Morita–Baylis–Hillman Reaction

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Morita–Baylis–Hillman Cyclizations of Arene–Ruthenium-Functionalized Acrylamides**

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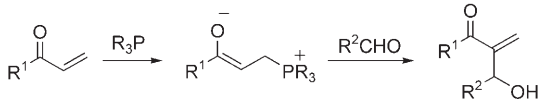
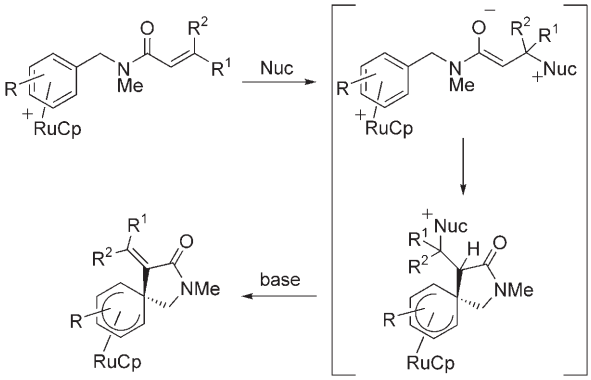
The conventional Morita–Baylis–Hillman (MBH) reaction entails condensation of an α,β-unsaturated carbonyl compound with an aldehyde to afford an α-hydroxyalkyl enone.[1] The reaction proceeds by initial conjugate addition between an enone and a nucleophilic promoter (usually a tertiary amine or trialkyl phosphine) to generate a zwitterionic enolate. Addition to an aldehyde electrophile and elimination of the nucleophilic promoter completes the reaction (Scheme 1). The products of MBH reactions are useful



Scheme 1. Conventional Morita–Baylis–Hillman reaction.

synthetic intermediates and building blocks; hence, considerable effort has been directed toward determining the mechanistic details of this transformation.[2] Variations of MBH reactions have been reported in which reactive enolates are prepared from enones in the presence of transition-metal or Lewis acid reagents.[1a] The range of electrophilic reaction partners also has been expanded to include activated ketones, other enones,[3] allylic electrophiles (including π-allyl–palladium complexes),[4,5] alkyl halides,[6] epoxides,[7] and aryl bismuth reagents.[8]

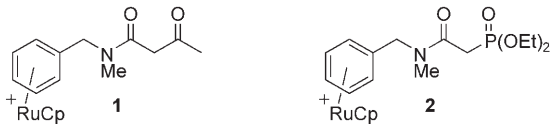
Despite these noteworthy advances, the MBH reaction remains limited in scope owing to the reluctant participation of nonactivated and/or substituted α,β-unsaturated carbonyl compounds. Acrylamides especially have proven to be particularly difficult substrates, and only a few examples of MBH reactions between simple acrylamides and activated aldehydes have been reported.[9] In contrast to this generally observed reactivity profile, we have found that *N*-benzyl acrylamides metalated with a {CpRu^{II}} fragment (Cp = cyclopentadienyl) readily undergo intramolecular MBH cyclizations in the presence of added nucleophile and base (Scheme 2). The ruthenium–arene fragment serves as the



Scheme 2. Ruthenium–arene-mediated intramolecular MBH reaction.

electrophilic reaction partner in these transformations, resulting in formation of ruthenium–cyclohexadienyl complexes as the initial products. Subsequent demetalation then delivers highly functionalized spirolactams. These transformations represent the first examples of direct metal–arene participation in MBH-type reactions.[10]

We first became interested in exploring the feasibility of the reaction sequence shown in Scheme 2 after discovering that both *N*-benzyl acetoacetamides (**1**) and *N*-benzyl-β-amidophosphonates (**2**) can be converted to 2-azaspirocyclic cyclohexadienyl complexes by an initial nucleophilic aromatic



addition followed by enolate trapping and olefination, respectively.[11,12] Generation of a reactive enolate by means of an MBH-type reaction of a coordinated acrylamide, however, offers a more direct and potentially more versatile entry into the azaspiro[4.5]decane framework. Initial attempts to effect the conversion of the simple (*N*-benzyl acrylamide)–ruthenium complex **3** to the corresponding spirocyclic derivative under MBH conditions seemingly confirmed the sluggish reactivity of unsaturated amide substrates. After considerable experimentation, however, we were pleased to find that the reaction conditions shown in Equation (1) delivered the desired product **4** in good yield after a relatively short reaction time. As expected, nucleophilic addition to the ruthenium–arene fragment occurred diastereoselectively from the face opposite the metal center,

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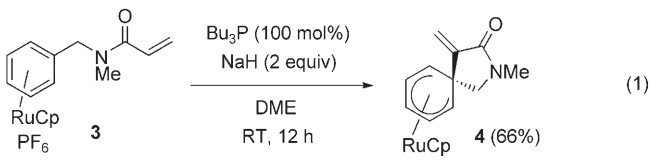
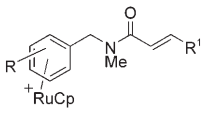
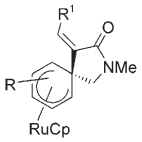
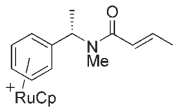
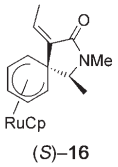
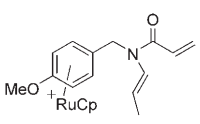
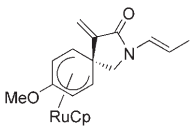


and the resulting cyclohexadienyl complex was spectroscopically indistinguishable from material prepared previously by reaction of **2** and formaldehyde.[12] The choice of solvent proved to be critical for the success of this transformation. While reactions performed in CH_3CN also provided **4** (albeit in diminished yield relative to that in dimethoxyethane (DME)), the use of CH_2Cl_2, THF, or dimethylformamide (DMF) resulted in no reaction. Besides Bu_3P, 4-dimethylaminopyridine (DMAP) also was found to promote the reaction. Other amines (1,4-diazabicyclo[2.2.2]octane (DABCO), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), Hünig's base) were ineffective.

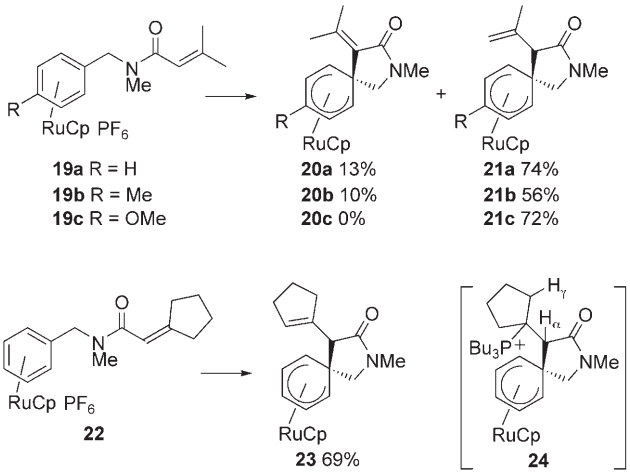
The conversion of substituted ruthenium–arene complexes to the corresponding spirocyclic cyclohexadienyl complexes under the conditions shown in Equation (1) was next examined.[13] As illustrated in Table 1, *para*- and *ortho*-substituted arene complexes were efficiently converted to spirolactams **6**, **8**, and **10** (entries 1–3, Table 1). Significantly, substitution at the β position of the acrylamide was also tolerated as evidenced by the isolation of ethylidene-functionalized lactams **12**, **14**, and **16** (entries 4–6, Table 1; *Z* isomers were obtained in each case). The success of these latter transformations is noteworthy in view of the deleterious effect that enone substitution normally has upon conventional MBH reactions.[1] Benzylic substitution is also tolerated as demonstrated in entry 6. The final entry in Table 1 illustrates incorporation of a removable nitrogen protecting group.

Table 1: (Spirolactam)ruthenium complexes prepared under MBH reaction conditions (100 mol% PBu_3, 2 equiv NaH, DME, RT).

Entry	Substrate	Product	Yield [%]
			
1	**5**, R = 4-OMe, R^1 = H	**6**	60
2	**7**, R = 4-Me, R^1 = H	**8**	71
3	**9**, R = 2-Cl, R^1 = H	**10**	61
4	**11**, R = H, R^1 = Me	**12**	96
5	**13**, R = 4-OMe, R^1 = Me	**14**	56
6	 (*S*)–**15**	 (*S*)–**16**	47
7	 **17**	 **18**	55

Treatment of *N*-allyl-*N*-benzyl acrylamide with $[(CH_3CN)_3RuCp][PF_6]$ resulted in η^6-arene coordination along with concomitant allyl isomerization to afford enamide **17**. Spirocyclization under our standard MBH conditions then gave the expected product **18**.

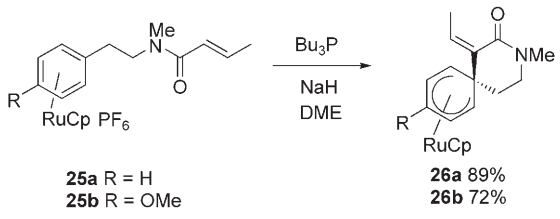
The successful use of crotyl amide substrates in these reactions prompted us to explore the suitability of β,β-disubstituted acrylamides as spirocyclization precursors. In the event, dimethyl acrylamide complexes **19a**,**b** were found to give a mixture of separable spirolactam isomers in favor of β,γ-unsaturated derivatives **21a**,**b** in good yields (Scheme 3).



Scheme 3. MBH-type cyclizations of β,β-disubstituted acrylamide complexes (see [Eq. (1)] for reaction conditions).

The 4-methoxy substrate **19c** afforded only the 2-isopropenyl lactam **21c**. Likewise, the cyclopentylidene derivative **22** was smoothly converted to complex **23**, and the conjugated amide isomer was not detected. Presumably steric constraints in the putative intermediate **24** are such that base-induced elimination of PBu_3 occurs by loss of H_γ rather than loss of H_α.[14] Structurally related β,γ-unsaturated products were not observed in reactions involving *N*-benzyl crotyl amide complexes (entries 4–6, Table 1). The observation that β-mono- and β,β-disubstituted acrylamides participate in the reaction is notable since they are less electrophilic than unsubstituted acrylamides.

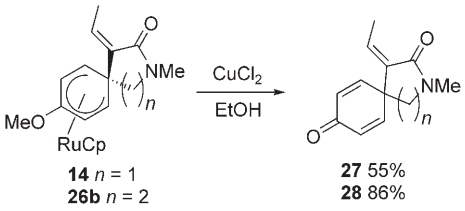
The construction of 6,6-spiro-fused heterocycles has also been briefly examined. Crotyl amide (arene)ruthenium complexes **25a**,**b** were prepared from phenethylamine and subjected to our standard cyclization reaction conditions (Scheme 4). In each case an efficient spirocyclization was



Scheme 4. Preparation of 6,6-spiro-fused complexes.

observed, and the corresponding cyclohexadienyl complexes **26a**,**b** were isolated in good yield. Thus, the greater conformational mobility of the ethyl-linked crotyl amide side chain does not appear to adversely affect the spirocyclization reaction manifold. In contrast, structurally related acetoacetamide complexes prepared from phenethylamine (i.e., analogues of **1**) are not observed to participate in spirocyclization reactions.[11] Additional work is planned in order to identify the origin of the divergent reactivity exhibited in these complexes.

We have previously reported methods for converting ruthenium–cyclohexadienyl complexes to metal-free azaspiro[4.5]decane derivatives.[12,15] These procedures are applicable to the products of MBH-type spirocyclizations as well. For example, mild oxidation of **14** and **26b** cleanly delivered the demetalated dienones **27** and **28**, respectively (Scheme 5). This reaction is facilitated by the presence of a

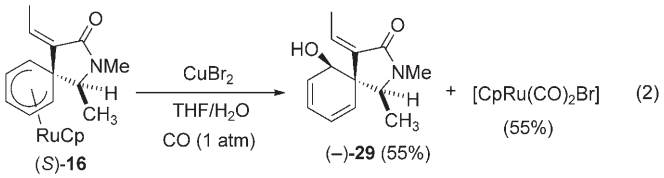


14 $n = 1$
26b $n = 2$

27 55%
28 86%

Scheme 5. Oxidative demetalation of methoxy-substituted cyclohexadienyl complexes.

methoxy substituent in the periphery of the cyclohexadienyl ligand. Substrates lacking such electronic activation are also amenable to oxidative demetalation. A particularly salient example is illustrated in Equation (2), in which chiral nonracemic (*S*)-**16** is converted to enantiomerically pure (−)-**29**



with recovery of the {CpRu} fragment.[12] Thus, this combination of metal-assisted cyclization followed by oxidative demetalation results in heterocycle construction by means of net Ru-mediated dearomatization.[16]

The facility with which *N*-benzyl and *N*-phenethyl acrylamide complexes participate in the spirocyclizations described above is in stark contrast to the sluggish reactivity normally displayed in conventional MBH-type reactions.[1,9] The origin of this enhanced reactivity may lie both in the intramolecular nature of these transformations and in the choice of electrophilic partner (i.e., an ruthenium–arene cation). While the mechanism of the conventional MBH reaction appears to be more complex than originally envisaged, there is general agreement that the rate-determining step involves the addition of aldehyde to a zwitterionic intermediate (step 2 in Scheme 1).[2] Activation of the aldehyde reactant (e.g., by the use of protic solvents) is often attempted as a means to increase the rate and yield of MBH reactions. In our system such tactics are not needed owing to the use of a metalated arene as the electrophile. Thus, the generation of a reactive nucleophile by conjugate addition of the tributylphosphine promoter to the acrylamide moiety may now be the rate-determining step. Consonant with this notion, a competition experiment was performed in which **3** was treated with Bu_3P and NaH in the presence of *p*-nitrobenzaldehyde. After 12 h, complex **4** was obtained as the sole isolable product along with unreacted *p*-nitrobenzaldehyde, thus establishing the superiority of the intramolecular reaction manifold. Additionally, exposure of metal-free *N*-benzyl acrylamide and *p*-nitrobenzaldehyde to Bu_3P in DME resulted in recovery of unreacted starting materials. This outcome may simply reflect the unsuitability of these substrates in a conventional MBH reaction. It is also possible that inductive effects operative in metal-coordinated analogues (such as **3**) may enhance the electrophilicity of the acrylamide moiety and facilitate addition of Bu_3P. Future studies will address this issue.

In summary, an intramolecular organometallic variation of the Morita–Baylis–Hillman reaction has been developed in which an ruthenium–arene complex is employed as an electrophile capable of trapping an enolate ion generated in situ. Studies aimed at expanding the scope of the intramolecular reaction and extending the process to include intermolecular additions are in progress. Additionally, the significant challenge of developing metal-catalyzed dearomatization reactions remains to be addressed.

Experimental Section

Preparation of **4**: To a solution of **3** (0.147 g, 0.300 mmol) in anhydrous DME (5 mL) was added Bu_3P (0.061 g, 0.300 mmol) and NaH (60%, 0.015 g, 0.600 mmol). The mixture was stirred at room temperature for 12 h. The solvent was evaporated and the residue partitioned with CH_2Cl_2 and brine. The organic phase was separated, dried over Na_2SO_4, filtered, concentrated, and purified by flash column chromatography (hexanes/EtOAc 1:1). Isolated **4** (0.070 g, 66%) was spectroscopically identical with material previously reported.[12]

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