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Acceleration of the Morita−Baylis−Hillman Reaction by a Simple Mixed Catalyst System

Alejandro Bugarin and Brian T. Connell*

Department of Chemistry, Texas A&M University, P.O. Box 30012, College Station, Texas 77842-3012

connell@mail.chem.tamu.edu

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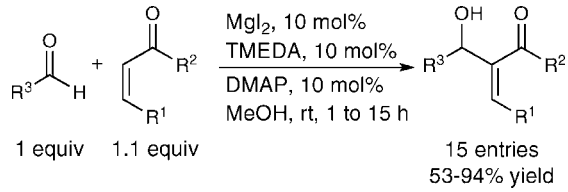

By using a catalytic amount of 4-dimethylaminopyridine (DMAP) as a nucleophile in the presence of an equal amount of tetramethylethylenediamine (TMEDA) and MgI_2, Morita−Baylis−Hillman adducts can be obtained in good to excellent yields from various aromatic and aliphatic aldehydes and cyclic enones/enoates at room temperature after convenient reaction times.

The Morita−Baylis−Hillman (MBH) reaction is an important carbon−carbon bond-forming reaction between electron-deficient alkenes, such as α,β-unsaturated ketones, and aldehydes or activated ketones. The products of MBH reactions are highly functionalized and hence can be used as components of further reactions such as aldol, Michael, Diels−Alder, or 1,2-additions, for instance, which in turn can lead to the synthesis of biologically important materials or natural products, such as furaquinocins.[1] The reaction is catalyzed by nucleophilic amines or phosphines, most commonly DABCO (1,4-diazabicyclo-[2.2.2]octane) or tertiary phosphines.[2]

The mechanism of the MBH reaction is believed to proceed through a conjugate addition followed by an aldol addition, and then β-elimination.[3] Various efforts have been made to accelerate this reaction sequence by using Lewis acid cocatalysts.[4] The Lewis acid catalyst is generally believed to activate electron-deficient alkenes to facilitate the conjugate addition of the nucleophile catalyst. This activation allows for the use of weaker nucleophiles or less electron-deficient alkenes in the MBH reaction.[5]

For example, in 1998, Aggarwal et al. reported the use of $La(OTf)_3$ (5 mol %) and triethanolamine (50 mol %) to accelerate the reaction rates for the MBH reaction between aldehydes and vinyl esters in the presence of DABCO (100 mol %). While successful MBH adducts were obtained with these conditions, excess DABCO was required to maximize the reaction rates due to the association of DABCO with the metal at equimolar ratios.[6]

In 1999, Kobayashi et al. reported the use of $LiClO_4$ as the Lewis acid in the presence of DABCO to catalyze the MBH reaction between aldehydes and vinyl esters in good yields. However, extended reaction times were required, and for some activated alkenes the use of excess Lewis acid was required.[7]

In addition, other strategies to mediate the MBH reaction have been examined, including the use of amino- or phosphino-type catalysts as nucleophiles,[8] ionic liquids as both a nucleophile and solvent system,[9] as well as biocatalysis.[10] Generally, each of these approaches faces certain limitations, although there is notable effort in this area,[11] there has yet to be developed a general, enantioselective version of the MBH reaction.

We were interested in developing a catalytic system for the MBH reaction, which would be amenable to asymmetric catalysis in a straightforward manner. Here we report the use of a mild catalytic system that combines equimolar amounts of the Lewis acid MgI_2, the electron-donating ligand TMEDA, and the nucleophile DMAP to promote the MBH reaction in a reasonable reaction time.

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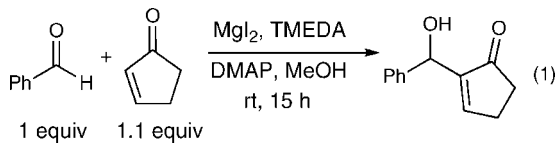
TABLE 1. MBH Reaction between Cyclopenten-2-one and Benzaldehyde in the Presence of MgI_2, TMEDA, and DMAP



entry	% MgI_2	% TMEDA	% DMAP	% yield[a]
1			10	NR
2		10		NR
3		10	10	NR
4	10	10	10	91
5	10	20		54
6	10		20	36

[a] Isolated yield after purification by silica gel chromatography.

Our initial studies identified several Lewis acidic metal salts which were capable of catalyzing the reaction of benzaldehyde with cyclopentenone in the presence of TMEDA and a catalytic Lewis base (DMAP). The metal salts $NiCl_2$, $PdCl_2$, $SnCl_4$, LiCl, $LiClO_4$, $Cu(OTf)_2$, and SmI_2 catalyzed MBH reactivity under these conditions, but the yields were low. No reactions were observed when Zn(II) halides were employed, but unfortunately $Zn(OTf)_2$ catalyzed the quantitative dimethylacetalization of benzaldehyde. However, Mg(II) salts proved to be quite reactive, with MgI_2 showing higher reactivity than its congeners $MgBr_2$ and $MgCl_2$.

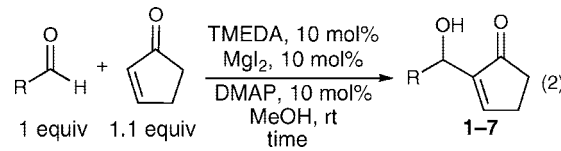
Potential nucleophiles, including DABCO, DBU, triethylamine, Hünig's base, and pyridine, were screened for compatibility with the combination of Lewis acidic MgI_2 and TMEDA. The strong base DBU deactivates the catalyst, whereas weak nucleophiles like triethylamine and pyridine show very low reaction rates and Hünig's base shows no reaction at all. It was found that the MBH reaction was accelerated dramatically by using MgI_2 and DMAP as catalytic partners.

No reaction was observed between benzaldehyde and cyclopentenone in the absence of MgI_2 (10 mol % of DMAP or 10 mol % of TMEDA) in MeOH (eq 1). However, the addition of 10 mol % of MgI_2 to the reaction mixture afforded the adduct in low yield when combined with either 20 mol % of DMAP (36% yield) or 20 mol % of TMEDA (54% yield). Increasing the amount of DMAP present provided no improvement in reaction yields. On the other hand, the use of equimolar amounts of Lewis acid, ligand, and Lewis base in the system afforded the adduct in 91% yield (Table 1, entry 4).

After optimizing the Lewis acid and nucleophile used as catalysts, various solvent systems were investigated. It was observed that the reaction was faster in MeOH than in THF, EtOAc, CH_2Cl_2, or dioxane. Although beneficial in other systems, a mixed solvent system of MeOH−H_2O also afforded lower yields in this system.[12]

We investigated the scope of the MgI_2/TMEDA/DMAP-catalyzed MBH reaction by examining a variety of electrophiles (Table 2). For electron-deficient aldehydes, the system is very efficient; the MBH adduct of *p*-nitrobenzaldehyde and cyclopentenone was obtained after only 5 h in 94% yield (Table 2, entry 4). Additionally, this system afforded reasonable yields for electron-rich aldehydes. The MBH adduct for the aromatic aldehyde *p*-methoxybenzaldehyde was obtained in 67% yield (Table 2, entry 6), and the MBH adducts for the aliphatic

TABLE 2. MBH Reaction of Cyclopenten-2-one



entry	R	time, h	product	% yield[a]
1	$(CH_3)_2CH-$	15	1	62
2	$Ph(CH_2)_2-$	15	2	89
3	$Ph(CH)_2-$	15	3	93
4	*p*-$NO_2(C_6H_4)-$	5	4	94
5	$(C_6H_5)-$	15	5	91
6	*p*-$MeO(C_6H_4)-$	15	6	67
7	*p*-$MeO(C_6H_4)-$	48	6	83
8	$(C_6H_{11})-$	15	7	66
9	$(C_6H_{11})-$	48	7	91

[a] Isolated yield after purification by silica gel chromatography.

aldehydes cyclohexane carboxaldehyde and isobutyraldehyde were obtained in 66% and 62% yields, respectively (Table 2, entries 8 and 1). The system was also efficient for α,β-unsaturated aldehydes; the MBH adduct for *trans*-cinammaldehyde was obtained in 93% yield (Table 2, entry 3). It is worth mentioning that the lower yields obtained for several of the MBH adducts were the result of incomplete reaction. The presence of starting materials was observed after 15 h for all entries with yields lower that 90%. This reaction time of 15 h was used as benzaldehyde, a moderately reactive aldehyde with neither electron-rich nor electron-poor characteristics, was completely consumed after this time period. By performing all reactions in this 15 h time window, we could compare the effects of electron-donating or electron-withdrawing functionalities on the rate of reaction.

To further examine the scope and utility of these catalytic reaction conditions, a variety of α,β-unsaturated ketones, esters, and thioesters were treated with benzaldehyde under the same reaction system conditions (Table 3). Again, most reactions were quenched after 15 h for comparison purposes, although starting material was still remaining. In all cases, the reaction proceeds smoothly in the presence of catalytic amounts of equimolar Lewis acid, ligand, and the nucleophile to afford the corresponding adducts in good to high yields at room temperature.

Notable examples from Table 3 include reactions with γ-disubstituted enones such as 4,4-dimethylcyclopenten-2-one (Table 3 entry 1) and 4,4-dimethylcyclohexen-2-one (Table 3, entry 3), which gave 86% and 75% yield, respectively, after 15 h.

The reactivity of transformations was also shown for cyclic enones, which contain five- (Table 2, entry 5), six- (Table 3, entry 2), and seven-membered rings (Table 3, entry 4) in moderate to high yields of 91%, 84%, and 56%, respectively.

The synthesis of xanthenes starting from 2-hydroxybenzaldehydes and 2-cyclohexenone with DABCO as catalyst has previously been reported by Brase et al.[13] He employed DABCO (50 mol %) as a catalyst in water under sonication conditions to obtain 2,3,4,4a-tetrahydro-1*H*-xanthen-1-one (**15**) in 83% yield after 48 h by a presumed sequence of MBH, conjugate addition, and elimination reactions. When we investigated this sequence under our reaction conditions, we obtained the product

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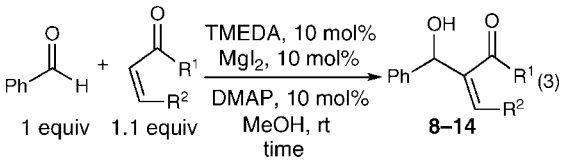
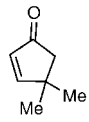
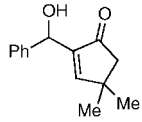
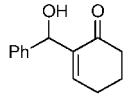
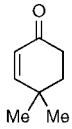
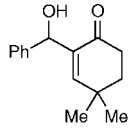
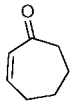
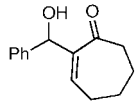
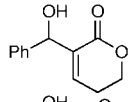
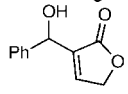
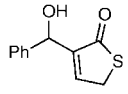
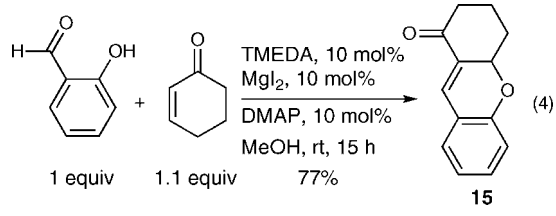
TABLE 3. MBH Reaction of Benzaldehyde



entry	enone/enoate	product		time, h	%yield[a]
1			**8**	15	86
2			**9**	15 48	84 89
3			**10**	15 48	75 91
4			**11**	15	56
5			**12**	15 48	47 78
6[b]			**13**	2	53
7[b,c]			**14**	1	92

[a] Isolated yield after purification by flash silica gel chromatography. [b] EtOH solvent. [c] Reaction performed at −15 °C.

SCHEME 1. Reaction of Cyclohexen-2-one and Salicylaldehyde



(Scheme 1) in 77% yield in significantly less time (15 h) and under milder reaction conditions.

Additions to acyclic enones and enoates under catalytic conditions is a longstanding problem. Scheidt and co-workers have recently begun to overcome this limitation by utilizing the addition of silyloxyallenes to aldehydes, specifically normally unreactive β-substituted substrates.[14] We envisioned that our catalytic system might also address this limitation. Unfortunately, our current system is not capable of accelerating the MBH reaction of acyclic enones or acrylates with aldehydes.

Elucidation of the mechanistic details of this system are currently in progress. We surmise that a TMEDA-bound MgI_2 is likely to be the active Lewis acid catalyst. Formation of a complex of TMEDA:MgI_2 is clearly visible in the ^1H and ^{13}C NMR spectra of a 1:1 mixture of the two (see the Supporting Information), as expected by the wealth of data on chelating amine/Mg(II) complexes in the literature.[15] Further studies will be necessary to adequately support or refute this hypothesis.

In summary, this new reaction system employing a 1:1:1 ratio of catalytic amounts (10 mol %) of MgI_2, TMEDA, and DMAP proved to be highly effective at promoting the reaction of a variety of electrophiles, including both electron-poor and electron-rich aldehydes, with various cyclic enones as the nucleophilic substrate in the MBH reaction. Both α,β-unsaturated esters and thioesters were also shown to undergo the MBH sequence even more readily. Furthermore, these studies provide a valuable platform for the development of chiral ligands to promote enantioselective MBH reactions, as chiral TMEDA-equivalent ligands are well-known.[16]

Experimental Section

Typical Reaction Procedure for known compounds 1−12 and 15. To a stirred mixture of aldehyde (0.5 mmol) and activated alkene (0.55 mmol) in MeOH (1.2 mL) at room temperature under argon was added a solution of magnesium iodide (13.9 mg, 0.05 mmol) and TMEDA (8.3 mg, 0.05 mmol) in MeOH (0.2 mL), followed by dropwise addition of a solution of 4-dimethylaminopyridine (6.1 mg, 0.05 mmol) in MeOH (0.1 mL). Afterward the mixture was stirred for 15 h at rt under argon. The reaction was quenched by addition of saturated aqueous NH_4Cl solution (1.0 mL). The solution mixture was extracted twice with dichloromethane (5.0 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash silica gel column chromatography (20% EtOH/hexanes or dichloromethane).

3-(Hydroxy(phenyl)methyl)furan-2(5*H*)-one (13). To a stirred mixture of benzaldehyde (53 mg, 0.5 mmol) and furan-2(5*H*)-one (46.2 mg, 0.55 mmol) in EtOH (1.2 mL) at room temperature under argon was added a solution of magnesium iodide (13.9 mg, 0.05 mmol) and TMEDA (8.3 mg, 0.05 mmol) in EtOH (0.2 mL) followed by dropwise addition of a solution of 4-dimethylaminopyridine (6.1 mg, 0.05 mmol) in EtOH (0.1 mL). Afterward the mixture was stirred for 2 h at rt under argon. The reaction was then quenched by addition of saturated aqueous NH_4Cl solution (1.0 mL). The solution mixture was extracted twice with dichloromethane (5.0 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash silica gel column chromatography (dichloromethane) to give compound **13** (50.4 mg, 53%) as a colorless oil: IR (thin film) 3424, 2869, 1745, 1201 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.43−7.31 (m, 5 H), 7.19 (q, J = 1.55 Hz, 1 H), 5.56 (s, 1 H), 4.78 (t, J = 2.0 Hz, 2 H), 3.45 (d, J = 4.0 Hz, 1 OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 146.0, 140.0, 136.3, 128.5, 128.2, 126.3, 70.5, 69.0; MS (ESI) calcd for $C_{11}H_{10}O_3$ + Li requires *m/z* 197.0790, found 197.0795.

3-(Hydroxy(phenyl)methyl)thiophen-2(5*H*)-one (14). To a stirred mixture of benzaldehyde (53 mg, 0.5 mmol) and thiophen-2(5*H*)-one (55 mg, 0.55 mmol) in EtOH (1.2 mL) at −15 °C under

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argon was added a solution of magnesium iodide (13.9 mg, 0.05 mmol) and TMEDA (8.3 mg, 0.05 mmol) in EtOH (0.2 mL) followed by dropwise addition of a solution of 4-dimethylaminopyridine (6.1 mg, 0.05 mmol) in EtOH (0.1 mL). Afterward the mixture was stirred for 1 h at −15 °C under argon. The reaction was quenched by addition of saturated aqueous NH_4Cl solution (1.0 mL). The solution mixture was extracted twice with dichloromethane (5.0 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash silica gel column chromatography (dichloromethane) to give compound **14** (94.8 mg, 92%) as a pale yellow oil: IR (thin film) 3419, 2918, 1659, 1170 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.42−7.32 (m, 5 H), 7.16 (m, 1 H), 5.63 (s, 1 H), 3.98 (t, J = 1.08 Hz, 2 H), 3.20 (d, J = 3.63 Hz, 1 OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.9, 148.9, 147.7, 140.6, 128.6, 128.1, 126.4, 70.1, 35.5; MS (ESI) calcd for $C_{11}H_{10}O_2S$ + Li requires m/z 213.0562, found 213.0573.

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Supporting Information Available: Experimental procedures for the preparation of MBH adducts and copies of ^1H and ^{13}C NMR spectra of all new and known compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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