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# Copper-Catalyzed One-Pot Borylative Aldolisation β-Fluoride Elimination for the Formal Addition of Acrylates to Carbonyl Moieties

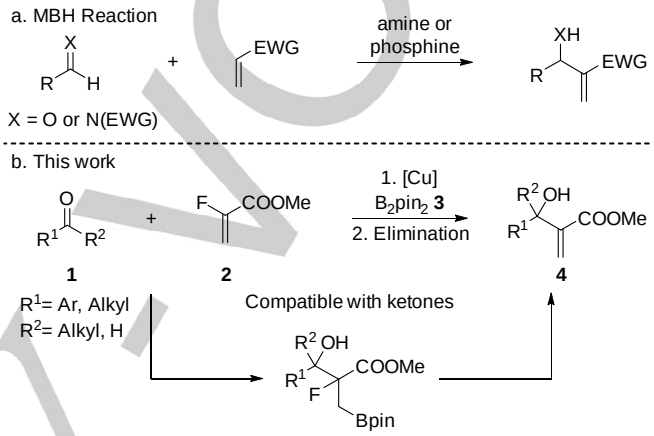
Corentin Rasson, Adrien Stouse, Arnaud Boreux, Virginie Cirriez and Olivier Riant*[a]

**Abstract:** Herein, we report the copper-catalyzed domino borylation/aldolisation of methyl 2-fluoroacrylate with carbonyl compounds followed by an elimination to afford Morita-Baylis-Hillman (MBH) analogs. The optimal conditions described were shown to be compatible with a wide range of aldehydes and ketones. Unprecedented MBH adducts derived from ketones were efficiently synthesized.

Recently domino reactions have emerged as highly efficient tools for the synthesis of complex structures.[1] The most prominent categories are the cationic[2], anionic[3], radical[4], pericyclic[5], photochemically induced[6] and transition metal-catalyzed[7] domino reactions. This last category relies mostly on expensive palladium[8], ruthenium[9] and rhodium[10] catalysts. More recently, copper-mediated conjugate additions have been exploited in the initiating step of the domino process. Several nucleophilic copper(I) species such as Cu-B[11], Cu-C[12], Cu-H[13] and Cu-Si[14] have been successfully employed in this strategy.

The Morita-Baylis-Hillman (MBH) reaction[15] , a well-known domino reaction that allows the formal condensation of a Michael acceptor and an aldehyde or an aldimine (Scheme 1a), is now recognized as one of the powerful synthetic tool of organic synthesis. However, this reaction still suffers from certain limitations such as high catalyst loading, low reaction rates, and, notably, its poor applicability to ketones. Numerous studies focused on modifying different parameters of the reaction have been realized[16] to try to overcome those drawbacks. Other synthetic routes have also been designed such as a nickel-catalyzed hydroxycarboxylation of allenes,[17] hydroalumination of acetylenic esters[18] or aldol reactions using sulfurated or selenated substrates followed by oxidation/elimination.[19]

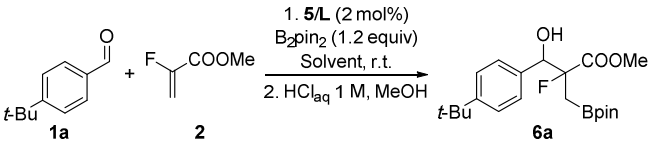
Inspired by a report from the group of Ogoshi[20] on the concomitant β-elimination of boron and fluoride from a trifluoromethyl moiety, we realized that an analogous method could lead to the generation of an acrylate from an α-fluoro-β-borylester. Such patterns can be obtained by the addition of Cu-B species onto an α-fluoro-acrylate **2**. The combination of this β-borylation with an aldolisation on carbonyl **1** followed by a subsequent elimination would yield MBH adduct **4** (Scheme 1b).




**Scheme 1.** a. Classical MBH reaction. b. Synthesis of MBH analogs *via* a copper catalyzed one-pot 1,4-addition/aldolisation/elimination.

In order to develop this new approach we first focused on the domino borylation/aldolisation step using 4-*t*-Bu-benzaldehyde as a model substrate (Table 1). As a starting point, we applied the conditions we previously described[14b] for catakytic alkyne borocupration using 2 mol% of the copper catalyst $CuF(PPh_3)_3{\cdot}2MeOH$ (**5**), 2 mol% of (*rac*)-BINAP (**L1**), 1.2 equivalent of diboron **3** in THF or toluene at room temperature (entries 1 and 2).

**Table 1.** Selected experiments from the optimization of copper-catalyzed 1,4-borylation/aldolisation between **1a** and **2**.

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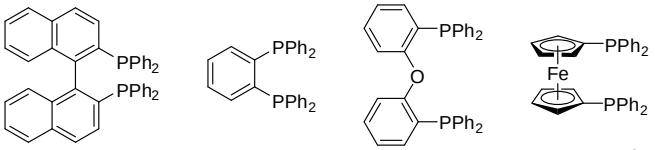
| Entry | Ligand | $B_2pin_2$ (equiv) | Solvent | Yield [%][a] |
|---|---|---|---|---|
| 1 | **L1** | 1.2 | THF | 70 |
| 2 | **L1** | 1.2 | Toluene | 78 |
| 3 | **L1**[b] | 1.2 | Toluene | 0 |
| 4 | - | 1.2 | Toluene | 48 |
| 5 | **L2** | 1.2 | Toluene | 36 |
| 6 | **L3** | 1.2 | Toluene | 68 |
| 7 | **L4** | 1.2 | Toluene | 87 |
| 8 | **L4** | 1.0 | Toluene | 58 |
| 9 | **L4** | 1.5 | Toluene | 89 |

[a] Yield determined by $^1$H NMR with 3,4,5-trimethoxybenzaldehyde as internal standard. [b] With no copper source.

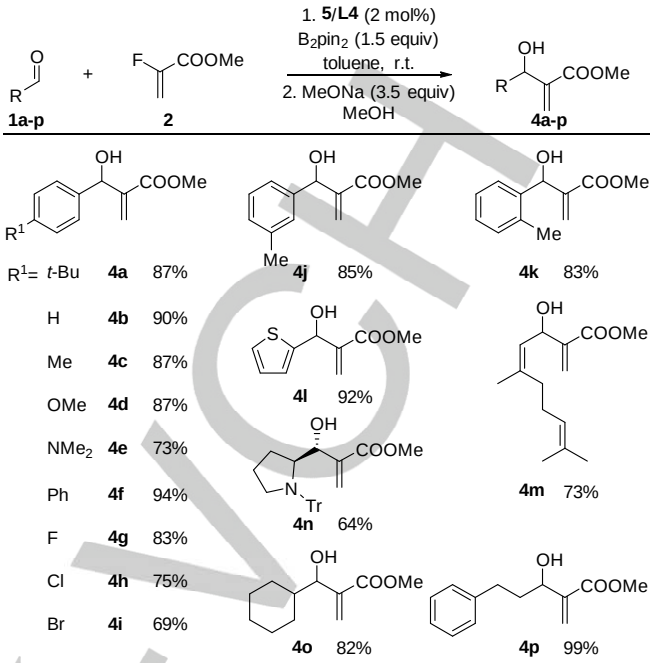



**L1** **L2** **L3** **L4**

Toluene proved to be a more suitable solvent than THF, affording **6a** in 78% yield by NMR. We then studied the influence of the metal and ligand. The metal is essential for this reaction. When no copper was used (entry 3) no product was observed. Similarly, in the absence of a ligand (entry 4) we observed a significant drop in the yield. Several other phosphine ligands were screened: dppbz (**L2**) or DPEphos (**L3**) gave lower yield than (**L1**) (entry 5-6) while dppf (**L4**) gave a very good result with 87% yield (entry 6). To further improve this transformation we modified the stoichiometry of $B_2pin_2$ **3**. Notably, using 1.5 equivalents of **3** affords slightly better yield (entry 9).

Following the successful optimization of the borylation/aldolisation step, we moved to the elimination step using several nucleophiles known to interact with borylated compounds (See supporting information). After extensive tests we found that using 3.5 equivalents of sodium methoxide in methanol afforded the MBH adduct in 81% yield. This yield was further improved by using 1.5 equivalent of aldehyde **1a** to obtain **4a** in 87% isolated yield.

With the optimized conditions in hand we started to investigate the scope of the reaction by testing different aldehydes (Scheme 2).




**Scheme 2.** Scope for aldehydes. Reaction conditions: **1** (0.75 mmol, 1.5 equiv), **2** (0.5 mmol, 1 equiv), $B_2pin_2$ (0.75 mmol, 1.5 equiv), CuF(PPh3)3·2MeOH **5** (0.01 mmol, 2 mol%), 1,1'-bis(diphenylphosphino)ferrocene **L4** (0.01 mmol, 2 mol%) in 2,5 mL toluene, room temperature, 18 h. NaOMe (1.75 mmol, 3.5 equiv) in 2.5 mL MeOH, room temperature, 24h. Yields of isolated products are given.

Benzaldehyde and simple alkyl substituted aromatic aldehydes were readily converted into the corresponding MBH adduct **4a-c** and **4j-k** (83 to 90% yield). For non-bulky groups such as methyl, the substitution in ortho, meta or para position seems to have no significant influence on the yield of the reaction (**4c,j,k**). Additionally, the presence of halogens is well tolerated with only a minor decline in efficiency observed with larger halogens (**4g-i**). Even deactivated aldehydes (**1d-e**) gave good yields of the desired products. This result is noteworthy, especially for 4-dimethylaminobenzaldehyde **1e** which typically does not react at all in the MBH reaction. Heteroatoms are well tolerated with 2-thiophene carboxaldehyde **1l** giving 92% yield of **4l** and *N*-trityl prolinal yielding **4n** in 64% and only one diastereosiomer. α-β-unsaturated aldehyde **1m** and alkyl aldehyde **1o-p** also readily react under the reaction conditions to give **4o-p** in 82% and 99% yield, respectively.

Based on the high reactivity observed for the unactivated aldehydes, we postulated that these conditions might allow extending the scope of the reaction to substrates where the MBH reaction is usually poorly applicable, notably ketones. To test this, we applied the optimized conditions to acetophenone **7a** as a model substrate (Table 3).

**Table 3.** Selected experiments from the optimization reactions using ketones.

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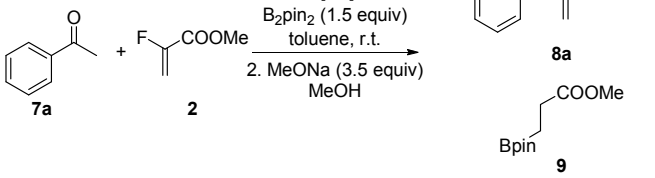
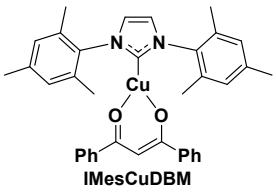
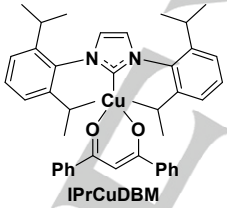



| Entry | [Cu] (mol %) | L (mol%) | **7a** (equiv) | **2** (equiv) | Yield [%][a] | |
|---|---|---|---|---|---|---|
| | | | | | **8a** | **9** |
| 1 | **5** (2) | **L4** (2) | 1.5 | 1 | 49 | 28 |
| 2 | **5** (2) | **L4** (2) | 1 | 1 | 48 | 33 |
| 3 | **5** (2) | **L1** (2) | 1 | 1 | 29 | 45 |
| 4 | **IMesCuDBM** (2) | | 1 | 1 | 23 | 32 |
| 5 | **IPrCuDBM** (2) | | 1 | 1 | 57 | 27 |
| 6 | **IPrCuDBM** (5) | | 1 | 1 | 70 | 4 |
| 7 | **IPrCuDBM** (7) | | 1 | 1 | 79 | 4 |
| 8 | **IPrCuDBM** (7) | | 1 | 1.2 | 83 | 11 |

[a] Yield determined by $^1$H NMR with 3,4,5-trimethoxybenzaldehyde as internal standard.



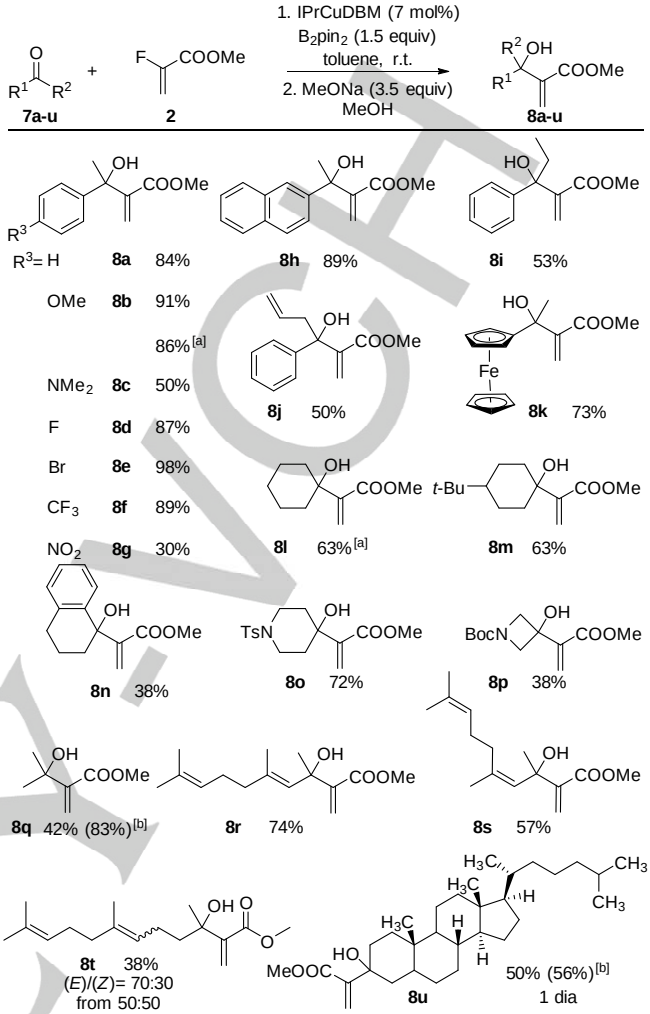
**IMesCuDBM**



**IPrCuDBM**

We were delighted to observe the formation of **8a**. However, the lower reactivity of ketones compared to aldehydes also lead to byproduct **9**. The use of 1 or 1.5 equivalents of **7a** yielded similar results (entries 1-2). To see if different ligands could prevent the formation of **9** and improve the reaction, various phosphine ligands and NHCs were tested. The phosphines and IMes gave lower yields for **8a**, while the use of IPrCuDBM gave a better yield (57%) of the product but did not change the amount of **9** formed. However, upon using a higher catalyst loading (entry 6-7) the yield of **8a** increased and the formation of **9** could be significantly supressed. The best result (83%) was obtained when 1.2 equivalent of **2** was used.

Using these new optimized conditions we started to investigate the scope of the reaction towards other ketones (Scheme 3).




**Scheme 3.** Scope for ketones. Reaction conditions: **7** (0. 5 mmol, 1 equiv), **2** (0.6 mmol, 1.2 equiv), $B_2pin_2$ (0.75 mmol, 1.5 equiv), IPrCuDBM (0.035 mmol, 7 mol%) in 2,5 mL toluene, room temperature, 18 h. NaOMe (1.75 mmol, 3.5 equiv) in 2.5 mL MeOH, room temperature, 24h. Yields of isolated products are given. [a] On a 5 mmol scale. [b] $^1$H NMR yield with 3,4,5-trimethoxybenzaldehyde as internal standard.

Impressively, aromatic ketones bearing electron-withdrawing or electron-donating groups (**8a-h**) were well-tolerated and gave good to excellent yields with the exception of *p*-nitro-substituted acetophenone (**8g,** 30%). Even modification of $R^2$ from a methyl to an ethyl or allyl (**8i-j**) gave acceptable yields. Alkyl ketones (**8m-q,u**) gave in most cases moderate to good yields except for azetidinone **7p** (38%) and tetralone **7n** (38%). Interestingly, the use of **7r-s** showed a better reactivity of (*E*)-enone (74%) compared to the (*Z*) counterpart (57%). This difference in reactivity is also seen with use of a 50:50 mixture of **7t** to give a 70:30 ratio in the final product **8t**.

On the basis of *in situ* NMR analysis and precedent in the literature, we can postulate a general mechanism for this transformation. We previously described a mechanism for the borylation/aldolisation leading to **A**.[11b] Upon treatment with NaOMe in MeOH, **A** undergoes a nucleophilic attack from two methoxide ions on both borons to give the bis-boronate **B**. Following a cleavage of a B-O bond to give an alcohol, the other

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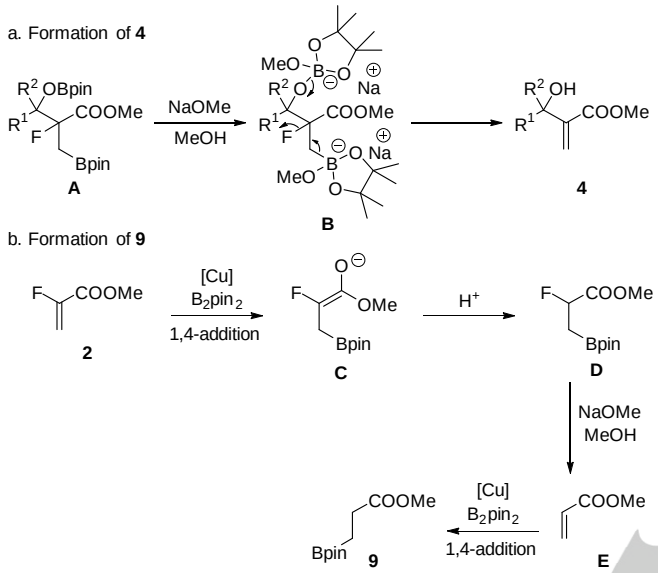
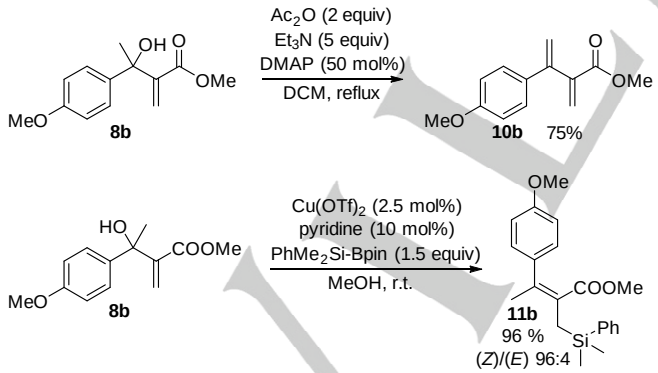
boronate undergoes a concomitant elimination of the fluoride and the boron moiety to give **4** (Scheme 4a). The formation of side product **9** was also studied by NMR (see supporting information). **9** is obtained by the conjugate addition of Cu-Bpin on **2** to give the enolate **C** which will trap a proton from the reaction media to give **D**. Upon treatment with NaOMe in MeOH methyl acrylate **E** is obtained and reacts with a Cu-Bpin species to give **9**.




**Scheme 4.** Mechanism for the formation of **4** and **9**

Having synthesized products **8** we started to study their potential as starting material for further transformation in useful compounds. We therefore devised a reaction to obtain diene **10b** *via* an acetate elimination and applied a previously reported silylation/elimination procedure to obtain the tetrasubstituted allylsilane **11b** with high yield and selectivity.[21]




**Scheme 5.** Transformation of **8b** into **10b** and **11b**

In conclusion, we have developed a highly efficient and broadly applicable alternative route to the classical MBH reaction. We describe this new approach as a one-pot domino borylation/aldolisation elimination process. This new approach tolerates a wide range of substituents on the substrates and importantly permits the use of normally unreactive substrates including ketones and deactivated aldehydes. Work is now in progress to devise an enantioselective version and to further study the potential of transformations of our adducts into synthetically useful intermediates.

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**Keywords:** copper • catalysis • borylation • Morita-Baylis-Hillman • domino

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**Copper-Catalyzed One-Pot Borylative Aldolisation β-Fluoride Elimination for the Formal Addition of Acrylates to Carbonyl Moieties**

Herein we report the copper-catalyzed domino borylation/aldolisation of methyl 2-fluoroacrylate with carbonyl compounds followed by an elimination to afford Morita-Baylis-Hillman (MBH) analogs. The optimal conditions described were shown to be compatible with a wide range of aldehydes and ketones. Unprecedented MBH adducts derived from ketones were efficiently synthesized.