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Expedient synthesis of thioether-functionalized hydrotris(indazolyl)borate as an anchoring platform for rotary molecular machines

Guillaume Erbland,[a] Yohan Gisbert,[a] Gwénaël Rapenne [a,b] and Claire Kammerer*[a]

Abstract: Major improvements in the synthesis of surface-mounted rotary molecular machines based on ruthenium(II) complexes are reported. The development of a one-pot indium(III)-mediated "*N*-deprotection / ester reductive sulfidation" sequence allowed step economy, reproducibility and high efficiency in the synthesis of the thioether-functionalized tripodal ligand. Switching to the thallium salt of hydrotris(indazolyl)borate and to microwave heating further optimized the preparation of the common intermediate in the modular synthesis of symmetric and dissymmetric molecular motors and gears. The penta(4-bromophenyl)cyclopentadienyl ruthenium(II) key precursor is now reproducibly synthesized in 5 steps and 31% overall yield on the longest linear sequence. Subsequent five-fold Suzuki-Miyaura coupling with ferroceneboronic acid led to a new C_5-symmetric penta-ferrocenyl molecular motor.

Introduction

The field of artificial molecular machines has witnessed a tremendous development over the last two decades, with an initial impetus related to the synthesis of mechanically interlocked systems allowing to control the motion of (at least) one of their components.[1,2] Among nanomachines, artificial molecular motors are expected to transform the supplied energy into a unidirectional translational or rotational motion, ultimately leading to recovery of the work performed.[3] Pioneering examples of chemically- and light-fuelled rotary motors were reported as early as in 1999 by the groups of Kelly[4] and Feringa,[5] respectively, exhibiting controlled unidirectional motion in solution. Although many very elegant molecular rotary motors using chemical or light energy have been developed ever since[3] and have shown interesting applications,[6] the exploitation of electronic energy is still rare and only scarce examples have been reported at the single molecular scale[7-9] or in self-assembled monolayers.[10] Sykes and co-workers employed a butyl methyl sulfide single-molecule chemisorbed on a Cu(111) surface as a rotor and used the tip of a Scanning Tunneling Microscope (STM) to trigger an electrically-driven rotation.[7] As a result, one of the enantiomeric surface-bound molecules underwent rotary motion with 5% directionality, which has been ascribed to the intrinsic chirality of the STM tip. In 2011, Feringa incorporated four overcrowded alkene-based motors acting as wheels into a molecular car scaffold and proved that the electrically-driven rotary motion of the motors can be converted into directional translation of the nanovehicle on a Cu(111) surface.[8]

In this context, we reported the design and synthesis of electron-fueled molecular motor **1** displaying a dissymmetrically-substituted cyclopentadienyl rotor, a scorpionate ligand as the stator and a ruthenium(II) center as a joint allowing the rotary motion of the upper part with respect to the lower one (Figure 1).[11] The tripodal stator was functionalized with thioether groups to ensure a strong anchorage on gold surface *via* chemisorption. This molecular motor was indeed studied at the single molecule scale at low temperature (5 K) under Ultra-High Vacuum (UHV) by STM.[9] The latter was used not only to image the molecular motor, but above all to trigger its rotation *via* the injection of tunneling electrons. Most importantly, it was discovered that the dissymmetric character of the rotor, with four phenyleneferrocenyl groups and a truncated tolyl arm, is of paramount importance. On the one hand, it allows a direct monitoring of the rotation (and of its direction) by following the position of the shorter arm, which serves as a tag. On the other hand, it was discovered that this dissymmetry induces a reversible behaviour, with a direction of rotation which depends on the location of the tip during the pulse (above one of the longer ferrocenyl-appended arms, or above the shorter truncated arm).

This motor belongs to a broader family of motors that have been reported along the years (Figure 1).[12] This family mostly involves C_5-symmetric rotors, with arms of various lengths and nature.[11,13] Indeed, while the dissymmetric motor **1** displays a diameter of about 2 nm with a single *para*-phenylene separating the cyclopentadienyl and ferrocenyl units, several motors with longer arms have been reported. These C_5-symmetric rotors included phenylethynyl linkers[13b] but also insulating groups such as bisethynyl *trans*-platinum(II)[13b] or bicyclooctyl[13c] spacers. Moreover, most of the motors had been originally designed to be deposited on insulating oxide surfaces and therefore display ester anchoring groups.

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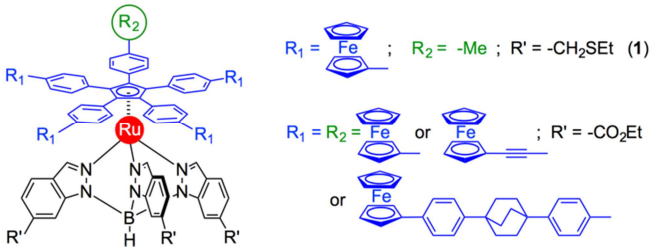
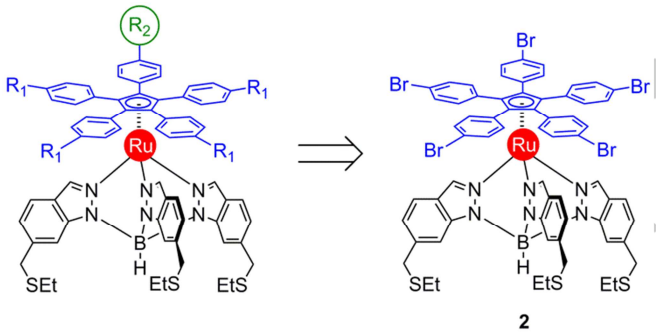


Figure 1. Structure of the unidirectional and reversible tetraferrocenyl molecular motor **1** and of symmetric Ru(II)-based molecular motors incorporating ester anchoring groups on the scorpionate ligand, and arms of various lengths and nature connected to the cyclopentadienyl core.

However, the technology is currently not mature enough to address horizontally an electron-fueled rotary motor located between two electrodes on an insulating surface (*i.e.* a nanojunction). Our efforts are thus currently focused on the development of new symmetric and dissymmetric structures of motors and gears,[12b,c] specifically designed for an optimal interaction with metallic surfaces such as gold (Scheme 1).

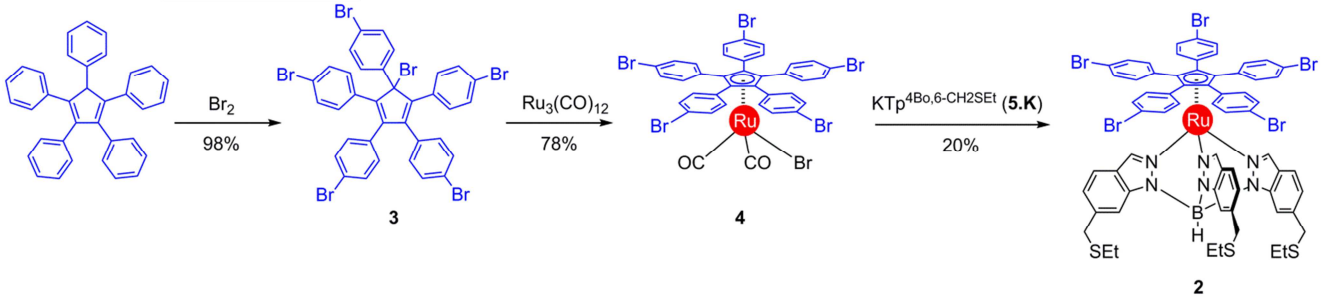


Scheme 1. Structure of symmetric (R_1 = R_2) or dissymmetric (R_1 ≠ R_2) molecular motors and gears, and related retrosynthetic analysis leading back to common key intermediate **2**.

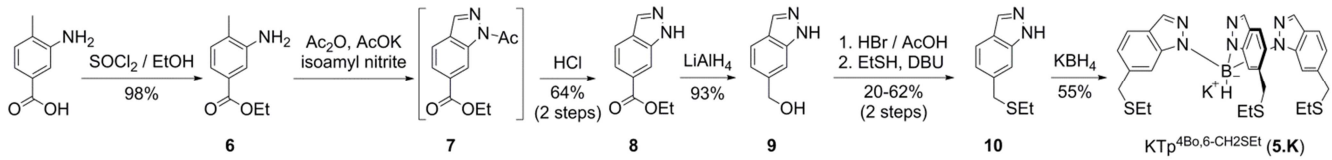
From a retrosynthetic point of view, all the structures including a C_5-symmetric rotor stem from key intermediate **2**, displaying aryl bromide functions on each arm, ready for various cross-coupling reactions. This strategy was successfully applied to the synthesis of our family of symmetric motors, starting from pentaphenylcyclopentadiene (Scheme 2).[11] The latter is first brominated on the phenyl *para*-positions and on the cyclopentadiene core using neat bromine giving an hexabrominated compound (**3**) in a nearly quantitative yield. Subsequent oxidative addition on ruthenium(0) cluster $Ru_3(CO)_{12}$ leads to complex **4**,[14] in accordance with the method reported by Connelly and Manners.[15] Conversion of this piano-stool complex into the key intermediate **2** is finally achieved *via* ligand exchange in the presence of the potassium salt of thioether-functionalized hydrotris(indazolyl)borate (**5.K**). Although this synthetic route suffers from the low yield of the last step, it allows the formation of the cyclopentadienyl-Ru(II) complex, which appeared impossible under other tested conditions due to the strong steric hindrance of the five phenyl rings attached to the cyclopentadienyl core.

By contrast, the synthesis of the dissymmetric motor **1** (with R_1 = Fc and R_2 = Me) involved the introduction of the tolyl group corresponding to the truncated arm at a very early stage.[11] In addition to an evident lack of modularity, it was observed that the oxidative addition of the dissymmetric cyclopentadienyl bromide on the $Ru_3(CO)_{12}$ cluster was less efficient (43%) than with the corresponding symmetric precursor **3** (78%). This tendency was confirmed by other attempts with cyclopentadienyl bromides involving one longer and potentially coordinating arm.[16] In view of future developments of dissymmetric motors and gears based on the ruthenium cyclopentadienyl scaffold, the latter approach is not reliable and modular enough. It is thus envisioned to exploit penta-bromide key intermediate **2** and perform a first statistical single cross-coupling to generate the differentiated arm. The remaining four activated positions could then undergo cross-couplings reactions to yield various dissymmetric rotors.

This renewed strategy towards dissymmetric motors and gears highlights the need for important amounts of key intermediate **2**. It thus appeared necessary not only to increase the efficiency of the coordination of the tripodal ligand (only 20%, Scheme 2) but also to optimize the synthesis of potassium hydrotris[6-((ethylsulfanyl)methyl)indazolyl]borate **5.K** by itself. The latter is a bifunctional platform combining anchoring groups and coordinating sites pointing in opposite directions. The anchoring groups are necessary to efficiently restrict the possible translation, rotation and rocking motions of molecules on a surface. While a single binding point only prevents translation motions and a second one additionally blocks the rotation of the molecule, a minimum of three points of anchoring are necessary to preclude rocking motion. In our design, the rigid hydrotris(indazolyl)borate scaffold bears three functional thioether pendant groups well oriented at the 6-position of the indazole core to very efficiently immobilize this platform on metallic surfaces such as gold, silver or copper (Scheme 1). On the opposite side of the ligand, three nitrogen atoms belonging to the indazole cores are available to coordinate a metal center such as ruthenium. This tripodal chelating unit thus allows the covalent binding of coordination complexes on a surface, as in



Scheme 2. Synthesis of key intermediate **2** starting from pentaphenylcyclopentadiene.



Scheme 3. Synthetic route toward the potassium salt of hydrotris(indazolyl)borate **5.K**, starting from 3-amino-4-methylbenzoic acid.

the surface-mounted molecular gears or motors reported previously.[12] Furthermore, lifting the metallic center away from the surface allows minimizing interferences caused by metal-surface interactions. In this context, rotors (in the case of rotary motors) or cranked wheels (in the case of gears) can be efficiently deposited, anchored and studied without almost any interaction with the surface, which is particularly important for Scanning Probe Microscopy experiments.

Herein we present our results towards higher efficiency and step-economy in the preparation of tripodal ligand **5** and of the ruthenium penta-bromide derivative **2**, which serves as a central platform in the modular synthesis of various molecular motors and gears. As an application, the synthesis of a new symmetric penta-ferrocenyl motor with three thioether pendant groups (Scheme 1, $R_1 = R_2$ = ferrocene) is reported.

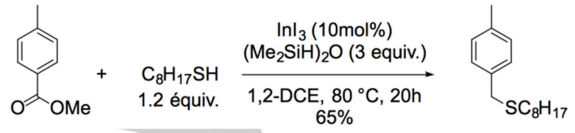
Results and Discussion

As mentioned above, one of our aims was to optimize the synthetic route towards hydrotris(indazolyl)borate **5** in terms of efficiency and reproducibility. Indeed, the preparation of such scorpionate ligand involved 7 steps starting from 3-amino-4-methylbenzoic acid (Scheme 3).[17] The latter was almost quantitatively protected as an ethyl ester and subsequently converted to the 1*H*-indazole **8** by a Jacobson reaction followed by acidic hydrolysis of the intermediate acetamide **7** (64% over two steps). Functional group manipulation to convert the ethyl ester into the desired ethyl thioether then involved the reduction of the ester to the corresponding alcohol **9**, bromination and subsequent nucleophilic substitution with ethanethiol. The thioether-appended 1*H*-indazole **10** was finally reacted with KBH_4 under solvent-free conditions at 200 °C to afford selectively the potassium hydrotris(indazolyl)borate $KTp^{4Bo,6-CH2SEt}$ (**5.K**) which was purified by sublimation of unreacted indazole **10**.

This synthetic sequence has been intensely used in our group as a standard way to prepare indazole-derived scorpionate ligands carrying either ester (from a direct reaction between KBH_4 and **8**) or thioether anchoring groups. Now that our main interest lies in molecular machines to be studied on metallic surfaces, it was desirable to renew the synthetic route towards thioether-appended indazole **10**, especially as a lack of efficiency and reproducibility of the ethanethiol-mediated nucleophilic substitution was observed throughout the years.

Improved synthetic route to thioether-appended indazoles

Interestingly, Sakai *et al.* recently reported the direct conversion of esters into sulfides *via* an indium-catalyzed reductive sulfidation reaction (Scheme 4).[18] The ester is directly reacted with the appropriate thiol in 1,2-dichloroethane (1,2-DCE) in the presence of a catalytic amount of indium(III) iodide as Lewis acid and an excess of 1,1,3,3-tetramethyldisiloxane (TMDS) as reducing agent.[19] After overnight heating, thioethers deriving from aliphatic and aromatic esters and thiols are obtained in good to excellent yields.



Scheme 4. Example of the indium(III)-catalyzed reductive sulfidation of methyl *p*-methylbenzoate with 1-octanethiol, as reported by Sakai *et al.*[18]

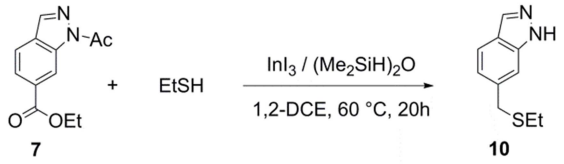
This method is thus of high synthetic utility since it avoids the common sequence involving the reduction of the ester, subsequent conversion of the alcohol into a (pseudo)halide and final substitution by a sulfur nucleophile.

The efficiency and the scope of this transformation drew our attention since this would allow the direct conversion of indazolyl ester **8** to thioether **10** (Scheme 3) in a single step (instead of three), although Sakai *et al.* did not mention any test on heteroaromatic derivatives.

In order to prevent the coordination of free 1*H*-indazole to the In(III) center, the reaction was first tested with the *N*-acetyl-protected indazolyl ester **7**. When reproducing the conditions reported by Sakai *et al.*, *i.e.* 10 mol% indium(III) iodide in combination with ethanethiol (1.2 equiv.) and 1,1,3,3-tetramethyldisiloxane (TMDS, 3 equiv. *i.e.* 6 *Si-H* equiv.) in 1,2-dichloroethane at 60 °C for 20h, a complex mixture was obtained as observed by ^{1}H NMR spectroscopy of the crude product (Table 1, entry 1). Careful analysis revealed the presence of traces amounts of unconverted starting material (**7**). Since no further signal corresponding to an acetamide moiety was detected, it was concluded that the expected *N*-acetyl protected indazole carrying the ethyl thioether function had not been formed. To our delight, it appeared that the free 1*H*-indazole scaffold bearing the thioether function was present in the mixture, although in traces amounts. This indicates that the desired reductive sulfidation takes place, although with a concomitant deprotection of the *N*-acetyl group which most probably consumes both the thiol and the silane. Indeed, increasing the quantity of thiol and silane to 2.2 and 6 equivalents, respectively, the free 1*H*-indazole **10** was gratifyingly formed as major product and isolated in 57% yield (entry 2). To check if the possible coordination of the free 1*H*-indazolyl ester **8** or thioether **10** formed during the reaction might deactivate the indium(III) catalyst and thus hamper the reaction, indium(III) iodide was introduced in slight excess (1.1 equivalent) compared to the substrate (entry 3). Under otherwise unchanged conditions, only a minor improvement of the isolated

yield was obtained (65%). In this reaction, a by-product (**13**) was formed in a ratio of 1:4 compared to product **10** according to the ^{1}H NMR spectrum of the crude mixture. This by-product had already been observed in various amounts under catalytic conditions and corresponds to the *N*-ethyl derivative of **10**. The *N*-ethyl moiety in **13** most probably results from a direct reduction of the acetamide group, as already reported under similar conditions.[20] To overcome this unproductive side reaction, the quantity of nucleophile was increased to 4 equivalents and the desired free 1*H*-indazole **10** was obtained as a single product in 86% yield (entry 4). Finally, in view of the synthesis of scorpionate ligands on a large scale, the same reaction was run on 1.5 g (compared to 150 mg in entries 1-4) to give rise to thioether indazole **10** in a comparable 85% isolated yield (entry 5).

Table 1. Optimization of the reaction conditions for the direct conversion of indazolyl ester **7** to thioether **10**,[a] in one single step instead of four.



Entry	InI_3 (equiv.)	EtSH (equiv.)	$(Me_2SiH)_2O$ (equiv.)	Yield (%)[b]
1	0.1	1.2	3	Traces
2	0.1	2.2	6	57[c]
3	1.1	2.2	6	65[c]
4	1.1	4	6	86
5[d]	1.1	4	6	85

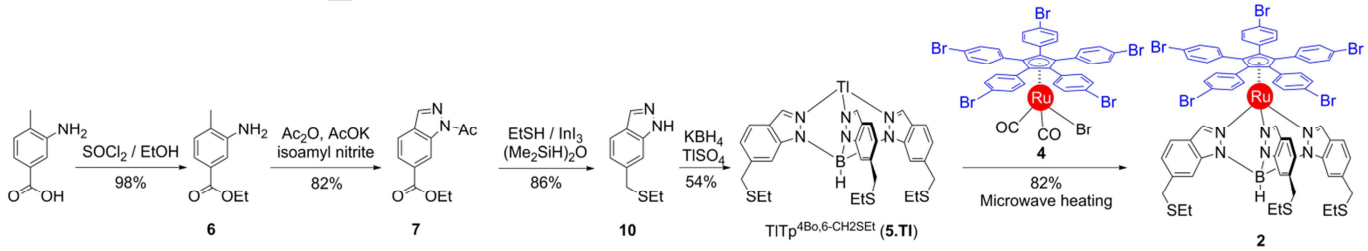
[a] The reactions were run on a 150 mg (0.65 mmol) scale unless otherwise stated. [b] Isolated yield unless otherwise stated. [c] By-product **13** resulting from the direct reduction of the *N*-acetyl group into an *N*-ethyl moiety was detected in the crude mixture. [d] The reaction was run on a 1.5 g (6.5 mmol) scale.

Application of the reaction conditions for the reductive sulfidation of esters developed by Sakai *et al.* and subsequent optimization now allow for a direct conversion of *N*-acetyl indazolyl ester **7** into the corresponding *N*-deprotected indazolyl thioether **10** in high yield and in a single step. This one-pot deprotection / reductive sulfidation not only shortens the synthetic route towards tripodal ligand **5.K** but also avoids the tedious isolation of 1*H*-indazolyl ester **8**. The thioether-functionalized indazole (**10**) is now very conveniently prepared in three steps on the gram scale starting from 3-amino-4-methylbenzoic acid in a reproducible 70% overall yield (Scheme 5), instead of six steps and a non-reproducible overall yield of 12 to 36% previously.

Following this improvement, the reproducibility of the synthesis of the hydrotris(indazolyl)borate salt **5.K** and the efficiency of the subsequent ligand exchange to yield key intermediate **2** were tackled.

Beneficial use of the thallium salt of the tripodal ligand as intermediate in the synthesis of rotor 2

Hydrotris(pyrazolyl)borates and by extension hydrotris(indazolyl) borates, are mostly prepared by heating an excess of the appropriate pyrazole (respectively indazole) with KBH_4 or $NaBH_4$ under neat conditions, as described above for the synthesis of the potassium salt **5.K**.[21] However, the thallium(I) salts of such derivatives have appeared as mild and valuable reagents for the transfer of the scorpionate ligands onto various transition metals, as they exhibit a lower reducing ability than the corresponding alkali metal salts.[22] The crystallinity of the thallium(I) complexes also renders their isolation more easy, and we thus envisioned the synthesis of the thallium salt $TlTp^{4Bo,6\text{-}CH2SEt}$ **5.Tl**. The thallium salts of scorpionate ligands are usually obtained by cation exchange, reacting the alkali metal salt with $TlNO_3$. In 2008, two new methods were reported by Kitamura *et al.*: i) preparation and isolation of thallium borohydride $TlBH_4$ and subsequent reaction with pyrazole or indazole derivatives[23] or ii) a solvent-free one-pot method using KBH_4 and Tl_2SO_4 in a 2:1 ratio to yield the thallium hydrotris(pyrazolyl)- or hydrotris(indazolyl)borate *via* an *in-situ* cation exchange.[24] Given the toxicity of thallium(I), the latter one-pot procedure was selected to avoid the isolation of the thallium borohydride reagent. Indazole **10** was thus reacted in the presence of potassium borohydride and thallium sulfate to give rise to thallium hydrotris(indazolyl)borate **5.Tl** in 54% yield (Scheme 5). Generating the thallium salt instead of the potassium salt leads to a comparable yield (54% vs 55%, respectively) but avoids the tedious and non-reproducible sublimation procedure as the thallium salt is efficiently recrystallized. However, the main advantage of using the thallium intermediate **5.Tl** lies in the ligand exchange step. Indeed, the reaction of 2 equivalents of thallium hydrotris(indazolyl)borate **5.Tl** with 1 equivalent of the ruthenium cyclopentadienyl complex **4** in THF at 100 °C for 48h afforded the target compound **2** in 67% yield, compared to 20% with the potassium salt **5.K** under otherwise similar conditions (Scheme 2). To our delight, the efficiency of this reaction was even further increased to 82% replacing classical heating with



Scheme 5. Optimized synthetic route yielding the key penta-bromide rotor **2** in 5 steps and 31% overall yield in the longest linear sequence (instead of 8 steps and maximum 4% yield previously).

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microwave heating (100 °C, 3 x 10 min) in acetonitrile as solvent (Scheme 5).

The indium(III)-mediated one pot deprotection / reductive sulfidation sequence followed by the preparation of the thallium salt of the scorpionate ligand has significantly shortened the synthetic route to the penta-bromide rotor **2** and increased its efficiency. Indeed, this key building block towards molecular motors and gears is now prepared in 5 steps in 31% overall yield in the longest linear sequence, compared to 8 steps and a maximum 4% overall yield formerly.

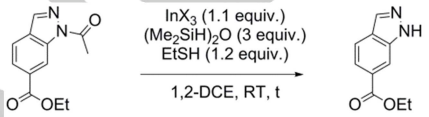
Extension of the indium(III)-mediated methodology to the synthesis of ester-appended scorpionate ligands

During our work towards the reductive sulfidation of indazolyl ester **7**, it was observed that the deprotection of the *N*-acetylindazole to give the corresponding 1*H*-indazole **8** occurs prior to the effective transformation of the ester. Deprotection of the *N*-acetyl protecting group is most commonly performed under drastic basic (hydroxide, alkoxide) or acidic (HCl) conditions,[25,26] provided that these conditions are compatible with additional functional groups. For instance, in our synthetic route towards hydrotris(indazolyl)borates, the crude *N*-acetylindazole obtained *via* the Jacobson reaction was deprotected using concentrated HCl at 60 °C (Scheme 3). The 1*H*-indazole **8** was obtained in a moderate 64% yield over two steps, and it was observed that a significant amount of product was lost during the acidic deprotection step, possibly *via* hydrolysis of the ester.

Since the amide function appears more reactive than the ester towards In(III)/TMDS/EtSH reaction conditions, the possible selective deprotection of the indazole core under mild conditions was investigated.

In a first test, the slight excess of indium(III) iodide (1.1 equiv.) was maintained while the amounts of ethanethiol and TMDS were reduced to 1.2 and 3 equiv. respectively, in order to favor the single reaction of the amide function (Table 2, entry 1). After 16h at room temperature, the starting material was fully converted but a mixture of products was obtained, including **10** resulting from the *N*-deprotection / reductive sulfidation sequence. The desired deprotected indazolyl ester **8** was isolated in 28% yield. Less reactive indium(III) species were tested next in order to avoid the conversion of the ester moiety. In the presence of indium(III) acetate and triflate, the conversion was very low after 4h at room temperature (entries 2 and 3). Conversely, indium(III) chloride promoted a smooth reaction with 91% conversion of the starting material after 20h (entry 4). Increasing the reaction time to 48h led to full conversion and the desired deprotected 1*H*-indazole **8** was isolated in a satisfactory 96% yield (entry 5). Blank experiments were next carried out in order to assess the role of each reagent. As expected, omission of the Lewis acidic indium(III) species totally prevented the reaction (entry 6). In the absence of thiol, the major product was *N*-ethylindazolyl ester (**14**), resulting from the complete reduction of the carbonyl moiety to the corresponding methylene (entry 7).[20] Finally, the reducing agent is also crucial in this procedure as no reaction occurs in the absence of hydrosilane (entry 8). It is thus assumed that this deprotection reaction is formally a reductive sulfidation of the acetamide moiety, with the indazole core playing the role of the leaving group.

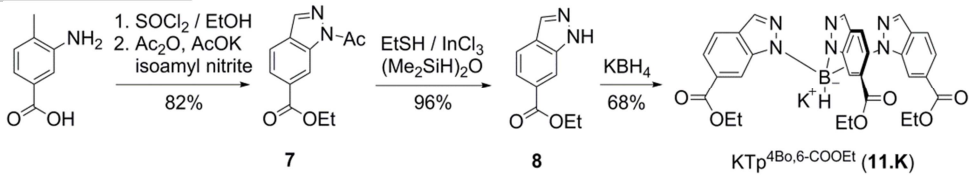
Table 2. Screening of conditions for the *N*-deprotection of *N*-acetylindazole **7** and corresponding blank experiments.[a]



Entry	InX_3	t (h)	Conv. (%)[b]	Yield (%)[c]
1	InI_3	16	100	28[d]
2	$In(OAc)_3$	4	0	-
3	$In(OTf)_3$	4	5	nd[e]
4	$InCl_3$	20	91	nd
5	$InCl_3$	48	100	96
6	-	48	0	-
7[f]	$InCl_3$	48	96[g]	5
8[h]	$InCl_3$	48	0	-

[a] The reactions were run on a 150 mg scale (entries 1-5) or on a 75 mg scale (entries 6-8). [b] Conversion of the starting material **7** as determined by ^{1}H NMR spectroscopy. [c] Isolated yield. [d] The desired product **8** was formed along with reductive sulfidation product **10** (13% isolated yield) and other unidentified products, as observed by ^{1}H NMR spectroscopy of the crude product. [e] Not determined. [f] Ethanethiol was omitted. [g] *N*-ethylindazolyl ester **14** and the desired product **8** were obtained in the crude mixture, in a 2:1 ratio. [h] 1,1,3,3-Tetramethyldisiloxane was omitted.

With these new deprotection conditions in hand, indazolyl ester **8** is now efficiently synthesized in 79% overall yield starting from 3-amino-4-methylbenzoic acid (Scheme 6), as compared to the 63% obtained previously (Scheme 3). The preparation of ester-appended hydrotris(indazolyl)borate **11.K**, used as stator in studies on insulating surfaces, will benefit from this improvement implying an increase from 43% to 54% of the overall yield on this four-step sequence.



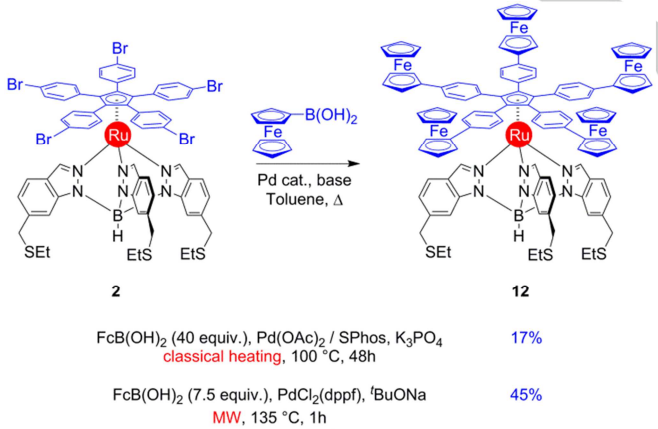
Scheme 6. Optimized synthetic route towards the potassium salt of ester-functionalized hydrotris(indazolyl)borate **11.K**.

Test-reaction: Synthesis of a new molecular motor and last major improvement using microwave activation

So as to probe the efficiency of a complete synthetic sequence up to molecular machines, the preparation of the new molecular motor **12** incorporating a symmetric rotating subunit was tackled (Scheme 7).

The penta-bromide rotor **2**, displaying a thioether-functionalized tripodal ligand, was submitted to Suzuki-Miyaura coupling conditions in the presence of a large excess of ferroceneboronic acid, using palladium diacetate / SPhos as catalytic system, potassium phosphate as base in anhydrous toluene. Penta-aryl bromide **2** thus underwent five successive Suzuki-Miyaura couplings to give rise to the desired penta-ferrocenyl molecular motor **12** in 17% yield after 48h at 100 °C (Scheme 7, classical heating).

Considering the future preparation of motors and gears that may involve more complex and expensive boronic acid derivatives, decreasing the amount of such partner was highly desirable. New reaction conditions were thus developed, involving 7.5 equiv. of ferroceneboronic acid (*i.e.* 1.5 equiv. per aryl bromide), sodium *tert*-butylate (22.5 equiv.) as base and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium $PdCl_2$(dppf) (20 mol% per aryl bromide) as catalyst in anhydrous toluene. Microwave heating at 135 °C for 1 h gave rise to the desired penta-ferrocenyl product in a highly satisfactory 45% yield (Scheme 7, microwave heating). This step leads to the formation of five new C-C bonds in a single synthetic operation, with a yield of 85% per Suzuki-Miyaura cross-coupling in spite of the steric hindrance. These new coupling conditions now allow an expedient synthesis of this symmetric molecular motor, displaying short ferrocenylphenylene arms, in 6 steps in the longest linear sequence with an overall yield of 14%.



Scheme 7. Synthesis of the new molecular motor **12** *via* a five-fold Suzuki-Miyaura cross-coupling under classical or microwave heating.

The new molecular motor **12** was fully characterized and exhibits free rotation at room temperature as shown by NMR spectroscopy. Its properties will be investigated by Scanning Probe Microscopy techniques in the near future.

Conclusions

In this work, high efficiency and step-economy was achieved in the preparation of thioether-functionalized hydrotris(indazolyl) borates to be used as anchoring platforms in surface-mounted rotary molecular machines, but also as a general platform to anchor various metallic centers on gold, silver or copper surfaces. Indeed, the development of a one-pot "*N*-deprotection/ ester reductive sulfidation" sequence allowed the direct conversion of the *N*-acetylindazolyl ester precursor into the corresponding 1*H*-indazolyl thioether in a single high-yielding step mediated by indium(III) iodide. The thioether-functionalized indazole is now very conveniently prepared in three steps on the gram scale starting from 3-amino-4-methylbenzoic acid in a reproducible 70% overall yield, instead of six steps and a non-reproducible overall yield of 12 to 36% previously. Furthermore, milder conditions involving indium(III) chloride and the same TMDS/EtSH system were identified for the selective cleavage of the *N*-acetyl protecting group leading to the free 1*H*-indazolyl ester in excellent yield, which is of interest for the synthesis of ester-appended scorpionate ligands.

In view of the synthesis of families of ruthenium(II) complexes based on a thioether-functionalized stator and a penta-aryl cyclopentadienyl rotor, the preparation of the penta(4-bromophenyl)cyclopentadienyl common intermediate was improved to reach 31% overall yield in the longest linear sequence (5 steps), instead of a maximum of 4% (over 8 steps) previously. A five-fold Suzuki-Miyaura cross-coupling of this key precursor gave rise to a new C_5-symmetric molecular motor with five ferrocenylphenylene arms, proving that molecular machines can now be obtained efficiently in 6 steps via our renewed synthetic route. The modular synthesis of various symmetric and dissymmetric molecular gears, exploiting the same synthetic strategy, is now underway.

Experimental Section

General methods: All commercially available chemicals were of reagent grade and were used without further purification. Isoamyl nitrite, anhydrous 1,2-dichloroethane, anhydrous THF, anhydrous acetonitrile, anhydrous toluene, ethanethiol, potassium phosphate and sodium *tert*-butoxide were purchased from Aldrich. 3-Amino-4-methylbenzoic acid, potassium borohydride, thallium(I) sulfate and 1,1'-bis(diphenylphosphino)ferrocenepalladium(II) dichloride (dichloro-methane adduct) Pd(dppf)Cl_2·CH_2Cl_2 were purchased from Acros. Trichloroindigane, triiodoindigane and ferroceneboronic acid were purchased from Alfa Aesar. 1,1,3,3-Tetramethyldisiloxane and palladium(II) acetate were purchased from ABCR. Potassium acetate was purchased from Lancaster, acetic anhydride from Fluka and 2-dicyclohexylphosphino-2'-6'-dimethoxybiphenyl (SPhos) from TCI. Compounds **3**,[14] **4**,[14] **6**,[17] and **11.K**[17] were prepared according to the corresponding published procedures. All reactions were carried out using standard Schlenk techniques under an argon atmosphere. Thin layer chromatography (TLC) was performed on pre-coated aluminum-backed silica gel 60 UV_{254} plates (Macherey-Nagel) with visualization effected using ultraviolet irradiation (λ = 254, 366 nm). Flash column chromatography was carried out on 230-400 mesh silica gel (Aldrich) unless otherwise stated. Microwave reactions were carried out using CEM Discover LabMate. NMR, IR and mass spectra were recorded by the appropriate services of the Toulouse Institute of Chemistry (ICT - FR2599). NMR spectra were recorded with a Bruker Avance 300 or Avance 500 spectrometer and full assignments were made with the

assistance of COSY, HMBC and HSQC spectra when necessary. ^{1}H and ^{13}C NMR chemical shifts (δ) are reported in ppm relative to the signal of tetramethylsilane (TMS). Residual solvent signals were used as an internal reference. Coupling constants (J) are given in Hz and the following abbreviations have been used to describe the signals: singlet (s); doublet (d); triplet (t); quadruplet (q); quintuplet (quint); multiplet (m). The numbering system used for the assignment of signals in new compounds **5.Tl**, **7** and **12** is provided in the supporting information document, along with the corresponding spectra. IR spectra were recorded with a Nicolet 6700 FTIR-ATR. Only selected characteristic peaks are recorded. High-resolution mass spectra (HRMS) were performed with a Waters GCT Premier spectrometer for desorption chemical ionization (DCI/CH_4) and with a Waters Xevo G2 QTof spectrometer for electrospray ionization (ESI). Melting points were measured with a Krüss M5000 melting-point apparatus or with a Kofler hot bench and are uncorrected. UV/Vis spectra were recorded with a Shimadzu UV-26000 spectrometer (sh=shoulder, ε [$mol^{-1}dm^3cm^{-1}$] is reported in parentheses).

Compound 2: In a dry tube designed for microwave irradiation and under argon, compound **5.Tl** (160 mg, 0.20 mmol, 2.0 equiv.), ruthenium(II) complex **4** (110 mg, 0.10 mmol, 1.0 equiv.) were introduced and degassed anhydrous acetonitrile (4 mL) was added. The tube was sealed and the reaction mixture was heated under microwave irradiation at 100 °C for 3 x 10 min. A pressure of 5 bar was achieved due to the CO evolution and this pressure was released between heating cycles. The completion of the reaction was monitored by TLC. The resulting mixture was diluted with CH_2Cl_2 and filtered through a pad of silica gel. The solvents were removed under reduced pressure and the residue was purified by column chromatography (CH_2Cl_2/cyclohexane gradient from 0:100 up to 30:70) to afford compound **2** (128 mg, 0.08 mmol, 82%) as an orange solid. R_f=0.3 (CH_2Cl_2/cyclohexane 30:70); ^{1}H NMR (300 MHz, CD_2Cl_2, 25°C): δ=7.88 (bs, 3H), 7.80 (d, ^{4}J = 0.5 Hz, 3H), 7.35 (dd, ^{3}J = 8.4 Hz, ^{4}J = 0.5 Hz, 3H), 7.21 (m, 20H), 7.04 (dd, ^{3}J = 8.4 Hz, ^{4}J = 1.4 Hz, 3H), 3.90 (s, 6H), 2.46 (q, ^{3}J = 7.4 Hz, 6H), 1.27 (t, ^{3}J = 7.4 Hz, 9H); ^{13}C NMR (125 MHz, CD_2Cl_2, 25°C): δ=143.6, 140.2, 137. 8, 135.1, 132.1, 130.6, 122.3, 122.0, 121.9, 120.0, 110.9, 87.1, 37.4, 25.3, 14.3; UV/Vis (CH_2Cl_2): λ_{max} (ε)= 298 (26800), 312 nm (25600 $mol^{-1}dm^3cm^{-1}$); HRMS (ESI+): calcd for $C_{65}H_{54}BBr_5N_6RuS_3$ $[MH]^+$:1528.8674, found: 1528.8652. The data match those reported in the literature.[11]

Thallium hydrotris{6-[(ethylsulfanyl)methyl]indazol-1-yl} borate (5.Tl): 6-[(Ethylsulfanyl)methyl]-1*H*-indazole **10** (530 mg, 2.76 mmol, 3.0 equiv.), KBH_4 (61 mg, 1.11 mmol, 1.2 equiv.) and Tl_2SO_4 (285 mg, 0.565 mmol, 0.6 equiv.) were successively placed in a dry Young-type Schlenk tube. The mixture was stirred at 140 °C for 1h under an argon stream in an open system, and the Schlenk tube was then sealed and heated for 2h at 180 °C. The mixture was allowed to cool to room temperature. The Schlenk tube was connected to an argon line, and the internal pressure, which had been raised by the evolution of hydrogen gas, was carefully released. Subsequent heating of the closed system during 3h at 180 °C followed by cooling to room temperature yielded a white solid. Chloroform (10 mL) was added and the resulting suspension was transferred to a conical centrifuge tube. After centrifugation at 3000 rpm for 30 min, the supernatant (8 mL) was separated and 8 mL of chloroform were added. The operation was repeated three times. The combined supernatants were evaporated to dryness. The residue was solubilized in a minimum amount of CH_2Cl_2, and MeOH was then added (v/v = 1:1). The thallium salt **5.Tl** crystallized by slow evaporation to give white crystals (392 mg, 0.496 mmol) in 54% yield. ^{1}H NMR (300 MHz, CD_2Cl_2, 25°C): δ=8.05 (d, ^{4}J = 0.8 Hz, 3H, H_a), 8.01 (m, 3H, H_d), 7.62 (dd, ^{3}J = 8.3 Hz, ^{4}J = 0.8 Hz, 3H, H_b), 7.11 (dd, ^{3}J = 8.3 Hz, ^{4}J = 1.4 Hz, 3H, H_c), 3.93 (s, 6H, H_e), 2.46 (q, ^{3}J = 7.4 Hz, 6H, H_f), 1.25 (t, ^{3}J = 7.4 Hz, 9H, H_g); ^{13}C NMR (75 MHz, CD_2Cl_2, 25°C): δ=144.9 (C_2), 137.6 (C_1), 133.5 (C_5), 122.7 (C_7), 122.5 (C_4), 121.0 (C_3), 112.4 (C_6), 37.0 (C_8), 25.7 (C_9), 14.7 (C_{10}); HRMS (ESI-): calcd for $C_{30}H_{34}BN_6S_3$ $[M\text{-}Tl]^-$:584.2136, found: 584.2136.

Ethyl 1-acetyl-1*H*-indazole-6-carboxylate (7): A dry three-necked round bottom flask was successively charged with ethyl 3-amino-4-methylbenzoate **6** (2.0 g, 11.2 mmol, 1.0 equiv.), anhydrous toluene (50 mL), potassium acetate (1.1 g, 12.3 mmol, 1.1 equiv.) and acetic anhydride (3.8 mL, 40.5 mmol, 3.6 equiv.). Isoamyl nitrite (3.0 mL, 22.3 mmol, 2.0 equiv.) was then added dropwise over 15 min. The resulting gelatinous mixture was stirred and heated at reflux for 16h with a 15% NaOH trap. The completion of the reaction was monitored by TLC. The solution was then evaporated to dryness to give an orange-brownish solid. The crude product was dissolved in 50 mL of CH_2Cl_2, filtered on a pad of silica gel and concentrated under reduced pressure. The residue was purified by column chromatography (CH_2Cl_2/pentane gradient from 30:70 up to 70:30) to give compound **7** (2.1 g, 9.2 mmol) as an orange solid in 82% yield. R_f=0.6 (ethyl acetate/cyclohexane 30:70); m.p. 95 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ=9.07 (m, 1H, H_d), 8.15 (d, ^{4}J = 0.9 Hz, 1H, H_a), 8.02 (dd, ^{3}J = 8.3 Hz, ^{4}J = 1.4 Hz, 1H, H_c), 7.75 (dd, ^{3}J = 8.3 Hz, ^{4}J = 0.8 Hz, 1H, H_b), 4.43 (q, ^{3}J = 7.1 Hz, 2H, H_f), 2.80 (s, 3H, H_e), 1.43 (t, ^{3}J = 7.1 Hz, 3H, H_g); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ=171.0 (C_8), 166.3 (C_{10}), 139.4 (C_1), 138.8 (C_2), 131.5 (C_5), 129.0 (C_7), 125.5 (C_3), 120.7 (C_4), 117.2 (C_6), 61.6 (C_{11}), 23.1 (C_9), 14.5 (C_{12}); IR (ATR): $\tilde{\nu}$=1715 cm^{-1} (C=O); HRMS (DCI/CH_4): calcd for $C_{12}H_{13}N_2O_3$ $[MH]^+$:233.0926, found: 233.0935.

Ethyl 1*H*-indazole-6-carboxylate (8): In a dry Schlenk tube under argon were successively added ethyl 1-acetyl-1*H*-indazole-6-carboxylate **7** (150 mg, 0.65 mmol, 1.0 equiv.), trichloroindigane $InCl_3$ (157 mg, 0.71 mmol, 1.1 equiv.) and anhydrous 1,2-dichloroethane (2 mL). Ethanethiol (60 µL, 0.78 mmol, 1.2 equiv.) and 1,1,3,3-tetramethyldisiloxane (TMDS) (353 µL, 1.94 mmol, 3.0 equiv.) were then successively added and the reaction mixture was stirred at room temperature for 16h. The completion of the reaction was monitored by TLC and the reaction medium was then evaporated to dryness. The crude product was dissolved in CH_2Cl_2 (10 mL), transferred to a separatory funnel and water (3 mL) was added. The layers were separated and the aqueous phase was then extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by column chromatography (ethyl acetate/cyclohexane 1:1). to afford compound **8** (118 mg, 0.62 mmol) as a white solid in 96% yield. R_f=0.32 (ethyl acetate/cyclohexane 30:70); m.p. 125°C; ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ=10.25 (br s, 1H), 8.28 (m, 1H), 8.15 (d, ^{4}J = 0.8 Hz, 1H), 7.88 (dd, ^{3}J = 8.5 Hz, ^{4}J = 1.3 Hz, AB system, 1H), 7.81 (dd, ^{3}J = 8.5 Hz, ^{4}J = 0.8 Hz, AB system, 1H), 4.44 (q, ^{3}J = 7.1 Hz, 2H), 1.44 (t, ^{3}J = 7.1 Hz, 3H).; ^{13}C NMR (63 MHz, $CDCl_3$, 25°C): δ=166.8, 139.5, 135.0, 129.0, 125.7, 121.6, 120.7, 112.1, 61.3, 14.4; IR (ATR): $\tilde{\nu}$=3317 (N-H), 1688 cm^{-1} (C=O). The data match those reported in the literature.[17]

6-[(Ethylsulfanyl)methyl]-1*H*-indazole (10): In a dry Schlenk tube under argon were successively added ethyl 1-acetyl-1*H*-indazole-6-carboxylate **7** (150 mg, 0.65 mmol, 1.0 equiv.), triiodoindigane InI_3 (352 mg, 0.71 mmol, 1.1 equiv.) and anhydrous 1,2-dichloroethane (2 mL). Ethanethiol (0.2 mL, 2.6 mmol, 4.0 equiv.) and 1,1,3,3-tetramethyldisiloxane (TMDS) (0.7 mL, 3.9 mmol, 6.0 equiv.) were then added and the reaction mixture was heated at 60 °C during 16h. The completion of the reaction was monitored by TLC and the reaction medium was evaporated to dryness. The crude product was dissolved in CH_2Cl_2 (10 mL), transferred to a separatory funnel and water (3 mL) was added. The layers were separated and the aqueous phase was then extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The product was purified by column chromatography (ethyl acetate/cyclohexane 20:80) to yield compound **10** (107 mg, 0.56 mmol, 86%) as a white solid. R_f=0.3 (ethyl acetate/cyclohexane 30:70); m.p. 66-67°C; ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ=10.09 (bs, 1H), 8.05 (d, ^{4}J = 0.9 Hz, 1H), 7.71 (dd, ^{3}J = 8.3 Hz, ^{4}J = 0.9 Hz, 1H), 7.44 (m, 1H), 7.18 (dd, ^{3}J = 8.3 Hz, ^{4}J = 1.4 Hz, 1H), 3.87 (s, 2H), 2.46 (q, ^{3}J = 7.4 Hz, 2H), 1.25 (t, ^{3}J = 7.4 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$, 25°C): δ=140.4, 138.0, 134.4, 122.7, 122.4, 120.8,

109.6, 36.3, 25.4, 14.3; IR (ATR): $\tilde{\nu}$=3183 cm^{-1} (N-H); HRMS (DCI/CH_4): calcd for $C_{10}H_{13}N_2S$ $[MH]^+$:193.0799, found: 193.0799. The data match those reported in the literature.[17]

Compound 12:

Conditions A (classical heating): In a dry Schlenk tube under argon, penta-arylbromide **2** (26 mg, 17 µmol, 1.0 equiv.), palladium(II) acetate (3.9 mg, 17 µmol, 1.0 equiv.), K_3PO_4 (72 mg, 340 µmol, 20 equiv.), ferroceneboronic acid (156 mg, 680 µmol, 40 equiv.) and 2-dicyclohexylphosphino-2'-6'-dimethoxybiphenyl (SPhos) (14 mg, 34 µmol, 2.0 equiv.) were successively introduced and degassed anhydrous toluene (1.5 mL) was added. The resulting suspension was stirred at 100 °C for 48 hours and the completion of the reaction was monitored by TLC. The reaction mixture was allowed to cool to room temperature, filtered on a neutral alumina pad (using CH_2Cl_2) and evaporated in vacuo. The residue was purified by column chromatography (neutral alumina, CH_2Cl_2/cyclohexane 30:70) followed (if required) by a recrystallization in a heptane/MeOH mixture (1:1). Complex **12** was obtained as an orange-red solid (6 mg, 2.9 µmol, 17%).

Conditions B (microwave irradiation): In a dry tube designed for microwave irradiation and under argon, penta-arylbromide **2** (50 mg, 33 µmol, 1.0 equiv.), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane $PdCl_2(dppf)\cdot CH_2Cl_2$ (27 mg, 33 µmol, 1.0 equiv.), sodium *tert*-butoxide (71 mg, 740 µmol, 22.5 equiv.), ferroceneboronic acid (57 mg, 246 µmol, 7.5 equiv.) were successively introduced and degassed anhydrous toluene (3.6 mL) was added. The tube was sealed and the reaction mixture was heated under microwave irradiation at 135 °C for 1h (a pressure of 5 bar was achieved). The reaction mixture was allowed to cool to room temperature, filtered on a neutral alumina pad (using CH_2Cl_2) and evaporated in vacuo. The residue was purified by column chromatography (neutral alumina, CH_2Cl_2/cyclohexane 30:70) followed (if required) by a recrystallization in a heptane/MeOH mixture (1:1). Complex **12** was obtained as an orange-red solid (30 mg, 15 µmol, 45%). R_f=0.2 (CH_2Cl_2/cyclohexane 30:70, SiO_2); ^{1}H NMR (500 MHz, CD_2Cl_2, 25°C): δ=8.11 (br s, ~3H, H_a), 7.92 (bs, 3H, H_d), 7.36 (m, 13H, H_b and H_h), 7.20 (d, ^3J = 8.5 Hz, 10H, H_i), 6.99 (dd, ^3J = 8.4 Hz, ^4J = 1.3 Hz, 3H, H_c), 4.55 (dd, ^3J = 1.9 Hz, ^4J = 1.8 Hz, 10H, H_j), 4.24 (dd, ^3J = 1.9 Hz, ^4J = 1.8 Hz, 10H, H_k), 3.94 (s, 25H, H_l), 3.90 (s, 6H, H_e), 2.48 (q, ^3J = 7.3 Hz, 6H, H_f), 1.28 (t, ^3J = 7.3 Hz, 9H, H_g); ^{13}C NMR (125 MHz, CD_2Cl_2, 25°C): δ=144.1 (C_2), 140.4 (C_1), 138.6 (C_{15}), 137.6 (C_5), 133.9 (C_{13}), 132.4 (C_{12}), 125.1 (C_{14}), 122.6 (C_7), 122.4 (C_4), 120.4 (C_3), 111.4 (C_6), 87.8 (C_{11}), 84.7 (C_{16}), 70.2 (C_{19}), 69.6 (C_{17}), 66.7 (C_{18}), 36.9 (C_8), 25.7 (C_9), 14.8 (C_{10}); UV/Vis (CH_2Cl_2): λ_{max} (ε)= 292 (30300), 340 nm (16000 $mol^{-1}dm^3cm^{-1}$); HRMS (ESI+): calcd for $C_{115}H_{99}BFe_5N_6RuS_3$ $[MH]^+$:2053.3108, found: 2053.3103.

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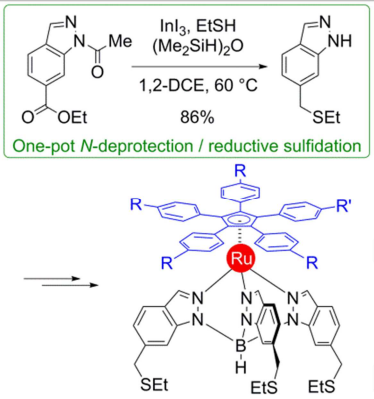
The development of a one-pot indium(III)-mediated "*N*-deprotection / ester reductive sulfidation" sequence led to major improvement in the synthesis of thioether-functionalized hydrotris(indazolyl)borate ligands, used as anchoring platforms in a family of surface-mounted rotary molecular motors and gears.



Molecular machines

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Expedient synthesis of thioether-functionalized hydrotris(indazolyl)borate as an anchoring platform for rotary molecular machines