Pd-Catalyzed Direct Deoxygenative Arylation of Non-π-Extended Benzyl Alcohols with Boronic Acids via Transient Formation of Non-Innocent Isoureas

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Pd-catalyzed, direct deoxygenative arylation of non-π-extended benzyl alcohols with boronic acids via transient formation of non-innocent isoureas

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Non-innocent electrophiles, palladium, cross-coupling, base-free, carbodiimide.

ABSTRACT: We report the direct arylation of non-derivatized alcohols with boronic acids and demonstrate that a Pd catalyst, in combination with a carbodiimide, can be used to forge a C−C bond via the transient formation of non-innocent isoureas from the corresponding alcohols. Besides further polarizing the C−O bond, the transiently generated isourea contains a masked base which is released during the reaction to enable catalytic turnover under exogenous base-free conditions. The developed concept was benchmarked against the coupling of non-π-extended benzyl alcohols and boronic acids and led to the formation of a C−C bond between differently decorated coupling partners. Notably, the strategic generation of non-innocent isoureas endows this C−O cleavage reaction with high orthogonality over conventional electrophiles, and enables the employment of highly base-sensitive boronic acids. Additionally, the preformed isoureas can be leveraged for rapid (5 min reaction time) exogenous base-free coupling reactions which work under conventional thermal conditions and do not rely on customized catalysts nor specialized equipment. The synthetic investigations were also complemented by preliminary mechanistic studies. More broadly, the presented work bridges a conceptual gap between two important research areas, i.e. carbodiimide-mediated alcohol activation and deoxygenative transition-metal catalyzed coupling chemistry, providing a promising blueprint for direct catalytic deoxygenative reactions.

Introduction

Alcohols represent privileged entities across the molecular sciences that are ubiquitous[1] and are also accessible from abundant and renewable sources[2]. Despite the significant polarization of the C−O bond, which should in principle prime it for activation through oxidative addition, the direct use of non-derivatized alcohols as electrophiles in transition-metal catalyzed coupling reactions still represents a challenge in the field due to the high bond dissociation energy of the C−O bond as well as the poor leaving group ability of the hydroxy group. Although elegant strategies have recently been developed in this area[3], the field remains largely underdeveloped compared to the plethora of methodologies that make use of pre-activated, derivatized alcohols, such as sulfonates or carboxylates.[4] The latter approach requires prior functional group interconversion strategies to turn the hydroxy group into a suitable leaving group, which is time- and resource-intensive. Therefore, approaches that enable the direct employment of alcohols, without the need for a separate pre-activation step, are highly desirable (Figure 1A).[5] Based on the transdisciplinary relevance of C–C bond forming coupling reactions[6] and the abundance of alcohol feedstocks, the direct use of alcohols to forge a new C–C bond is of particular importance. Therefore, the development of novel, enabling strategies is imperative.[7] One widespread C–C bond forming coupling reaction is the Suzuki-Miyaura coupling (SMC). Since its disclosure, the use of boron nucleophiles for the construction of C–C bonds has become an indispensable tool in modern organic synthesis.[8] However, one of the major drawbacks of the SMC is the requisite for base.[8-10] Recently, numerous research groups have tackled the 'base problem' and developed a variety of innovative strategies for circumventing the use of exogenous bases.[3b,10]

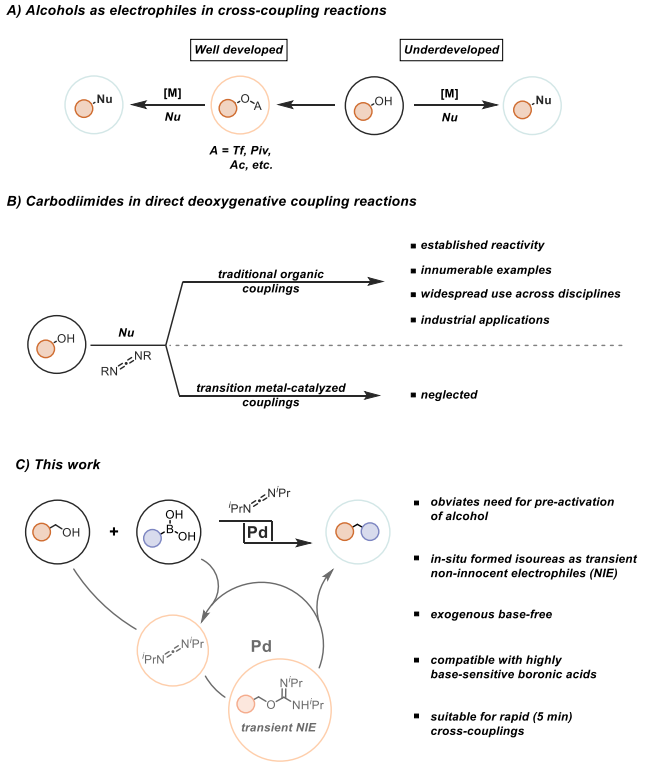


Figure 1 Context of the work.

Nevertheless, due to the inherent role of the base in the SMC, the development of base-free conditions for this useful reaction still represents a challenging task and most often requires pre-functionalization of native moieties such as alcohols.

In contrast to transition-metal catalyzed coupling reactions, the direct exchange of a free OH group for another functional moiety is well established in classical organic couplings such as amide or ester couplings.[11] Carbodiimides have played an enabling role in this field, as they were among the first reagents used for such deoxygenative couplings, and methods based on these useful reagents have since become a mainstay in synthesis.[12] As a consequence, the use of carbodiimides has enabled fundamental developments across numerous important research areas, e.g. pharmaceutical synthesis[13], peptide synthesis[14], oligonucleotide synthesis[15], solid-phase synthesis[16], chemical biology[17], and by that shaped essential disciplines such as biochemistry, pharmacology and medicine.

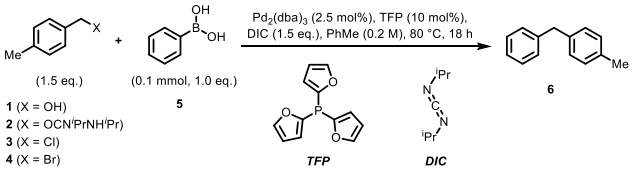
As opposed to their widespread impact on classical organic deoxygenative couplings, to date, the promising features of carbodiimideshave been neglected in transition-metal catalyzed deoxygenative coupling reactions (Figure 1B), although certain other coupling reagents have found some utility in acyl SMCs of carboxylic acids.[18] Recognizing their untapped potential, we envisaged the strategic use of carbodiimides for the direct transition-metal catalyzed arylation of non-derivatized alcohols with boronic acids (Figure 1C). Besides the unprecedented nature of this approach, an additional anticipated challenge could be catalyst deactivation induced by the high reactivity of carbodiimides towards transition metals.[19] However, if this challenge could be overcome, we envisaged the carbodiimide to first react with the alcohol to transiently form the corresponding isourea which in turn would serve as an appropriate electrophile for the deoxygenative coupling with the boronic acid. Based on pioneering work by Inoue and co-workers using preformed allylisoureas in exogenous base-free Tsuji-Trost type allylation reactions[20], we further surmised that our strategy could also tackle the 'base problem' through the non-innocent behavior[21] of the transiently formed isourea, which would release its masked base, allowing for catalytic turnover under exogenous base-free conditions. Based on this conceptual blueprint, we started our investigation by undertaking a proof of principle study. Pioneering seminal work by the group of Shi, which made use of a different strategy, demonstrated the Pd-catalyzed coupling of benzyl alcohols with arylboroxines under exogenous base-free conditions, however their strategy was limited to π-extended systems as alcohol coupling partners.[3b] Moreover, Rao *et al.* reported a Cu-catalyzed protocol for the exogenous base-free coupling of diarylmethanols with boronic acids.[3l] We therefore sought to benchmark our concept against the coupling of benzyl alcohols with boronic acids.[3e]

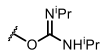
Results and Discussion

Proof of principle

We selected the coupling of 4-methylbenzyl alcohol **1** and phenylboronic acid **5** assisted by diisopropylcarbodiimide (DIC) as a model reaction and evaluated different reaction conditions. Initially, we tested a bimetallic system comprised of CuCl and $Pd(PPh_3)_4$ based on the facts that Cu^I salts have proven efficient catalysts for isourea formation[22] and Pd^0 complexes represent prototypical catalysts for SMCs[8]. This study provided lead results as the bimetallic system indeed afforded the desired coupling product **6** in 57% yield. Thereafter, we set out and performed an optimization study, which quickly, yet surprisingly, revealed that CuCl was not essential for the reaction (see Supporting Information).

Table 1 Optimized conditions and control reactions.



Entry	X	Deviation	Yield 6 / %[a]
1		-	87 (84)
2		w/o $Pd_2(dba)_3$	<5
3	OH	w/o TFP	<5
4		w/o DIC	<5
5		at r.t.	52
6		w/o DIC	89
7	Br or Cl	-	<5

[a]GC yield (isolated yield in parentheses).

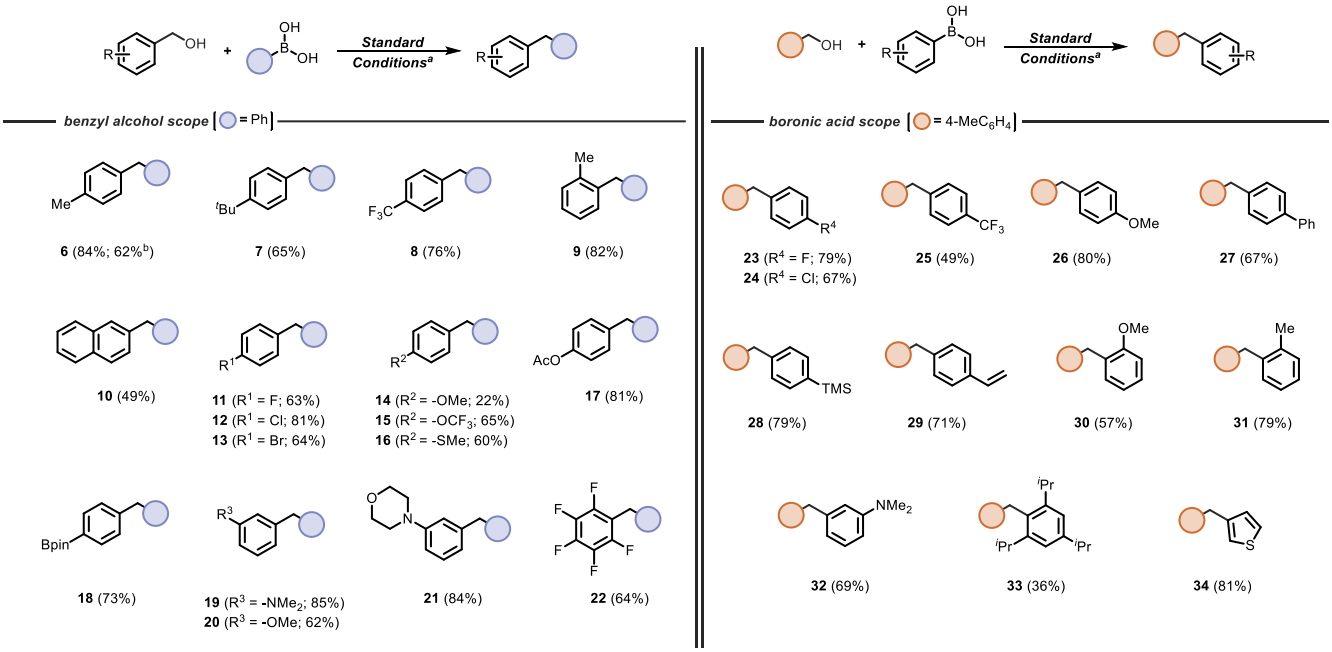
Finally, we found that a catalytic system consisting of $Pd_2(dba)_3$ and tri-2-furylphosphine (TFP) in combination with a slight excess of benzyl alcohol **1** and DIC afforded diarylmethane **6** in 87% yield (Table 1, Entry 1). Control experiments revealed that all reaction components are essential for the coupling (Table 1, Entries 2-4). Notably, it was found that the coupling even occurs at room temperature albeit with

reduced yield compared to 80 °C (Table 1, Entry 5). Furthermore, a reaction with preformed isourea **2** in the absence of DIC afforded coupling product **6** in comparable yield to the model reaction, suggesting the actual intermediacy of this compound in the one-pot process (Table 1, Entry 6). Importantly, prototypical conventional electrophiles such as benzyl chloride **3** or benzyl bromide **4** were not suitable for the coupling highlighting the unique reactivity of the non-innocent isourea electrophile (Table 1, Entry 7).

Scope investigation

With the optimized conditions in hand, we ventured into the scope investigation. Regarding the electrophilic coupling partner, an array of differently substituted primary benzyl alcohols could be employed and gave straightforward access to a library of diversely decorated diarylmethanes in good to moderate yields (Table 2, left). Electron-withdrawing functional groups such as a 4-trifluoromethyl group (**8**) as well as 4-halide substitution (**11** - **13**) were compatible. Notably, the coupling proved to be highly chemoselective even in presence of other electrophilic moieties, such as chloride **12** and bromide **13**, that are known to undergo oxidative addition in the presence of a low-valent Pd catalyst in canonical SMC couplings.[8] Moreover, very electron-poor systems could be employed enabling the synthesis of polyfluorinated diarylmethane **22**. Electron-donating functional groups such as 4-methoxy, on the other hand, performed sluggishly (**14**).

Table 2 Scope of the reaction with respect to both coupling partners.



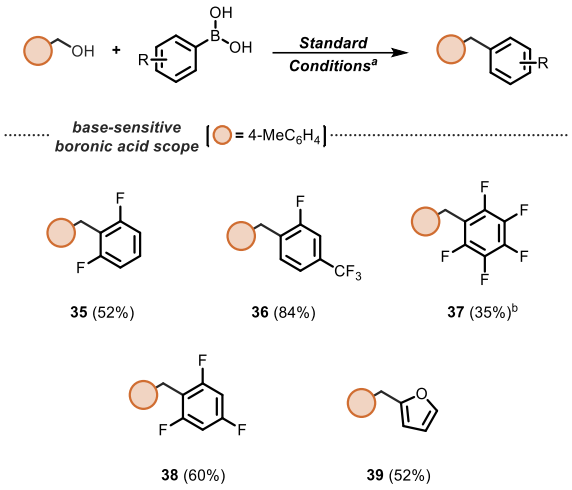
[a]$Pd_2(dba)_3$ (2.5 mol%), TFP (10 mol%), DIC (1.5 eq.), alcohol (1.5 eq.), boronic acid (0.5 mmol, 1.0 eq.), PhMe (0.2 M), 80 °C, 18 h. [b]7.5 mmol scale. Isolated yield in parentheses.

In contrast, 4-trifluoromethoxy as well as 4-methylthioether substituted benzyl alcohols performed well (**15** and **16**). Notably, base-sensitive acetoxy groups were compatible with the reaction conditions (**17**). In addition to the chemoselectivity over conventional electrophiles, the coupling proved to be equally chemoselective for boronic acids as pinacol boronates (**18**) did not react, giving rise to orthogonal coupling strategies on both coupling partners. Finally, the model reaction was readily scaled up 15-fold affording diarylmethane **6** in 62% yield. Next, we studied the scope of the nucleophilic coupling partner and tested various boronic acids for the coupling with 4-methylbenzyl alcohol **1** under otherwise standard conditions. Halide substituted boronic acids proved suitable for the reaction and afforded the corresponding products in good yields (**23** and **24**). High chemoselectivity towards electrophilic moieties was also observed for the nucleophilic coupling partner of the reaction as highlighted in the case of diarylmethane **24**, i.e. the benzyl alcohol moiety against the chloride moiety. Moreover, 4-(trifluoromethyl)phenylboronic acid could be employed (**25**). Strongly electron-donating functional groups such as 4- and 2-methoxy led to the corresponding products in good yields (**26** and **30**). Moreover, the coupling performed well despite increased steric bulk next to the reaction center (**30** and **31**), even in the case of highly sterically demanding 2,4,6-triisopropyl substitution (**33**). Trimethylsilyl as a functional handle[23] proved to be orthogonal to the reaction conditions as shown in the synthesis of diarylmethane **28**. In addition, heteroaromatic boronic acids such as 3-thienyl boronic acid could be employed (**34**).

Next, we tested whether the exogenous base-free reaction conditions are suitable for the coupling of highly base-sensitive boronic acids, as this represents a considerable challenge in the field (Table 3).[8-10] Seminal studies have shown that protodeboronation of certain boronic acids under basic reaction conditions is very fast with individual half-lives in the milliseconds range.[9] Therefore, we selected representative base-sensitive boronic acids and subjected them to the standard conditions using again 4-methylbenzyl alcohol **1** as the electrophilic coupling partner. The strategy was indeed suitable and a range of base-

sensitive boronic acids could be successfully coupled. Employment of 2-fluoro-4-trifluorophenyl boronic acid and 2-furanyl boronic acid gave straightforward access to diarylmethanes **36** and **39**.

Table 3 Application of the strategy to the coupling of highly base-sensitive boronic acids.

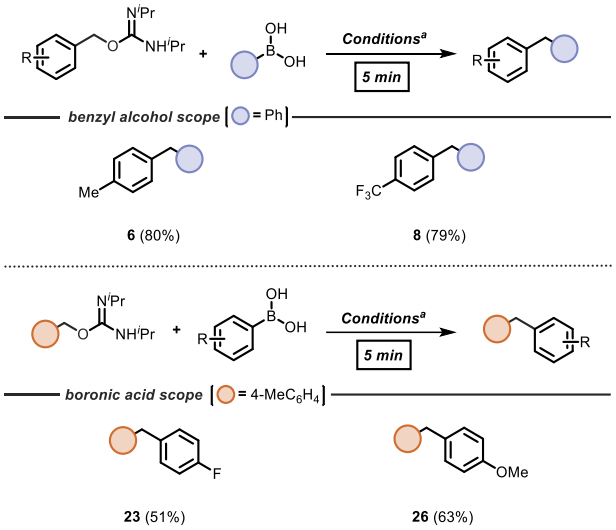


[a]$Pd_2(dba)_3$ (2.5 mol%), TFP (10 mol%), DIC (1.5 eq.), alcohol (1.5 eq.), boronic acid (0.5 mmol, 1.0 eq.), PhMe (0.2 M), 80 °C, 18 h; [b]$Pd_2(dba)_3$ (2.5 mol%), TFP (10 mol%), DIC (2.0 eq.), alcohol (1.0 eq.), boronic acid (2.0 eq.), PhMe (0.2 M), 80 °C, 18 h. Isolated yield in parentheses.

Importantly, polyfluorinated boronic acids such as 2,6-difluorophenyl boronic acid and 2,4,6-trifluorophenyl boronic acid proved compatible and allowed for the synthesis of coupling products **35** and **38**. After slight adjustments, diarylmethane **37** could be synthesized demonstrating that even pentafluorophenyl boronic acid is compatible with the reaction. Furthermore, an additive study with base-sensitive functional groups such as enolizable ketones, esters, epoxides and trifluoroacetamides was conducted and revealed that the reaction is compatible with these moieties (see Supporting Information).

Finally, it was found that the employment of preformed isoureas enabled rapid (5 min reaction time) exogenous base-free cross-couplings with boronic acids which was demonstrated for several coupling partners (Table 4). Notably, these couplings were performed using a conventional catalyst under thermal conditions and thus do not rely on customized catalysts or specialized equipment such as a microwave oven or continuous-flow platforms.

Table 4 Rapid cross-couplings of preformed isoureas and boronic acids.

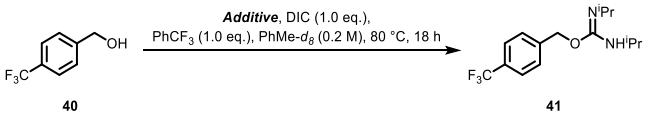


[a]$Pd_2(dba)_3$ (2.5 mol%), TFP (10 mol%), isourea (1.5 eq.), boronic acid (0.1 mmol, 1.0 eq.), PhMe (0.2 M), 80 °C, 5 min. GC yield in parentheses.

Mechanistic Interrogation

Having demonstrated that the method is compatible with various motifs across both coupling partners and offers orthogonal coupling strategies for the electrophilic as well as the nucleophilic part, we performed a preliminary mechanistic investigation of the underlying reaction pathways.

Table 5 Investigation of the isourea formation.



Entry	Additive	Yield 41 / %[a]
1	-	<5
2	$Pd_2(dba)_3$ (2.5 mol%)	<5
3	TFP (10 mol%)	<5
4	$Pd_2(dba)_3$ (2.5 mol%), TFP (10 mol%)	>95

[a] ^{19}F NMR yield using $PhCF_3$ as an internal standard.

Since the overall transformation, according to our working hypothesis, can be divided into two parts, i.e. isourea formation and SMC, we first investigated which reaction components are responsible for the isourea formation. Therefore, 4-trifluoromethylbenzyl alcohol **40** was taken as a model substrate and isourea formation with DIC was studied by ^{19}F NMR spectroscopy (Table 5). It was found that without any additive, alcohol **40** and DIC failed to produce isourea **41** which is in line with literature reports (Table 5, Entry 1).[22] Moreover, catalytic amounts of $Pd_2(dba)_3$ or TFP were equally unable to promote the generation of isourea **41** (Table 5, Entry 2 & 3). In contrast, the combination of $Pd_2(dba)_3$ and TFP led to quantitative formation of isourea **41** (Table 5, Entry 4).

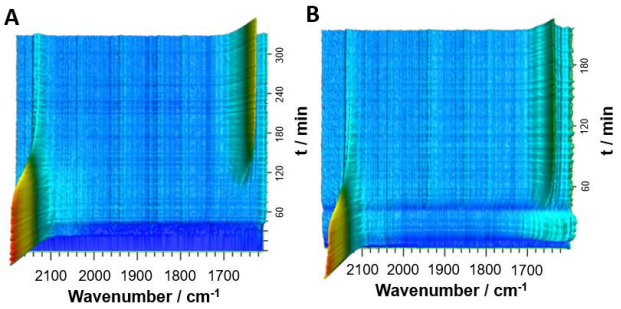
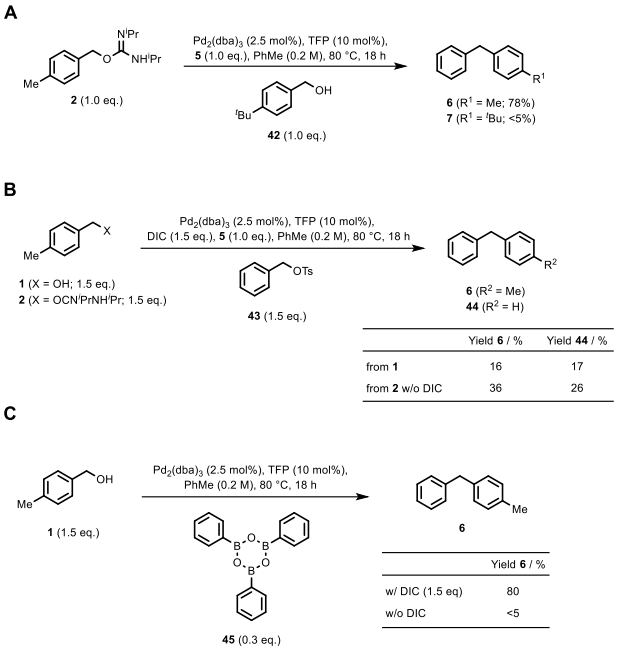


Figure 2 Time-resolved in-situ IR spectra of the isourea formation promoted by $Pd_2(dba)_3$/TFP (A) and phenylboronic acid (B).

This was corroborated by time-resolved in-situ IR spectroscopy showing the complete disappearance of the diagnostic band (ν(C=N) = 2106 cm^{-1}) of DIC over time and the appearance of a new band at 1665 cm^{-1} corresponding to isourea **41** (Figure 2A). Notably, combinations of Pd(0) complexes and tertiary phosphines have, to the best of our knowledge, never been reported to catalyze isourea formation. Additionally, it is worth pointing out the promiscuity of this catalytic system enabling two distinct reactions, i.e. the isourea formation as well as the SMC. Finally, the effect of the boronic acid was studied via time-resolved in-situ IR spectroscopy and indicated that phenylboronic acid **5** can also promote isourea formation (Figure 2B).

We next probed whether isourea formation is reversible under the reaction conditions by conducting a crossover experiment (Figure 3A). 4-*tert*-Butylbenzyl alcohol **42** and isourea **2** were subjected to the standard reaction conditions without the addition of DIC and the product distribution was analyzed. Since control reactions demonstrated early-on that DIC is essential for the coupling (Table 1, Entry 5), we hypothesized that diarylmethane **7** could only form in case the isourea formation would be reversible, thereby releasing DIC from isourea **2** and in turn enabling the generation of the corresponding isourea of 4-*tert*-butylbenzyl alcohol **42**. Postreaction analysis demonstrated that diarylmethane **6** was formed in 78% yield, whereas only traces of diarylmethane **7** could be detected. Consequently, isourea formation can be considered irreversible under the reaction conditions.



	Yield **6** / %	Yield **44** / %
from **1**	16	17
from **2** w/o DIC	36	26

	Yield **6** / %
w/ DIC (1.5 eq)	80
w/o DIC	<5

Figure 3 Control experiments. A: Reversibility of the isourea formation. B: Base liberation pathway. C: Boroxine generation via dehydration.

Next, we studied the base generation pathway of the reaction. First, experiments revealed that model isourea **41** is thermally stable under the reaction conditions as no significant degradation, i.e. <5%, could be detected (see Supporting Information). Next, a crossover experiment was designed in order to probe the base generation pathway. Accordingly, conventional benzyl tosylate **43** was added to the model coupling and the product distribution was analyzed (Figure 3B). Since conventional electrophiles do rely on exogenous base for catalytic turnover, the detection of the corresponding coupling product **44** would point towards the liberation of the urea anion during the reaction. Benzyl tosylate **43** was chosen as the electrophile since the tosylate anion is poorly nucleophilic and would thus be unlikely to interfere with the experiment through a nucleophilic substitution at the isourea moiety, which could otherwise liberate the base through a different mechanism. As a result, postreaction analysis revealed that the coupling product of benzyl tosylate **43**, i.e. diarylmethane **44**, was indeed formed alongside diarylmethane **6** which is in line with a dissociative mechanism. In a complementary crossover experiment starting from isourea **2** and omitting DIC, diarylmethane **44** could again be detected, yet with a higher yield further supporting the dissociative scenario.

Finally, control experiments were performed to rule out a reaction pathway in which DIC would primarily serve as a dehydrating agent for the in-situ generation of boroxine **45** (Figure 3C).[3b] Accordingly, 4-methylbenzyl alcohol **1** was reacted with boroxine **45** under standard conditions in presence and in the absence of DIC. Boroxine **45** proved to be a competent coupling partner in the presence of DIC and diarylmethane **6** was formed in comparable yields to the model coupling. However, in the absence of DIC diarylmethane **6** could not be detected which is in line with the prior observations and further supports an isourea formation pathway.

Conclusion

In summary, we have developed the first carbodiimide assisted strategy for the direct arylation of non-derivatized alcohols with boronic acids introducing the benefits of carbodiimides to the realm of transition-metal catalyzed coupling chemistry, ultimately bridging a longstanding conceptual gap. The newly developed strategy makes use of transiently formed non-innocent isoureas which contain a masked base that is released during the reaction. This feature enables the omission of an exogenous base while conserving catalytic turnover. Additionally, the reaction allows for the direct use of the corresponding alcohol. We have showcased the potential of the concept by successfully coupling a range of differently substituted non-derivatized benzyl alcohols and boronic acids. Notably, the approach proved orthogonal to multiple canonical cross-coupling moieties on both coupling partners and allowed for the employment of highly base-sensitive boronic acids. Furthermore, a platform for rapid (5 min reaction time) cross-couplings was developed employing preformed isoureas which does neither rely on customized catalysts nor specialized equipment. Preliminary mechanistic investigations elucidated the key aspects of this unprecedented class of reaction and revealed a complex interplay between the individual reactants. In a broader context, we believe that the presented work demonstrates the potential of carbodiimides for deoxygenative transition-metal catalyzed coupling reactions and will serve as a conceptual blueprint for further developments.

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Notes

The authors declare no competing financial interest.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, compound characterization data, detailed mechanistic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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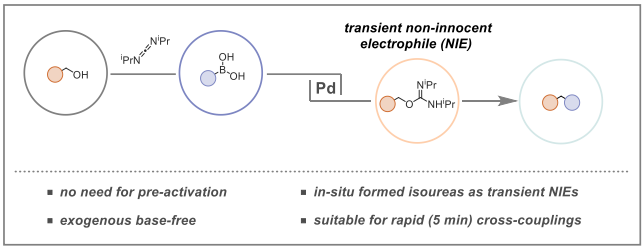
transient non-innocent
electrophile (NIE)
OH
iPrN
NiPr
OH
B
OH
Pd
NiPr
O
NHiPr
no need for pre-activation
exogenous base-free
in-situ formed isoureas as transient NIEs
suitable for rapid (5 min) cross-couplings