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COMMUNICATION

Phosphine-boronates: efficient bifunctional organocatalysts for Michael addition†‡

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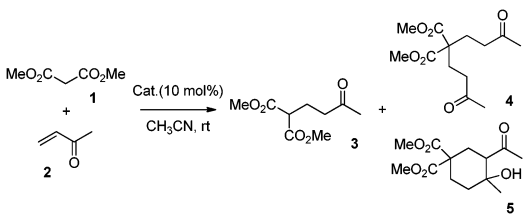
Phosphine-boronates $R_2P(o\text{-}C_6H_4)B(OR')_2$ have been evaluated as bifunctional organocatalysts for the Michael addition of malonate pronucleophiles to methylvinylketone. The presence of the Lewis acidic boron center adjacent to phosphorus significantly improves catalytic performance. Isolation and complete characterization of a key intermediate, namely a β-phosphonium enolate, substantiate the role of the Lewis acidic moiety in the catalytic process.

In recent years, cooperation between Lewis acids and Lewis bases has attracted considerable interest, and so-called Frustrated Lewis Pairs and ambiphilic derivatives have been shown to exhibit unique chemical behavior.[1,2] In this context, our group has been particularly interested in phosphine-boranes connected by an *ortho*-phenylene bridge, the close proximity of the two reactive sites being anticipated to amplify their cooperativity. In addition to possessing original and versatile ligand properties,[2,3] $R_2P\text{-}(o\text{-}C_6H_4)BR'_2$ derivatives have been found to efficiently stabilize reactive intermediates derived from phosphines.[4,5]

Phosphines have emerged over the past few decades as powerful nucleophilic catalysts for a variety of CC coupling reactions.[6] Taking into account the great potential of cooperative multi-center organocatalysis,[7] a few bifunctional phosphine catalysts have also been applied to the formation of carbon–carbon bonds.[8] Essentially protic moieties (such as phenolic OH groups) have been involved as ancillary activating sites, but to the best of our knowledge, the association of phosphines with Lewis acidic boron centers has not been considered thus far in this area. With the aim of further extending the synthetic interest of ambiphilic compounds, we became interested in evaluating PB derivatives towards catalytic CC coupling reactions. Herein we report our first catalytic results and mechanistic investigations in this area.

Phosphines have been recognized quite early on as competent organocatalysts for the Michael addition of active methylene compounds to electron-poor olefins.[9] For this study, the reaction of dimethylmalonate **1** with methylvinylketone (MVK) **2** was chosen as model reaction (Scheme 1). Our investigations began with the recently described phosphine-boronate **Ph_2PBpin** (Fig. 1).[10] All catalytic tests were performed at room temperature with a catalyst loading of 10 mol%. The influence of the solvent was studied and the molar ratio of the substrates was varied (Table S1, ESI‡). The best results were obtained in acetonitrile, using two equivalents of MVK with respect to dimethylmalonate. Accordingly, the desired addition product **3** was obtained in 67% yield within 9 h. Notably, **Ph_2PBin** performs slightly better than PPh_3 indicating some positive influence of the boronate moiety.

Then, the nature of the boronate group was varied and its influence on the catalytic performance was evaluated (Fig. 1, Table 1). Not surprisingly, reducing the steric demand of the boronate ester was found to increase the activity of the PB derivatives. The phosphine-boronate **Ph_2PBNeo** exhibited the highest activity (97% conversion of the malonate was achieved



Scheme 1 Catalytic Michael addition of dimethylmalonate **1** to methylvinylketone **2**.

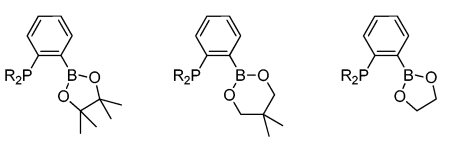


Fig. 1 Phosphine-boronates evaluated as organo-catalysts for the Michael addition.

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‡ Electronic supplementary information (ESI) available: Experimental details and characterization data, including crystallographic data for **8**. See DOI: 10.1039/c2cc30399j

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Table 1 Catalyst survey for the Michael addition of dimethylmalonate **1** to MVK[a]

Entry	Ratio **1** : **2**	Catalyst	Time/h	Conv[b]	**3**[c] (%)	**4**/**5**[c] (%)
1	1 : 2	**Ph_2PBNeo**	3.5	97	57	28/12
2	1 : 2	**Ph_2PBGly**	3.5	75	65	7/nd[d]
3	1 : 2	**Ph_2PBPin**	3.5	61	49	5/1
4	1 : 2	**PPh_3**	3.5	32	28	<5
5	1 : 2	**Me_2PBGly**	1	98	29	17/52
6	1 : 1	**Me_2PBGly**	1	77	58	7/nd[d]
7	1 : 1	**Me_2PBNeo**	1	82	69	2/10
8	1 : 1	**Me_2PBPin**	1	77	60	7/7
9	1 : 1	**Me_2PPh**	1	62	50	5/6

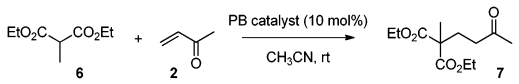
[a] Reactions were carried out with **1** (0.2 mmol) at 25 °C in acetonitrile (0.4 mL). [b] Determined by ^{1}H NMR. [c] Yields determined by ^{1}H NMR using mesitylene as internal standard. [d] Not detected.

in only 3 h 30 min), but led to poor selectivity (40% of the double Michael adducts **4** and **5**, resulting from intramolecular aldol reaction[9a]). A much better compromise was met with **Ph_2PBGly**, compound **3** being obtained in 65% yield within 3h30, with minimal amounts of the side-products **4**/**5** (<10% overall). Comparatively, **Ph_2PBpin** and PPh_3 afforded **3** in only 49% and 28% yields, respectively. These results confirm that the introduction of a boronate moiety can improve the catalytic performance of the phosphine, and thereby substantiate some cooperative behavior of the nucleophilic and Lewis acidic moieties of the PB organocatalyst.[11]

With the aim of further increasing the catalytic activity of the phosphine-boronates, we then envisioned to replace the Ph substituents at phosphorus for alkyl groups. The known (*o*-bromophenyl)-dimethylphosphine $Me_2P(o\text{-}C_6H_4)Br$[12] was used as a key precursor. Halogen–lithium exchange followed by electrophilic trapping with trimethoxyborate and subsequent transesterification with the appropriate diol afforded the desired compounds **Me_2PBpin**, **Me_2PBNeo** and **Me_2PBGly**. These new phosphine-boronates were isolated in pure form and characterized by multi-nuclear NMR and HRMS.‡

Compound **Me_2PBGly** was first evaluated in the catalytic Michael addition (Table 1, entry 5). Complete conversion was achieved within only 1 h at room temperature, but at the expense of selectivity. The major products are actually the double adducts **4** and **5** rather than the monoadduct **3**. To circumvent this limitation, an equimolar ratio of methylvinylketone **2** was used with respect to malonate **1**. Gratifyingly, all dimethylphosphine-boronates were found to efficiently promote the Michael reaction under these conditions with good selectivity in favor of the monoadduct **3** (entries 6–8). Here **Me_2PBNeo** provided the best results, affording **3** in 69% yield and only 12% of side-products **4** and **5** (entry 7). A comparable selectivity, but significantly lower yield was obtained using Me_2PPh as catalyst (entry 9).

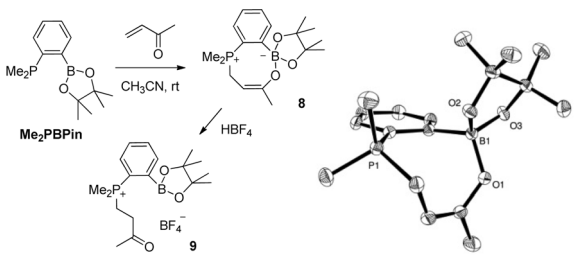
The fact that the double adducts **4** and **5** were obtained as major products in the presence of two equivalents of MVK indicates that the dimethylphosphine-boronate **Me_2PBGly** is able to effectively promote Michael addition with unsubstituted as well as substituted malonate derivatives. This prompted us to evaluate the catalytic performance of PB compounds towards a more challenging Michael addition, namely the reaction of methyl diethylmalonate **6** with MVK **2** (Scheme 2; Table S2, ESI‡). Long reaction times were required with the diphenylphosphine-boronate catalysts, in line with the formation of only small amounts of



Scheme 2 Catalytic Michael addition of the substituted malonate **6** to methylvinylketone **2**.

double adducts upon reacting **1** with **2**. Compounds **Ph_2PBGly** and **Ph_2PBNeo** featuring non-sterically hindered boronate moieties significantly outperformed **Ph_2PBPin** and PPh_3, affording the desired product **7** in 82 and 95% yields, respectively, after 62 h. The corresponding dimethylphosphine-boronates also proved to be efficient catalysts for the Michael addition of the substituted malonate **6**, and as expected, the reaction proceeds much faster than with the diphenylphosphine-boronates. The steric demand for the boronate moiety seems to play a pivotal role. Indeed, after 5 h at room temperature, the Michael adduct **7** was obtained in up to 95% yield with **Me_2PBNeo**, but only 50% with **Me_2PBpin**. These results further emphasize the participation and beneficial influence of the boronate moiety in the catalytic transformation. And preliminary studies substantiate the ability of the PB compounds to catalyze the Michael addition of other substrates.‡

To try to get some insight into the role of the bifunctional phosphine-boronate, stoichiometric reactions were then performed. According to *in situ* NMR monitoring in deuterated acetonitrile, **Ph_2PBpin** reacts readily with MVK **2** at room temperature. The diagnostic signals for **Ph_2PBpin** (δ ^{31}P −5.4 and ^{11}B 33.7 ppm) disappear progressively in favor of two new signals (δ ^{31}P 34.2 and ^{11}B 6.6 ppm), suggesting the quaternarization of both the phosphorus and boron atoms. Side-reactions and decomposition prevent gaining more information about the formed compound, but pleasingly, a cleaner reaction was observed with **Me_2PBpin**. Addition of MVK induced the instantaneous formation of a new compound **8**. Its ^{31}P (δ 31.5 ppm) and ^{11}B (δ 6.6 ppm) NMR data are very similar to those observed with **Ph_2PBpin**, and consistent with the presence of phosphonium and borate moieties. In addition, signals clearly attributable to a P–CH_2–CH=C_q skeleton were identified by ^{1}H [δ 3.56 ppm (m, 2H, PCH_2), 4.20 (pseudo-quartet, $^3J_{H-H}$ = $^3J_{H-P}$ = 7.3 Hz, CH =)] and ^{13}C NMR [δ 160.6 (d, $^3J_{C-P}$ = 10.6 Hz, C =), 87.6 (d, $^2J_{C-P}$ = 12.6 Hz, CH)]. X-Ray diffraction analysis unambiguously confirmed the molecular structure of **8** (Scheme 3).‡ Formal 1,4-addition of the PB derivative to MVK results in an eight-membered ring system. In other words, nucleophilic attack of the phosphorus atom of **Me_2PBpin** on MVK forms a β-phosphonium enolate which is stabilized intramolecularly by the boronate moiety. Strong interaction



Scheme 3 Synthesis, X-ray structure (ellipsoid drawing at 50% probability; hydrogen atoms omitted for clarity) and protonation of the β-phosphonium enolate **8**.

between the enolate moiety and the boron center is apparent from the short O1B bond [1.509(2) Å] and from the pyramidalization of the boron environment (the sum of bond angles for the CBpin fragment = 326.25°). Compound **8** stands as a very rare example of a β-phosphonium enolate. Such zwitterionic derivatives are usually unstable and exist as cyclic pentavalent phosphoranes. To the best of our knowledge, the only unambiguously characterized precedents were reported recently by Kwon *et al.* from three-component reactions involving triphenyl, trimethyl or tributyl-phosphine, methylpropionate and 4-pyridinecarboxaldehyde.[13,14] Note also that the formation of **8** from **Me_2PBpin** and MVK nicely complements the results observed recently by Erker and co-workers upon reacting the ethylene-bridged phosphine-borane $Mes_2PCH_2CH_2B(C_6F_5)_2$ with α,β-unsaturated carbonyl derivatives.[15]

After nucleophilic attack at the electron-poor alkene, phosphine-catalyzed Michael additions are supposed to proceed *via* acid–base exchange with the malonate derivative.[9] To check the ability of the β-phosphonium enolate **8** to participate in such acid–base reaction, it was treated *in situ* with HBF_4. The corresponding γ-keto phosphonium **9** was readily and cleanly formed and its structure was unambiguously established spectroscopically.[16] Note that traces of **9** are also detected upon reaction of **Me_2PBPin** with MVK, probably as a result of protonation of the β-phosphonium enolate **8** with adventitious proton sources.

To verify that derivative **8** can be effectively considered as an intermediate in the catalytic cycle, it was evaluated itself for the coupling of dimethylmalonate **1** and MVK **2**. Within the margin of error, the MVK adduct **8** and phosphine-boronate **Me_2PBpin** gave identical catalytic results in terms of activity and selectivity (with **8**, products **3**, **4** and **5** were obtained in 61, 15 and 10% yields, respectively, as to compare with entry 8, Table 1).

In conclusion, introduction of a boronate moiety in the *ortho*-position of phenylphosphines was shown to enhance their catalytic performance towards Michael addition. The role of the Lewis acidic moiety is supported by the isolation of a key β-phosphonium enolate intermediate upon reaction of the phosphine-boronate $Me_2P(o\text{-}C_6H_4)$Bpin with methylvinylketone. Following the seminal contribution of D. W. Stephan and G. Erker, PB derivatives and related Frustrated Lewis Pairs have been successfully applied to metal-free hydrogenation of a variety of organic substrates.[1] The results reported here extend the scope of such bifunctional organocatalysts to the formation of carbon–carbon bonds. Future work will aim at evaluating PB derivatives in other CC bond-forming reactions, including in asymmetric versions.[17]

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