C–C Activation

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Rhenium-Catalyzed C–H and C–C Bond Activation

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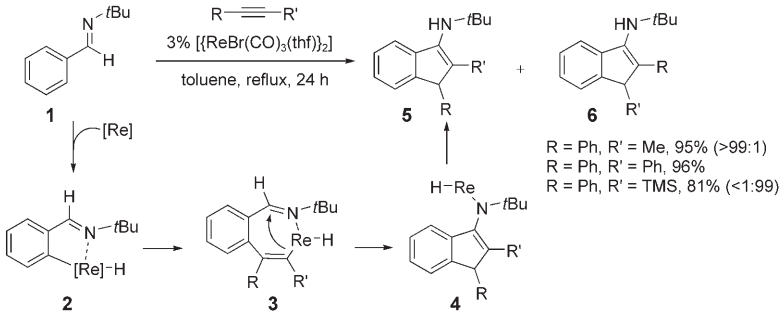
The principles of atom economy and environmentally benign chemical reactions have generated substantial interest in the development of methods based on the functionalization of carbon–hydrogen bonds.[1] To date, however, there have been far fewer reports on the functionalization of carbon–carbon single bonds. This is no surprise given the paramount steric obstacles a catalyst must overcome along the path to carbon–carbon bond activation. In early work in this area, Tipper and Bergman studied stoichiometric C–C bond activation,[2] and subsequently, a variety of strategies addressing catalytic C–C bond activation have been devised. To date, however, no truly general methods exist, and this area remains a major challenge for organic synthesis.[3] Of the systems developed thus far most have benefitted from ring strain,[4] chelation assistance,[5] or the formation of metal alcoholates to β-alkyl elimination[6] to allow for the selective cleavage of the C–C single bond.

Recent reports by Kuninobu and Takai on the rhenium(I)-catalyzed C–C bond formation by direct C–H activation illustrate a unique mode of reactivity. The reaction of aldimine **1** with acetylenes using $[\{ReBr(CO)_3(thf)\}_2]$ as the catalyst afforded indene derivative **5** with excellent regioselectivity (Scheme 1).[7] The yield of the reaction was improved when a CO ligand was removed from the active catalyst which presumably results in a vacant coordination site for the binding of the imine nitrogen. In support of this hypothesis, rhenium complexes such as $[Re_2(CO)_{10}]$, $[ReBr(CO)_3(CH_3CN)_2]$, $[ReCp^*(CO)_3]$ ($Cp^* = C_5Me_5$), and $[ReCl_3(PMe_2Ph)_3]$, which dissociate CO only upon photolysis,[8] did not show any catalytic activity under the same reaction conditions. It was found that the regioselectivity was reversed, without any significant loss in yield, when the reaction was carried out with 1-phenyl-2-(trimethylsilyl)acetylene under the same conditions.



Scheme 1. [3+2] Annulation of an aromatic aldimine and various acetylenes. TMS = trimethylsilyl.

In contrast to the indene formation observed with rhenium(I), when $[Ru_3(CO)_{12}]$ was used as the catalyst C–H bond activation and alkyne coupling occurred without imine migratory insertion, ultimately providing **9** after reductive elimination (Scheme 2).[9] Although similar metalated intermediates **3** and **8** were proposed in the rhenium- and ruthenium-catalyzed reactions, only the vinyl rhenium intermediate **3** underwent the intramolecular addition to the imine moiety to afford **4**. Reductive elimination and 1,3-rearrangement in **4** occurred successively to form **5** and **6** (Scheme 1). The different reactivity of the rhenium and ruthenium catalysts was proposed to reflect greater polarity of the rhenium–carbon bond relative to that of the ruthenium–carbon bond. Acetylenes bearing at least one aryl group were necessary to give the corresponding indene derivatives, as alkyl-substituted alkynes such as 6-dodecyne, propyne, or 1-trimethylsilyl-1-propyne did not provide the desired indene derivatives. This study marks the first example of intramolecular nucleophilic cyclization of an organometallic intermediate derived from the *ortho*-C–H bond activation of imines.

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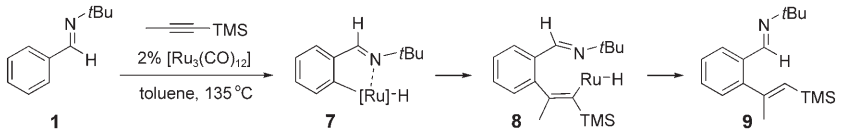
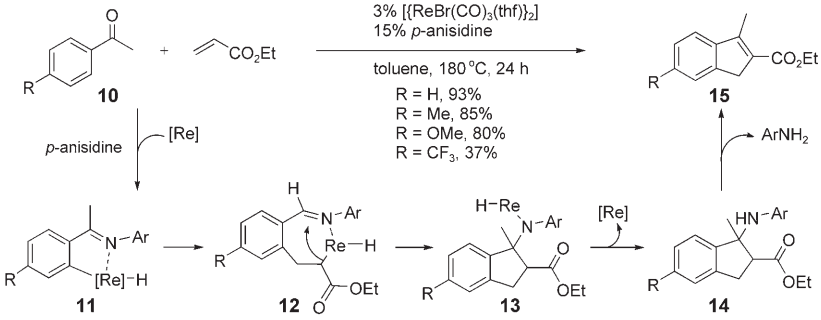


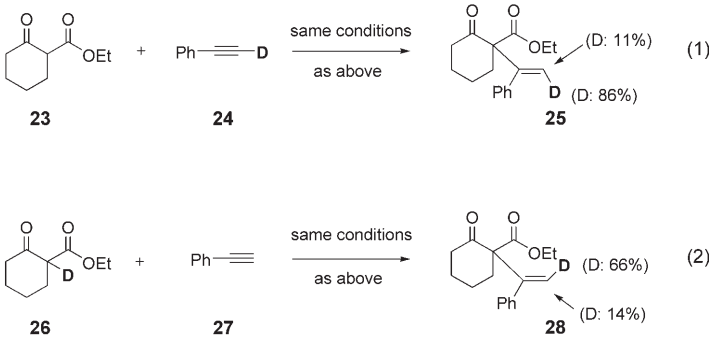
Scheme 2. Ruthenium-catalyzed C–H/alkyne coupling.

The same rhenium(I) complex was employed as a catalyst in the synthesis of indene derivatives from aromatic ketones (**10**) and α,β-unsaturated esters (Scheme 3). The annulations were accomplished with a co-catalytic amount of *p*-anisidine in toluene at 180 °C.[10] The reaction proceeds via the ketimine **11** formed by the reaction of acetophenones with *p*-anisidine. The imine functionality then acts as a directing group in the C–H activation step (→ **12**) and as an electrophile in the subsequent cyclization (→ **13**).

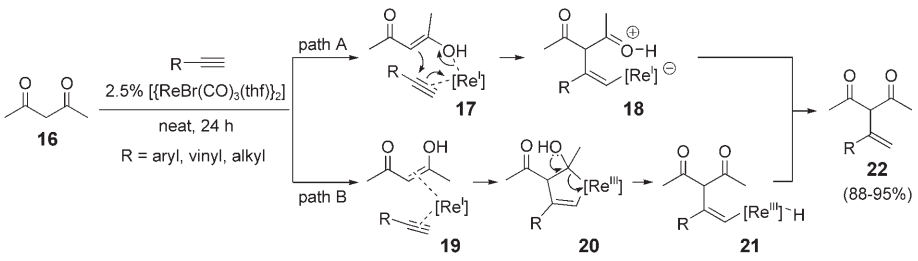


Scheme 3. Rhenium-catalyzed annulation of aromatic ketones with α,β-unsaturated esters.

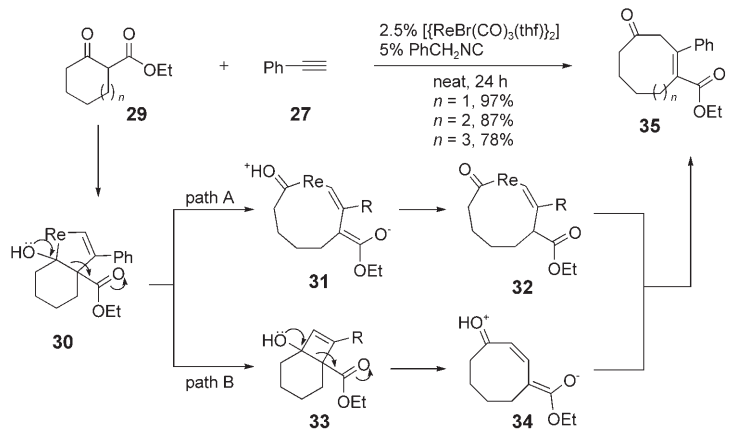
Complementing previously developed gallium- and indium-catalyzed vinylation of 1,3-dicarbonyl compounds,[11,12] rhenium(I) complexes also promote α-vinylation of 1,3-diketones (e.g., **16**) or β-keto esters with acetylenes to give **22** (Scheme 4).[13] Mechanistic studies were carried out with the deuterium-labeled substrates **24** and **26**. The reaction of deuterated phenylacetylene **24** with **23** afforded **25**, in which the deuterium is selectively located *anti* to the β-keto ester group [Eq. (1)]. Alternatively, reacting the deuterated 1,3-dicarbonyl compound **26** with **27** gave the **28** with deuterium incorporated *syn* to the β-keto ester group [Eq. (2)]. The observed scrambling of deuterium may result from the stabilization of **18** by back bonding from rhenium(I) which facilitates rotation about the double bond.[8a]



In 1974 the first ring-expansion reaction of cyclic 1,3-dicarbonyl compounds by reaction with and acetylenic esters in the presence of base was reported by Proctor et al.,[14] and very recently Shimizu and co-workers have reported a similar ring-expansion reaction of cyclic 1,3-dicarbonyl compounds with alkynyl imines.[15] Until recently, catalytic systems for this class of ring-expansion reactions were unknown. Addressing this, Kuninobu and Takai found that rhenium-catalyzed ring-expansion reactions of cyclic 1,3-dicarbonyl compounds and acetylenes proceeded in the presence of an isocyanide as a ligand. Thus, treatment of cyclohexanone-2-carboxylic acid ethyl ester **29** ($n=1$) with phenylacetylene in the presence of catalytic amount of [{$ReBr(CO)_3(thf)$}$_2$] and benzyl isocyanide as a ligand, under solvent-free conditions, afforded the eight-membered-ring compound **35** (Scheme 5).[16] Notably, in the absence of isocyanide as a ligand, only the α-vinylated adduct was obtained, demonstrating the necessity of the isocyanide ligand.[17] Two possible reaction pathways including ring opening by a retro-aldol reaction from **30** (path A) and the de Mayo-type reaction (path B) were proposed. Although experimental data to differentiate between the two proposed mechanisms has not been discussed, mechanistic studies on a related ruthenium-catalyzed [2+2] cycloaddition reactions of olefins with acetylenes[18] are consistent with the de Mayo



Scheme 4. Rhenium-catalyzed alkenylation of 2,4-pentanedione with phenylacetylene. β-Keto esters are also readily converted in this reaction.



Scheme 5. Ring expansion of cyclic 1,3-keto esters with phenylacetylene.

reaction (path B). While $[ReBr(CO)_5]$ and $[MnBr(CO)_5]$ also catalyze the synthesis of **35** in modest yield (45% and 59%, respectively), neither $[Ru_3(CO)_{12}]$, $[RuH_2(CO)(PPh_3)_3]$, $PtCl_2$, $AuCl_3$, nor $GaCl_3$ promote formation of **35** under identical reaction conditions.

Many challenges must still be overcome if rhenium(I) catalysts are to be made practical for C–H and C–C bond functionalization. However, rhenium can now be added to the growing list of metals capable of promoting reactions involving directed aromatic C–H bond activation. Moreover, the pioneering and efficient methodology featuring insertion of terminal acetylenes into unactivated C–C single bonds of non-strained cyclic compounds developed by Kuninobu and Takai opens up the new possibilities for future development. The innovations discussed herein are among the most efficient strategies for the synthesis of indene derivatives and the construction of medium-size cyclic compounds from readily available substrates.

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