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Journal of Organometallic Chemistry 653 (2002) 200–208

Journal of Organometallic Chemistry

www.elsevier.com/locate/jorganchem

Mini review

C–C Cross-coupling reactions for the combinatorial synthesis of novel organic materials

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Received 18 September 2001; accepted 1 October 2001

Abstract

To accelerate the development process to organic materials combinatorial strategies and screening methodologies have been representatively elaborated for coumarin dyes and oligothiophenes. Pd-catalyzed cross-couplings of Suzuki, Sonogashira–Hagihara and Heck type were utilized to substitute the coumarin scaffold. Optimized synthetic protocols were applied to construct in a parallel manner in solution diverse libraries of more than 150 coumarin derivatives. To evaluate the fluorophore ensemble, the coumarins were screened for optical properties and several library members with high fluorescence quantum yields were identified. Using solid-phase synthesis, a 256-membered library of quater(3-arylthiophene)s was generated by using both the parallel and the 'mix-and-split' technique. Suzuki type couplings were employed for the stepwise oligomer growth using diverse aryl substituted thiophene boronic esters as building blocks. The rapid screening for electrochemical properties was facilitated by using an automated screening device. The data analysis led to the development of structure–property relationships on which to base future material design.

Keywords: Combinatorial chemistry; Coumarins; Cyclic voltammetry; Fluorescent dyes; High-throughput-screening; Oligothiophenes; Organic materials; Palladium-catalyzed cross-couplings

1. Introduction

Palladium-catalyzed cross-coupling reactions are an extensively used subset of the synthetic repertoire of an organic chemist. These reactions are primarily utilized for the formation of carbon–carbon [1], carbon–nitrogen [2] and carbon–oxygen bonds [3]. Employed for the generation of complex natural products [1] and material-related structures [4] these synthetic transformations are characterized by mild reaction conditions, a broad tolerance for functional groups and high reaction conversions. Due to these unique characteristics palladium-catalyzed cross-couplings were recently recognized as suitable reactions to create combinatorial libraries of various pharmaceutically interesting lead structures [5,6].

The paradigm of combinatorial chemistry and high-throughput screening now being well-established in the pharmaceutical drug discovery process [7] has recently been shown to enable the acceleration of the whole development process to mainly inorganic materials and catalysts [8]. These pioneering combinatorial approaches inspired us to develop and to evaluate novel methods that provide for both rapid compound generation and subsequent screening of the organic materials. For this type of materials, the most common routes to lead discovery and optimization are often empirical exploration and serendipity rather than rational design based on structure–property relationships. Consequently, our recent research efforts have addressed the general question of whether the applicability of combinatorial methodologies can be significantly extended to the development of organic materials. As a proof of concept study we developed approaches for the combinatorial synthesis and screening of fluorescent dyes [9] and π-conjugated oligomers [10]. To generate the material libraries, we applied palladium-catalyzed cross-coupling reactions in two different ways: semiautomated parallel synthesis in solution and 'mix-and-split' synthesis on solid support. These synthetic strategies, together

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0022-328X/02/$ - see front matter
PII: S0022-328X(02)01153-1

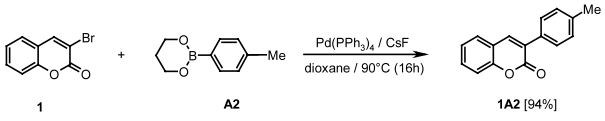
with advanced screening procedures, are further discussed in this paper.

2. Combinatorial libraries of organic materials

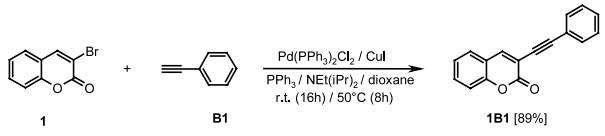
2.1. Fluorescent dyes

The natural product coumarin and its synthetic derivatives represent an important class of benzopyrones that have found extensive application as therapeutic agents [11], optical bleaching agents [12], active media for tunable dye lasers [13] and as luminescence labels for biochemical studies [14]. To date, a correlation between optical properties, in particular the fluorescence quantum yield, and the molecular structure of these chromophores is not predictable by current theories. The combinatorial generation of a diverse library based on the coumarin scaffold and its subsequent screening for optical properties should provide a data set whose analysis could pave the way for the development of reliable structure–property relationships.

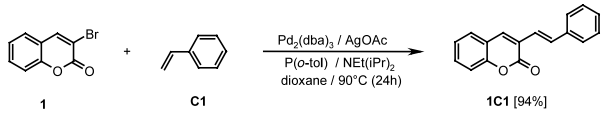
To vary the electronic structure of the coumarin core in a combinatorial manner, we developed synthetic protocols to substitute the 3-position of several coumarin scaffolds by C–C cross-coupling reactions of the Suzuki, Sonogashira–Hagihara and Heck type. Using these Pd-catalyzed transformations the attachment of (het-)arylene, ethynylene and ethenylene moieties was expected to significantly alter the electronic structure of the parent chromophore. In the first step, optimized synthetic protocols for all three coupling reactions were elaborated. In sharp contrast to the classical organic synthesis where reaction conditions are optimized individually for each reaction component, synthetic procedures for parallel syntheses are generalized for a representative set of building blocks that cover a wide reactivity range. In the following paragraphs, these optimizations are representatively discussed for 3-bromocoumarin **1** [15].



Scheme 1. Suzuki cross-coupling of 3-bromocoumarin **1** and boronic ester **A2**.



Scheme 2. Sonogashira–Hagihara cross-coupling of 3-bromocoumarin **1** and phenylacetylene **B1**.



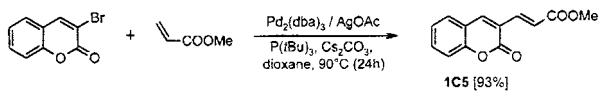
Scheme 3. Heck cross-coupling of 3-bromocoumarin **1** and styrene **C1**.

When attaching (het-)arylene substituents to the coumarin core, the effectiveness of Suzuki cross-couplings was evaluated by using *p*-tolyl boronic ester **A2** as coupling component. Since among various reactions conditions, $Pd(PPh_3)_4$ as catalyst and CsF as base are very efficient in cross-couplings of aromatics and heterocycles with a wide range of sterically and electronically different boron compounds [16], we applied this protocol to the coumarin scaffold. Among the solvents tested (DMF, THF and dioxane), dioxane appeared to be the most appropriate due to its higher boiling point with respect to THF and higher conversion rates with respect to DMF. These optimized reaction conditions allowed the isolation of the *p*-tolyl substituted coumarin **1A2** in 94% yield (Scheme 1).

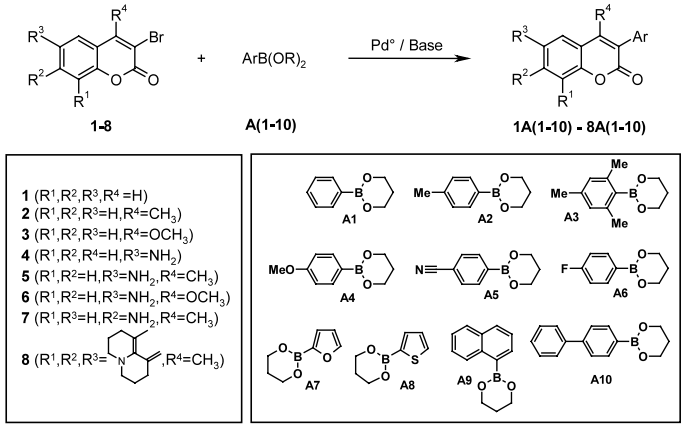
The introduction of ethynylene moieties at the coumarin core **1** by using Sonogashira–Hagihara-type reactions was optimized by utilizing phenylacetylene **B1** as the representative coupling component yielding phenylacetylene-substituted coumarin **1B1**. As a result, catalytic system $Pd(PPh_3)_2Cl_2/PPh_3/CuI$ and $NEt(iPr)_2$ as a base proved to be the most appropriate reaction conditions (89% yield, Scheme 2).

In order to evaluate the effectiveness of Heck reactions with 3-bromocoumarin **1**, styrene **C1** was representatively employed for the cross-coupling of ethylene derivatives. As reaction parameters we varied the catalyst [$Pd(PPh_3)_2Cl_2$, $Pd(PPh_3)_4$, $Pd_2(dba)_3$], the ligand [PPh_3, P(*o*-tol)$_3$] and the base [NEt_3, $NEt(iPr)_2$]. Careful analysis of the optimization reactions revealed that the system $Pd_2(dba)_3/AgOAc/P(o\text{-tol})_3/NEt(iPr)_2$ is the most efficient to furnish the desired styryl substituted coumarin **1C1** (Scheme 3). The cross-coupled product is formed isomerically pure (E-form) in 94% yield.

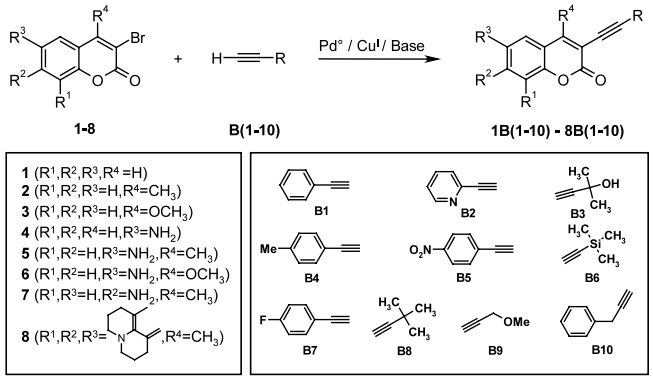
Since Heck couplings are known to be particularly sensitive to the electronic nature of the alkene component [17], we investigated the cross-coupling of coumarin **1** and acrylic acid methyl ester **C5** which is more electron-deficient than styrene **C1**. Indeed, this cross-coupling resulted in a diminished yield (17%) of acrylic ester substituted coumarin **1C5** when the aforementioned reaction conditions were applied. Cognizant of this situation, we refined the protocol for electron-poor alkenes and found that the system $Pd_2(dba)_3/AgOAc/P(tbu)_3/Cs_2CO_3$ is much more appropriate. The yield of coumarin **1C5** could be increased to 93% (Scheme 4). Vice versa, under these conditions styrene only gave 12% of ethenylated coumarin **1C1**.



Scheme 4. Heck cross-coupling of 3-bromocoumarin **1** and acrylic ester **C5**.



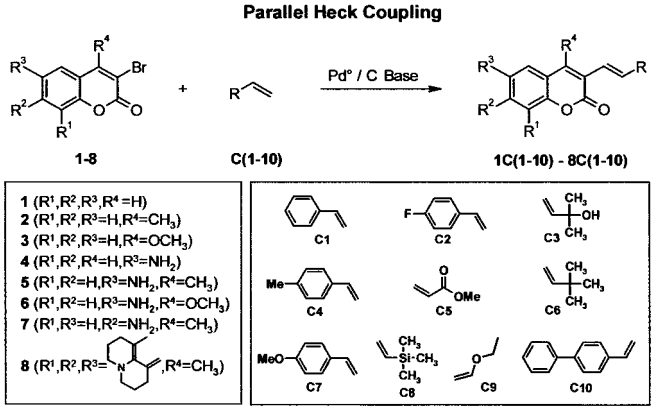
Scheme 5. Coumarin sublibrary generated by parallel Suzuki reactions of 3-bromocoumarins **1**–**8** and boronic ester **A(1**–**10)**.



Scheme 6. Coumarin sublibrary generated by parallel Sonogashira–Hagihara reactions of 3-bromocoumarins **1**–**8** and acetylenes **B(1**–**10)**.

In order to assess the reliability of the optimized reactions conditions for the three Pd-catalyzed cross-couplings, three different 10-membered model libraries based on 3-bromocoumarin **1** were generated by reaction with 10 boronic esters **A(1**–**10)** (Suzuki coupling, Scheme 5), with 10 acetylenes **B(1**–**10)** (Sonogashira–Hagihara coupling, Scheme 6) and 10 olefins **C(1**–**10)** (Heck coupling, Scheme 7) [18] in an automated parallel synthesizer. Building blocks **A(1**–**10)**, **B(1**–**10)** and **C(1**–**10)** from which diversity emerged were selected for their difference in electronic and steric properties. Following a parallel pre-purification by means of solid phase extraction, the three libraries were analyzed and purified by automated HPLC–MS. For the library constructed by Suzuki couplings the isolated yields of the 10 (het-)arylated coumarins **1A(1**–**10)** ranged from 67 to 97%. Similarly, Sonogashira–Hagihara coupling furnished a 10-membered library of 3-ethynylated coumarins **1B(1**–**10)** in isolated yields of 74–95%, whereas Heck-coupling gave the 10-membered library of 3-(*E*)-ethenylated coumarins **1C(1**–**10)** in 30–94%. In total, all 30 expected coupling products were obtained in high purity and in most cases in high yield. Thus, the preparation of model libraries **1A(1**–**10)**, **1B(1**–**10)** and **1C(1**–**10)** served as a standard for further chromophore libraries.

Due to the efficiency of the optimized synthetic protocols we aimed to generate a further seven coumarin libraries based on 3-brominated coumarins **2**–**8** [19]. The variation at the coumarin core by electron-donating substituents in 4-, 6-, 7- and 8-position results in a high diversity which should decisively influence the electronic structure and the associated dye properties. At the same time, however, also the reactivity of the coumarin in the Pd-catalyzed reactions was expected to be altered. The Suzuki coupling proved to tolerate the various electron-donating abilities of methyl, methoxy, amino and dialkylamino groups attached to the coumarin scaffold and gave libraries **2A(1**–**10)**–**8A(1**–**10)** in high conversions. In contrast to the Suzuki coupling, Sonogashira–Hagihara and Heck reactions almost completely failed under the conditions optimized for 3-bromocoumarin **1**. Consequently, it was necessary to further optimize the reaction conditions for these 3-bromocoumarins. Depending on the substitution pattern, three different sets of protocols were developed for both reaction types: (1) Sonogashira–Hagihara coupling of 3-bromocoumarins **2**–**8**: $Pd(PPh_3)Cl_2/PPh_3/CuI/Et_3N$; (2) Heck coupling of non-amino substituted 3-bromocoumarins **2** and **3**: $Pd(OAc)_2/P(o\text{-tol})_3/NEt(iPr)_2$; (3) Heck coupling of amino substituted 3-bromocoumarins **4**–**8**: $Pd(OAc)_2/n\text{-}Bu_4NCl/LiCl/NaHCO_3$. By applying these reaction conditions for the preparation of libraries **2B(1**–**10)**–**8B(1**–**10)** and



Scheme 7. Coumarin sublibrary generated by parallel Heck reactions of 3-bromocoumarins **1**–**8** and olefins **C(1**–**10)**.

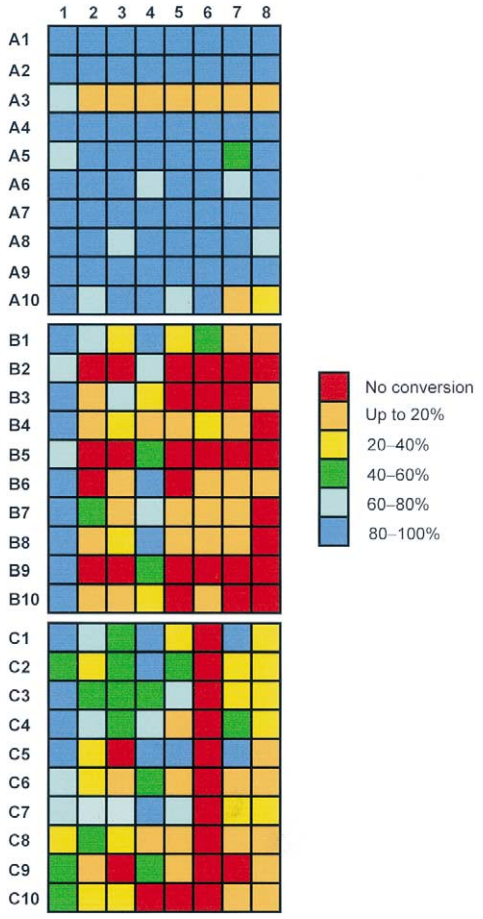


Fig. 1. Color-coded matrix which represents the reaction conversions (determined with HPLC) of all 'combinations' of 3-bromocoumarins **1**–**8** with coupling components **A(1**–**10)**, **B(1**–**10)** and **C(1**–**10)** as a 'map'. 3-Bromocoumarins **1**–**8** are plotted along the abscissa, coupling components **A(1**–**10)**, **B(1**–**10)** and **C(1**–**10)** along the ordinate.

2C(1–**10)**–**8C(1**–**10)** we were able to finally isolate after HPLC-purification 151 (63%) of 240 possible coumarin derivatives in purities $>99\%$. Among those, 127 library members are not reported in the literature. The isolation of the other compounds was not possible due to separation problems and/or low conversions during the reaction.

For the three Pd-catalyzed cross-coupling reactions several trends became evident when HPLC-determined reaction conversions of all 240 transformations were analyzed and compared. As mentioned above, the Suzuki-type cross-coupling is characterized by a broad tolerance with respect to electronic features of both the 3-bromocoumarins **1**–**8** and the boronic esters **A(1**–**10)**. The influence of the steric effects became apparent when the sterically demanding mesityl boronic ester **A3** was utilized. In these cases, relatively poor conversions were observed for the reaction with **1**–**8**. By contrast, cross-coupling reactions of the Sonogashira–Hagihara and the Heck type show diminished conversions with increasing overall electron-donating ability of the substituents in 4-, 6-, 7- and 8-position of the coumarin core. A decreasing conversion is found when aminocoumarin **4** without an substituent in the 4-position is compared to aminocoumarins **5**–**8** bearing a methyl or a methoxy substituent at the 4 position of the coumarin scaffold. In Fig. 1, the conversions of all synthetic transformations are summarized in a color-coded matrix which illustrates the aforementioned trends.

2.2. π-Conjugated oligomers

π-Conjugated oligomers appear ideally suited for a combinatorial approach. Their construction generally involves only an iterative two-step sequence for oligomer growth and the screening for optical and electronic properties should be amenable to automation. π-Conjugated oligomers have attracted much attention recently due to their possible application in molecular-based and -scale electronic devices [20] and for the construction of nanoarchitectures [21]. Moreover, these structurally-defined and monodisperse oligomers serve as model compounds for the corresponding polydisperse bulk polymers [4,20,22].

Recent examples of solid-phase synthesis demonstrated the successful incorporation of C–C cross-coupling reactions for the synthesis of one-step coupling products including bisarene, vinylarene and phenylacetylene moieties and for the generation of π-conjugated oligomers [5,23,24]. In particular for the synthesis of π-conjugated oligomers one can profit from the general advantages of solid-phase synthesis: (1) oligomer growth reactions can be driven to completion by using reagents in excess which can be easily removed by filtration; (2) purification of the growing oligomers is simplified by washing the polymer support with appropriate solvents; (3) an optimized solid-phase protocol can be easily translated into a combinatorial synthesis and is amenable to automation. These advantages prompted us to translate the optimized protocols for the oligomer synthesis in solution to solid phase supported chemistry. While in solution site-specific functionalized monomer building blocks or the use of protecting groups is crucial for the oligomer growth in one direction, an appropriate linker system is a prerequisite for the successful synthesis on solid support. Both a carboxy linker and a traceless silyl ether linkage were employed for the solid-phase synthesis of regioregular head-to-tail coupled oligo(3-alkylthiophene)s [25] and oligo(3-arylthiophene)s [26], respectively (Fig. 2).

Whilst the carboxy linkage provides a functionalized oligomer after cleavage from solid support, non-functionalized oligomers are obtained with the traceless silyl linker. Both target structures were generated by using an iterative sequence of iodinations and Suzuki cross-coupling reactions. The synthetic route for the *p*-tolyl substituted oligomers (R=CH_3) is shown in Scheme 8.

After the attachment of a chlorosilylthiophene to hydroxymethylated polystyrene, resin-bound thiophenes were iodinated after metalation with LDA or by a two-step electrophilic substitution using mercuric hexanoate and iodine. The oligomer elongation was achieved using a thiophene boronic ester (R=CH_3), $Pd(PPh_3)_4$ as the catalyst and aqueous $NaHCO_3$ as the base. The tetraarylated quaterthiophene could be isolated (after cleavage from solid support with TFA or TBAF and chromatographic purification) in 48% overall yield which corresponds to an average yield of 91% over eight reaction steps.

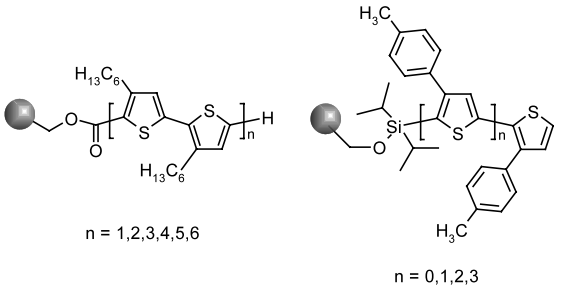
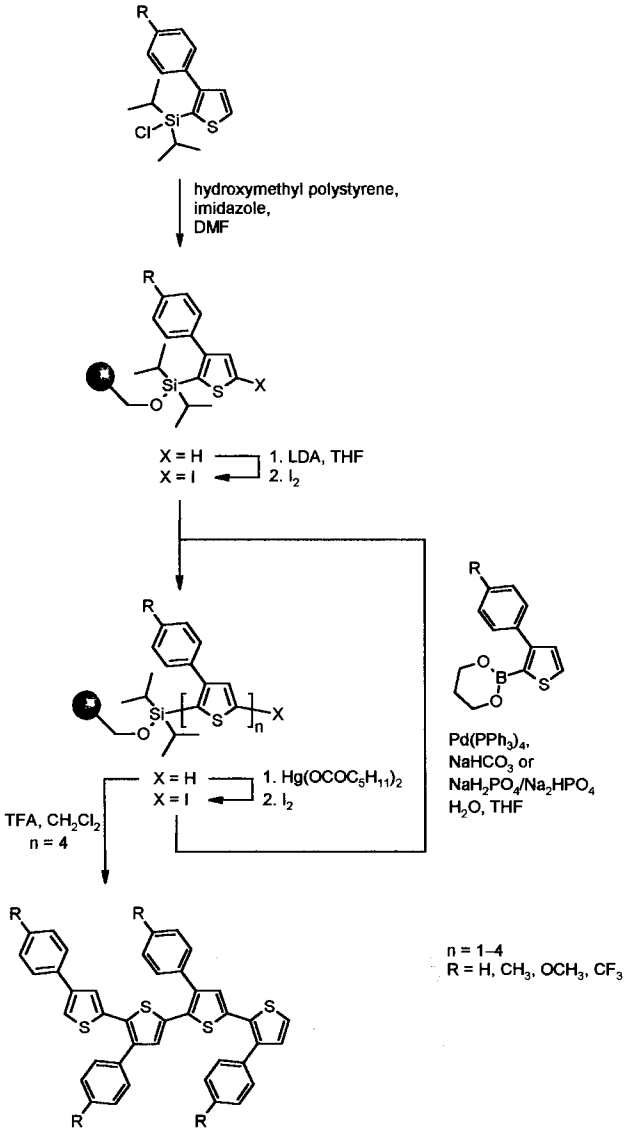


Fig. 2. Resin-bound regioregular head-to-tail coupled oligo(3-akylthiophene)s and oligo(3-arylthiophene)s generated by solid-phase synthesis.



Scheme 8. Solid-phase synthesis of oligo(3-arylthiophene)s.

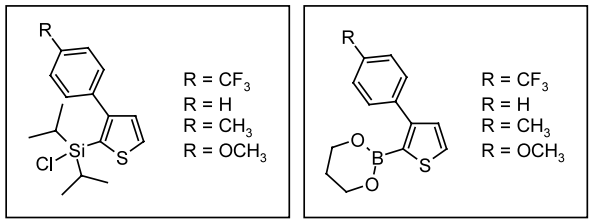


Fig. 3. Diversity building blocks for the construction of the oligothiophene library.

Since various substituents are used to modify the properties of conducting oligomers and polymers [20,22], it would be of great value to get a detailed insight into the substituent effects to increase the knowledge of structure–property relationships. Towards this goal, an oligo(3-arylthiophene) library was designed and generated to explore these substituent effects on the energy levels of the frontier orbitals as well as the associated energy gap. Based on the aforementioned solid-phase synthesis of oligo(3-arylthiophene)s we developed a general synthetic protocol for the library construction of quaterthiophenes bearing electronically different substituents in the *para* positions of the four 3-phenyl substituents (Scheme 8). The building blocks synthesized for the library generation are depicted in Fig. 3. With the four different substituents the electronic behavior of the resulting oligomers was expected to be systematically altered whereas the overall geometry of the quaterthiophenes should remain almost constant.

Investigating the feasibility of the Suzuki cross-coupling reaction employing these four electronically different building blocks clearly revealed the influence of the electronic nature of the substituents on reactivity. In particular, the reactivity of the four boronic esters was substantially altered so that the synthetic protocol needed to be further optimized. Phenyl and *p*-tolyl substituted boronic esters underwent smooth cross-coupling with resin-bound iodothiophenes under the standard reaction conditions: boronic ester (2.5 equivalents), sodium hydrogencarbonate (10 equivalents), $Pd(PPh_3)_4$ (5 mol%), THF–H_2O. After 8 h, nearly complete conversion to the corresponding polymer-bound oligomers was observed, independent of the electronic nature of the immobilized iodinated compound. Cross-coupling with the electron-rich anisyl substituted thiophene boronic ester was found to pro-

ceed more slowly. In this case, quantitative conversion could be achieved when the components were reacted for a prolonged reaction time. In contrast, the trifluoromethyl substituted phenylthiophene boronic ester proved to be critical in achieving complete conversions. In this case, desired oligomers were obtained in moderate to poor conversions when the standard conditions were applied. The incomplete conversions were a result of the rapid deboronation of the coupling component. The protiodeboronation could be effectively suppressed when utilizing an aqueous buffer solution of sodium dihydrogenphosphate (four equivalents) and disodium hydrogenphosphate (eight equivalents). In conclusion, two different Suzuki cross-coupling conditions were necessary for a high-yielding oligomer growth: aqueous sodium hydrogencarbonate as the base for electron-rich phenyl, *p*-tolyl and *p*-anisyl substituted thiophene boronic esters and aqueous hydrogenphosphate–dihydrogenphosphate buffer system as the base for the thiophene boronic ester bearing the electron-withdrawing trifluoromethylphenyl group.

To generate all possible permutations of the thiophene silylchloride and boronic ester building blocks, 256 quaterthiophenes needed to be synthesized. Both the parallel and the well-established directed sorting variant of the 'mix-and-split' methodology was employed to synthesize the compound ensemble [27]. The synthesis of the iodobithiophenes was performed in parallel, the oligomer growth to the 256 desired quaterthiophenes used the directed sorting strategy. In the latter, the individual compounds are synthesized in solvent-permeable microreactors each labeled with a unique radiofrequency tag for identification. This technique allows several reactions (one per microreactor) to be carried out in the same reaction vessel simultaneously. Only seven parallel reaction steps yielded all 256 different polymer-bound tetramers reflecting the high efficiency of the combinatorial synthesis. Following the cleavage of the individual oligomers using TFA, the tetraarylated quaterthiophenes were purified by automated HPLC and a coupled MS detector allowed the structure validation. The overall isolated yields of the purified library members ranged from 2 to 51% (over eight reaction steps).

3. Library screening

In order to accelerate the whole combinatorial development loop and not to shift a bottleneck within the loop, it is essential to subject the generated library members to a powerful screening procedure. Ideally, an efficient screening process should allow the automated parallel or rapid sequential probe analysis with a high sample throughput. With the advent of combinatorial chemistry in the fields of pharmaceutical chemistry, solid-state materials science and catalysis, numerous powerful screening methodologies have been developed that are now well-established. These include enzymatic assays [28], colorimetric assays [29], IR thermography [30]. For inorganic solid-state material libraries several 'on-chip' screenings for superconductivity, magnetoresistance, dielectricity, ferrocelectricity and luminescence have been reported [31]. By contrast, the development of efficient screening methodologies for organic materials is in its infancy and even less advanced than the methodology utilized for the library construction [32]. Recently, Schmitz and Schmidt reported an elegant manufacturing and evaluation of a spatially addressable library of organic light-emitting devices [33]. This approach illustrated the feasibility of combinatorial strategies for the optimization of organic electron transport materials and device configurations in complex multiparameter systems.

For the aforementioned libraries of fluorescent dyes and π-conjugated oligomers we were interested in the optical and electrochemical properties such as absorption and emission maxima, fluorescence quantum yields and redox potentials. Absorption and fluorescence spectroscopy and cyclic voltammetry were chosen for the systematical investigation of these electronic features.

Using an automated microplate reader coupled to a fluorescence spectrometer the rapid sequential screening of the ensemble of coumarin dyes was conducted. The subsequent data analysis resulted in the identification of several hits. Fluorescent dyes with good to excellent fluorescence quantum yields and emissions in the yellow, green and blue range of the spectrum were obtained. Some of these screening 'hits' are displayed in Fig. 4. For example, 3-phenylethynyl-coumarin **7B1** exhibits an even higher fluorescence quantum yield ($\phi_f = 0.98$) than the commercially available laser dye coumarin 120 ($\phi_f = 0.88$) [34]. Moreover, the data analysis provided the relationship between the chemical structure and molecular parameters such as absorption and emission maxima, stokes shifts etc.

In contrast to the coumarin library in which the data analysis of the screening results allowed identification of individual 'hits' with a specific property, no such hit identification was targeted for the oligomer library. Here, we aimed to deduce detailed structure–property relationships on which to base future material design. For the electrochemical screening of the oligo(3-arylthiophene) library we constructed an apparatus for the sequential recording of cyclic voltammograms [35]. The fully automated screening device is comprised of a 96-well plate which was used as an array of electrochemical cells, a three-electrode setup (Pt-working, Pt-counter, Ag–AgCl reference electrode), a solvent dispenser, a potentiostat and a computer for data acquisition. The tailored software allowed to precisely position the electrode-setup into the wells of the microt-

iter plate, the dosing of the electrolyte and the acquisition of the cyclovoltammetric data.

Typical cyclic voltammograms obtained by the aforementioned automated screening process are exemplified in Fig. 5. These voltammograms are representative examples which are observed for the library members. In panel A of Fig. 5, the voltammogram of the quaterthiophene bearing two trifluoromethylphenyl, a tolyl and an anisyl group reveals two reversible oxidation waves at $E_1^\circ = 0.58$ and $E_2^\circ = 0.84$ V. These reversible redox waves can be unambiguously ascribed to the formation of the quaterthiophene radical cation and its subsequent oxidation to the corresponding dication. Depending on the substitution pattern, some oligomers exhibit an irreversible first oxidation (panel B of Fig. 5; quaterthiophene bearing three anisyl and a trifluormethylphenyl group). In the case of an irreversible first oxidation, a second irreversible oxidation wave appears at around $E_p = 1.1$ V. This wave can be attributed to the generation of a σ-dimer which is formed by the dimerization of the radical cations. Such σ-dimers are currently discussed as intermediates of the oxidative polymerization process to conducting polymers including polythiophenes [36].

The first oxidation potentials of the library members span the range of $E_{ox}^\circ = 0.42$–0.68 V. This range clearly indicates the electronic influence of the substituents on the core structure. The four substituents substantially alter the redox potentials in dependence of their respective electron-donating or -accepting ability. On first inspection, the electronic nature of the four substituents appears to be strictly additive. However, the comparison of the oxidation potentials of isomeric oligomers reveals that the substitution pattern, i.e. the sequence of the four substituents, is a second determinant of the oxidation potential.

4. Conclusions

To accelerate the pace of the discovery process to novel organic materials, more efficient strategies must be developed that provide for both a rapid compound generation and evaluation. Towards this goal, we generated material libraries of fluorescent coumarins and oligothiophenes using well-established C–C cross-coupling reactions of the Heck-, Sonogashira–Hagihara- and Suzuki-type. Subsequent screening of the purified libraries for optical and electrochemical properties al-

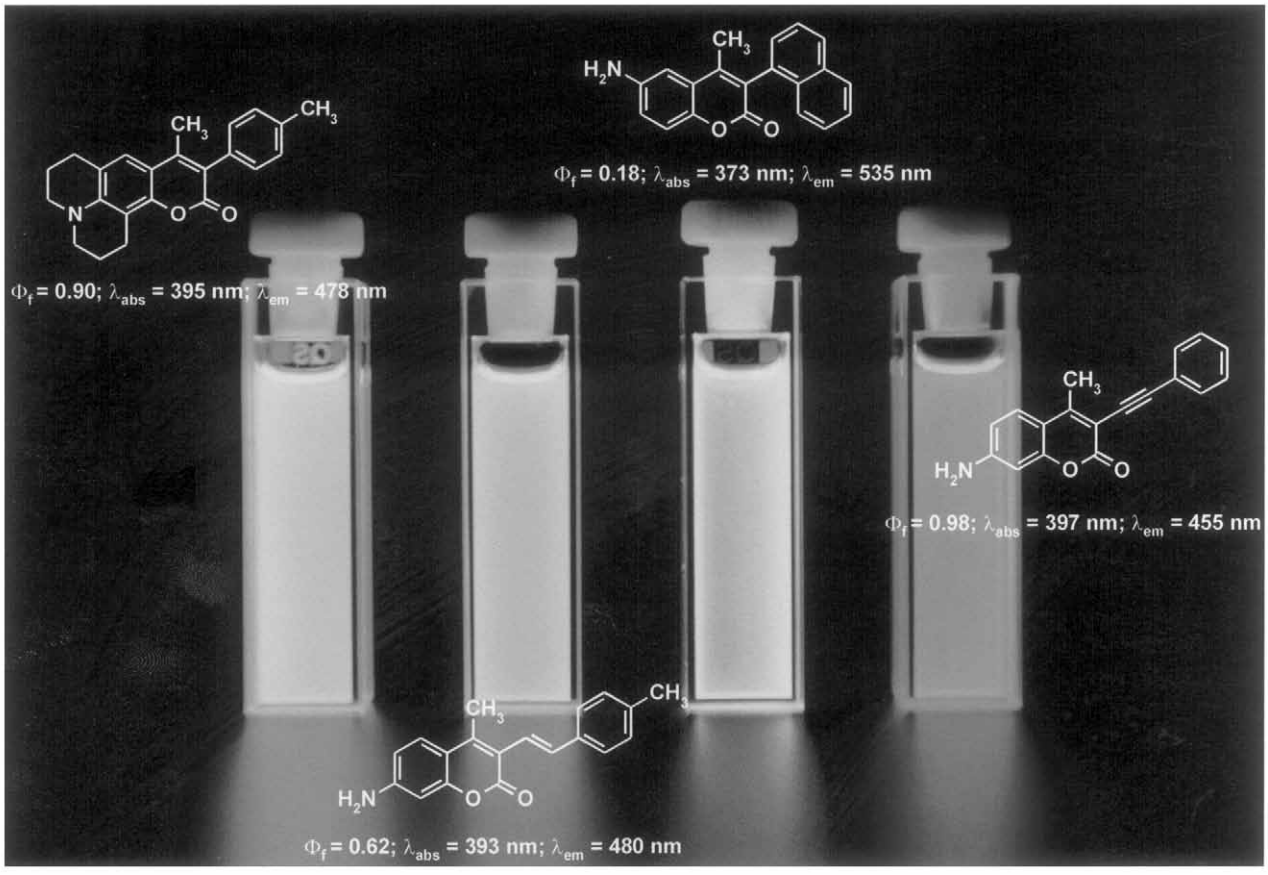


Fig. 4. Identified hits of the coumarin library.

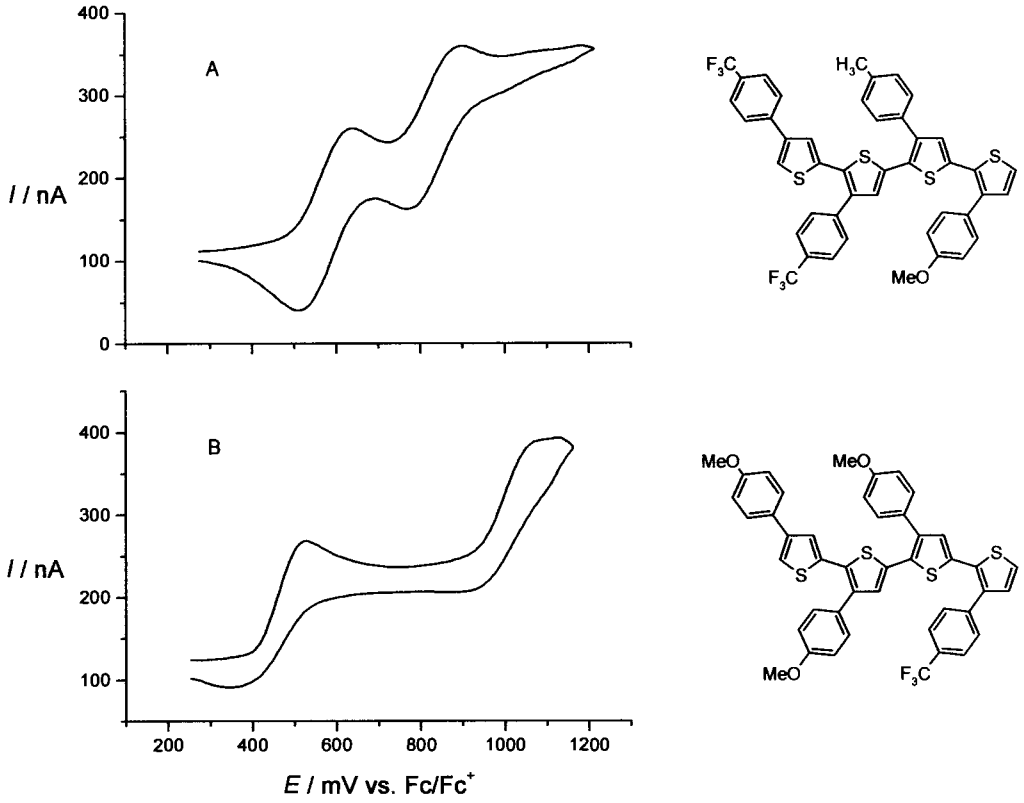


Fig. 5. Typical cyclic voltammograms of quater(3-arylthiophene)s measured in CH_2Cl_2 (0.1 M Bu_4NPF_6, $v = 100$ mV s^{-1}).

lowed the identification of 'hits' of novel coumarins with high fluorescence quantum yields and the development of detailed structure–property relationships for the π-conjugated oligomers. The results presented here clearly demonstrate that combinatorial strategies are promising avenues of research to address the challenge of material design and development.

Acknowledgements

We gratefully acknowledge the financial support of the Fonds der Chemischen Industrie and the BMBF (Kekulé grant to C.A.B.).

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