Unlocking copper catalysis with nitro compounds: Synthesis of functionalized allylboranes from allylic nitroalkanes

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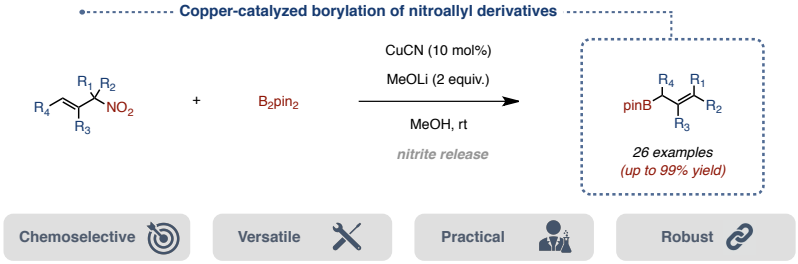
Supporting Information

ABSTRACT: A copper-catalyzed borylation of allylic nitroalkanes is reported. The method, which exploits the high versatility of the nitroalkane precursors, tolerates a variety of functional groups and allows a straightforward access to diversely substituted allylboronic esters in high yields. This unprecedented reactivity towards copper complexes has been further exploited in the synthesis of a number of γ-fluoroallyl boronic esters starting from readily available α-fluoroallyl nitroalkanes, as well as in various post-functionalizations towards synthetically useful building blocks. Both the reaction mechanism and the chemoselectivity have been rationalized experimentally and through DFT calculations.



KEYWORDS: Copper catalysis, borylation, nitroalkanes, allylboronic esters, fluoroallyl boronic esters

■ INTRODUCTION

Allylboronic esters are an important class of compounds used in a variety of transformations. Their moderate nucleophilic character offers a high functional group tolerance, making them ideal for the synthesis of structurally complex molecules.[1] Allylboronic esters are also commonly used to react with aldehydes, ketones and imines to form the corresponding homoallylic derivatives with high levels of enantio- and diastereocontrol.[2] Hence, the development of new methods allowing a straightforward, sustainable and ideally inexpensive access to these compounds is of great importance. Several strategies have been reported over the years.[3-6] The first one involves the addition of highly reactive organometallic species such as Grignard reagents on trialkoxyboranes and subsequent addition of a diol,[3] however, although effective, this approach suffers from an easy 1,3-metallotropic shift of the organometallic species, which leads to a mixture of the linear and the branched allylboranes, thus limiting this method to the simplest allylboronic esters. Since the mid-90s and the pioneering work of Miyaura[4] and Ito[5] on the palladium- and copper-catalyzed borylation of allylic acetates (Figure 1. **A**), the development of transition metal-catalyzed borylation of allylic derivatives has tremendously facilitated the synthesis of these compounds. As a matter of fact, these two seminal works have prompted the development of several other borylation reactions using either different transition metal catalysts such as Fe, Co, Pt and Ni, or other leaving groups such as a phosphates, ketals and fluoride.[6] These methods are however usually limited in scope due to the syntheses of the allylic precursors which often require the use of strong nucleophiles or reducing agents, ultimately restricting the functional group tolerance. The development of a borylation reaction involving allylic nitroalkanes appeared to us as a promising alternative as it would circumvent all these issues and provide a direct access to highly functionalized allylboranes. Indeed, the acidity of the protons α to the nitro group allows an easy functionalization of the allylic position using reactions that are mostly compatible with a large variety of functional groups such as the Henry and the Mannich reactions, the Knoevenagel condensation or the Michael addition just to name a few.[7] This approach appeared slightly counter-intuitive at first as there was evidence of redox incompatibility between the nitro group and diborane species leading to the formation of reduced compounds as shown by Niggemann[8] and Wu[9] (Figure 1. **B**). Nonetheless, by

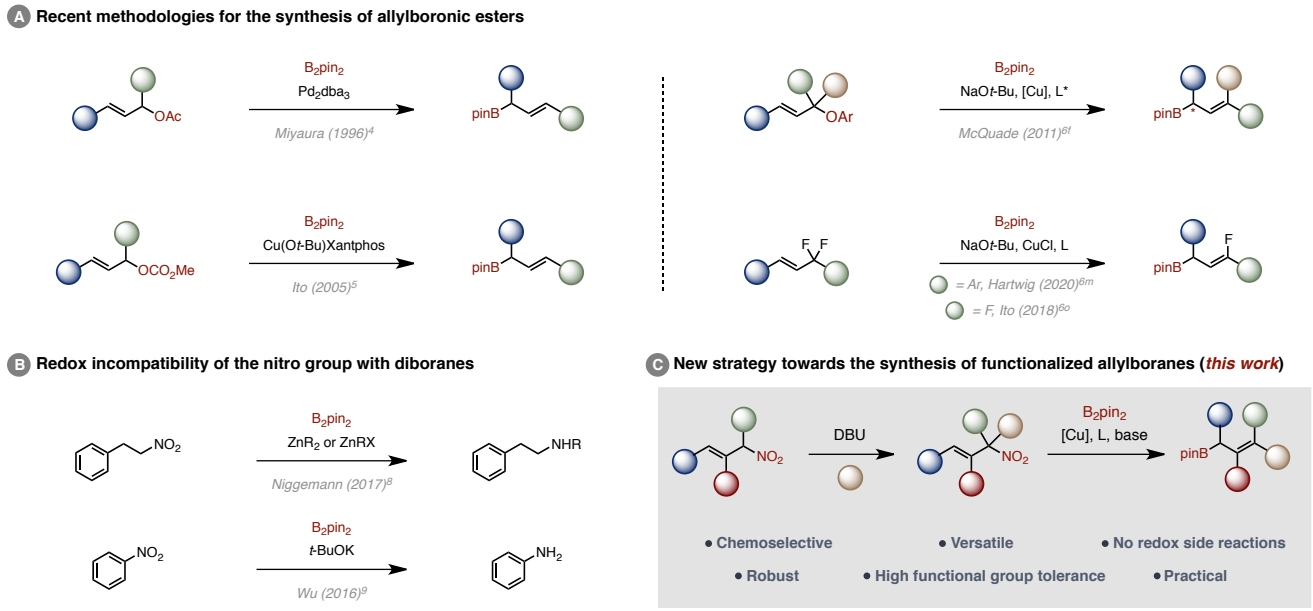


Figure 1. Strategies for the synthesis of allylboronic esters.

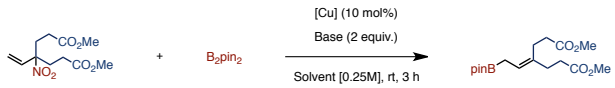
taking advantage of the kinetics of the borylation reaction, we believed we can tame the reducing ability of the boronate species and favour the borylation process over the reduction of the nitro group.

■ RESULTS AND DISCUSSION

Our journey began with the evaluation of the redox compatibility of allyl nitroalkanes with B_2Pin_2 in the presence of various copper salts. We chose allyl nitroalkane **1a** as our model substrate. The latter was prepared in four steps and 28% overall yield starting from nitromethane (see SI for more details). Our first borylation reaction run in THF at rt using 10 mol% of CuI and 2 equiv. of *t*-BuOLi led to the desired allylboronic ester **2a**, albeit in only 18% yield (Table 1, entry 1). Interestingly, changing the solvent to methanol considerably increased the yield to 72% (Table 1, entry 3). A similar result was also observed when replacing *t*-BuOLi with *t*-BuOK, MeOLi or Cs_2CO_3 (Table 1, entries 4-6). In sharp contrast, the use of a weaker base such as NaOAc did not lead to any product formation (Table 1, entry 7). The nature of the copper salt was also examined. Hence, replacing CuI by $Cu(OAc)_2$ (Table 1, entry 8) appeared to be detrimental, while Cu(I) salts bearing a hard counter anion demonstrated a better catalytic activity as showcased by the use of CuCN, which led to full conversion and 89% isolated yield (Table 1, entry 10). The reaction could also be run using only 2 mol% of CuCN, however longer reaction times were required (Table 1, entry 11). Finally, CuClXantphos (Table 1, entry 12), which was also employed by Ito and co-workers in the first borylation of allylic carbonates, demonstrated a similar efficacy but was discarded for a question of cost and practicality.

With these first results in hand, we next explored the scope of the reaction by subjecting a variety of allylic nitroalkanes to our optimized borylation conditions [CuCN (10 mol%), MeOLi (2 equiv.), B_2pin_2 (2 equiv.), MeOH, rt]. As shown in Figure 2, all the resulting allylboranes **2a-g** were obtained in high yields independently of the nature of the starting terminal olefin **1a-g**. In the case of non-symmetrical α-disubstituted nitro allyl derivatives, the two resulting diastereoisomers were generally obtained in a roughly 4:1 ratio, although in the case of compound **1f**, the two stereoisomers were obtained in equal amounts, thus suggesting the importance of the size of the substituents on the selectivity outcome. Interestingly, in the case of compound **1g** bearing a silyl-protected allylic alcohol, the two stereoisomers were obtained in a roughly 1:1 ratio, but the *Z* isomer further reacted to afford the corresponding dihydro-oxaborinin product **2g'**.

Table 1. Systematic study[a]



Entry	[Cu]	Base	Solvent	Conversion (%)[b]	Yield (%)[b]
1	CuI	*t*-BuOLi	THF	100	18
2	CuI	*t*-BuOLi	DMF	100	55
3	CuI	*t*-BuOLi	MeOH	85	72
4	CuI	*t*-BuOK	MeOH	85	63
5	CuI	MeOLi	MeOH	85	72
6	CuI	Cs_2CO_3	MeOH	85	72
7	CuI	NaOAc	MeOH	0	0
8	$Cu(OAc)_2$	MeOLi	MeOH	80	55
9	CuBr·Me_2S	MeOLi	MeOH	85	72
10	**CuCN**	**MeOLi**	**MeOH**	**100**	**91 (89[c])**
11	CuCN	MeOLi	MeOH	100	85[d]
12	CuClXantphos	MeOLi	MeOH	95	85
13	-	MeOLi	MeOH	0	0
14	CuCN	-	MeOH	0	0

[a]**Reaction conditions: 1a** (0.2 mmol, 1 equiv.), B_2pin_2 (0.4 mmol, 2 equiv.), base (0.4 mmol, 2 equiv.), solvent (0.8 mL), rt, 3 h. [b]Determined by NMR using 1,3,5-trimethoxybenzene as an internal standard. [c]Isolated yield. [d]Reaction run using 2 mol% of [Cu].

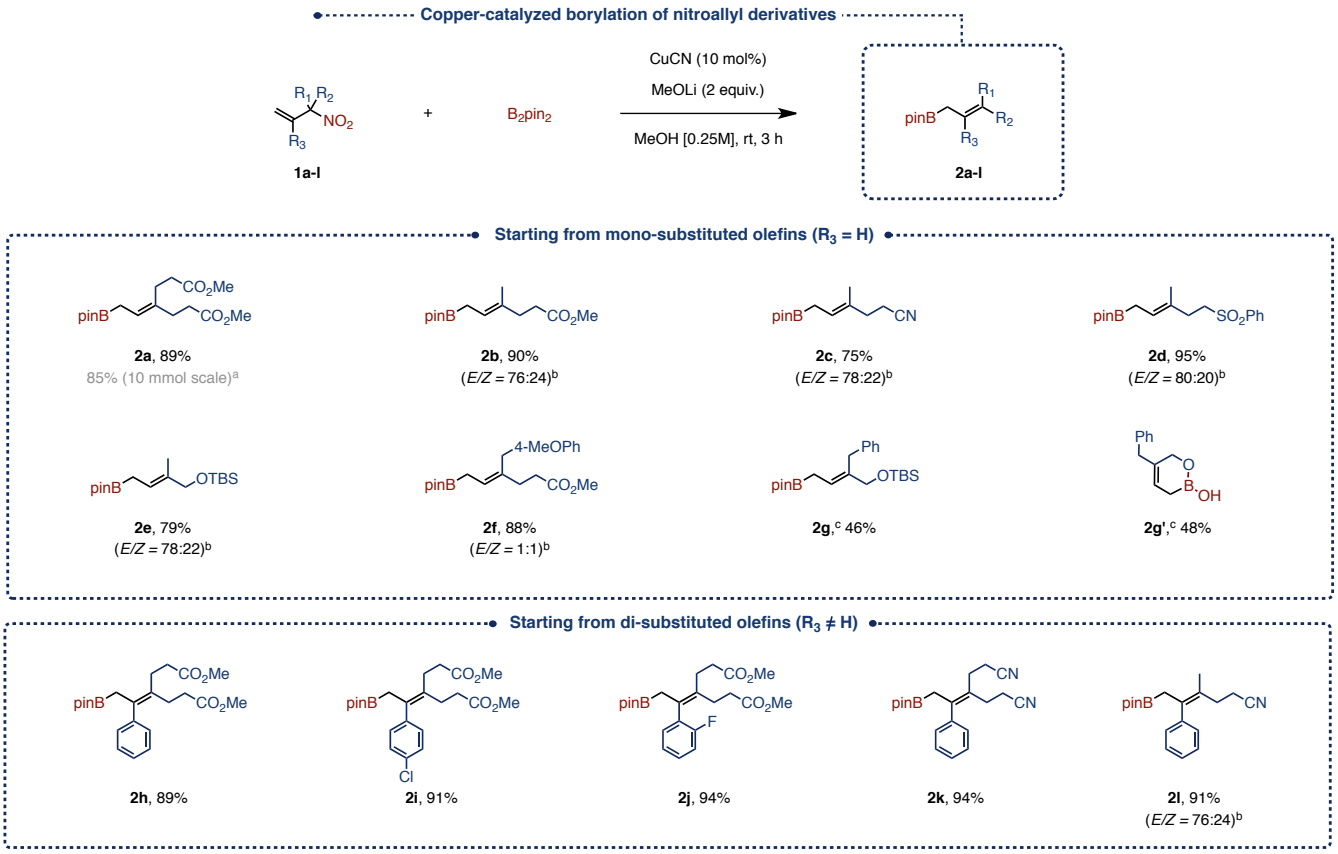


Figure 2. Substract scope. [a]Reaction run using 2 mol% of CuCN. [b]Determined by ^{1}H NMR on the crude reaction mixture. [c]Reaction run over a period of 24 h.

The reaction also proved equally effective when applied to gem-disubstituted terminal olefins such as **1h-l**. Indeed, the corresponding allylboranes **2h-l** were obtained in high yields ranging from 89 to 94% with once again a roughly 3:1 ratio of the two diasteroisomers in the case of the non-symmetrical α-disubstituted precursors.

Finally, the reaction proved to be easily scalable as the borylation of nitroalkane **1a** run on a 2.6 g scale (10 mmol) afforded the corresponding borylated product **2a** in 85% isolated yield.

Overall and as anticipated, the use of nitro allyl precursors allowed to easily introduce functional diversity around the allyl moiety with groups such as esters, cyanides, sulfones and silyl-protected alcohols. But most importantly, our borylation method proved particularly effective as all the allylic nitroalkanes tested readily underwent borylation independently of the substitution pattern on the allyl moiety thus offering a straightforward access to tri- and tetrasubstituted allylboranes in usually excellent yields. This appeared to be all the more appealing that this allylic substitution approach offers a new entry to functionalized tetrasubstituted allylboronates.[10]

Reaction mechanism study. In contrast to other leaving groups employed in previous borylation studies,[6d-g,11,12] we can reasonably expect the NO_2 moiety to interact with the metal at different stages of the mechanism and potentially favor one pathway over another. To address this question, we modeled the entire reaction mechanism by means of DFT calculations. We used the ωB97X-D functional together with the 6-31G(d) basis set (see SI for more details).[13] We chose 3-methyl-3-nitrobutene as a model substrate and CuXantphos(Bpin) as the active organometallic species.

As shown in the free energy profile represented in Figure 3A, the reaction starts with the activation of the catalyst followed by its coordination with the substrate through a highly stabilizing process (–32 kcal.mol^{-1}). This leads to the formation of the reactive complex, which exhibits two conformers noted **R-*syn*** and **R-*anti*** that differ by the relative positioning of the NO_2 group with respect to the Cu. While we expected the **R-*syn*** conformer to favor the coordination of the metal by the NO_2 moiety, it turned out that the **R-*anti*** conformer was more stable by 3.1 kcal.mol^{-1}.

The following chemical step, namely the cupro-borylation of the alkene moiety, is then initiated from either the **R-*syn*** or the **R-*anti*** conformer. This results in a transition state that is slightly higher in free energy for the *syn*-cupro-borylation (**TS1-*syn***) than for its *anti*-counterpart (**TS1-*anti***). However, it is worth stressing that despite these differences in energy, both the *anti*- and the *syn*-cupro-borylation pathways exhibit very fast kinetics owing to very small energy barriers (<10 kcal.mol^{-1}) and are therefore almost equally likely to occur.

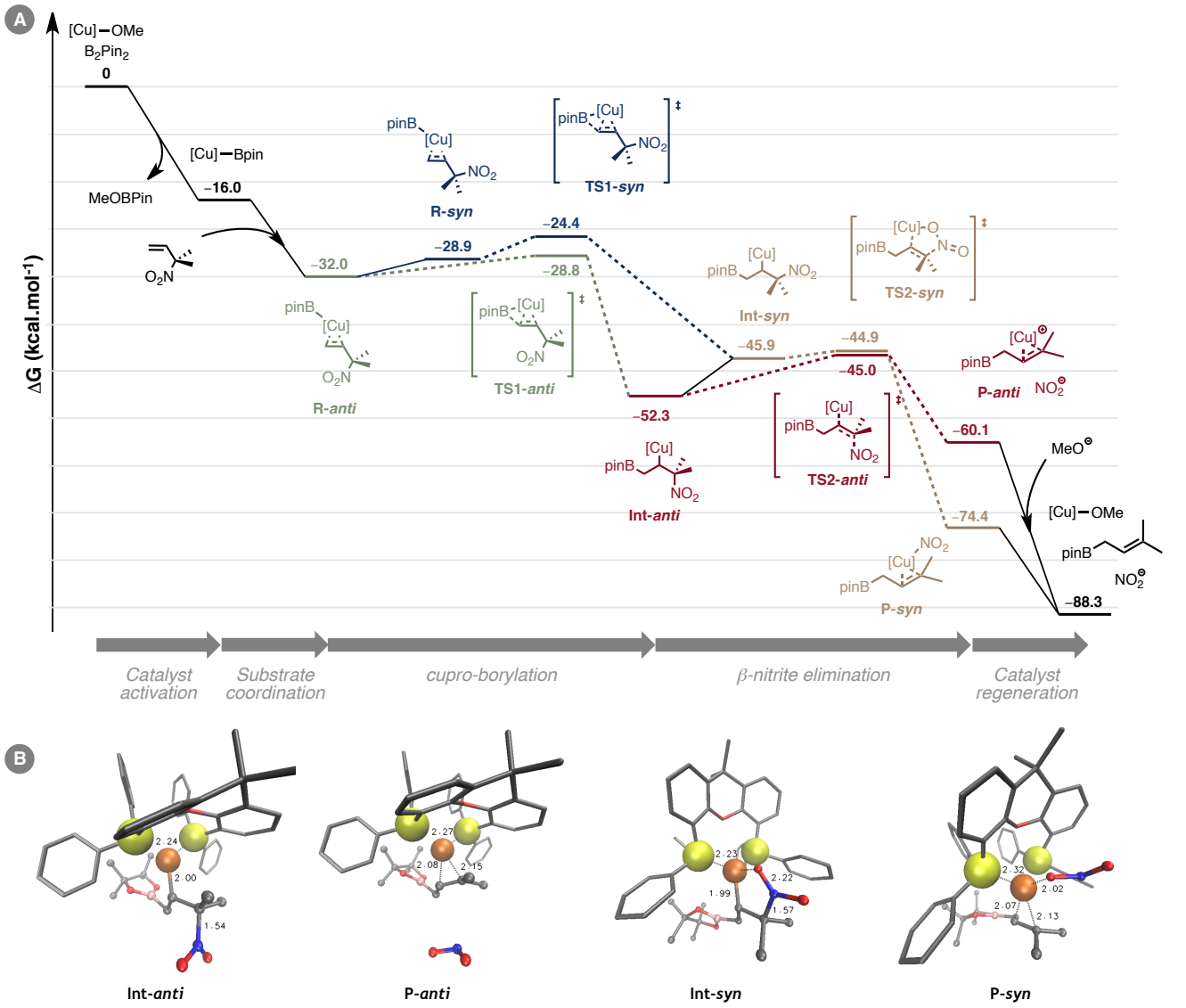


Figure 3. DFT study of the complete reaction mechanism of the cupro-borylation of the alkene moiety followed by the β-nitrite elimination leading to the allylborane. (**A**) Computed free energy profiles. Conformational equilibrium and chemical reactions are represented with plain lines and dashed lines, respectively. (**B**) Relevant structures for the rationalization of the energy differences during the *syn* and *anti* elimination step of the NO_2 group. For sake of clarity, hydrogen atoms were omitted. All the 3D structures for all the stationary points are provided in the SI (Table S1).

The cupro-borylation step leads to the formation of two conformers of the same alkyl copper intermediate noted **Int-*syn*** and **Int-*anti***. These two conformers are in thermal equilibrium prior to the next chemical step. **Int-*anti*** is the most stable and is a local resting state of the system with a stabilization free energy of –20 kcal.mol^{-1} with respect to **R-*anti***. The relative stability of **Int-*anti*** *vs* **Int-*syn***, was rationalized in terms of internal non-covalent interactions within the complex. We evaluated the strength of these interactions by means of additional DFT calculations involving the so-called NCIPLOT analysis (see SI for more details).[14] Our calculations revealed that **Int-*syn*** exhibits a local Pauli repulsion between the electron cloud of the Cu atom and that of the nearby oxygen of the NO_2 group (see Figure S2 in the SI). There is indeed no stabilizing interaction between the two moieties.

The next chemical step is the β-nitrite elimination, which again proceeds through either an *anti*- or a *syn*-type mechanism. The two alternative pathways, namely **Int-*anti*** → **TS2-*anti*** and **Int-*anti*** → **Int-*syn*** → **TS2-*syn*** exhibit virtually the same small activation barrier of roughly 7 kcal.mol^{-1}. In both cases, the chemical step leads to a Cu complex, **P-*anti*** or **P-*syn***, which ultimately decomposes to form the final allylborane through a highly stabilizing process.

Overall, after considering the four pathways (two chemical steps, each with either a *syn* or an *anti* mechanism), we were able to show that in the case of the symmetrical allylic nitroalkanes, the reaction proceeded through the four pathways with no significant discrimination.

Extension of the scope. Encouraged by these results, we decided to extend the method to fluorinated allylic nitroalkanes as this would provide a straightforward access to

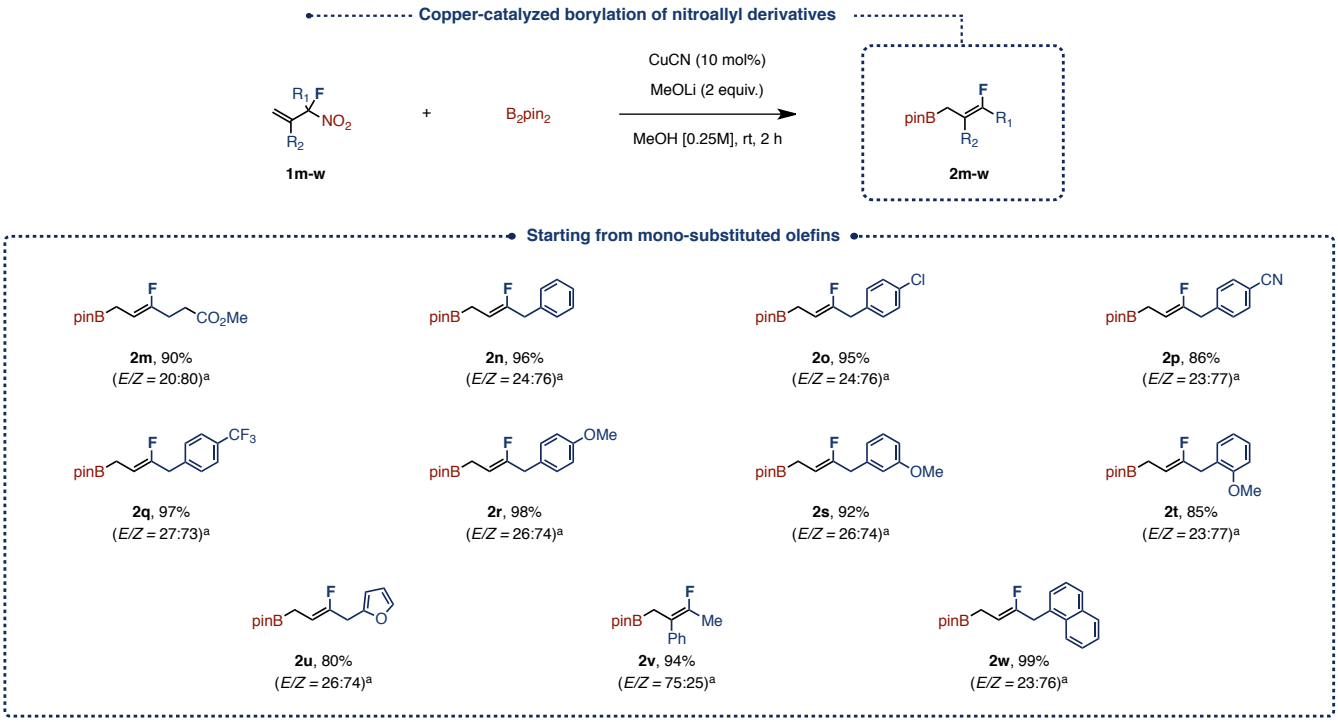


Figure 4. Synthesis of γ-fluoroallyl boronic esters. [a]Determined by ^{1}H NMR on the crude reaction mixture.

γ-fluoro-allylboronic esters. To that effect, a fluorination procedure was developed on various nitro olefin precursors using SelectFluor as an electrophilic source of fluorine.[15] The corresponding fluorinated nitro allyl derivatives **1m-w** were obtained in high yields (see SI for full details). The latter were engaged in our borylation reaction under the previously optimized conditions, affording the exclusive formation of the γ-fluoro-allylboronic esters **2m-w** in excellent yields ranging from 85 to 99% (Figure 4). Once again, the reaction tolerated a variety of functional groups including cyanides, esters and halogens and didn't lead to any loss of fluorine during the process, which was one of the risks as fluoro-allyl derivatives are known to readily undergo borylation under Cu-catalysis.[6k-l,12a-b]

Rationalization. To rationalize the excellent chemoselectivity observed, we performed additional DFT calculations. Both the *syn*- and *anti*-elimination pathways of the nitrite and the fluoride were modeled using the same computational setup as previously. The corresponding free energy profiles are represented in Figure 5, **A**. As a general trend, our calculations show that the *syn*-elimination is always favored independently of the leaving group for thermodynamic reasons; the relative free energies of each product are such that $\Delta G_{P\text{-}syn\text{-}F} \approx \Delta G_{P\text{-}syn\text{-}NO2} << \Delta G_{P\text{-}anti\text{-}NO2} << \Delta G_{P\text{-}syn\text{-}F}$. In addition, **TS-*syn*-F** is higher in free energy than **TS-*syn*-NO$_2$** by 4 kcal.mol^{-1}. This difference in activation energies between the two *syn* elimination pathways can be rationalized by analyzing the structural reorganizations that are required to reach these transition states, from the initial most stable conformer ***anti*-NO$_2$**. It is worth noting that the *syn* elimination of the NO_2 group first requires a conformational transition, namely ***anti*-NO$_2$ → *syn*-NO$_2$**, that is significantly destabilizing (+6.6 kcal.mol^{-1}). This destabilization is due to a Pauli repulsion between the electron cloud of the nitro group and the Cu center, in a similar way to the case of 3-methyl-3-nitrobutene discussed above. The same initial conformational transition that is required for the *syn* elimination of the fluorine, namely ***anti*-NO$_2$ → *syn*-F**, is less destabilizing by +4.9 kcal.mol^{-1} due to the weaker Pauli repulsion between the fluorine atom and the copper as suggested by the longer distance between the copper and the fluorine atom (2.82 Å) compared to the one observed in ***syn*-NO$_2$** between the copper and the NO_2 group (2.33 Å) (Figure 5, **B**). However, once ***syn*-F** is obtained, the system needs to go through a strained 4-membered ring transition state, namely **TS-*syn*-F**, to complete the chemical step. In contrast, the transition state arising from ***syn*-NO$_2$**, namely **TS-*syn*-NO$_2$**, is a five-membered ring which turns out to be significantly more stable by 4 kcal.mol^{-1} than **TS-*syn*-F**.

Extention of the method. Following these results, we decided to extend the method to 1,2-disubstituted allylic nitroalkane precursors with the idea to further extend the scope to secondary allylic boronic esters. To that effect, **3a** was prepared and subjected to our borylation conditions. Unfortunately, no conversion was observed and new conditions needed to be found (Figure 6, **A**). The typical reaction conditions developed by Ito and co-workers [B_2pin_2 (2 equiv.), MeOK (2 equiv.), CuClXantphos (5 mol%), THF, rt] led to only 20% conversion of the starting material and 12% yield (entry 1). Luckily, by switching the solvent to MeOH and

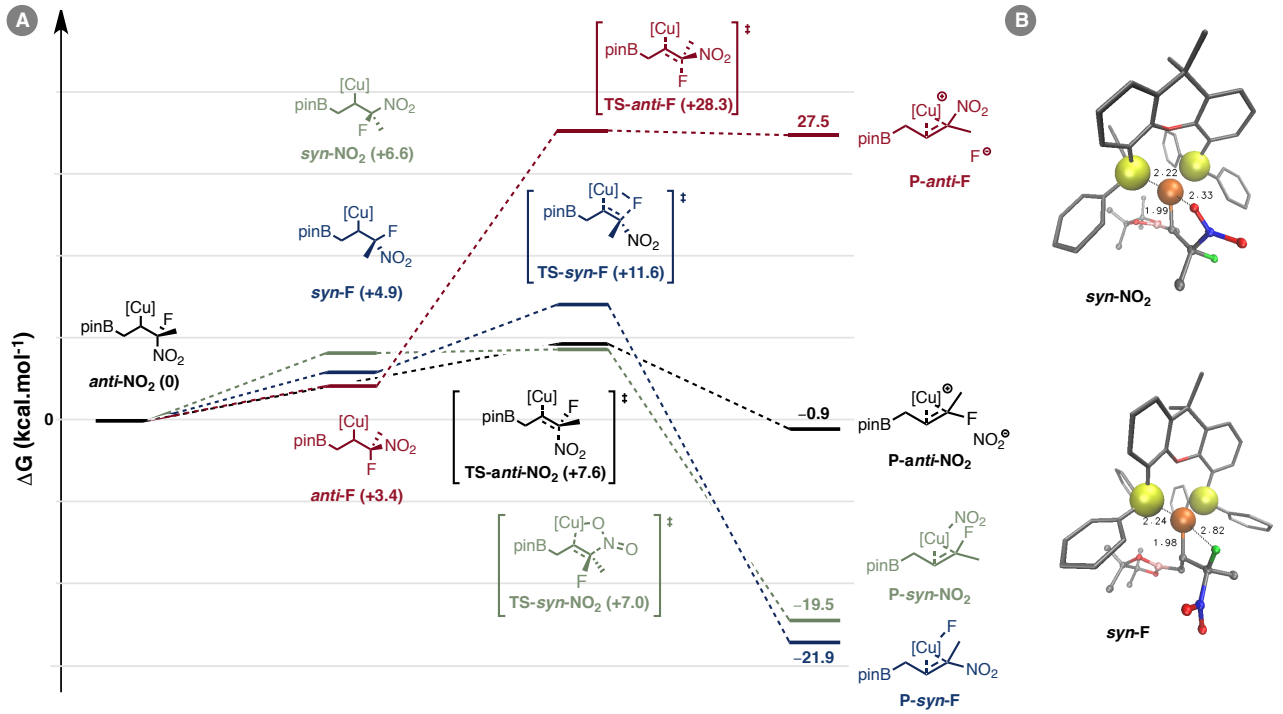


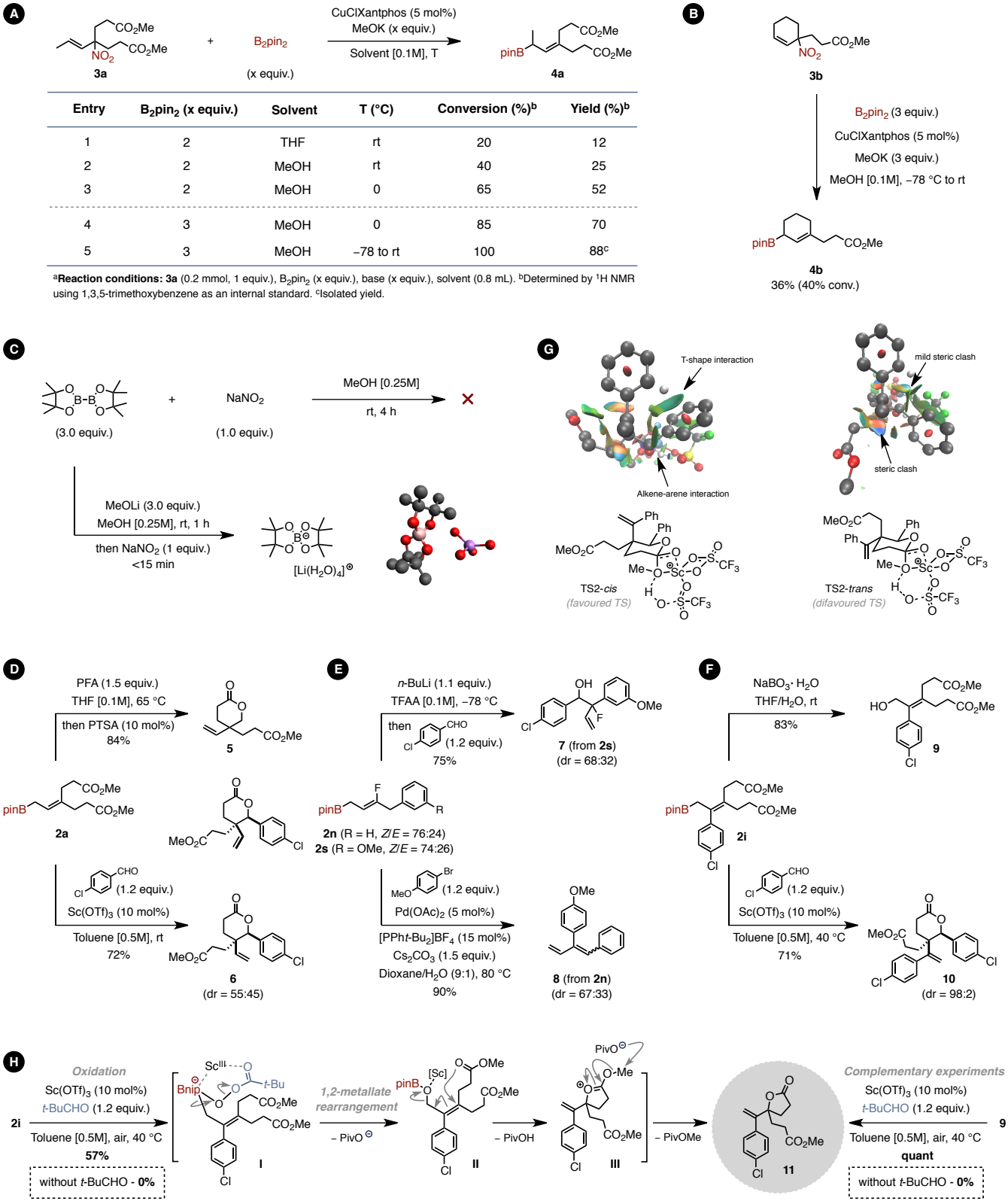
Figure 5. Comparison of the β-elimination pathways with the nitro and the fluorine leaving groups. (**A**) Free energy profiles. (**B**) Geometries of the *syn*-alkyl copper complexes for the *syn* nitrite elimination (top) and *syn* fluoride elimination (bottom). For sake of clarity, hydrogen atoms were omitted.

by running the reaction at 0 °C instead of rt, we were able to boost the yield to 52% (entry 3). Increasing the amount of B_2Pin_2 to 3 equiv. also improved the yield (70%, entry 4), however the best result was obtained by adding the base at –78 °C and letting the temperature slowly rise to rt. This afforded the desired allylboronic ester **4a** in 88% yield (entry 5). The same conditions were eventually applied to substrate the nitrocyclohexene derivative **3b** (Figure 6, **B**), however the reaction was more sluggish, affording **4b** in 36% yield (90% brsm).

To identify any off-cycle reaction that could consume B_2Pin_2 and thus explain the low conversions observed, we ran a series of test reactions (Figure 6, **C**). Based on previous reports describing the reduction of the nitro group by diborane species, we first envisioned that B_2Pin_2 could potentially interact with the allylic nitroalkane leading to the formation of reduced products. However, none were detected, even in trace amounts. Consequently, we hypothesized that the nitrite anion released during the reaction could perturb the catalytic cycle by interacting with the copper complex and B_2Pin_2. To test this hypothesis, we generated the ate complex in MeOH in the presence of sodium nitrite. Interestingly, after a few minutes, a slight increase in temperature was observed accompanied by gas evolution and the formation of a precipitate, which structure was confirmed by X-Ray analysis (Figure 6, **C**), thus demonstrating the presence of an off-cycle reaction leading to *in situ* B_2Pin_2 degradation. As a consequence, in the case of more hindered allylic nitroalkanes, which are arguably less reactive, the nitrite released during the reaction oxidizes the ate complex generated *in situ*, which inhibits the reaction and explains the poor conversion observed.

Post-functionalisations. With all these highly substituted allylboranes in hand, we were curious to exploit their inherent reactivity in various post-transformations. In this context, allylborane **2a** was easily converted to the corresponding δ-lactone **5** in presence of paraformaldehyde (1.5 equiv.) and PTSA (10 mol%) (Figure 6, **D**). When the reaction was run with *p*-chlorobenzaldehyde, the use of $Sc(OTf)_3$ was necessary to increase the rate of the reaction. The resulting δ-lactone **6** was obtained in a good 72% yield, albeit with a poor diastereoselectivity of 45:55 in favor of the *trans*-lactone.[16] Two γ-fluoroallylboranes (**2n** and **2s**) were also engaged in post-transformations (Figure 6, **E**). Hence, the use of **2s** in the allylation of *p*-chlorobenzaldehyde under the conditions developed by Aggarwal and co-workers[17] afforded the corresponding β-fluoro alcohol **7** in 75% yield. Compound **2n**, on the other hand, was engaged in a Pd-catalyzed Suzuki/dehydrofluorination cascade leading to the formation of diene **8**, which was obtained in an excellent 90% yield.

More hindered allylboranes such as **2i** were also very reactive (Figure 6, **F**). The C–B bond for instance was readily oxidized with $NaBO_3{\cdot}H_2O$ to afford the corresponding allylic alcohol **9** in 83% yield. The allylation of *p*-chloro benzaldehyde with **2i** afforded the corresponding δ-lactone **10** in 71% yield and an excellent 98:2 diastereoselectivity, which contrasts with the roughly 1:1 ratio obtained when the reaction was run on **2a**. This difference in diastereoselectivity can be explained by the presence of π-interactions between the two aryl moieties. This hypothesis was verified by modeling the two cyclization modes associated with the formation of the *trans* and the *cis* lactones (Figure 6, **G**). Analysis of non-covalent interactions using NCIPlot software (see *SI* for additional details) in the transition states of the



Entry	B_2pin_2 (x equiv.)	Solvent	T (°C)	Conversion (%)[b]	Yield (%)[b]
1	2	THF	rt	20	12
2	2	MeOH	rt	40	25
3	2	MeOH	0	65	52
4	3	MeOH	0	85	70
5	3	MeOH	−78 to rt	100	88[c]

[a]**Reaction conditions: 3a** (0.2 mmol, 1 equiv.), B_2pin_2 (x equiv.), base (x equiv.), solvent (0.8 mL). [b]Determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard. [c]Isolated yield.

Figure 6. (**A**) Optimization of the reaction conditions for 1,2-disubstituted alkenes. (**B**) Extension to internal alkenes. (**C**) Redox compatibility test between diborane species and sodium nitrite (top). Redox compatibility test between ate-complex and sodium nitrite (bottom). (**D**) Synthesis of δ-lactones *via* allylation and subsequent cyclization. (**E**) Derivatization of monofluoro allylboranes: allylation of *p*-chlorobenzaldehyde (*top*), synthesis of dienes through a Pd-catalyzed Suzuki/dehydrofluorination cascade (*bottom*). (**F**) Derivatization of tetrasubstituted allylboranes: oxidation to the corresponding allylic alcohol (*top*); synthesis of γ-lactones through an oxidation/lactonization cascade (*center*); diastereoselective synthesis of δ-lactones *via* allylation and subsequent cyclization. (**G**) NCIplot of transition states associated with the elimination of methanol: strong stabilizing interactions are highlighted in blue, weak interactions are highlighted in green and strong destabilizing interactions are highlighted in red. Transition state leading to the major compound with the two aryl rings in a *cis* conformation (*left*); Transition state leading to the formation of the minor compound with the two aryl rings in a *trans* conformation (*right*). (**H**) *t*-BuCHO/$Sc(OTf)_3$-mediated formal γ-oxidation/lactonisation of **2i** and **9** leading to γ-lactone **11**. [PFA = paraformaldehyde]

methanol elimination during the lactonization step revealed the presence of a T shaped π-stacking interaction between the aryl groups, as well as an alkene-arene π-stacking interaction during the formation of the *cis* lactone. These stabilizing interactions, which are not present in the TS leading to the formation of the *trans* lactone offer a free energy difference of 4.5 kcal.mol^{-1} in favor of the formation of the *cis* lactone.

Surprisingly, when **2i** was reacted with pivaldehyde, the expected allylation product could not be detected; instead we isolated γ-lactone **11** in 57% yield (Figure 6, **H**). To understand this unusual formal γ-oxidation/ lactonization cascade, we carried out a set of reactions. A first reaction run in the absence of pivaldehyde did not produce γ-lactone **11** but afforded alcohol **9** instead in 19% yield. Interestingly, when the latter was engaged in the same reaction, γ-lactone **11** was obtained quantitatively, while in the absence of pivaldehyde the reaction failed to produce the lactone, thus suggesting that pivaldehyde was crucial both for the oxidation of the allylboronate and the lactonization. With these results in hand, we propose a mechanism where pivaldehyde is first oxidized to the corresponding peracid, which then reacts with the pinacolboronic ester to form "ate" complex **I**. The latter undergoes a 1,2-metallate rearrangement to generate intermediate **II** along with a pivalate anion. In the presence of $Sc(OTf)_3$, the borylated alcohol is eliminated through an S_N2' type reaction facilitated by one of the ester groups, thus generating oxonium **III**. Finally, the pivalate anion released in the previous step abstracts the methyl group to produce the desired γ-lactone **11** along with methyl pivalate.

■ CONCLUSION

In summary, we have reported a novel reactivity for allylic nitroalkanes, which can now be used as valuable precursors for the synthesis of diversely substituted allylic boronic esters through a copper-catalyzed borylation. Moreover, this is the first time a metal is used to catalyze the borylation of nitro allyl derivatives. The method is chemoselective favouring C–NO_2 fragmentation over NO_2 reduction. It is high yielding, scalable, easy to set up, affordable, highly functional group tolerant and applicable to the synthesis of polysubstituted allylic boronic esters, which are valuable synthetic platforms as showcased in various post-transformations. The method is also highly versatile as the allylic nitro derivatives can be easily prepared from readily available nitroalkene precursors, a strategy best pictured in our fluorination/borylation process towards fluorinated allyl boronic esters. A comprehensive density functional theory study has helped us gather some valuable insights into the reaction mechanism and the origin of the diastereoselectivity. We believe this work will pave the way to further developments in the field of copper-catalyzed allylations.

■ ACKNOWLEDGMENTS

The authors gratefully thank Ecole Polytechnique, ENSTA-Paris and Queen Mary University of London for financial support.

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