Carbocycles Terminated by Ir-Catalyzed HAT (1.5 equiv of Coll·HCl, 3 equiv of Mn, 0.1 M THF, 4 atm H_2)

n = 1, R = CH_3 : **14**
n = 1, R = C_6H_5 : **16**
n = 2, R = CH_3 : **18**

n = 1, R = CH_3 : **15**
n = 1, R = C_6H_5 : **17**
n = 2, R = CH_3 : **19**

entry	substrate	conditions	product[a]
1	**14**[b]	10 mol % Cp_2TiCl_2, 1 mol % **1**	**15**, 60%[c]
2	**14**[b]	10 mol % Cp_2TiCl_2, 5 mol % **1**	**15**, 71%[c]
3	**14**[b]	15 mol % Cp_2TiCl_2, 5 mol % **1**	**15**, 88%[c]
4	**16**[d]	15 mol % Cp_2TiCl_2, 5 mol % **1**	**17**, 68%[e]
5	**18**[f]	15 mol % Cp_2TiCl_2, 5 mol % **1**	**19**, 91%[g]

[a] All products can be diastereoconvergently hydrogenated to the *trans* products with Crabtree's catalyst.[12] [b] dr = 96:4. [c] dr = 63:37. [d] dr = 99:1. [e] dr = 85:15. [f] dr = 98:2. [g] dr = 67:33.

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Supporting Information Available: Experimental details and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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