Scope and Mechanism of a True Organocatalytic Beckmann Rear-rangement with a Boronic Acid / Perfluoropinacol System under Ambient Conditions

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Supporting Information

ABSTRACT: Catalytic activation of hydroxyl functionalities is of great interest for the production of pharmaceuticals and commodity chemicals. Here, 2-alkoxycarbonyl- and 2-phenoxycarbonyl-phenylboronic acid were identified as efficient catalysts for the direct and chemoselective activation of oxime N-OH bonds in the Beckmann rearrangement. This classical organic reaction provides a unique approach to prepare functionalized amide products that may be difficult to access using traditional amide coupling between carboxylic acids and amines. Using only 5 mol% of boronic acid catalyst and perfluoropinacol as an additive in a polar solvent mixture, the operationally simple protocol features mild conditions, displays a broad substrate scope, and a high functional group tolerance. A wide variety of diaryl, aryl-alkyl, heteroaryl-alkyl and dialkyl oximes react under ambient conditions to afford high yields of amide products. Free alcohols, amides, carboxyesters, and many other functionalities are compatible with the reaction conditions. Investigations of the catalytic cycle revealed a novel boron-induced oxime transesterification providing an acyl oxime intermediate involved in a fully catalytic non-self-propagating Beckmann rearrangement mechanism. The acyl oxime intermediate was prepared independently and was subjected to the reaction conditions. It was found to be self-sufficient; it reacts rapidly, unimolecularly without the need for free oxime. A series of control experiments and ^{18}O labeling studies support a true catalytic pathway involving an ionic transition structure with an active and essential role for the boronyl moiety in both steps of transesterification and rearrangement. According to ^{11}B NMR spectroscopic studies, the additive perfluoropinacol provides a transient, electrophilic boronic ester that is thought to serve as an internal Lewis acid to activate the ortho-carboxyester and accelerate the initial, rate-limiting step of transesterification between the pre-catalyst and the oxime substrate.

INTRODUCTION

New catalytic modes of functional group activation can unlock unique reactivity in organic molecules and lead to novel bond-forming processes. When applied to safe and readily available substrates like alcohols and carboxylic acids, efficient and atom-economical methods can be developed that by-pass the use of toxic halide derivatives or stoichiometric reagents.[1] In this regard, the concept of boronic acid catalysis (BAC) exploits the tempered Lewis acidity of boronic acids along with their ability to form reversible covalent bonds with hydroxyl functionalities, thereby providing an opportunity for temporary activation of C–O bonds. Several applications of BAC have been demonstrated by our group and others.[2] For instance, we reported direct boronic acid-catalyzed transposition[3] and substitutions[4] of allylic alcohols, and Friedel-Crafts alkylation of neutral arenes with readily available allylic and benzylic alcohols.[5] With a view to expand BAC towards other dehydrative reactions of hydroxyl-containing functional groups, we considered the direct Beckmann rearrangement of ketoximes into secondary amides.[6] In its classical form, the Beckmann rearrangement is promoted by strong protic acids.[7] This important transformation is at the heart of the industrial synthesis of lactam monomers for the manufacture of nylon, and it also finds utility in the discovery and production of pharmaceuticals.[8] Mild catalytic manifolds are rare, and, oftentimes, pre-activation of the hydroxyl (i.e., tosylation) is required. Compared to the use of inorganic Lewis acids, organocatalysis offers notable advantages such as broader functional group compatibility and operational simplicity (ie., air- and moisture tolerance).

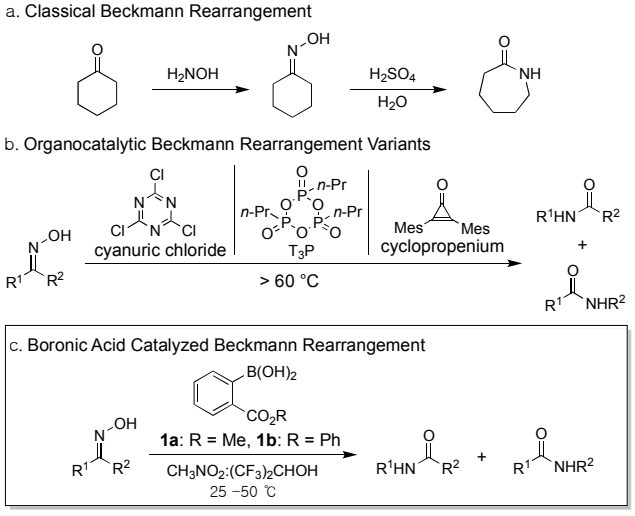


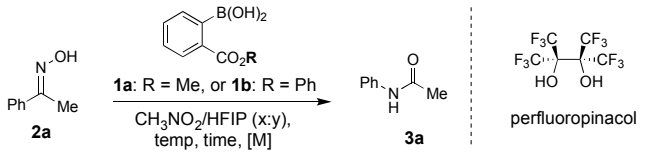
Figure 1. Classical and organo-mediated/catalyzed Beckmann Rearrangement procedures.

Reported procedures for the Beckmann rearrangement employing organic compounds as promoters, such as cyanuric chloride,[9] BOPCl,[10] triphosphazene,[11] tosyl chloride,[12] propylphosphonic anhydride (T3P),[13] TFA[14] or cyclopropenium salts[15] require an acid co-catalyst or elevated temperatures (60-100 °C) to achieve effective activation of oximes (Figure 1). Many of these reagents have been shown to act merely as initiators of the Beckmann rearrangement through a self-propagating mechanism involving a nitrilium intermediate, and are therefore not true catalysts.[12,15] These limitations, coupled with the significance of the Beckmann rearrangement as a unique method for the synthesis of amides, warrant the development of new organocatalytic procedures that can operate at or near ambient temperature for a wider variety of substrates. Herein, using the BAC concept, we report a direct Beckmann rearrangement procedure that displays high functional group tolerance under ambient conditions for diaryl, aryl-alkyl, heteroaryl-alkyl and dialkyl oximes, affording high yields of amide products.

RESULTS AND DISCUSSION

Optimization of Reaction Conditions. The initial optimization focused on the identification of effective boronic acids capable of mediating the prototypic Beckmann rearrangement of oxime **2a** into amide **3a** (Table 1). Over 20 functionalized aryl boronic acids[16] were screened in different solvents (see SI). Only 2-methoxycarbonylphenyl boronic acid (**1a**) provided a significant amount of the amide product. It was found to transform oxime **2a** into amide **3a** in good yield in a solvent mixture of 4:1 hexafluoroisopropanol (HFIP) and nitromethane at 50 °C after 72 hours (entry 1). The use of HFIP is vital to the reaction, and a higher conversion is achieved with a higher proportion of HFIP (entries 2-4). Further optimization showed that the concentration could be increased up to 1.0 M, thus providing substantial solvent economy without undermining the reaction yield (entry 5). However, the reaction exhibited lower efficiency when decreasing the reaction time and temperature (entry 6). We hypothesized that, in addition to providing a polar reaction medium, HFIP could form an electron-poor boronic ester and modulate the Lewis acidity of the boron atom. To this end, a catalytic amount of perfluoropinacol was added to promote a more stable cyclic boronic ester. Satisfactorily, product **3a** formed in higher conversion at room temperature after 24 hours (entry 7). With perfluoropinacol, catalyst loading could be decreased to 5 mol%, affording **3a** in high yield (entry 8). Further optimization of the boronic acid (see SI) led to the use of phenoxy ester **1b,** which considerably shortened the reaction time providing **3a** in high yield after only 6 hours (entries 9-10). It is noteworthy that the reaction appears to tolerate trace water (entry 11 vs entry 8), and the use of molecular sieves was found to have a negligible effect (see SI). Solvents need no exhaustive drying with this simple experimental procedure. Interestingly, 2-carboxyphenylboronic acid (**1c**) is ineffective (entry 12).

Table 1. Optimization of Boronic Acid Catalyzed Beckmann Rearrangement



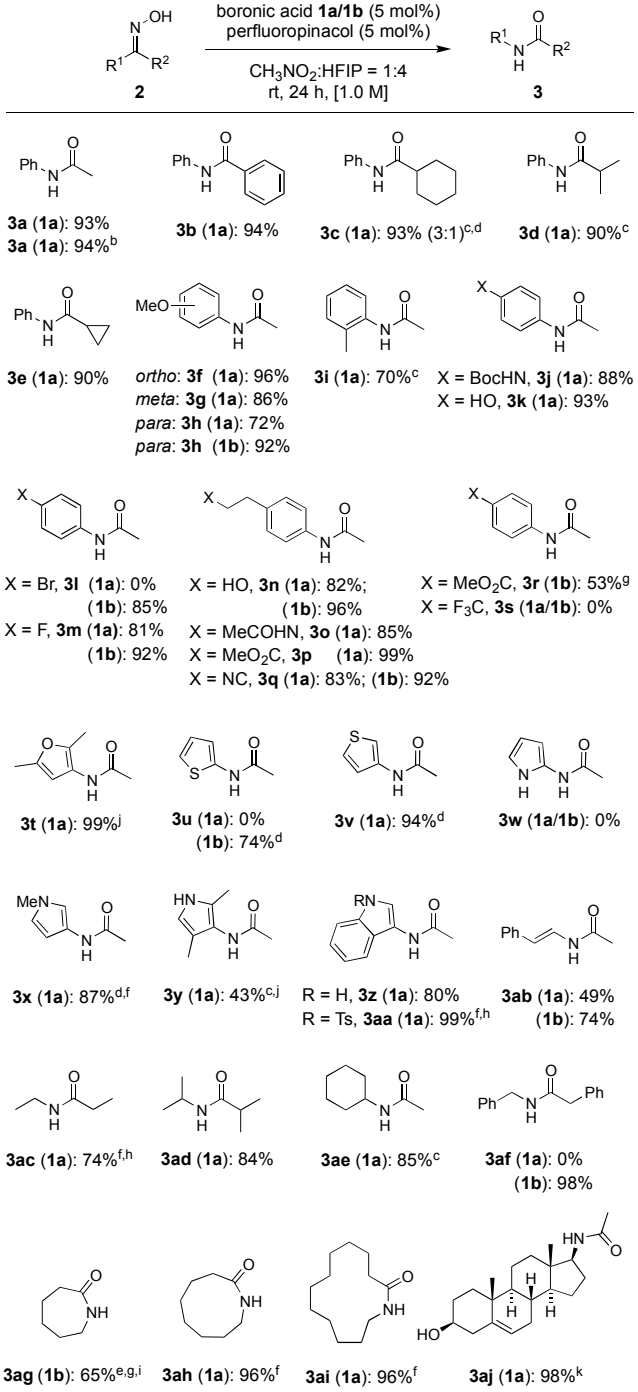
entry[a]	cat.	mol (%)	x:y	[M]	T (ºC)	t (h)	**3a**[b] (%)
1	**1a**	10	1:4	0.5	50	72	100
2	**1a**	10	1:2	0.5	50	72	93
3	**1a**	10	1:1	0.5	50	72	79
4	**1a**	10	4:1	0.5	50	72	60
5	**1a**	10	1:4	1.0	50	72	87
6	**1a**	10	1:4	1.0	rt	24	72
7[c]	**1a**	10	1:4	1.0	rt	24	94
8[d]	**1a**	5	1:4	1.0	rt	24	93[e]
9[d]	**1a**	5	1:4	1.0	rt	6	37[e]
10[d]	**1b**	5	1:4	1.0	rt	6	94
11[f]	**1a**	5	1:4	1.0	rt	24	86
12	**1c** (R=H)	20	1:4	0.5	50	72	0

[a]Reaction conditions: 0.5 mmol of oxime were dissolved in the indicated solvent mixture. [b]Yields were determined by ^{1}H NMR analysis of reaction mixture using 1,4-dinitrobenzene as internal standard. [c]Reaction was run with 10 mol% of perfluoropinacol. [d]Reaction was run with 5 mol% perfluoropinacol. [e]Isolated yield. [f]50 mol% of water was added to the solvent.

Examination of Substrate Scope. A representative panel of 36 aromatic and alkyl substituted oximes were tested in the boronic acid catalyzed Beckmann rearrangement under the optimal conditions from Table 1 (entry 8 or 10) using **1a** or **1b** as the catalyst. As shown in Scheme 1, in most cases the reaction proceeded efficiently at room temperature for both aryl and alkyl substituted substrates. As demonstrated with **3a**, this BAC procedure maintains its efficiency on gram-scale. A range of functional groups were found to be fully tolerant of these reaction conditions. A phenol-containing substrate underwent the rearrangement in 93% yield (**2k**). As shown with products **3l-3r**, halide, alcohol, amide, carboxyester, and nitrile groups are compatible. Moreover, a variety of common protecting groups were also tolerated, including acid sensitive Boc (**2j**) and Ts (**2aa**) groups. Pharmaceutically relevant heteroaromatic substrates also reacted efficiently, including the use of free pyrrole (**2y**) and indole (**2z**). These unprotected substrates offer significant synthetic advantage, in terms of step and atom economy, over amidation methods that require protected heterocycles. Hindered heteroaromatic amides like **3y** are unprecedented and would be difficult to prepare using standard amide coupling methods. The temperature sensitive enamide **3ab** was obtained in high yield under ambient conditions with this procedure. The steroid pregnenolone oxime **2aj** underwent the Beckmann rearrangement in 76% yield even without protection of the alcohol. Cyclohexanone oxime **2ag**, a notoriously challenging substrate,[9-12,15] gave a 65% yield under more forcing conditions. Additionally, the superiority of

catalyst **1b** over **1a** is clearly evidenced by the examples of oximes **2l**, **2u**, and **2af**. As expected, aromatic oximes with electron-withdrawing substituents are less reactive due to their inferior migratory aptitude. Although carboxyester-substituted aromatic ketone **2r** was successful at elevated temperature, no product was observed when the highly deactivated oxime **2s** was used under various conditions. Oxime **2w** was also unreactive, presumably due to catalyst inhibition from chelation of the boronic acid to the *ortho*-amine and the oxime moieties.

Scheme 1. Substrate Scope of Boronic Acid Catalyzed Beckmann Rearrangement[a]

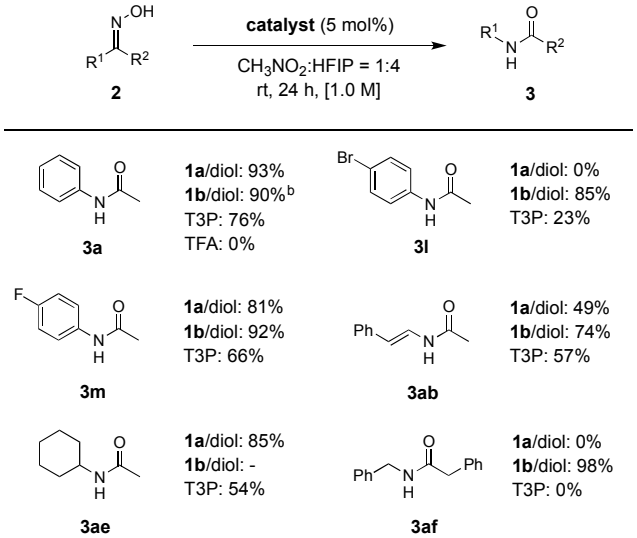


[a]Reactions performed on 0.5 mmol scale. Yields are reported after isolation unless otherwise noted; [b]Gram scale, 30 h; [c]Oxime was formed as a mixture of isomers, for ratios see SI, however, unless noted, a single amide product was observed; [d]The minor product resulted from migration of R^2; [e]Yield was determined by ^{1}H NMR analysis of the reaction mixture with 1,4-dinitrobenzene as internal standard; [f]50 ºC; [g]80 ºC; [h]With 10 mol% boronic acid and diol; [i]With 30 mol% boronic acid and diol; [j]20 mol% boronic acid, CH_3NO_2/HFIP (1:1), 50 ºC, 24 h; [k]HFIP, 50 ºC, 24 h.

Several of the oximes used in this study were formed as mixtures of *E*/*Z* isomers. Notably, in almost all cases the mixture of oximes resolved to a single major product with generally excellent selectivity based on the expected migratory aptitude of the R^1 and R^2 groups. The non-stereospecific nature of this Beckmann rearrangement method probably originates from the rapid interconversion of *E* and *Z* oximes under the reaction conditions.[17]

Due to the ability of HFIP to facilitate ionic reactions[18] the BAC conditions were compared with some of the most active Beckmann rearrangement promoters reported. When T3P and TFA were applied to a subset of oxime substrates, the results were clearly inferior to the new BAC method (Scheme 2). In fact, rearrangement of even the simplest of oximes, **2a**, failed with the use of catalytic or even stoichiometric amounts of TFA. [19] These results demonstrate that the exceptional activity of boronic acid catalysts **1a**/**1b** is not simply due to the unusual solvent system employed or to the presence of adventitious acid.

Scheme 2. Comparison of Organocatalysts for the Beckmann Rearrangement in CH_3NO_2/HFIP[a]

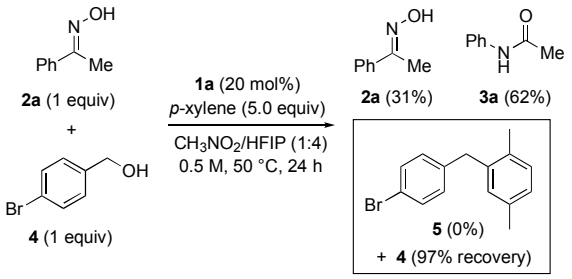


[a]Reactions performed on 0.5 mmol scale. Yields are reported after isolation unless otherwise noted; [b]Reaction was complete after 6 h.

Chemical Orthogonality with Alcohols. Electron-poor arylboronic acids are excellent catalysts for the activation of certain alcohols in Friedel-Crafts reactions.[5] We were interested in evaluating the potential of **1a** to act as a chemoselective activator of oxime N-OH units. To this end, boronic acid **1a**

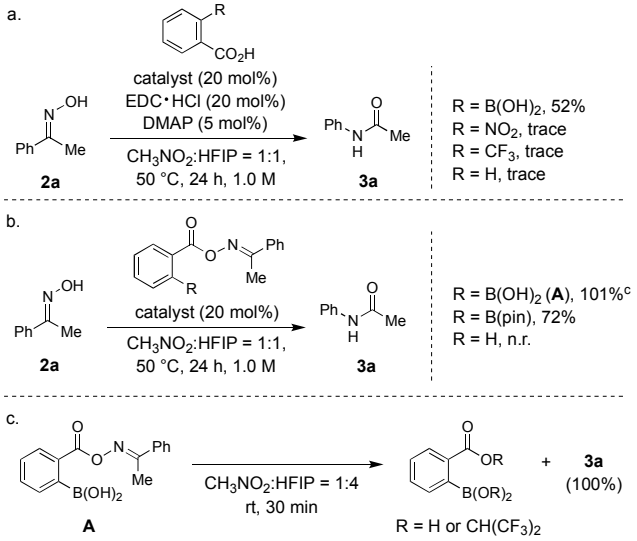
and oxime **2a** were subjected to Friedel-Crafts benzylation conditions with *p*-xylene and alcohol **4** as competing substrates (Scheme 3).[5b] Remarkably, only the amide **3a** was formed along with a good recovery of **2a** and alcohol **4**. None of the expected Friedel-Crafts product (**5**) was observed. This result highlights the potential of BAC in orthogonal catalysis of reactions with substrates containing multiple hydroxyl-containing functional groups.

Scheme 3. Chemoselectivity of Boronic Acid Catalyst **1a**



Investigation of the *ortho*-Boronyl Group. Preliminary experiments were performed in order to shed light on the mechanism. The unique structure and reactivity of 2-methoxy/phenoxycarbonyl-phenylboronic acids **1a** and **1b** led us to propose the formation of a *o*-boronyl oxime ester (**A** in Scheme 4c) as the key intermediate for this Beckmann rearrangement procedure. Oxime esters were shown by Kuhara in the early 1900s to be suitable precursors in the Beckmann rearrangement.[20] To support the intermediacy of an oxime ester, several control experiments were conducted. 2-Carboxyphenylboronic acid was found to be inactive under various conditions (see Table 1 and SI). However, when the reaction was performed in the presence of an esterification reagent to form the acyl oxime *in situ*, a moderate (52%) yield of amide product **3a** was observed (Scheme 4a). Removing or replacing the boronyl group with other electron withdrawing groups (e.g. NO_2 and CF_3) led to no product formation, which suggests a Lewis acidic role for the *ortho*-boronyl. Oxime ester **A** was prepared independently and shown to efficiently catalyze the rearrangement, which supports its intermediacy (Scheme 3b). Protecting catalyst **1a** with pinacol before use resulted in only a trace amount of product (see SI). However, when the pinacol boronate of **A** was subjected to the standard reaction conditions, 72% of amide **3a** was observed (Scheme 3b). Altogether these results indicate that a Lewis acidic boronate can facilitate the downstream Beckmann rearrangement, but a free boronic acid is preferred for effecting the oxime transesterification. When oxime ester **A** was exposed to the reaction solvent, spontaneous rearrangement occurred, forming **3a** and a mixture of the carboxylic acid and HFIP ester of the catalyst. The self-sufficiency and high reactivity of **A** support a unimolecular Beckmann rearrangement that does not require a second molecule of oxime as needed in the self-propagating 'nitrilium' mechanism.[12,15]

Scheme 4. Mechanistic Control Experiments[a,b]



[a]Reaction conditions: 0.5 mmol of oxime were dissolved in the indicated solvent mixture without further precautions. [b]Yields were determined by ^{1}H NMR analysis of reaction mixture using 1,4-dinitrobenzene as internal standard. [c]Reaction was run with the conditions of Table 1, entry 10.

Studies of the Role of HFIP and Perfluoropinacol. Use of HFIP as solvent has proven to be beneficial for cationic processes such as the Beckmann rearrangement.[17] In addition to its role as a polar solvent, we suspected that HFIP could also engage in reversible boronic ester formation with catalyst **1a** thus providing a highly electrophilic and Lewis acidic boron center (see SI). This idea led to the use of co-catalytic perfluoropinacol, which presumably forms a more stable 5-membered boronic ester (Table 1, entries 7-10). The partial formation of a reactive perfluoropinacol boronate is supported by NMR studies (Figure 2). Mixtures of boronic acid **1a** (δ = 30 ppm) and increasing amounts of perfluoropinacol in nitromethane-*d3* were subjected to ^{11}B NMR measurement (equation 1). A large shift in the ^{11}B NMR from 30 ppm to 15 ppm supports the presence of a tetrahedral boron atom arising from the coordination between the carbonyl and the Lewis acidic boron. The perfluoropinacol boronate was prepared independently from **1a** (equation 2), and it was also subjected to NMR analysis. The same characteristic ^{11}B NMR shift of 15 ppm confirms its formation in the titration studies. Downfield shifts in the ^{1}H and ^{13}C NMR signals for the carbonyl and methoxy groups also suggest an increase in the electrophilicity of the ester (Scheme 5a). These interactions are likely responsible for facilitating the transesterification and promoting the subsequent Beckmann rearrangement.

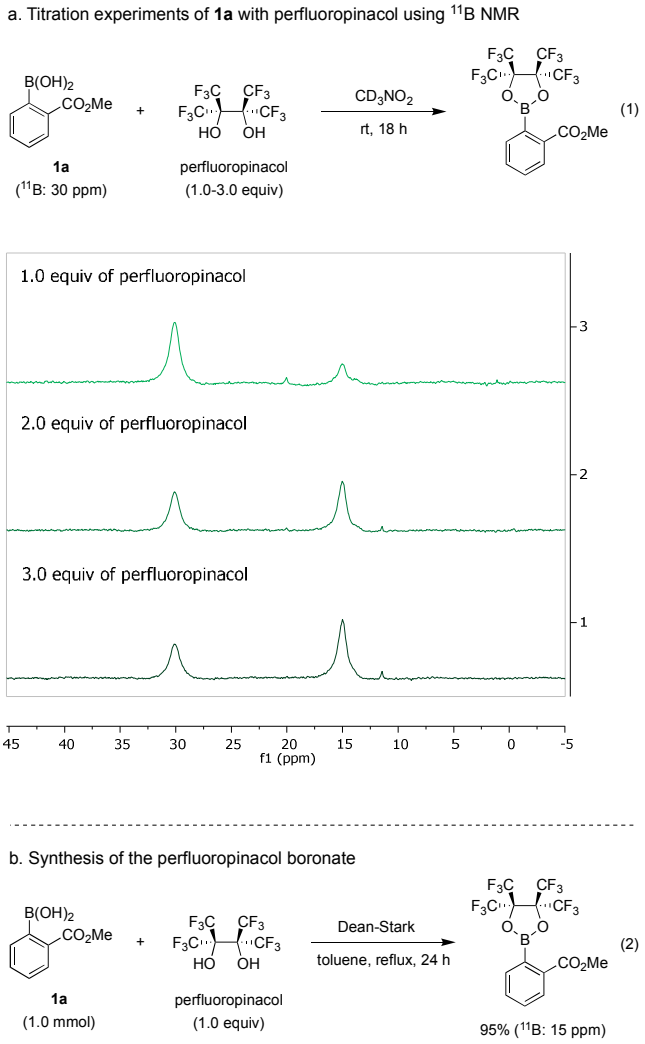
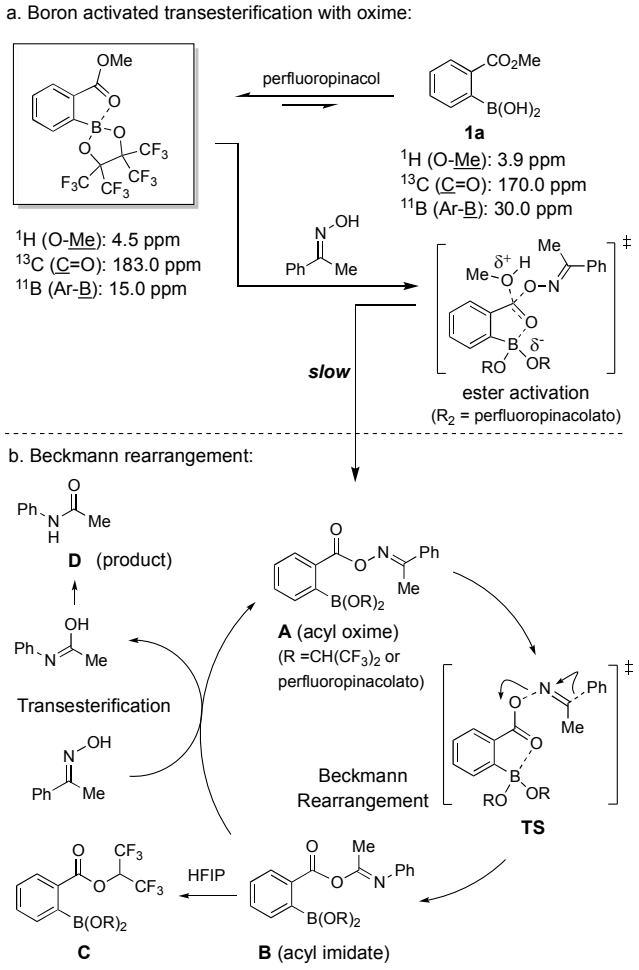


Figure 2. Titration of boronic acid **1a** with various amounts of perfluoropinacol via ^{11}B NMR.

Mechanistic Proposal: True Catalysis vs Self-propagation. Based on the above experiments, a catalytic cycle is proposed in Scheme 5. The catalyst undergoes boronic ester formation with perfluoropinacol resulting in a more electrophilic boron center, which mediates the oxime transesterification by activating the carboxyester and affording catalytic intermediate **A** (Scheme 5a). This boron-assisted oxime transesterification is likely to be the rate-limiting step, a notion supported by the superiority of pre-catalyst **1b** with a better leaving group (OPh). Based on the ability of **A** to rearrange spontaneously and quantitatively in the absence of free oxime (cf. Scheme 4c), this boronic acid induced Beckmann rearrangement likely proceeds via a fully catalytic, unimolecular mechanism. The reactivity of **A** does not support a stepwise bimolecular self-propagating mechanism involving the reaction of a free nitrilium ion with oxime substrate.[21] This sort of stepwise process has been previously shown to lead to dimerized side products with other organocatalysts.[9,12b] These byproducts were not observed when **1a** was used as the catalyst with cyclohexanone oxime, which further supports the proposed mechanism when using **1a**/**1b** as catalytic species.[22]

Although the role of the boronyl unit in the actual rearrangement is unclear, it is reasonable to assume that carboxyl coordination to the electrophilic boronate turns the acyl unit into a very reactive leaving group and thus facilitates the bond migration process (see **TS** in Scheme 5b). Other electron-withdrawing substituents such as nitro (cf. Scheme 3a) are incapable of this sort of internal Lewis acid-promoted activation. The rearranged acyl imidate **B** eventually releases the amide product (**D**) via exchange with another molecule of oxime. Acyl imidate **B** is expected to be a significantly more reactive ester compared to **1a**/**1b** and acyl oxime **A**. Thus, it reacts rapidly by transesterification with oxime substrate to recycle the effective catalyst, acyl oxime **A**. When no more oxime is available, esterification with HFIP, a much weaker nucleophile, leads to **C**, which was detected by MS and ^{1}H NMR (see SI).

Scheme 5. Proposed Catalytic Cycle of Boronic Acid Catalyzed Beckmann Rearrangement



A qualitative reaction progress kinetic analysis of the rearrangement step was performed by monitoring the decomposition of acyl oxime **A** into products **C** and **D** by LC-MS and UV detection (Figure 3). This study confirmed the rapid transformation of acyl oxime (**A**) into the amide and HFIP ester products at ambient temperature. Decay of **A** does not show the linear relationship expected of a zero-order rearrangement. This observation is most likely explained by the involvement of HFIP as a reactant in the probable rate-limiting transesteri-

fication of the acyl imidate intermediate (**B**), a step required to release **C** and **D**. When used as solvent, HFIP thus leads to a pseudo-first-order situation that is reminiscent of the exponential profiles of Figure 3.

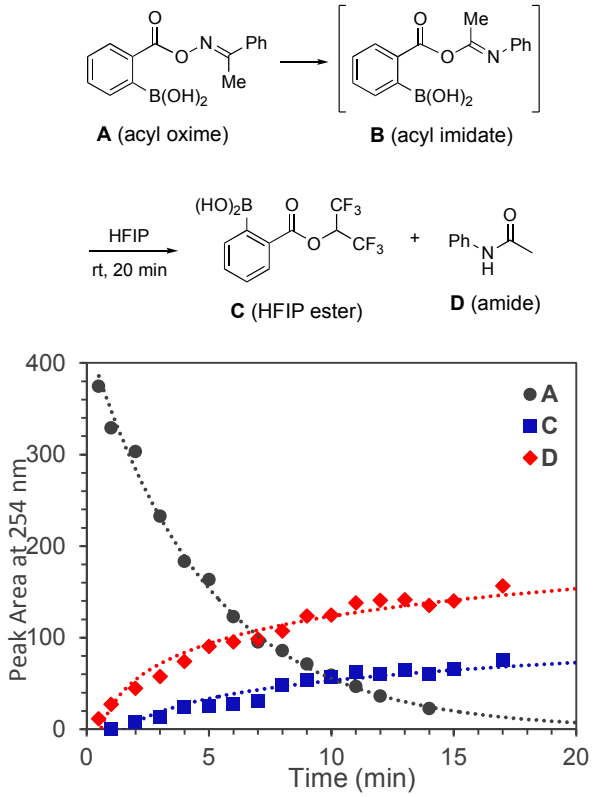
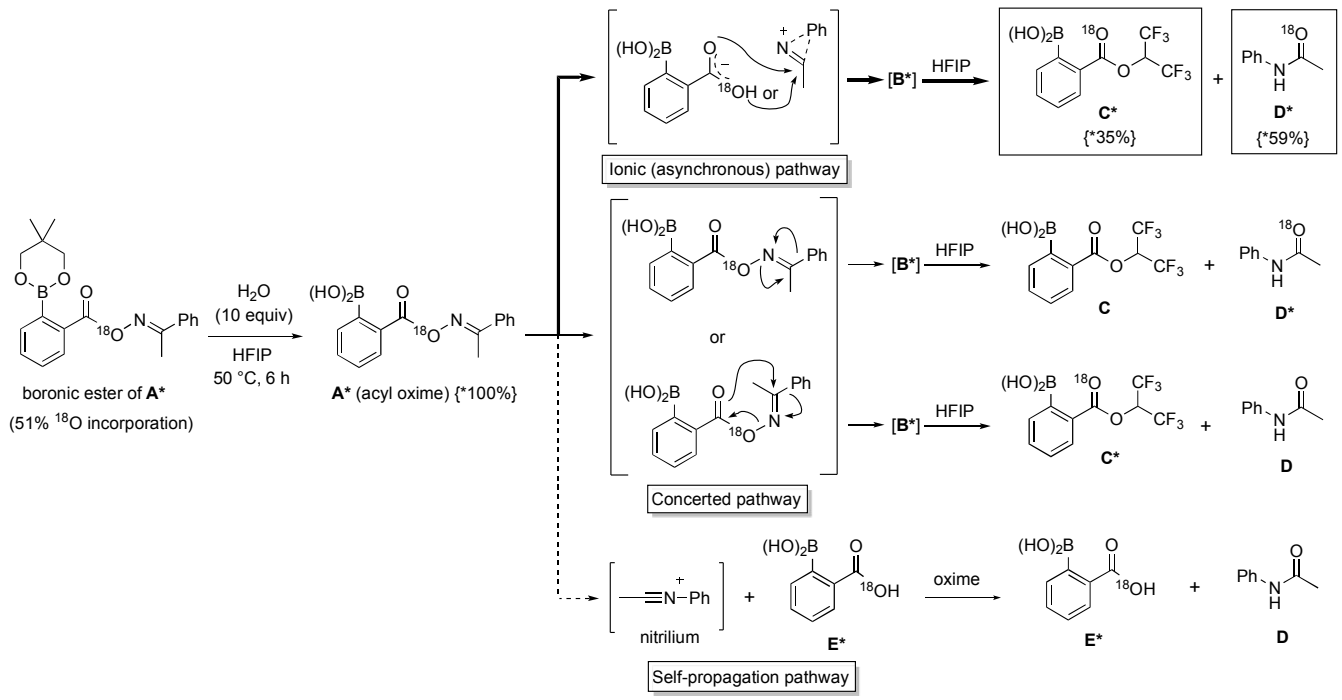


Figure 3. Reaction progress kinetic analysis of the model Beckmann rearrangement of the acyl oxime (**A**) of acetophenone. Relative peak areas on the graph are not normalized.

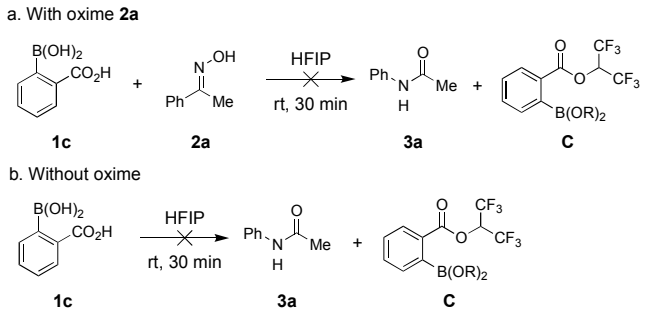
To further support the proposed Beckmann rearrangement mechanism, an isotope labeling study was conducted using ^{18}O-labeled acyl oxime (Scheme 6). If the rearrangement is unimolecular with ionic character, the label should distribute about equally into amide product **D*** and HFIP ester **C***. If the rearrangement step is concerted, depending on the migrating oxygen of the carboxylate unit, the label should be observed exclusively in amide **D*** or, if 1,3-migration of the carboxylate is preferred, it will be observed in HFIP ester **C***. With a self-propagating pathway, the label should be incorporated solely into carboxylic acid **E*** (**1c**). Acyl oxime **A*** was synthesized as a 2,2-dimethylpropanediol boronate with a ^{18}O label onto the sp^3 oxygen. It was prepared with 51% ^{18}O incorporation using a ^{18}O-labeled acetophenone oxime **2a*** made according to a literature procedure.[23] The results of this experiment, which was analyzed by HPLC-MS (selected ion monitoring mode), are shown in Scheme 6. Acyl oxime **B*** was treated in HFIP in the presence of a small amount of water to allow *in situ* boronate hydrolysis to the more reactive boronic acid. In our reaction optimization (cf., Table 1), water was shown not to significantly affect this Beckmann rearrangement procedure. Moreover, the presence of water in this investigation would allow us to confirm or rule out adventitious water as being the origin of the oxygen atom in the amide product. In the event, with **A*** normalized as 100% ^{18}O, less than 6% loss of the ^{18}O label was observed, and the ^{18}O ended up partitioning into HFIP ester **C*** (35%) and amide product **D*** (59%). A negligible amount (<2%) of carboxylic acid **E** was observed. These results confirm that the oxime oxygen atom is the one being incorporated into the amide product, not water, and it also rules out the self-propagating pathway commonly operative with other organocatalysts. Control analysis with authentic 2-carboxyphenylboronic acid (**E**) confirmed that if it formed, carboxylic acid **E** or its boronate form would be easily detected under the LC-MS conditions utilized (see SI). To confidently rule out the self-propagated mechanism, an assumption deduced by the absence of 2-carboxyphenylboronic acid (**E**) from the reaction mixture, it was necessary to confirm that **E** is unable to convert to **C** under the reaction conditions. Indeed, subjecting 2-carboxyphenylboronic acid (**E**) with and without oxime **2a** in HFIP did not lead to the formation of the HFIP ester **C** (Scheme 7).

Thus, product **D*** can only form through the fully catalytic, non-self-propagating mechanism. Partitioning of the ^{18}O label into **C*** and **D*** is in closer agreement with the ionic pathway. With the highly polar solvent used, it is reasonable to envisage that an asynchronous rearrangement through a short-lived ion pair consisting of the carboxylate and the pi-complex could occur. The slight deviation from a non-equal distribution of the label (ie., 59:35 as opposed to 47:47), may be rationalized through two possible explanations (Scheme 8). Because the ^{16}O oxygen is coordinated to the boron atom, the ^{18}O label is initially more "free" to collapse with the pi-complex and form the acyl imidate, thus leading to a disproportionate amount of ^{18}O label into amide **D*** (Scheme 8a). Alternatively, provided formation of the acyl imidate is reversible, complex kinetic isotopic effects and/or equilibrium isotopic effects could manifest and play a role leading to a small bias in favor of **C**/**D*** over **C***/**D**. Nevertheless, with proportions of labeled **B*** and **C*** that are quite similar, the rearrangement mechanism is consistent with the ionic pathway and a true catalytic cycle involving **1a**/**1b** as pre-catalysts and acyl oxime **A** as the effective catalytic species.

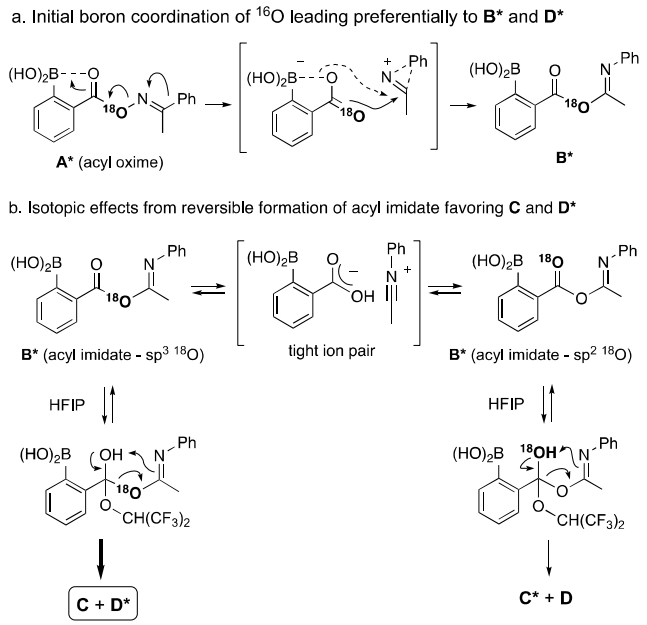
Scheme 6. Rearrangement of ^{18}O-Labeled Oxime **2a***



Scheme 7. Control reactions: non-formation of **C** from **1c**



Scheme 8. Possible pathways for uneven **C***:**D*** proportions



CONCLUSION

In summary, we have identified 2-methoxy/2-phenoxy-carbonyl-phenylboronic acids **1a**/**1b** with catalytic perfluoro-pinacol as chemoselective organocatalysts for the Beckmann rearrangement under mild conditions at ambient temperature. This operationally simple protocol requires no inert atmosphere or pre-drying of solvents and displays a broad scope of oxime substrates and a high functional group tolerance. Mechanistic studies suggest a novel organocatalytic pathway initiated by facile boron mediated transesterification of an oxime, followed by a unimolecular Beckmann rearrangement. The boronyl unit of catalyst **1a**/**1b** plays an active role in both steps of this unique and selective mode of N–OH bond activation. In light of the self-sufficiency and high reactivity of intermediate **A**, and ^{18}O labeling studies, this work identifies a true organocatalytic Beckmann rearrangement mechanism and further expands the scope and utility of the BAC concept.

ASSOCIATED CONTENT

Supporting Information. Experimental details, analytical and spectral reproductions for the prepared compounds. The Supporting Information is available free of charge on the ACS Publications website.

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Author Contributions

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Funding Sources

No competing financial interests have been declared.

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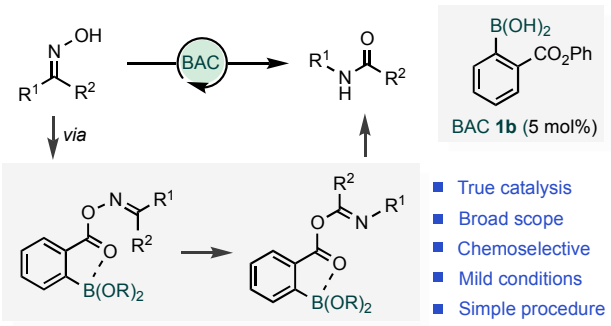
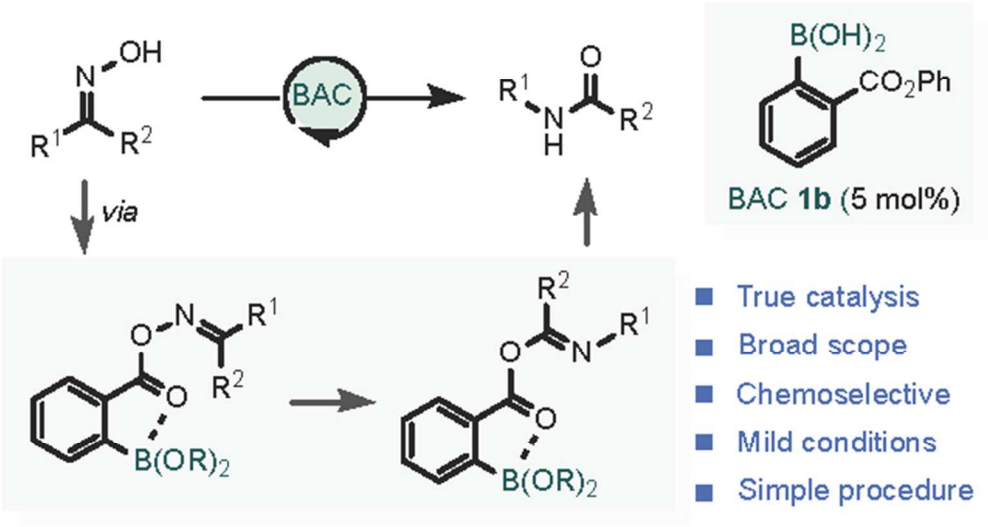
TOC Graphic


BAC
via
B(OH)2
CO2Ph
BAC 1b (5 mol%)
True catalysis
Broad scope
Chemoselective
Mild conditions
Simple procedure



82x44mm (200 x 200 DPI)