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Synthetic Methods

Synthesis of Ketones by C–H Functionalization of Aldehydes with Boronic Acids under Transition-Metal-Free Conditions

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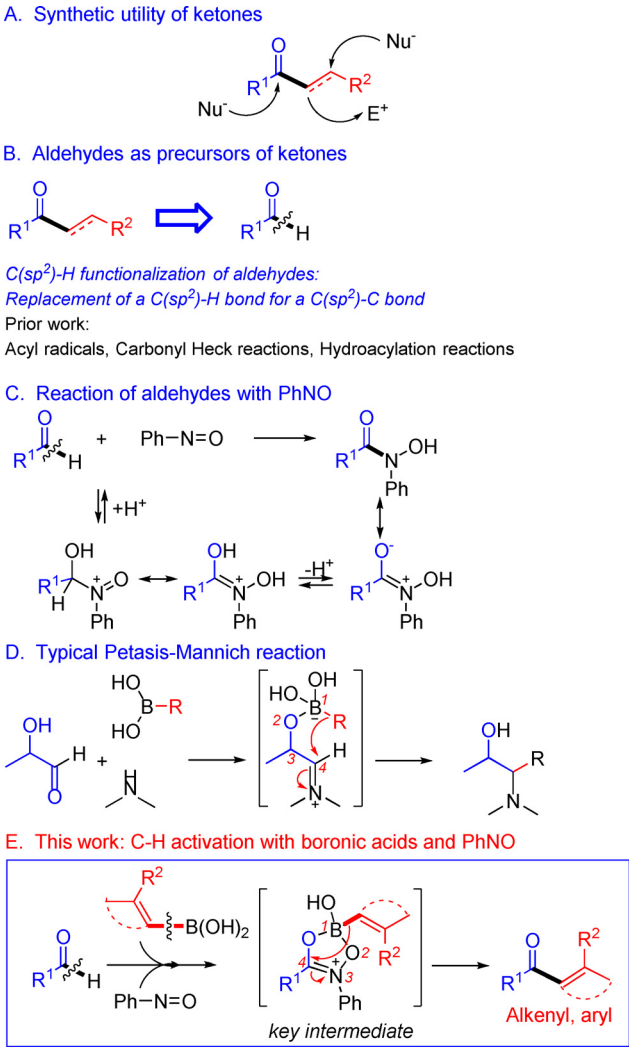
Abstract: *A method for the synthesis of ketones from aldehydes and boronic acids via a transition-metal-free C–H functionalization reaction is reported. The method employs nitrosobenzene as a reagent to drive the simultaneous activation of the boronic acid as a boronate and the activation of the C–H bond of the aldehyde as an iminium species that triggers the key C–C bond-forming step via an intramolecular migration from boron to carbon. These findings constitute a practical, scalable, and operationally straightforward method for the synthesis of ketones.*

Ketones are important structural motifs[1] and building blocks[2] in organic chemistry (Scheme 1a). Despite the many reactions available for their synthesis (e.g. reaction of carboxylic acid derivatives with organometallic reagents, transition-metal-catalyzed cross-couplings, Friedel–Crafts or Mannich reactions),[3,4] there is a continuous need for the development of new ways to improve their preparation in search of rapid methods that use readily available starting materials. This is the case of the C–H functionalization of aldehydes (Scheme 1b), that is, the replacement of their C(sp^2)–H bond for a C(sp^2)–C bond.[5] For this reaction to be highly efficient, it is imperative to find friendly-to-use reagents and avoid the use of toxic metals, cumbersome additives, or harsh reaction conditions.

Aldehydes have been used profusely as starting materials for the synthesis of ketones. Aside from the classic two-step procedure that consists of the addition of a carbon nucleophile, for example, a Grignard reagent, followed by the oxidation of the intermediate secondary alcohol,[6] aldehydes have been converted to ketones by making use of umpolung reactions that render acyl anion equivalents.[7,8] More recently, the use of acyl radicals,[9] carbonyl Heck reactions[10] and other related transition-metal-catalyzed additions[11] as well as hydroacylation reactions[12] have been gaining popularity for the direct synthesis of ketones from aldehydes. However, most of these methods rely on the use of strong bases, transition-metals, ancillary ligands, or harsh reaction conditions. Also, many of them are restricted to a particular type of aldehyde, either aliphatic or aromatic.

We became interested in exploiting the reaction between aldehydes and nitrosobenzene[13] (Scheme 1c) in connection with previous research concerning new reactions that involve boronic acids and nitroso compounds.[14] Boronic acids are well known for their ability to act as bench-stable carbon nucleophiles.[15] Due to their low reactivity,[16] they have mostly been used in combination with transition-metals. C–C bond formation using boronic acids as reagents under transition-metal-free conditions is comparatively rare.[17]



Scheme 1. A) Synthetic utility of ketones. B) Synthesis of ketones from aldehydes. C) Reaction intermediates in the formation of hydroxamic acids from aldehydes and nitrosobenzene. D) Typical mechanism of the Petasis-Mannich reaction. E) C(sp^2)-H aldehyde activation with boronic acids and nitrosobenzene leading to ketones.

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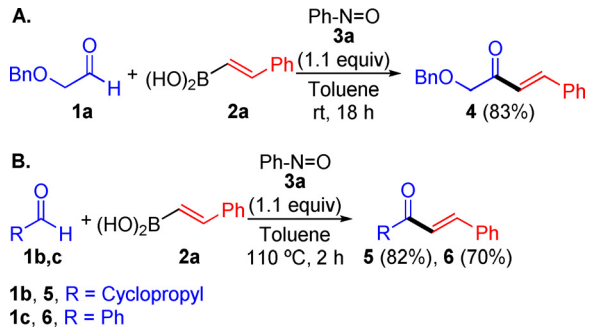
However, the interaction of the vacant orbital on the boron atom of boronic acids with a nucleophile renders boronates ("ate" complexes), which show enhanced nucleophilicities. The ability of boronates to engage in migration reactions triggered by the presence of a nearby electrophilic site is one of the most relevant reactions in boron chemistry.[18] In particular, the activation of boronic acids with oxygen nucleophiles permits the transformation of α-hydroxyaldehydes into amines (the Petasis-Mannich reaction).[19] In this reaction, coordination of a vinyl or aryl boronic acid to the hydroxy moiety generates a boronate intermediate that intermolecularly transfers its carbon group to the electrophilic iminium species formed by the interaction of the aldehyde with a primary or secondary amine (Scheme 1d). Recently disclosed reactions of other compounds that bear an oxygen site for coordination of the boronic acid and a nearby iminium-type functionality, such as heterocyclic N-oxides[20] or nitrile oxides,[21] follow related pathways.[22] We envisioned that the intermediates formed by the interaction of aldehydes with nitrosobenzene[13] could play a similar role. We report here (Scheme 1e) that the interaction of aldehydes with nitrosobenzene in the presence of boronic acids can lead to intermediates with boronate character that enable the activation of the aldehyde C–H bond via iminium-ion formation, giving rise to the transformation of aldehydes into ketones by a key 1,4-migration from boron to carbon in a one-pot procedure that takes place under mild conditions.

We started by selecting 2-benzyloxyacetaldehyde (**1a**) as the model aldehyde (Scheme 2a). This is a highly reactive aldehyde prone to self-condensation by aldol reactions under acidic or basic conditions. The C–H activation reactions of **1a** give rise to α-acyloxyketones, which are frequent motifs in biologically active natural products and pharmaceuticals.[23] Initial discovery and optimization experiments were carried out with 2-phenylvinylboronic acid (**2a**) using commercial-grade solvents without exclusion of air or humidity. A survey of the reaction conditions was performed (see the Supporting Information for details). Eventually, the optimized reaction conditions for the synthesis of ketone **4** emerged as 1.5 equivalents of alkenylboronic acid and 1.1 equivalents of nitrosobenzene in toluene at rt. However, when **1a** was replaced with the more encumbered cyclopropanecarbaldehyde (**1b**) or with benzaldehyde (**1c**) (Scheme 2b) yields at rt were significantly lower. We were pleased to find that in these cases an increase in temperature (toluene, 110 °C) allowed the obtainment of the corresponding ketones **5** and **6** in good yields and short reaction times (2 h, TLC following).

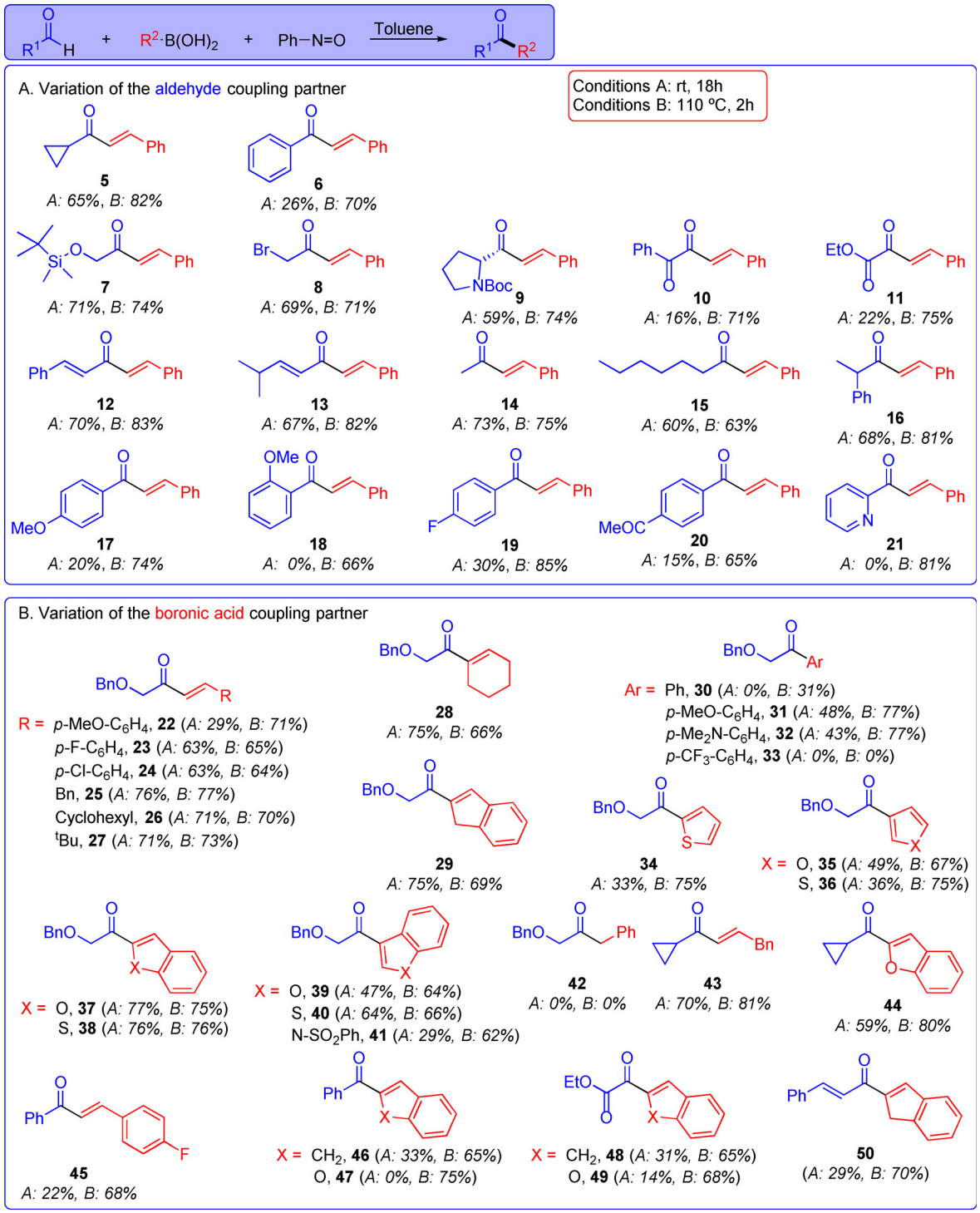


Scheme 2. Optimized reaction conditions.

With these observations in hand, we extended the reaction to a variety of aldehydes and boronic acids (Scheme 3). Keeping **2a** as the reaction partner, we observed that the reaction was very general for the aldehyde counterpart (Scheme 3a), tolerating other α-hetero functionalized aldehydes (**7**–**9**) that included the acid-labile TBSO group (**7**) and a proline derivative (**9**) that reacted without epimerization (see SI),[24] 1,2-dicarbonyl derivatives (**10**, **11**), α,β-unsaturated aldehydes (**12**, **13**), aliphatic aldehydes (**14**–**16**) and aromatic aldehydes (**6**, **17**–**21**) including examples with electron-donor substituents (**17**, **18**), *ortho*-substitution (**18**), and electron-accepting substituents (**19**–**21**). α-Hetero functionalized (**4**, **7**, **8**) aldehydes reacted with **2a** at rt allowing the synthesis of the corresponding ketones in good yields. More hindered (**5**, **9**, **16**) and α,β-unsaturated aldehydes (**12**, **13**) also reacted at rt but in moderate yields, which were increased upon heating. However, aromatic aldehydes (**6**, **17**–**21**) and 1,2-dicarbonyl derivatives (**10**, **11**) required the reaction to be performed at 110 °C. To demonstrate the potential synthetic utility of this methodology, two of the examples (**4** and **6**) were executed on a 1 g scale with similar yields (see the Supporting Information for details).

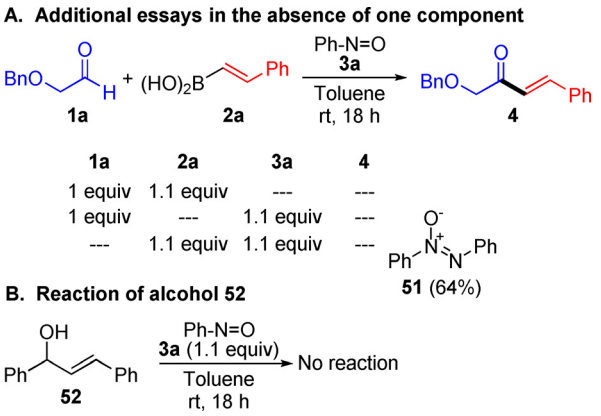
Next, using benzyloxyacetaldehyde (**1a**), cyclopropanecarbaldehyde (**1b**), benzaldehyde (**1c**), ethyl glyoxylate (**1d**), and cinnamaldehyde (**1e**) as representative examples of different types of aldehydes, we explored additional synthetic examples illustrating the reaction scope with regard to the boronic acid component **2** (Scheme 3b). The reaction was general with alkenylboronic acids, and ketones **22**–**27**, **43** and **45** were obtained in high yields both at rt (conditions A) and heating at 110 °C (conditions B). Concerning steric hindrance, we observed that substitution at the α-carbon was tolerated (**28**, **29**, **46**, **48**, **50**). The reaction also took place with phenylboronic acid (**30**) in moderate yield, but high conversions were obtained with arylboronic acids bearing electron-donor substituents (**31**, **32**). However, the presence of an electron-acceptor substituent on the benzene ring was not permitted (**33**). We were pleased to find that the reaction was also useful for the synthesis of ketones using heterocyclic boronic acids such as furan (**35**), thiophene (**34**, **36**), benzofuran (**37**, **39**, **44**, **47**, **49**) benzothiophene (**38**, **40**), and indole (**41**) derivatives, both with the boronic acid substituent at positions 2 (**34**, **37**, **38**, **44**, **47**, **49**) or 3 (**35**, **36**, **39**–**41**) of the heterocyclic ring. Unfortunately, the reaction did not take place with alkylboronic acids like benzylboronic acid (**42**).

We performed several additional experiments to gain insight into a plausible reaction course (see the Supporting Information for details). As expected, no reaction was observed upon mixing the aldehyde **1a** with the boronic acid **2a** in the absence of nitrosobenzene (**3a**) (Scheme 4a). No reaction was found between the aldehyde **1a** and nitrosobenzene (**3a**) in the absence of the boronic acid (**2a**) and the evolution of **3a** into azoxybenzene **51** was the only reaction observed upon mixing **3a** with **2a** in the absence of the aldehyde, which is consistent with the Lewis acid character of boronic acids.[25] We also checked that alcohol **52** was not oxidized by nitrosobenzene, discarding a reaction



Scheme 3. Scope and limitations. Conditions A: rt, 18 h. Conditions B: 110°C, 2 h. A) Variation of the aldehyde coupling partner. B) Variation of the boronic acid coupling partner. With the exception of compounds **4** and **6**, which were prepared on 1 g scale, yields are reported for isolated material following purification on a 0.20 mmol scale. See Supporting Information for full experimental details and conditions.

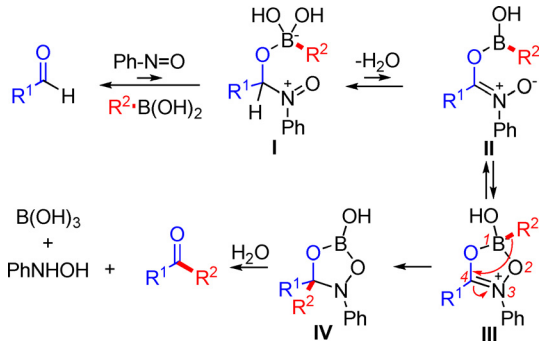
pathway with **52** as an intermediate in the synthesis of the corresponding ketone (Scheme 4b). The reaction was not inhibited in the presence of 1,4-benzoquinone or styrene which excluded a radical pathway that might have been induced by the redox properties of nitrosobenzene, and no variation in yield was observed when the reaction was executed in degassed anhydrous toluene or under oxygen atmosphere, which ruled out the participation of oxygen in the reaction course. These experiments did not permit the trapping of any reaction intermediate. In situ ^{1}H NMR spectroscopy in [D$_6$]benzene at rt revealed a slow conversion of the reactants benzyloxyacetaldehyde (**1a**), phenylvinylbor-



Scheme 4. Additional experiments. A) Reactions in the absence of one component. B) Attempted reaction of alcohol **52**.

onic acid (**2a**) and nitrosobenzene (**3a**) into ketone **4**, without evidence of any detectable intermediate. Control experiments using either the pinacol ester or potassium trifluoroborate analog of boronic acid **2a** failed to yield the expected ketone. This provides evidence towards the formation of an anionic nucleophilic boron species during the reaction mechanism, since pinacol boronic esters are reluctant to the formation of boronate species.[26] Also, the migration of the carbon backbone of the boronate in the key intermediate must be intramolecular since the highly nucleophilic trifluoroborate analog of **2a** did not react. Attempts to form a more electrophilic species (R^2BF_2) by treatment of the potassium trifluoroborate analog of **2a** with TMSCl or BF_3 led to multiple unidentifiable reaction products.[27] Additional spectroscopic and computational studies are underway in order to further delineate the mechanism of the reaction.

In light of these pieces of evidence and the above cited previous literature precedents concerning the reactions of aldehydes with nitrosobenzene[13] and the Petasis-Mannich reaction,[19,28] we concluded that coordination of the oxygen of the aldehyde with the boronic acid can trigger the nucleophilic addition of nitrosobenzene (Scheme 5), generating a low equilibrium concentration of the labile intermediate **I**, which has boronate character and an enhanced acidity of the original aldehyde hydrogen atom. Cyclization to **III** generates an iminium-type electrophile in the proximity of the nucleophilic boronate center, which rapidly evolves by 1,4-migration to **IV**. The collapse of this aminal-type intermediate upon hydrolysis renders the final ketone.



Scheme 5. Proposed reaction course.

In conclusion, we have demonstrated that aldehydes can be directly converted into ketones in a one-pot reaction with boronic acids in the presence of nitrosobenzene. The process takes place under mild conditions, does not require transition-metals, and is general for a wide variety of aldehydes, and for alkenyl and arylboronic acids, constituting a practical, scalable, and operationally easy method for the synthesis of ketones that can be particularly attractive from the standpoint of late-stage functionalization.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: aldehydes · boron · C–C coupling · ketones · synthetic methods

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