Rapid Automated Iterative Small Molecule Synthesis

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Abstract

Automated iterative small molecule synthesis has the potential to advance and democratize the discovery of new medicines, materials, and many other classes of functional chemical matter. But to date this approach has been limited by a requirement of about one day of time per C-C bond forming step. Here, we report a next-generation small molecule synthesizer which operates at an order of magnitude faster than prior systems through improvements in both chemistry and engineering. These findings move the field of small molecule synthesis a step closer to democratizing its core discovery engine.

Main

The automated synthesis of oligopeptides[1] and oligonucleotides[2] has transformed science, medicine, and technology,[3-5] and enabled creation of new fields such as proteomics, genomics, and synthetic biology[6-9]. After decades of optimization, the corresponding automated synthesizers are now general, efficient, and rapid. The resulting broadly available on-demand access to the corresponding biomolecules has shifted the bottleneck of scientific discovery from the synthesis process to the generation and testing of increasingly sophisticated hypotheses[10,11]. Substantial progress in these same directions has more recently been achieved with the more complex problem of automated oligosaccharide synthesis[12].

All of these approaches leverage the inherent strengths of modular iterative assembly, where prefabricated bifunctional building blocks are assembled under a unified process consisting of repeated deprotection, coupling, and purification steps. This approach trivializes synthesis planning while requiring optimization of only one type of bond-forming chemical reaction. Decades of focused effort to improve and generalize these platforms via

advances in both chemistry (e.g., reagents which minimize side reactions like PyBop[13]) and engineering (e.g., flow[14], microwaves[15], thermocycling[16]) have yielded synthesizers capable of making even very large target compounds in less than a day[14], a feat requiring cycle times on the order of minutes (Fig. 1a).

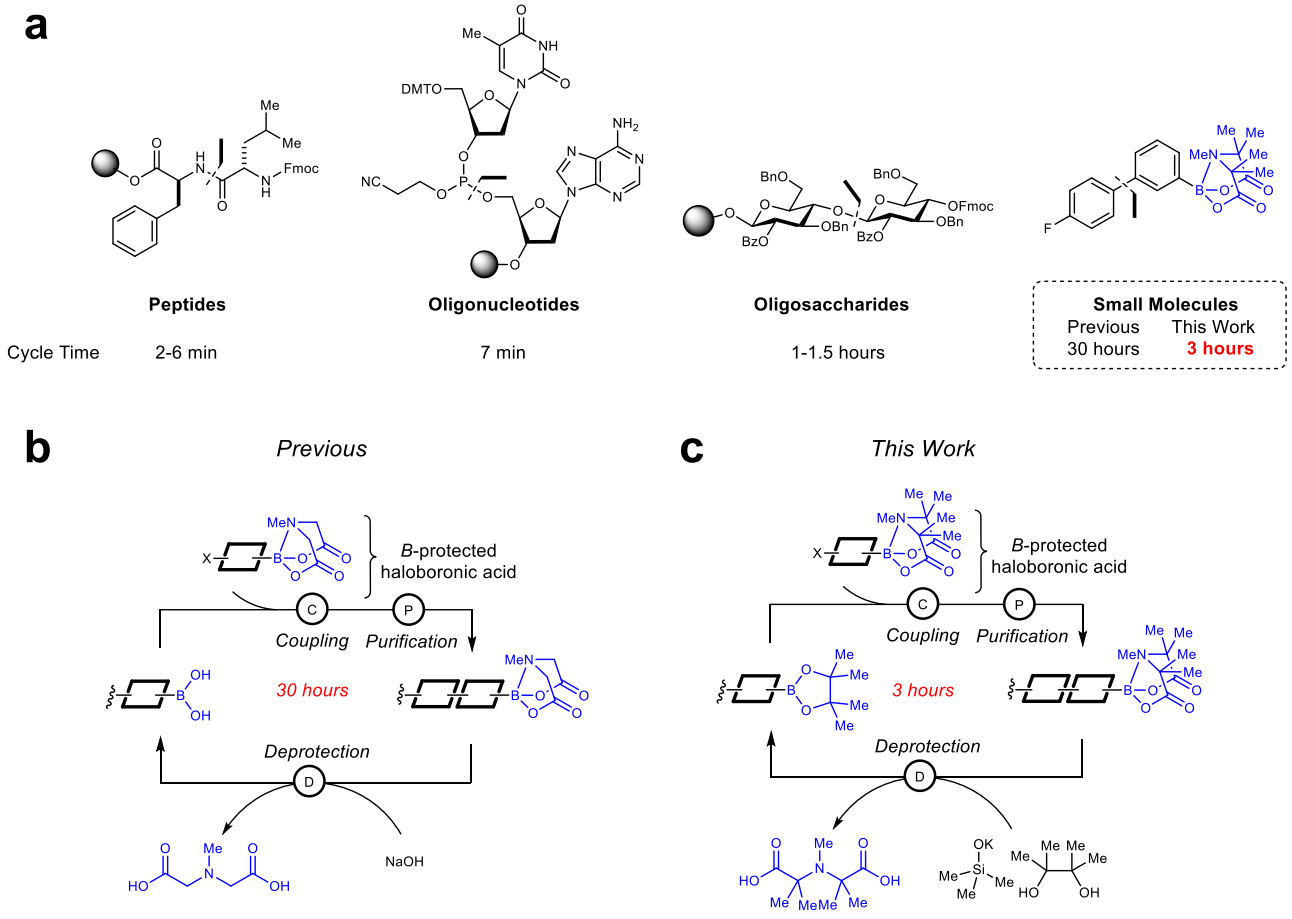

Fig. 1. **a**, Comparison of cycle time for one iteration of deprotection, coupling, and purification between automated iterative synthesizers for different classes of molecules. **b**, Iterative cross-coupling cycle reported previously[22] based on MIDA boronates and boronic acids. **c**, Iterative cross-coupling cycle reported in this work based on TIDA boronates and pinacol boronic esters.

In contrast, small molecules, a class of chemical matter that comprises the majority of known medicines[17], the core components of organic materials with myriad applications, and many other types of functional molecules, are still largely synthesized manually using customized strategies, even when aided by automation.[18] In 2007, we reported a general strategy for small molecule synthesis relying on iterative C-C bond formation via Suzuki-Miyaura cross-coupling (SMC) of bifunctional halo-N-methyliminodiacetic acid (MIDA) boronate building blocks[19-21]. In 2015, we reported a fully automated small molecule synthesizer employing this strategy[22], and in the years since we have expanded its capability to automate iterative Csp^3-C bond formation[23]) and demonstrated its utility in materials discovery[24,25] and its integration with AI-guided closed loop discovery engines[26]. Despite these advances, a key limitation of the platform is the long cycle time (more than one day) per C-C bond-forming step, owing principally to the slow and variable kinetics of SMC. This is at least an order of magnitude slower than analogous state-of-the-art peptide, oligonucleotide, and oligosaccharide synthesizers. Here we report a significant overhaul to the platform where each step of the iterative cycle has been reimagined and reoptimized for speed, efficiency, and generality. Key advances include our discovery that rapid SMC under

homogenous conditions[27-29], while not tolerated by MIDA boronates, are fully compatible with their more stable TIDA boronate counterparts[23], the development of a novel cartridge for rapid catch-and-release purification, and adaptation of AI-generated general reaction conditions for in-situ release cross-coupling of MIDA boronates[26] to enable final deprotection step-sparing direct coupling of penultimate TIDA boronate intermediates. Collectively these advances have yielded an order of magnitude rate acceleration per automated C-C bond forming step (Fig. 1a).

Results and Discussion

The principal components of an iterative SMC cycle can be broken down into deprotection (D), coupling (C), and purification (P). In our prior design[22,24] (Fig. 1b), deprotection occurs via the cleavage of the boron protecting group using aqueous base to furnish a reactive boronic acid which is then rigorously dried using magnesium sulfate followed by molecular sieves (4 hours). Afterwards, the coupling occurs under anhydrous SMC conditions via the slow addition of the freshly prepared boronic acid over 4 hours followed by 12 hours of reaction time with moderate heating (55 °C, 16 hours total). Finally, the purification occurs via harnessing the remarkable capacity for MIDA boronates to undergo catch-and-release on silica gel via 'catch' with diethyl ether/methanol then 'release' of the boronate product with tetrahydrofuran (4 hours) followed by concentration via argon sparging (6 hours). When deploying this technology in applied contexts, we observed some structure-dependent failures caused by protodeborylation, incomplete conversion, and/or insolubility. We hypothesized that many of these challenges stemmed from the sensitivity of the corresponding boronic acid intermediates, which are unstable species often not amenable to storage or isolation[30,31], with the propensity to form insoluble zwitterions[32,33], and necessitating slow addition as dilute solutions. To overcome these challenges, we envisioned redesigning the process around more stable intermediates, notably pinacol boronic esters[34] and tetramethyl-N-methyliminodiacetic acid (TIDA) boronates[23]. Following these design principles, we were ultimately able to discover substantially faster and broadly applicable iterative deprotection, coupling, and purification processes, which proceed in absence of water and through stable and isolable intermediates (Fig. 1c).

Rapid and homogenous iterative Suzuki-Miyaura cross-coupling

Our first goal was developing rapid and broadly applicable SMC conditions amenable to automation and iteration, as this step represented approximately two-thirds of the total cycle time. For these purposes, we required reaction conditions which proceeded rapidly while not degrading the TIDA boronate motif. We observed that SMC using weak, insoluble inorganic bases such as carbonates and phosphates proceeded slowly (hours) but preserved the boronate, while stronger bases such as hydroxides and alkoxides proceeded faster but rapidly degraded the boronate at elevated temperatures (>40 °C).[23] Following recent reports by the Denmark group that the soluble base potassium trimethylsilanolate (TMSOK) affords rapid SMC kinetics at mild temperatures[27-29], we investigated the compatibility of MIDA and TIDA boronates with this base. When subjected to TMSOK at ambient temperature, we observed nearly instantaneous degradation of the MIDA boronate, while the corresponding TIDA boronate appeared unchanged after 12 hours (Fig. 2a). Remarkably, the model SMC between 4-fluorophenyl neopentyl ester and *m*-bromophenyl TIDA boronate using TMSOK proceeded to full conversion and 95% isolated yield in 5 minutes (Fig. 2b). These SMC conditions also performed well when applied to a diverse set of aryl, heteroaryl, and vinyl nucleophiles and electrophiles, providing an average isolated yield of 86% across 20 substrates, with all reactions completing within 5 minutes (Fig. 2c). Lewis basic heteroarenes required mild heating (50-60 °C) but still proceeded to full conversion within 5 minutes. Notably, palladium catalyst-poisoning functional groups such as thioethers[35] were well tolerated. Using pinacol esters in place of neopentyl esters displayed similar performance upon increasing temperature to 60 °C and extending the reaction time to 10 min.

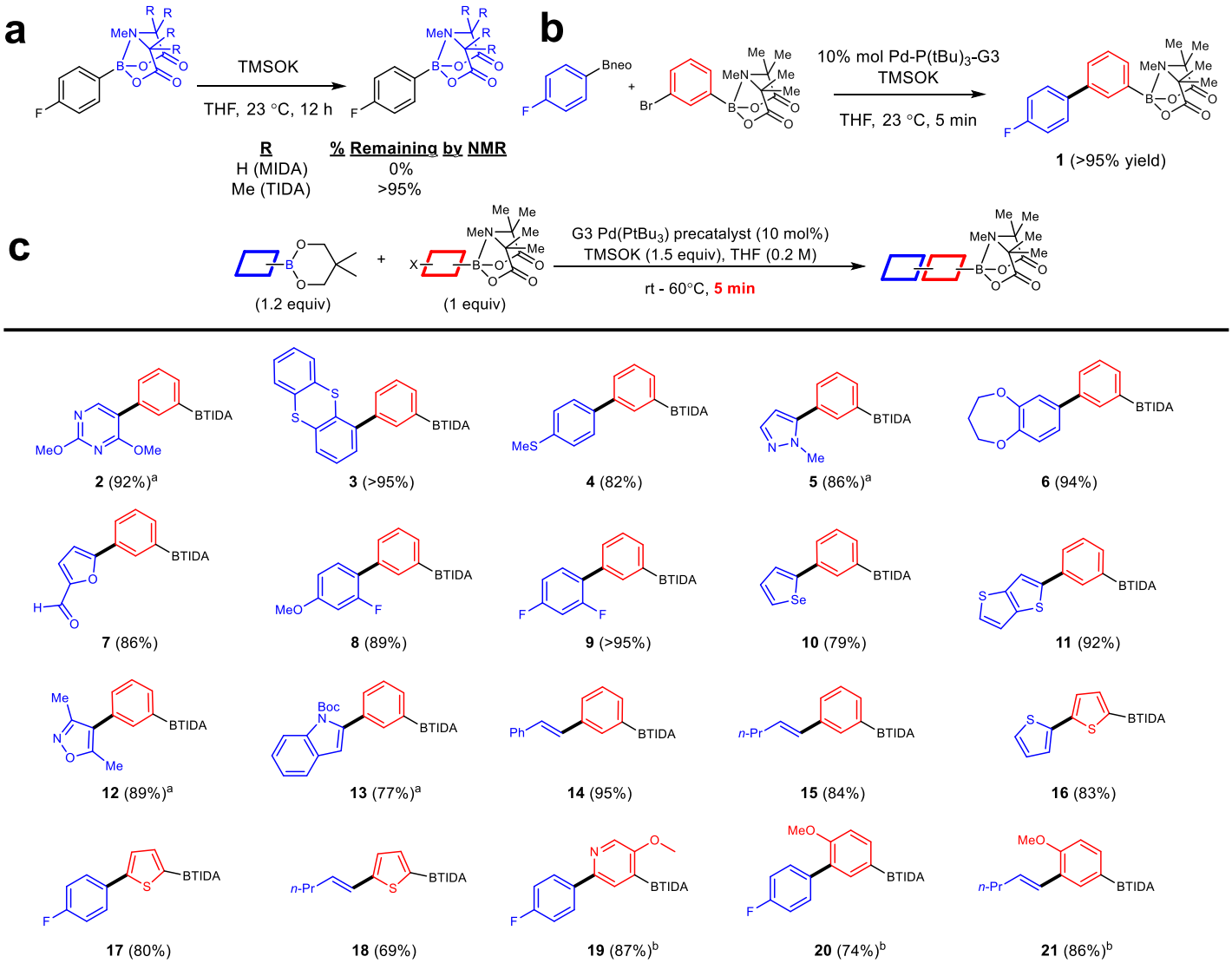

Fig. 2. **a**, Reaction of MIDA and TIDA boronates with TMSOK (2 equiv., monitored by ^{1}H NMR). **b**, Rapid, homogenous, and anhydrous TMSOK promoted cross-coupling in the presence of a TIDA boronate. **c**, Substrate scope of rapid iterative cross-coupling. Yields are isolated. For detailed experimental procedures see Supplementary Information. [a]50 °C. [b]60 °C.

Rapid and homogenous TIDA boronate deprotection

Our next goal was to develop a mild and rapid deprotection of TIDA boronates to pinacol boronic esters. We have previously demonstrated this reactivity can be achieved by the action of sodium hydroxide and pinacol[23], but this requires moderate heating (45 °C) and long reaction times (6 hours). While exploring the reactivity of TMSOK with TIDA boronates, we surprisingly observed that the base alone could deprotect TIDA boronates at 60 °C in 30 minutes, despite this not occurring during the SMC reaction at the same temperature (Fig. 3a). We hypothesized that the vacant p-orbital of the boronic ester coupling partner during SMC sequesters the silanolate base, preventing degradation of the TIDA boronate. As a control experiment, we heated a mixture of 4-fluorophenyl TIDA boronate, 4-fluorophenyl neopentyl ester, and TMSOK at 60 °C for 30 minutes, and did not

observe TIDA degradation products and successfully recovered 89% of the TIDA boronate in >95% purity, supporting our hypothesis (Fig. 3b). We also found that the combination of pinacol and TMSOK rapidly and cleanly deprotects TIDA boronates to pinacol esters, reaching full conversion within one hour at room temperature (Fig. 3c). The resulting reaction mixture can be quenched with a variety of reagents (e.g., $HCl_{(aq)}$, TMSCl, silica gel), however the use of calcium chloride buffered with sodium bicarbonate is preferably employed here as it is well tolerated even by sensitive polyene boronic esters[36].

Subsequent experiments revealed that three equivalents of TMSOK and pinacol are required to fully deprotect one equivalent of TIDA boronate (Supplementary Information Fig. S6). Accordingly, we hypothesized that the reaction yields one equivalent of TIDA dipotassium salt, two equivalents of trimethylsilanol, residual pinacol, and a TMSOK-bound pinacol boronate. Conveniently, treatment with calcium chloride resolved the reaction solution to clean and monomeric pinacol boronic ester isolated in near-quantitative yield, presumably via removing both diols and silanols (Fig. 3c). Studies of kinetics using ^{19}F NMR revealed that this reaction is second order in respect to the silanolate base and zero order in respect to the diol (Supplementary Information Section 2.2), suggesting some type of interesting dual role for TMSOK in the rate-determining step. While a specific interaction between the TIDA boronate cage and TMSOK prior to deprotection could explain the second-order rate dependence of the base (e.g., binding to the backside of the boronate cage[37]), such an interaction is not visible on the NMR time scale at ambient temperature (^{1}H, ^{13}C, ^{19}F, ^{11}B, ^{29}Si). We also found that aryl pinacol boronic esters were unstable to superstoichiometric silanolate base, but that addition of excess pinacol could render them more stable. Thus, 3-5 equivalents of both reagents are used in this work for optimal substrate stability and reaction time. Testing the reactivity of other soluble organic bases (potassium acetate, lithium isopropoxide, potassium phenoxide, potassium triethylsilanolate, and potassium dimethylvinyl silanolate) with TIDA boronates in presence of pinacol revealed that only the silanolates afforded pinacol ester product while the others afforded no reaction, suggesting that this reactivity is unique to this class of bases (Supplementary Information Table S1). TMSOK was utilized for the remainder of the study due to its desirable solubility, reactivity, and broad commercial availability.

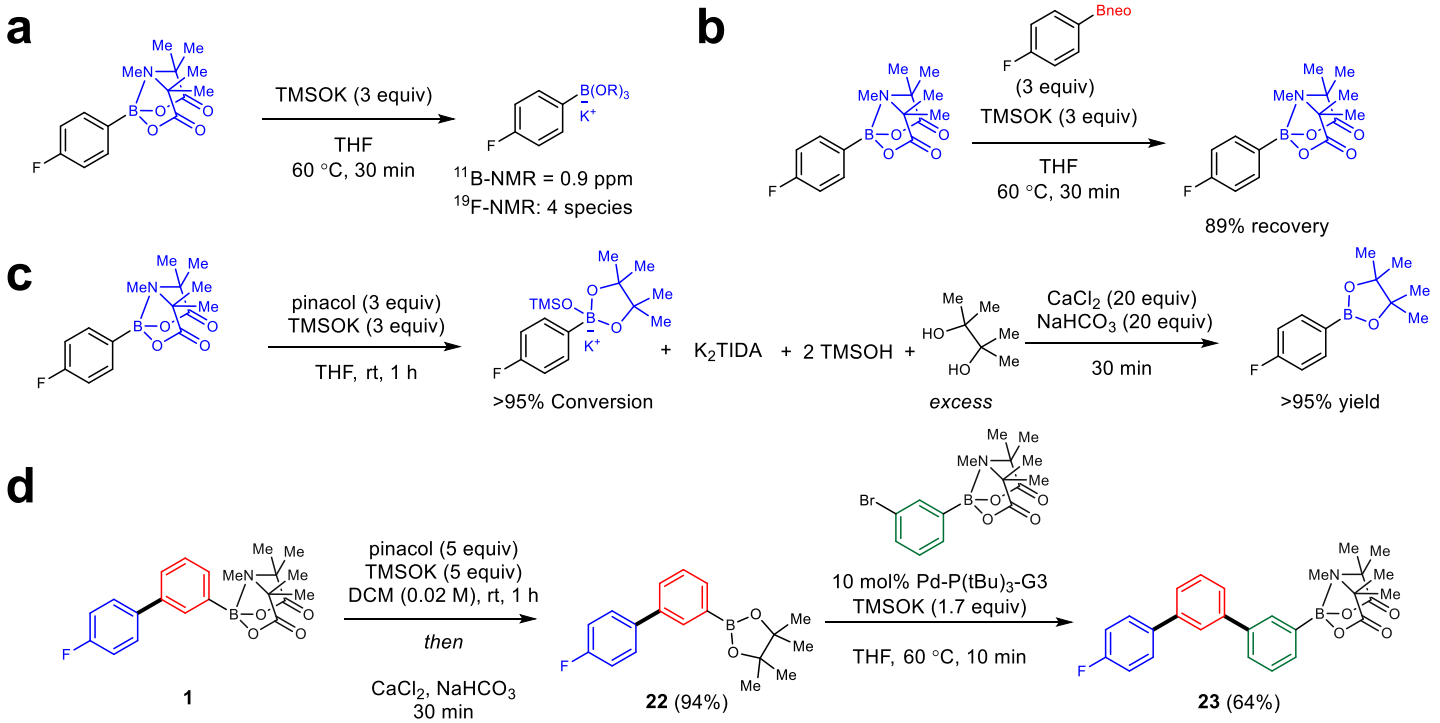

Fig. 3. **a**, Instability of TIDA boronates to TMSOK at 60 °C. **b**, Stability of TIDA boronates to TMSOK at 60 °C in the presence of boronic esters. **c**, Rapid deprotection of TIDA boronates to pinacol boronic esters at ambient temperature mediated by pinacol and TMSOK. **d**, Deprotection of a dimer TIDA boronate to a pinacol boronic ester and its competence in subsequent iterative SMC.

Robotic platform for rapid iterative cross-coupling

Optimization of the coupling and deprotection shifted the bottleneck of the process to the automated catch-and-release purification (previously 4 hours), which we envisioned we could hasten through reengineering. At the same time, we aimed to improve the robustness of the procedure by reducing instances of undesired physical behavior such as clogging, insolubility, and variable mass transfer. To accomplish these goals, we redesigned the process such that precipitation of the TIDA boronate product is afforded directly in the coupling reaction vessel after SMC, with subsequent purification occurring in-line through an extensively prototyped catch-and-release cartridge using vacuum filtration (Supplementary Information Fig. S27). This design eliminates slow syringe pump transfers and rinses/washes, while decoupling product solubility from the purification process. We also connected a rotary evaporator to the system, such that purified TIDA boronates could be eluted using acetone without affecting downstream chemistry. Together, these improvements result in near quantitative isolation of purified and coupled TIDA boronate products in a rapid and fully automated manner (1 hour).

Finally, we hypothesized that the TIDA boronate could be used as a direct coupling partner in the last step of an automated sequence, saving further time by simultaneously performing the deprotection and coupling steps. To accomplish this in-situ release cross-coupling, we discovered that our recently reported AI-optimized general reaction conditions employing MIDA boronates[26] are also compatible with TIDA boronates, and that the necessary reaction time is short (1 hour). Implementing this chemistry necessitated improving the design of the inert manifold used in previous instruments, such that dry and wet solvents could be simultaneously accommodated (Supplementary Information Section 2.3.1).With each elementary step optimized for speed, we next built and tested a next-generation small molecule synthesizer incorporating these advances (Fig. 4a). Translating the chemistry to the automated platform mainly required more dilute concentrations to ensure adequate mixing and high mass transfer between modules, as well as utilizing dichloromethane as a transfer solvent as it uniformly solubilizes TIDA boronates and is compatible with the deprotection and drying procedure. Next, we validated that the rapid automated SMC followed by automated purification affords clean TIDA boronates in high purity and yield (Fig. 4b), and that the rapid automated deprotection affords clean pinacol esters which perform competently in subsequent automated SMC (Fig. 4c). Finally, to draw a direct comparison to the previous platform,[22] we selected three representative oligomers: a natural product derivative, an organic electronic material, and a pharmaceutical, where the automated platform reported here uniformly synthesized these molecules in similar efficiency to our prior report but in significantly less total time (3 hours vs 60 hours previously, Fig. 4d). Each of these molecules was synthesized through a faster, fully automated sequence of coupling, purification, and in-situ deprotection-coupling. A comparative breakdown of individual step timing is shown in Supplementary Information Table S5.

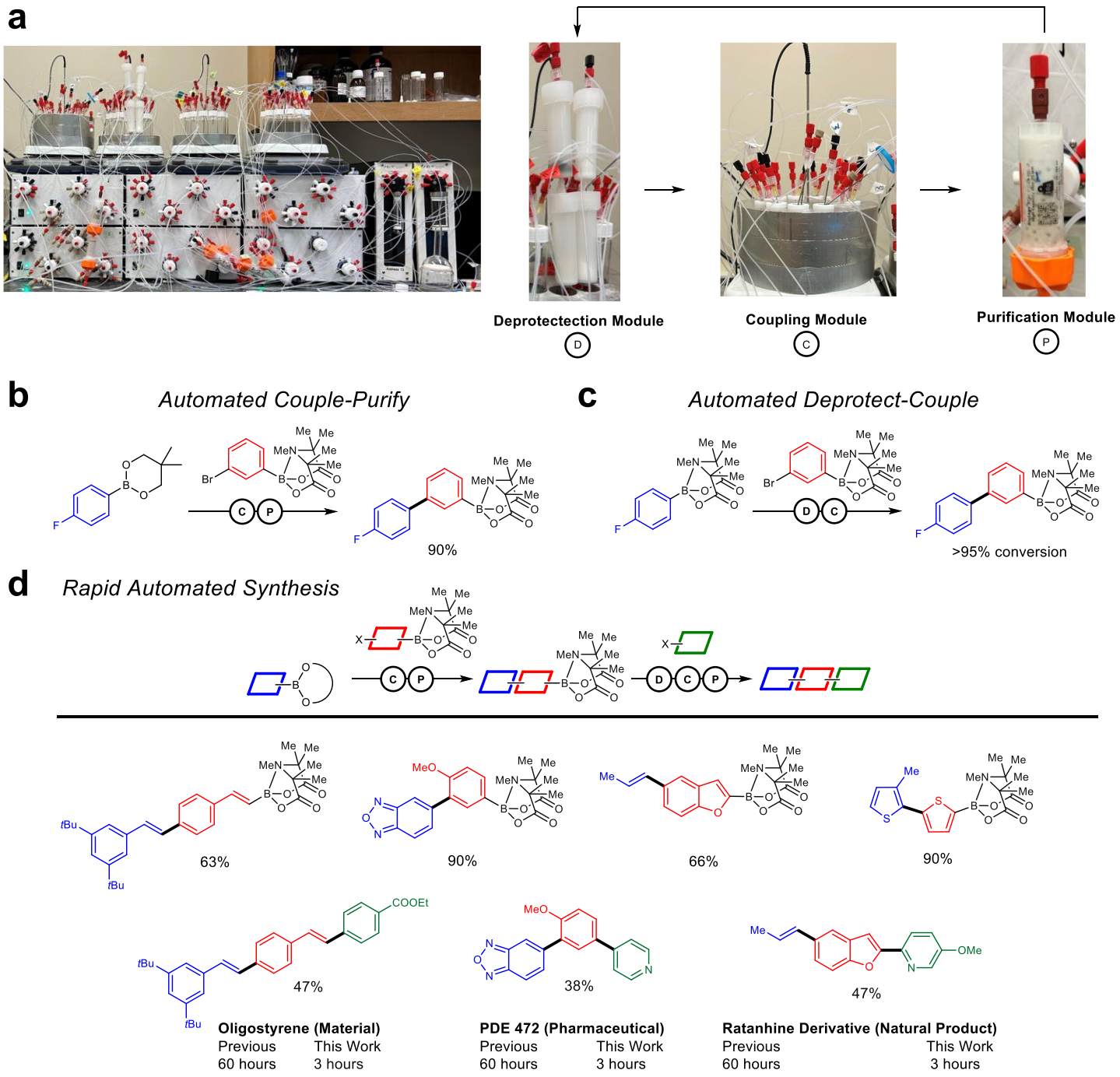

Fig. 4. **a**, The next-generation rapid small molecule synthesizer developed in this work. **b**, Automated cross-coupling followed by automated purification affords high yield and high purity TIDA boronate products. **c**, Automated deprotection followed by automated coupling affords high conversion to TIDA boronate products. **d**, Automated substrate scope. Yields are isolated. For automated synthesis procedures see Supplementary Information.

Conclusion

In conclusion, we have developed a rapid automated iterative cross-coupling platform that utilizes stable TIDA boronate building blocks and isolable pinacol ester intermediates to achieve an order of magnitude decrease in cycle time compared to the previous state-of-the-art. This is a significant step for automated iterative small molecule synthesis on its path towards achieving similar efficiency and societal impacts as iterative biomolecule synthesis. We expect the automated process reported here to be amenable to further miniaturization and parallelization due to its rapid kinetics and homogeneity. This technology is having measurable positive impact on our ongoing molecular discovery campaigns, particularly those including computer-aided design, which will be reported shortly.

Data Availability Statement

The data and methods that support the findings of this study are available in the Supplementary Information: manual and automated synthesis methods, kinetic studies, and control experiments.

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Competing Interests

The University of Illinois has filed patent applications related to MIDA and TIDA boronates with M.D.B. as inventor.

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