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$ZrCl_4$-catalyzed X–C/C–C bond formation for the geometric selective synthesis of (*E*)-β-iodo aza Morita–Baylis–Hillman (MBH) adducts

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Abstract—A geometric selective synthesis of (*E*)-β-iodo and β-alkyl vinyl ketones (MBH amino adducts) has been developed through a three-component Mannich-type reaction. The reaction was conveniently conducted by generating 3-iodo allenolate intermediates via the α,β-unsaturated addition of TMS-I to 3-butyn-2-one followed by a carbonyl addition onto *N*-aryl imines in the presence of $ZrCl_4$ catalyst. The resulting β-iodo allylic amines can be readily converted into β-alkyl Morita–Baylis–Hillman adducts by performing Suzuki and Kumada cross-couplings.

In the past decade, the Morita–Baylis–Hillman (MBH) and related reactions have received considerable attention among the organic and medicinal communities.[1–3] The MBH amino and hydroxyl adducts resulting from these reactions can be extensively utilized for the synthesis of numerous chemically and biologically important targets.[4]

Recently, our laboratories have been actively involved in the development of synthetic approaches to (*Z*)-β-halo MBH adducts, which cannot be obtained from classical Morita–Baylis–Hillman catalysis.[5,6] These methods are mainly based on the multicomponent couplings of α,β-acetylenic ketones or esters with aldehydes or activated imines in the presence of metal halides (Et_2AlI, MgI_2, etc.), which act as both Lewis acid promoters and halogen sources (Scheme 1). The presence of an extra halogen in the resulting MBH adducts enables a number of further synthetic transformations.

To extend the scope of our previous methods, we have been attempting to control the reaction toward the formation of β-iodo MBH amino adducts with dominant (*E*)-geometry without much success. In this paper, we are pleased to report our initial study for this purpose by using unactivated imines as electrophilic acceptors and softer Lewis acids. To the best of our knowledge, this could be the first example of using unactivated imines as electrophiles for the synthesis of β-halo MBH amino adducts.[7] This reaction can be readily performed by reacting 3-butyn-2-one and iodotrimethylsilane to generate β-iodo TMS-allenolate followed by its carbonyl addition onto imines in the presence of $ZrCl_4$ as the catalyst (Scheme 2). In addition, the subsequent cross-couplings using the β-iodo MBH amino adducts are also presented (Scheme 3).

The initial attempt at this reaction utilized the phenyl protected imine of benzaldehyde as the electrophile to react with β-iodo TMS-allenolate. Interestingly, in the absence of any catalyst the aza MBH product (**1a**) was obtained in a good chemical yield of 65% (Table 1, entry 1) under standard conditions.[8] Interestingly, the use of several typical Lewis acids, such as $SnCl_4$, $TiCl_4$, and $BF_3{\cdot}OEt_2$, diminished the reaction and resulted in a small amount of the desired product (Table 1, entries 2–4). However, after the Lewis acid catalyst was changed to $ZrCl_4$, which is a slightly softer Lewis acid, the reaction proceeded smoothly to give the desired aza

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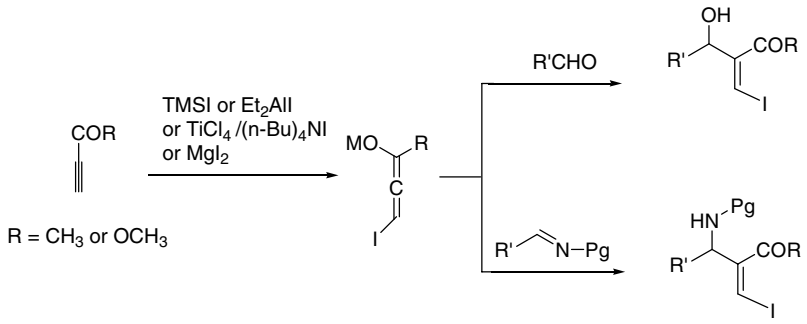
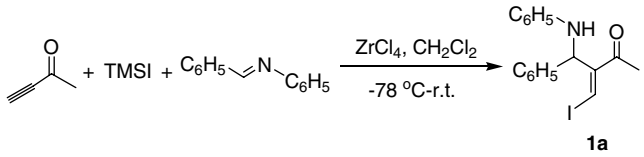


Scheme 1. Selective synthesis of (*Z*)-β-halo MBH adducts.



Scheme 2.

MBH product (**1a**) in an excellent chemical yield (97%, entry 5, Table 1). This excellent result can be explained by the fundamental principle of hard/soft interactions of acid and base in which the N atom can coordinate onto the Zr center more effectively than onto the Ti center.[12]

Under optimized conditions, we next attempted to extend the scope of substrates for this reaction. As summarized in Table 2, the carbonyl addition of β-iodo TMS-allenolate to those imines bearing electron-withdrawing groups on the aromatic ring proceeded smoothly to give the corresponding β-iodo Morita–Baylis–Hillman adducts (**1b–f**) in good to excellent yields (76–95%, entries 1–6, Table 2). However, when an electron-donating group attached aryl imine was subjected to the reaction under standard conditions, there was only a trace amount of the desired adduct formed. Considering the versatile utility of α-amino acid, the imine derived from ethyl glyoxylate was thus studied for this reaction. Unfortunately, the β-iodo MBH adduct (**1g**) was obtained in a poor chemical yield of 38% (entry 7, Table 2).

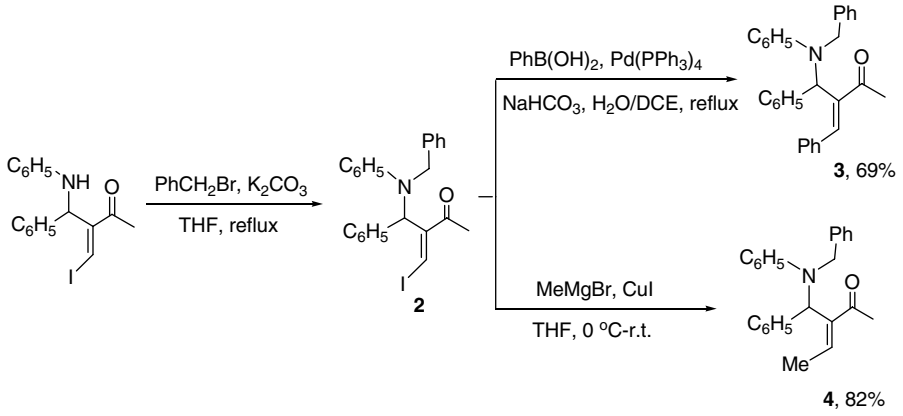
For each of the cases listed in Table 2, (*E*)-geometry was controlled very well. In fact, only (*E*)-isomer was observed as revealed by NMR analysis. (*E*)-Geometry of the β-iodo Morita–Baylis–Hillman product was unambiguously confirmed by NOESY spectroscopic analysis, and was proven to be opposite to that observed in our previous processes.[6a,b] Obviously, in the present system the exclusive *E*-selectivity of β-iodo MBH amino adducts is directed by the thermodynamic control and the room temperature condition accounts for this observation.

To further extend the application of the resulting aza MBH adducts, we also performed the cross-coupling reactions to generate (*E*)-β-alkyl and aryl MBH amino adducts,[9,10] which have not been documented well.

Table 1. Results of screening catalysts for the aza MBH synthesis[8]

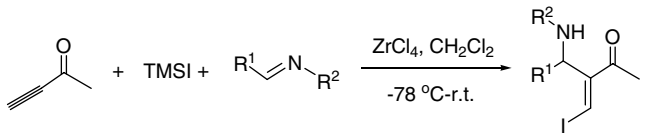
Entry	Catalyst	Yield[a,b] (%) **1a**
1	No cat.	65
2	$SnCl_4$	Trace
3	$TiCl_4$	16
4	$BF_3{\cdot}OEt_2$	Trace
5	$ZrCl_4$	97

[a] Isolated yields.
[b] The reaction mixture was maintained at −78 °C for 2 h before the imine and catalysts were added, then warmed to room temperature for an additional 2 h.



Scheme 3. Protection of the Mannich-type adduct and the subsequent cross-coupling reactions.

Table 2. Results of the three-component Mannich-type reaction



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Entry	R^1	R^2	Product	Yield[a,b] (%) **1**
1	C_6H_5	C_6H_5	**1a**	97
2	C_6H_5	4-BrC_6H_4	**1b**	95
3	C_6H_5	3-$CF_3C_6H_4$	**1c**	88
4	4-ClC_6H_4	C_6H_5	**1d**	84
5	2,4-$Cl_2C_6H_3$	C_6H_5	**1e**	82
6	4-$NO_2C_6H_4$	C_6H_5	**1f**	76
7	EtO_2C	C_6H_5	**1g**	38

[a] Isolated yields.

[b] The reaction mixture was maintained at −78 °C for 2 h before the imine and catalysts were added, then warmed to room temperature for an additional 2 h.

The first attempt to perform the Suzuki and Kumada couplings[11,12] were proven unsuccessful, which could be due to the active NH functional group. This functional group was next protected by treating with benzyl bromide in refluxing THF in the presence of potassium carbonate (Scheme 2). After it was protected, these two cross-couplings proceeded smoothly with phenylboronic acid and methylmagnesium bromide under the known conditions as reported by Rault[11] and Richards,[12] respectively. The corresponding products **3** and **4** were obtained in good yields of 69% and 82%, respectively (Scheme 3).

In conclusion, a stereoselective three-component Mannich-type reaction of imines, 3-butyn-2-one, and TMS-I using $ZrCl_4$ as the catalyst has been developed. This reaction provided an easy access to β-branched Morita–Baylis–Hillman (MBH) amino adducts. The reaction can be conveniently conducted under concise conditions. These products can be further subjected to the metal catalyzed cross-coupling reactions to afford novel β-alkyl and aryl MBH amino adducts in an exclusive *E*-geometric configuration.

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8. Typical reaction procedures for the synthesis of *E*-β-iodovinyl ketone **1a**: In a dry vial, under argon protection, iodotrimethylsilane (85 μL, 0.6 mmol) was added slowly to a solution of 3-butyn-2-one (47 μL, 0.6 mmol) in 2.0 mL of dichloromethane at −78 °C. The resulting solution was stirred for 2 h before 0.1 mmol of catalyst and imine (91 mg, 0.5 mmol) were charged. The reaction mixture was maintained at −78 °C for 2.0 h with stirring and allowed to warmup to room temperature for another 2 h. After quenching by 1.0 M of aqueous HCl solution (1.0 mL), the aqueous layer was extracted with EtOAc (3 × 5.0 mL). The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (neutral Al_2O_3 column, eluent: CH_2Cl_2/petroleum ether = 1/2) to provide the pure product.

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