Organic & Biomolecular Chemistry

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ROYAL SOCIETY OF CHEMISTRY

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Journal Name

RSCPublishing

View Article Online
DOI: 10.1039/C4OB02671C

ARTICLE

Gold-catalyzed Allene Cycloisomerization for Pyrrole Synthesis: Towards Highly Fluorinated BODIPY Dyes

Cite this: DOI: 10.1039/xoxxoooooox

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Received ooth January 2012,
Accepted ooth January 2012

DOI: 10.1039/xoxxoooooox

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A novel synthetic strategy toward highly fluorinated BODIPY dyes with exceptional photostabilities relying on sustainable gold catalysis has been developed. Key to the tailored pyrrole precursors is the gold catalysis performed in ionic liquids as reaction medium, allowing for a facile recycling of the catalysts. The dyes prepared are well-matching with the spectral windows of popular rhodamine dyes and possess a high brightness while showing a distinctly higher photostability than the rhodamines especially in aprotic solvents.

Introduction

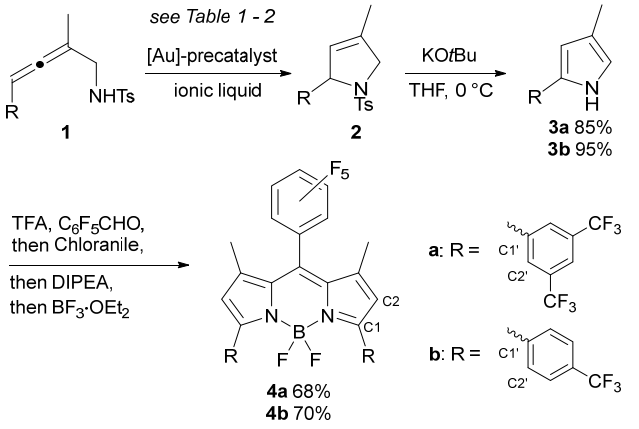
Sustainable metal catalysis has attracted general attention during the last years. Meanwhile also for gold catalysis powerful sustainable methods are known.[1] The use of ionic liquids (ILs) or micelles as reaction medium enables the stabilization of catalysts, preventing their undesired reduction to metallic gold. Previously, the unique stability and recyclability of these catalyst solutions was demonstrated.[2]

Novel sustainable synthetic routes are often also a key to success in advancing compounds of a certain class of specialty chemicals, for instance with unprecedented substitution patterns or improved reaction yields. In this regard, boron–dipyrromethene (BODIPY) dyes as one of the fastest growing classes of dyes[3] are very attractive targets. The popularity of BODIPY dyes is rooted in their outstanding absorption and fluorescence properties and high photo- and chemical stabilities, having resulted in a wide variety of applications. Besides bioimaging,[4] fluorescent indicators,[5] photodynamic therapy,[6] and organic photovoltaics,[7] highly fluorinated BODIPYs have been found recently to constitute a very promising class of multifunctional labeling agents.[8] One of the bottlenecks for novel BODIPYs is the availability of tailor-made pyrroles which constitute their core building blocks.

The expertise of our groups in sustainable metal catalysis[2] and the development of high-performance dyes[9] prompted us to embark on a collaborative approach toward new fluorinated BODIPY dyes **4** by gold-catalyzed cycloisomerization of α-aminoallenes **1** to 2,5-dihydropyrroles **2** in ionic liquids (Scheme 1). Although fluorinated BODIPYs possess many promising features, only a very limited number of fluorinated BODIPYs is known in literature.[8,10] Furthermore, the synthesis of pyrroles by cyclization reactions allows extensive structural variation and represents a valuable alternative compared to common strategies.[11]

Results and discussion

The cycloisomerization was carried out in ionic liquids (Table 1-3). Different gold catalysts and ionic liquids were examined for this purpose (Scheme 2).

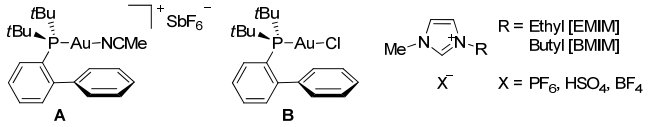


Scheme 1 Synthesis of BODIPY dyes.

The cyclization conditions were optimized with allene **1a** and cationic gold catalyst **A** (Table 1). Best results were achieved with [BMIM][PF_6] and [BMIM][HSO_4].

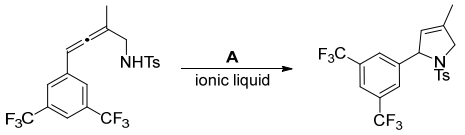
With 1 mol% of catalyst **A** in [BMIM][PF_6] complete conversion was observed after 24 h, while 2 mol% led to a shorter reaction time of 2 h (entries 1 & 2). The acidic ILs [BMIM][HSO_4] and [EMIM][HSO_4] were used at 60°C to attain a lower viscosity. Short reaction times of 15 min and 1h were obtained (entries 4 & 5), which

are comparable to [BMIM][PF_6] at the same temperature (entry 3). The acidic ILs do not mediate the cycloisomerization in the absence of the gold catalyst (entries 6 & 7).[12] In [BMIM][BF_4] and [EMIM][BF_4] no reaction was observed after 24 h at RT (entries 8 & 9). This may be due to a limited solubility of the gold catalyst in these more hydrophilic ionic liquids.



Scheme 2 Gold catalysts and ionic liquids used in this work.

Table 1 Influence of ionic liquids on the gold-catalyzed cycloisomerization of α-aminoallene **1a**

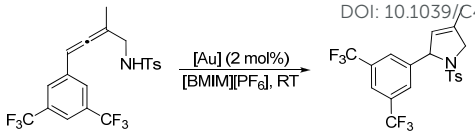


Entry	Ionic liquid	**A** (mol%)	*T* (°C)	*t* (h)	Conv.[a] (%)
1	[BMIM][PF_6]	1	25	24	100
2	[BMIM][PF_6]	2	25	2	100
3	[BMIM][PF_6]	2	60	0.25	100
4	[BMIM][HSO_4]	2	60	0.25	100
5	[EMIM][HSO_4]	2	60	1	100
6	[BMIM][HSO_4]	-	60	24	0
7	[EMIM][HSO_4]	-	60	24	0
8	[BMIM][BF_4]	2	25	24	0
9	[EMIM][BF_4]	2	25	24	0

[a] Conversion was determined by ^{1}H-NMR spectroscopy.

Allene **1a** and ionic liquid [BMIM][PF_6] were used for screening of the gold catalyst (Table 2). Except for $AuBr_3$ (entry 2), all catalysts examined gave short reaction times between 30 min and 2 h (entries 1, 3, 5 & 7). Both precatalyst **B** and Ph_3PAuCl were transformed into the corresponding cationic gold species with $AgSbF_6$. Without addition of a silver salt no reaction was observed (entries 6 & 8), whereas the silver salt alone induces only a very slow cyclization (entry 11). Beside the possibility of warming up (entry 10) and the addition of a small amount of toluene to give a solvent film led to decreased reaction times of 5 min (entries 4 vs. 3, 9 vs 7). This acceleration is probably caused by the two-phasic character of the reaction mixture. While the catalyst solvent system is a viscous solution, the allene is a solid and affords an emulsion during the reaction. The toluene seems to act as phase-transfer agent. These conditions were chosen for recycling experiments (Table 3).

Table 2 Influence of the gold catalyst on the cycloisomerization of α-aminoallene **1a** in [BMIM][PF_6][13]

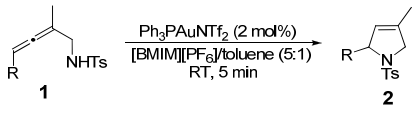


Entry	[Au]	Additive	*t*	Conv. (%)[a]
1	**A**	-	2 h	100
2	$AuBr_3$	-	48 h	30
3	$Ph_3PAuNTf_2$	-	1 h	100
4[b]	$Ph_3PAuNTf_2$	-	5 min	100
5	Ph_3PAuCl	$AgSbF_6$	1 h	100
6	Ph_3PAuCl	-	24 h	0
7	**B**	$AgSbF_6$	30 min	100
8	**B**	-	24 h	0
9[b]	**B**	$AgSbF_6$	5 min	100
10[c]	**B**	$AgSbF_6$	10 min	100
11	-	$AgSbF_6$	24 h	20

[a] Conversion was determined by ^{1}H-NMR spectroscopy.
[b] Toluene (ca. 20 Vol-%) was added. [c] Reaction temperature of 50 °C.

Previous investigations with $AuBr_3$ in [BMIM][PF_6] showed an extremely low catalyst leaching using hexane as extraction solvent.[2a] The pyrrolines **2** are not soluble in nonpolar solvents like hexane. Unfortunately, polar solvents like Et_2O cause a dramatic catalyst leaching. Therefore, the recycling was tested for 1**a** with toluene as extraction solvent and $Ph_3PAuNTf_2$ as gold catalyst. Over four runs excellent reactivity was observed (Table 3, entries 1-4). The reaction was stopped after 5 min in all runs, leading to quantitative conversion and high yield. A loss of reactivity was observed in the fifth run (entry 5), causing a lower yield of 80% (12% of allene **1a** were also recovered). Allene **1b** was cyclized under similar conditions with 90% yield in 5 min (entriy 6). A second run was carried out with a similar result (entry 7).

Table 3 Recycling of the catalyst/solvent system



Entry	Allene	Run	Yield[a] (%)
1	**1a**	1	91
2	**1a**	2	91
3	**1a**	3	98
4	**1a**	4	95
5	**1a**	5	80[b]
6	**1b**	1	90
7	**1b**	2	92

[a] Isolated yield. [b] 12% of **1a** was recovered.

The cyclization products are converted into the pyrroles using K*t*OBu in THF (Scheme 1).[14] According to common strategies, these were directly used in the BODIPY synthesis.[10a] In contrast to the literature method, however, oxidation times were extended and a second complexation step employed, finally providing the dyes in good yields of 68 and 70%.

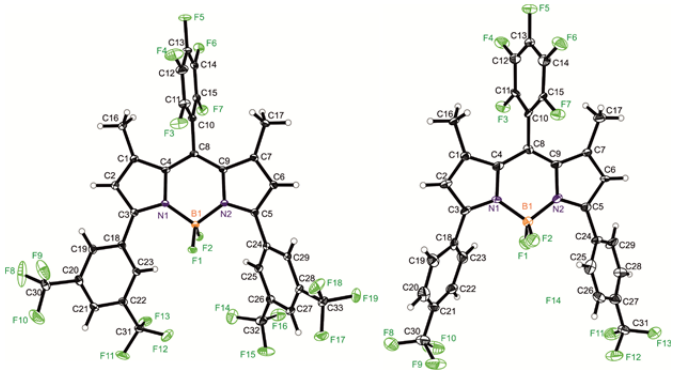


Figure 1 Ortep representation of **4a** (left) and **4b** (right) with atomic labeling shown with 30% probability displacement ellipsoids.

The molecular structures of **4a**,**b** were determined by single-crystal X-ray diffraction analysis and the corresponding molecular configurations are shown in Figure 1. Selected crystallographic data and structure refinement parameters are listed in Table S1. The observed geometric parameters of all crystal structures are generally comparable with those of other BODIPYs.[14-I,14-II] **4a** crystallizes in a monoclinic, **4b** in a triclinic space group with similar crystal packing. There are no significant interactions like hydrogen bonds or π-π interactions in the crystal lattice of both dyes. Only a weak π-π interaction occurs in **4a** with a plane-to-plane distance of 4.34 Å between the same pyrrole rings (N1, C1, C2 ,C3, C4) of two neighbouring pyrromethene fragments of the BODIPY core.

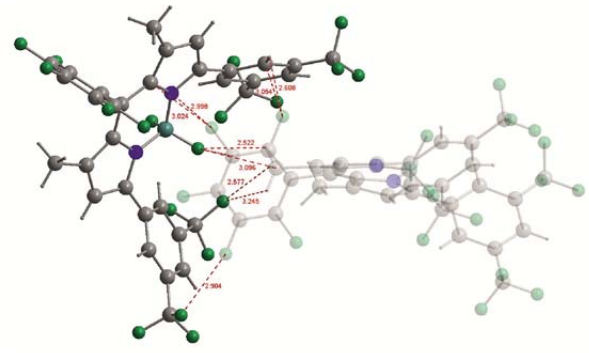


Figure 2 Short contacts in **4a** lead to a bowl-like conformation

The BODIPY skeleton formed by three conjugated heterocyclic rings is almost planar, with an rms deviation of 0.1260 and 0.1016 for **4a** and **4b**. Due to steric repulsion of the methyl groups attached to C1 and C7, the pentafluorophenyl moiety is strongly twisted out of the BODIPY mean plane, with dihedral angles of 88.35(05)° for **4a** and 76.73(10)° for **4b**, which is as expected more pronounced than for 1,7-H- and 3,5-diaryl-substituted dyes.[10e,14-III] An overlay of the two molecular configurations shows the differences in molecular conformation, i.e., the arrangement of the substituents attached at C3 and C5 (Figure S1). Whereas in **4b** the two phenyl rings are almost parallel with a dihedral angle of 28.09(22)°, the angle amounts to 86.24(07)° in **4a**. Because the arrangement of the molecules is head-to-tail, the short contacts from the pentafluorophenyl ring to the phenyl rings at C3,5 lead to a bowl-like conformation of **4a** (Figure 2). Such a bowl-type arrangement of head-to-tail aligned 3,5,8-phenyl-substituted BODIPYs has also been reported by Wakamiya very recently.[14-III]

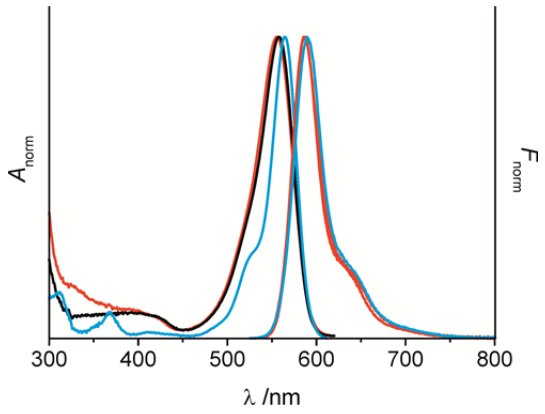


Figure 3 Absorption and fluorescence spectra of **4a** (black) and **4b** (red) in ethanol; the corresponding spectra of rhodamine 101 (blue) are included for comparison.

The spectroscopic properties of **4a** and **4b** are comparable with very little dependence on the solvent. The spectral envelopes shown in Figure 3 resemble classical BODIPY features. The high fluorescence quantum yields (Φ_f >0.85), long fluorescence lifetimes (τ_f ~5.5 ns) and high absorption coefficients ($\varepsilon_{\lambda max}$ ~50000 M^{-1} cm^{-1}), independent of solvent polarity and proticity, distinguish the dyes as bright emitter[15]s (comprehensive spectroscopic data of **4a**,**b** are collected in the ESI). Compared to their parent dye, 8-pentafluorophenyl-1,7,3,5-tetramethyl-BODIPY, that carries methyl groups instead of the trifluoromethylphenyl residues in the 3,5-positions,[8] the absorption maxima are shifted by ca. 40 nm and the absorption bands are significantly broadened. The Stokes shifts are increased from ca. 300 to 1000 cm^{-1}. In view of the color rules for BODIPY π system substitution,[16] these changes can be attributed to the extension of the fluorophores' π-system with the additional trifluorophenyl moieties and their enhanced rotational freedom. The comparatively small spectral differences between **4a** and **4b** despite the introduction of two additional CF_3 groups in the former is tentatively ascribed to the enhanced steric hindrance in case of 3,5-phenyl substitution at the BODIPY core.[17] The latter results in considerable (average) torsion angles around the C1–C1′ bond $<\theta_{C2-C1-C1'-C2'}>$ = 39° for **4a** and for 38° **4b** (for atom numbering pattern, see Scheme 1, bottom panel) and hence reduced electronic coupling

between BODIPY core and phenyl rings, diminishing the electron withdrawing effect of these substituents. These experimental findings are well reflected by quantum chemical calculations employing the density functional theory (DFT) method, revealing differences in the $S_1 \leftarrow S_0$ transition in the gas phase of only ca. 5 nm (Table S2, ESI). The latter are also the only oscillator-strong transitions in the 350–500 nm region for both dyes, involving HOMO and LUMO which are both centered almost exclusively on the 3,5-diphenyl-dipyrrin fragments for **4a**,**b** (Figure S2, ESI). Furthermore, with the corresponding triplet transitions being shifted for ca. 1.25 eV, the theoretical studies fully support the favorable spectroscopic properties found experimentally.

Dyes **4a** and **4b** absorb and emit in the green visible range, matching well the spectral region of prominent rhodamine dyes such as rhodamine 101, 6G, B or TRITC[18] and fitting perfectly to the output of green laser sources (e.g., the prominent 532 or 543 nm lasers, Figure 3). Compared to rhodamines the zwitterionic yet net uncharged BODIPYs are commonly well soluble in organic solvents across the entire polarity range,[3,19] broadening the areas of applications and offering potent alternatives to the search for hydrophobic rhodamine derivatives.[20] The most important feature of the newly synthesized fluorinated BODIPYs **4a**,**b** with regard to application is their excellent photostability, in particular when used in aprotic solvents. Figure 4 exemplarily combines photobleaching curves of **4a**,**b** and rhodamine 101 upon irradiation at 532 nm.

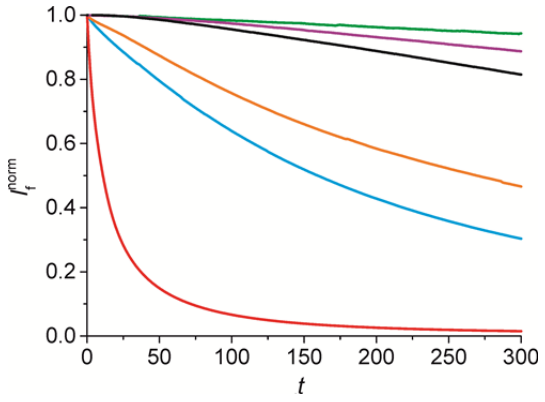


Figure 4 Photobleaching curves for irradiation at 532 nm (1W Laser power) in acetonitrile (**4a**: orange, **4b**: blue, rhodamine 101: red) and ethanol (**4a**: magenta, **4b**: green, rhodamine 101: black).

Conclusions

In the work presented here, two highly fluorinated and photo-stable BODIPY dyes with excellent spectroscopic properties have been prepared via gold catalysis in ionic liquids. While the use of sustainable gold catalysis is often strictly limited to the applied system, the possibility of recycling the catalyst solution was extended to more challenging allenes. Here [BMIM][PF_6] was found to be an excellent solvent system for gold catalysis and recycling. The fluorinated dyes possess an enormous potential for further applications such as functional group labeling or the staining of lipophilic compartments, for instance in cell imaging. Current work in our laboratories is directed toward both the synthesis of other functional BODIPYs and the application of the title dyes.

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Acknowledgements

Financial support by SusChemSys (which is co-financed by the Regional Development Fund (Investing in Your Future) of the European Union and the state of North Rhine-Westphalia), the European Metrology Research Programme (EMRP) (project IND15 SurfChem) and the Adolf-Martens-Fonds is gratefully acknowledged. The EMRP is jointly funded by the EMRP participating countries within EURAMET and the European Union.

Notes and references

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Electronic Supplementary Information (ESI) available: Full experimental details, including X-Ray structure analysis, Optical spectroscopy, Computational Studies, and NMR spectra. See DOI: 10.1039/b000000x/

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