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# Synthesis of 2,6-disubstituted BODIPY dyes using palladium-catalyzed cross-coupling reaction with indium organometallics and indium-catalyzed alkyne hydroarylation reactions

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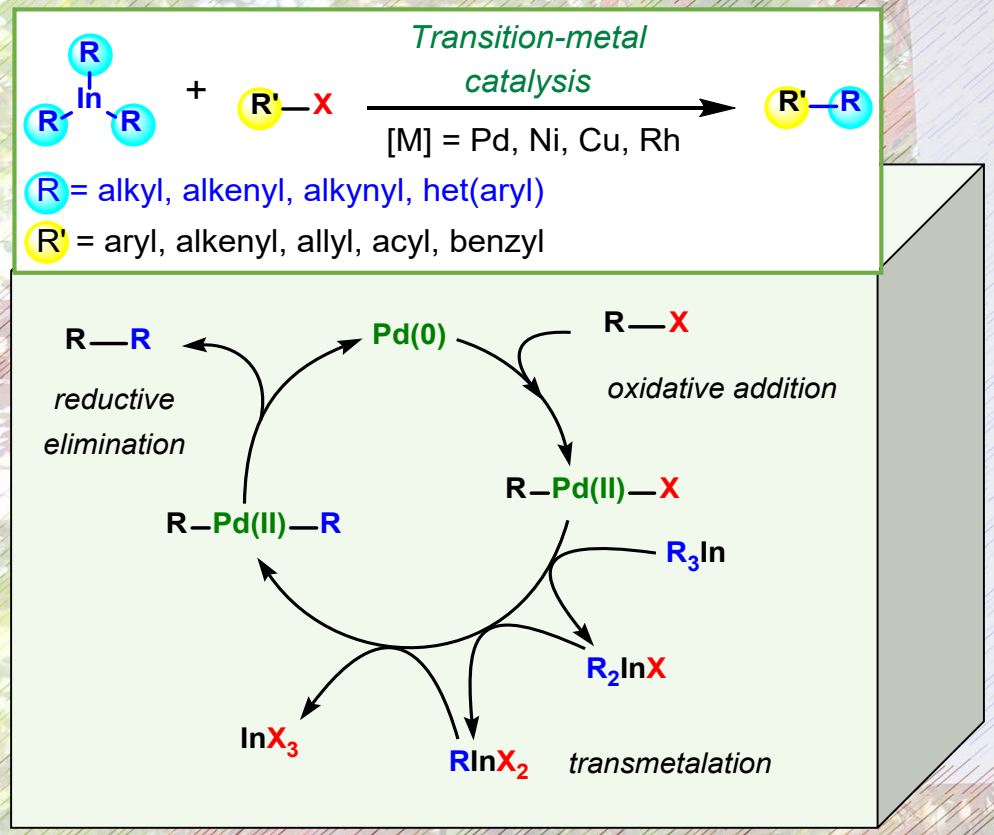
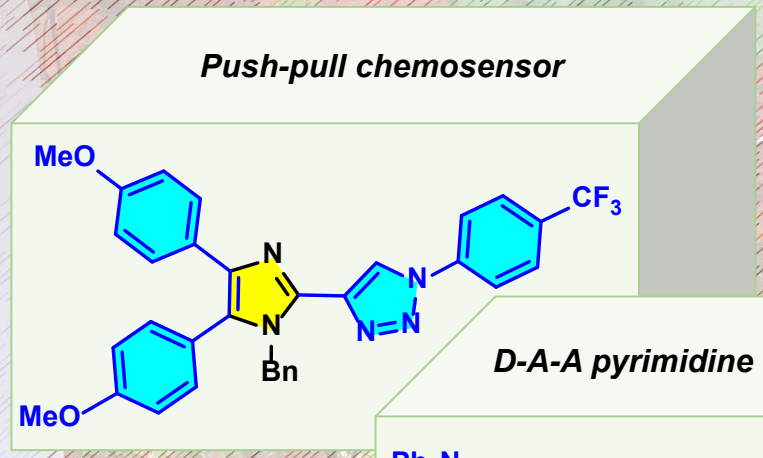
SynCatMeth | Synthetic and Catalytic Methods

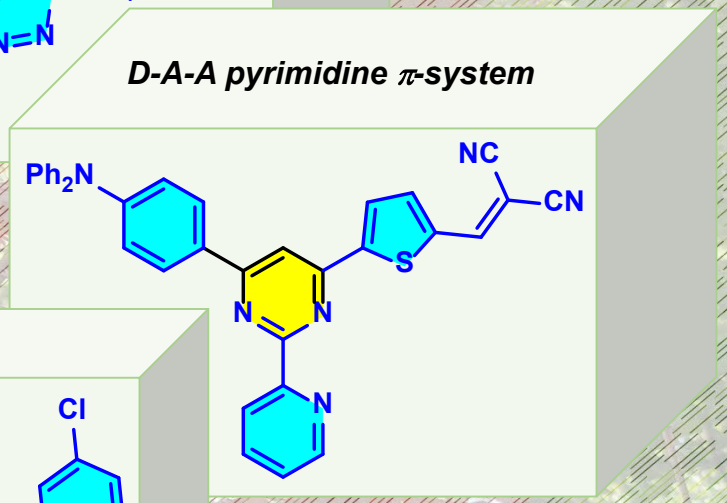
# Introduction

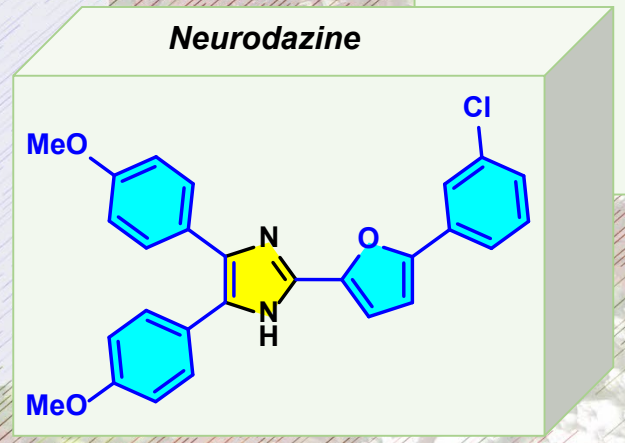
## Cross-coupling reactions using indium organometallics. Synthetic applications

Indium organometallics ($R_3In$) useful reagents in metal-catalyzed cross-coupling reactions



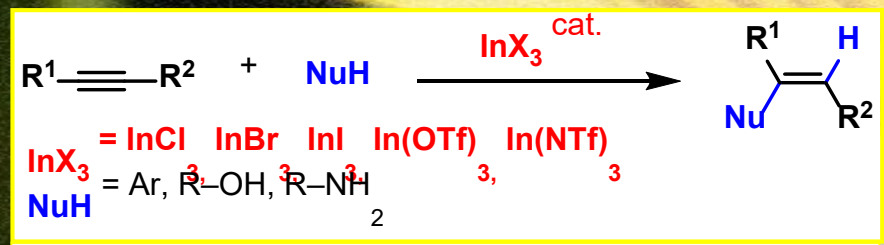



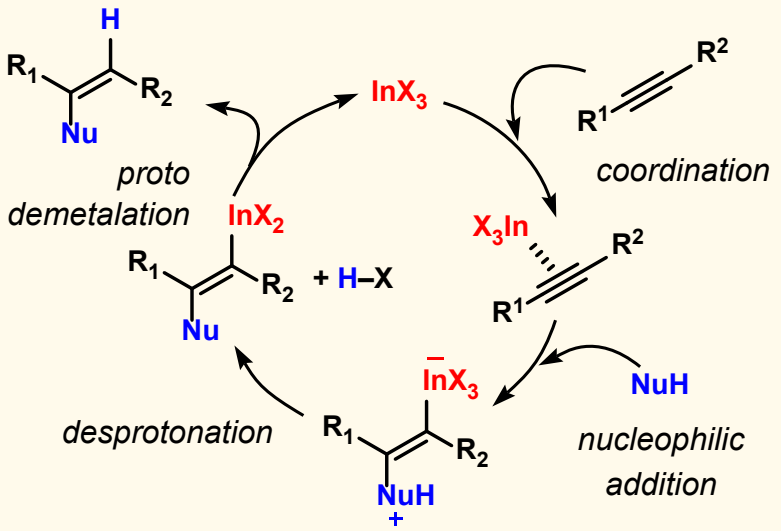

*Adv. Organomet. Chemi.* **2023**, 80, 177.

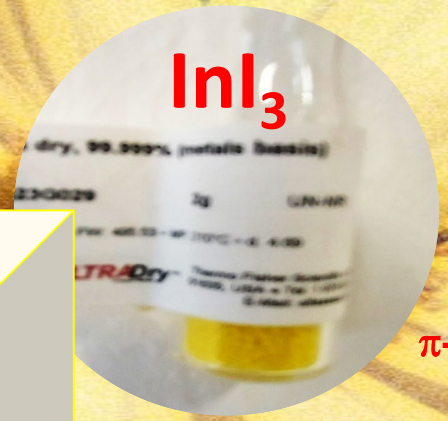
# Electrophilic activation of C–C unsaturated bonds using indium(III)

Metal-catalyzed hydroarylation of alkynes is an efficient methodology for the insertion of a C–C triple bond into a C–H bond of aromatic and heteroaromatic compounds.

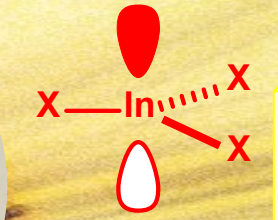
Indium(III) salts alternative catalysts to transition metals in catalysis.
Efficient π-acids for the electrophilic activation of alkynes.



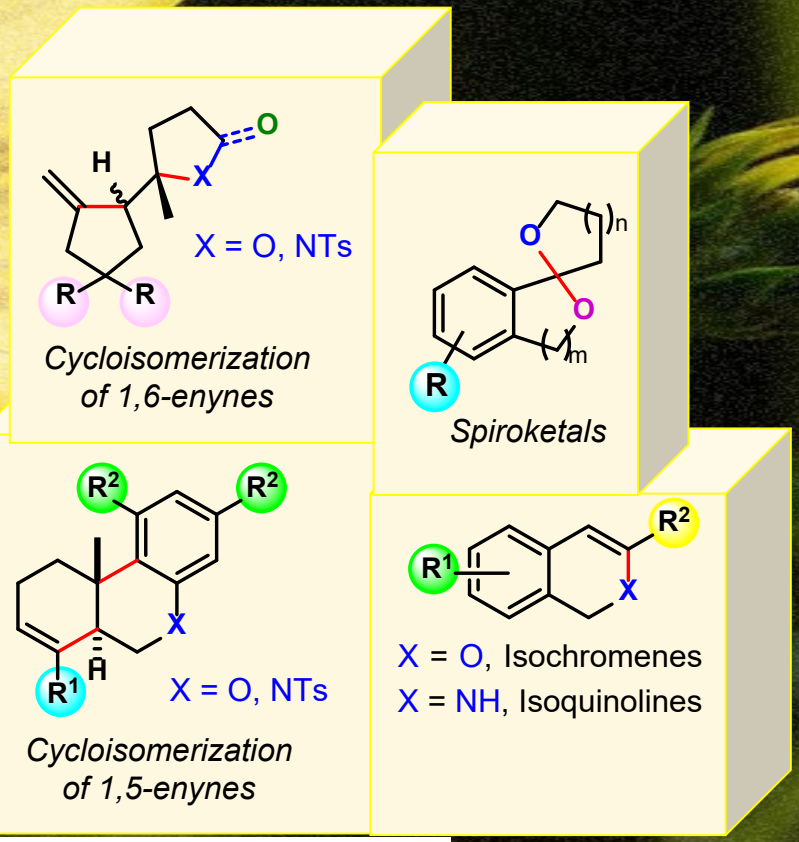




Indium(III)
Lewis acid




π-interaction

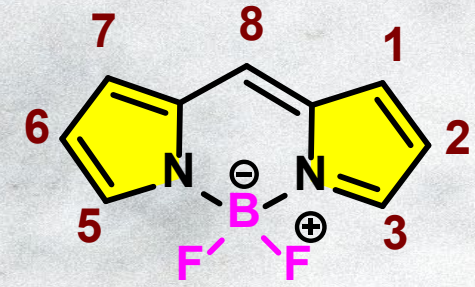




*Org. Biomol. Chem.* **2018**, *16*, 5733; *J. Org. Chem.* **2021**, *86*, 9515; *Org. Chem. Front.* **2022**, *9*, 6894; *Synthesis* **2023**, *55*, 1714; *Adv. Synth. Cat.* **2024**, 366, 852.

# BODIPY scaffold: properties and applications

## Properties

- Neutral total charge
- High brightness
- Large fluorescent quatum yields
- Photochemical stability
- High lipophilicity
- Chemical robustness
- Synthetic versatility




**BODIPY**

**4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene**

## Applications

- Fluorescent sensors
- Imaging probes
- Optoelectronic devices
- Photoredox catalysis
- Photodynamic therapy sensitizers
- Theranostic agents
- NIR probes to diagnose Alzheimer disease

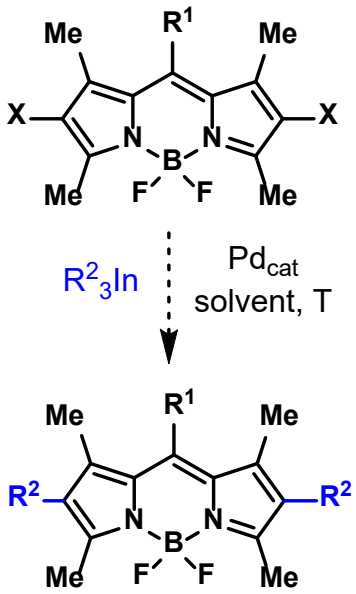
Boens, *N.et al*. Coord. *Chem. Rev*. **2019**, *399*, *Coord. Chem. Rev*. **2020**, *419*, 213375.

# Objective

**Synthesis of 2,6-disubstituted BODIPY dyes by palladium-catalyzed cross-coupling reactions using indium organometallics ($R_3In$) and indium(III)-catalyzed alkyne hydroarylation reactions**

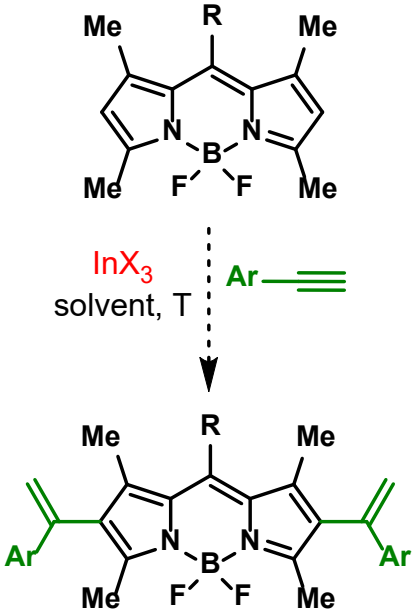
## Palladium-catalyzed cross-coupling reactions using $R_{3}In$o

$R_3In$




## Indium(III)-catalyzed alkyne hydroarylation reactions

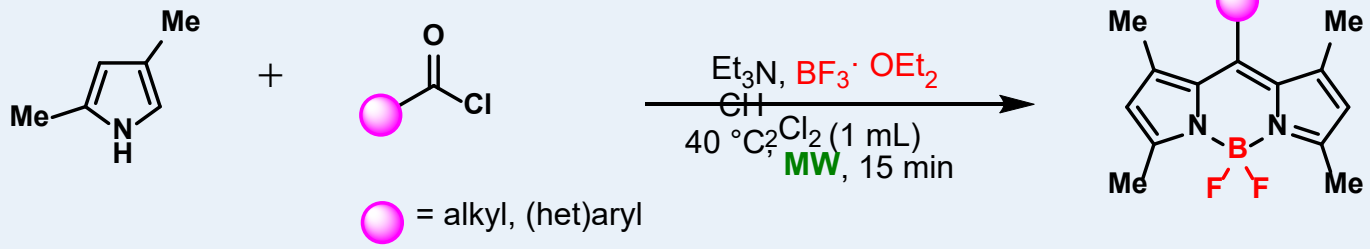
$InX_3$

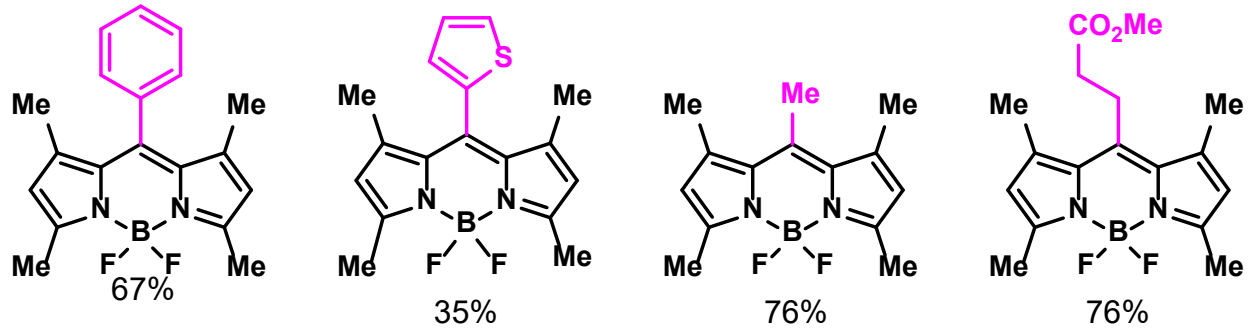


# Results

**1**

## Synthesis of *meso*-substituted BODIPY dyes by microwave-assisted direct synthesis





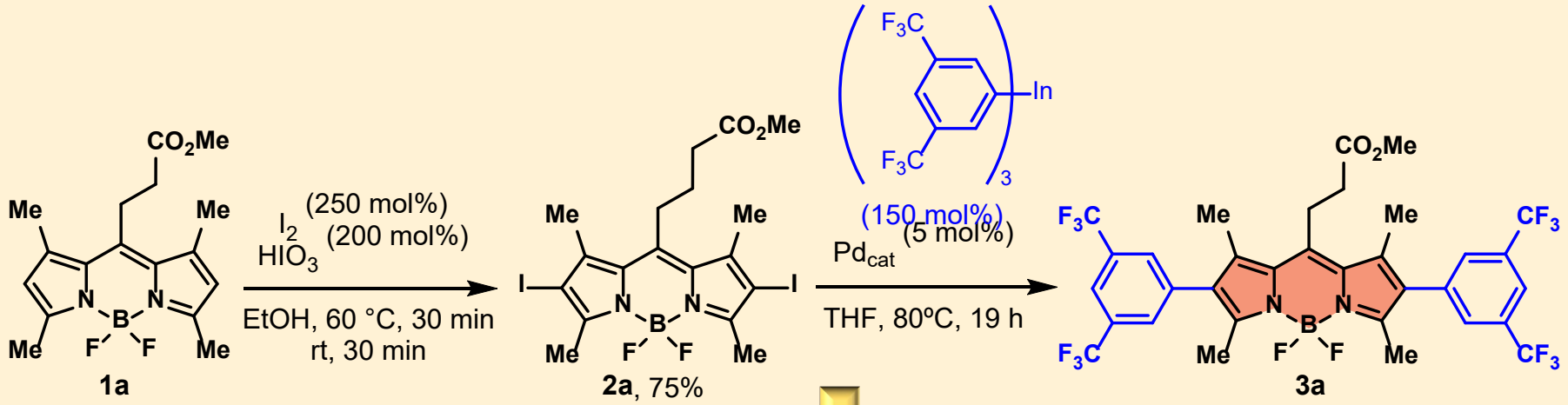
- + One step
- + Short reaction times
- + Low temperatures
- + Minimum amount of solvent
- + Broad scope
- + Good yields
- + Scalability

*Org. Biomol. Chem.* **2022**, *20*, 9132.

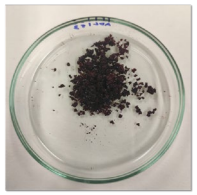
# Results

2

**Synthesis of 2,6-disubstituted BODIPY dye 3a from 1a through iodination followed by cross-coupling with tris[3,5-bis(trifluoromethyl)phenyl]indium**




BODIPY **1a**



BODIPY **3a**

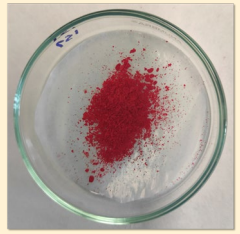
**Optimization**

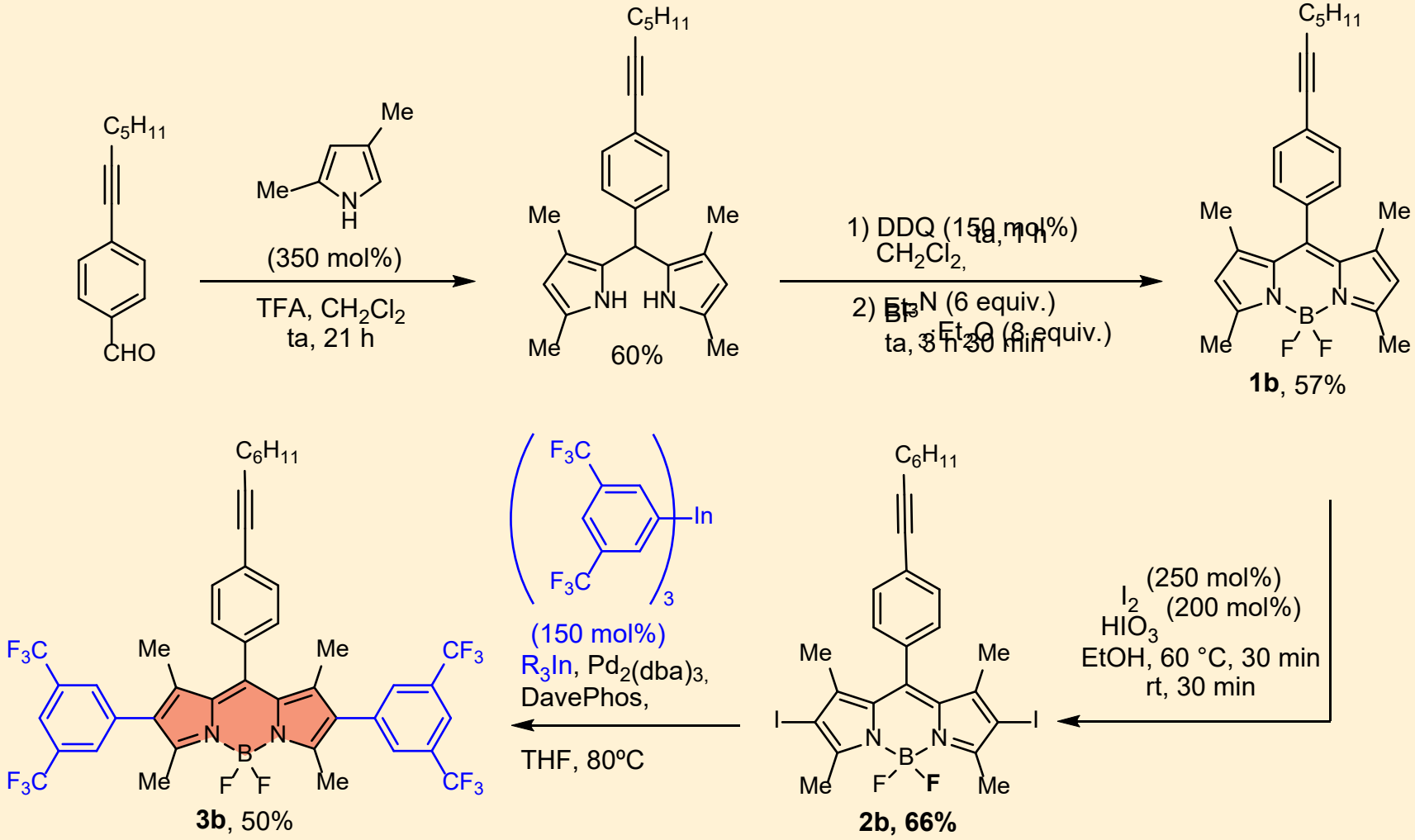
- $Pd(PPh_3)_4$ (traces of **3a**)
- $PdCl_2(PPh_3)_2$ (traces of **3a**)
- $Pd_2(dba)_3$, DavePhos (10 mol%) (**3a**,31% yield)

# Results

2

## Synthesis of 2,6-disubstituted BODIPY dye 3b

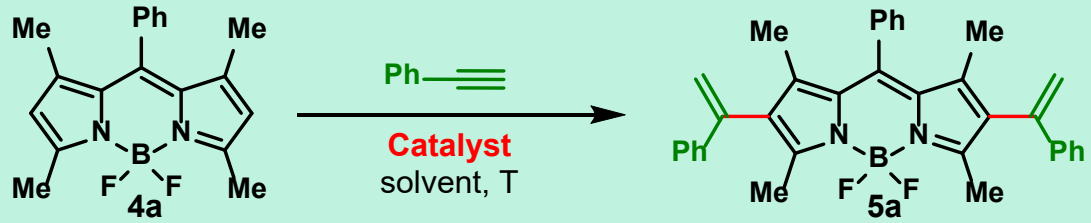




# Results

**Synthesis of 2,6-disubstituted BODIPY dye 5a from 4a by indium(III)-catalyzed phenylacetylene hydroarylation**

3




**Optimal conditions:**
**$InI_3$ (20 mol%), DCE, 80 ºC, 8 h**

## Optimization

**5-20 mol% Cat.**

$InCl_3$, $InBr_3$, $InI_3$,
$In(OTf)_3$,
$GaCl_3$, $Bi(OTf)_3$,
$Au(PPh_3)Cl/AgSbF_6$
$AuCl_3$, $PtCl_2$

**Solvent**

DCE, toluene, $CH_3CN$

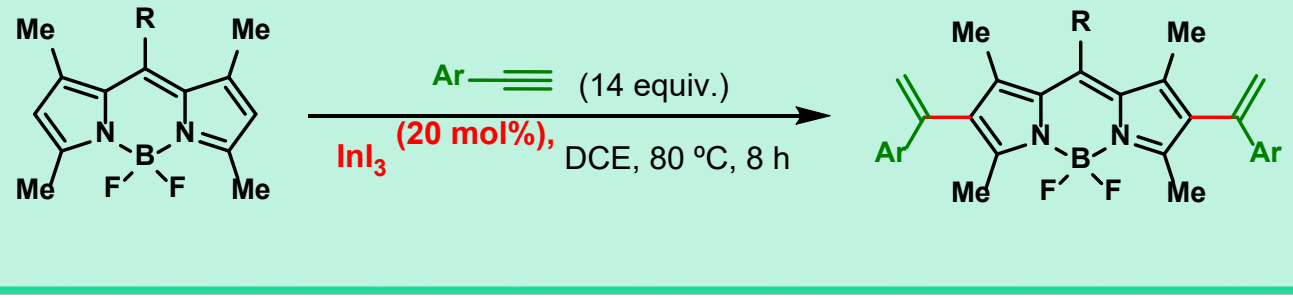
**Temperature**

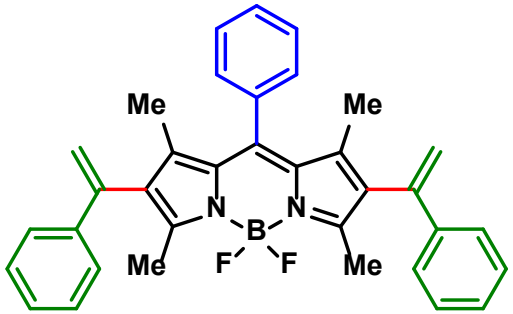
RT, 80 ºC, 100 ºC

# Results

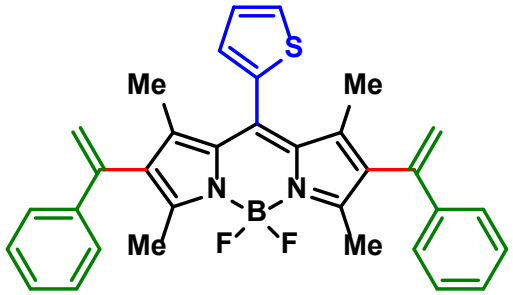
**Synthesis of 2,6-disubstituted BODIPY dyes by indium(III)-catalyzed arylalkyne hydroarylation**

**4**

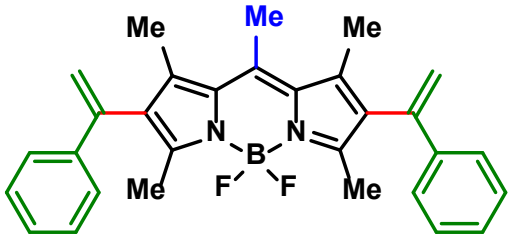


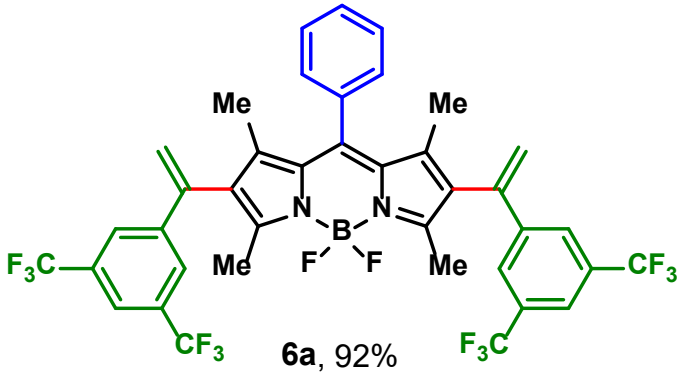

**5a**, 90%




**5b**, 61%




**5c**, 73%

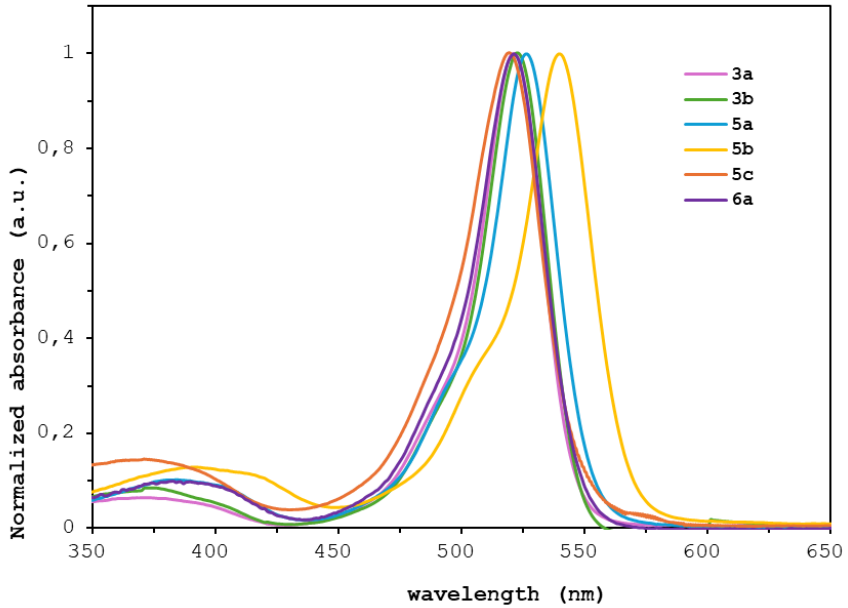


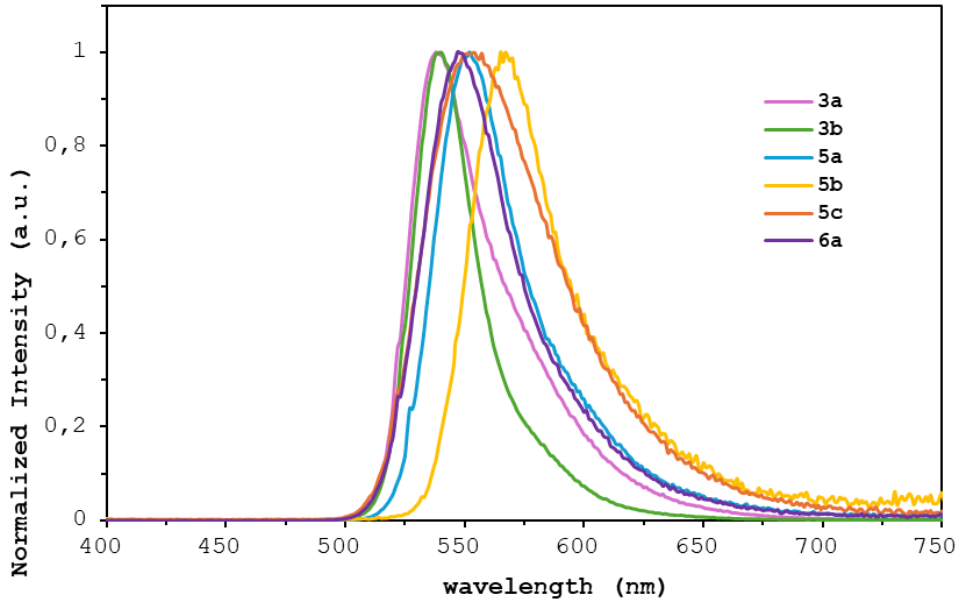

**6a**, 92%

*J. Org. Chem.* 2024, 89, 7, 4702

# Results

## 5 Photophysical properties




| Comp. | $\lambda_{max}^{Abs}$ (nm) ($\varepsilon$($M^{-1}$ $cm^{-1}$)) | $\lambda_{max}^{PL}$ (nm) | $\Phi_F$ |
|---|---|---|---|
| 3a | 521 (65030) | 538 | 0.78[b] |
| 3b | 523 (75594) | 540 | 0.79[b] |
| 5a | 526 (64944) | 552 | 0.72[c] |
| 5b | 540 (77698) | 565 | 0.14[c] |
| 5c | 520 (38421) | 554 | 0.96[c] |
| 6a | 523 (79174) | 543 | 0.79[c] |

- Spectra were recorded in $CHCl_3$ solutions at room temperature at $7.5 \cdot 10^{-7}$ M for UV-Vis and PL spectra, excited at the respective under $\lambda_{max}$.
- Fluorescence quantum yields for **3a-3b** were determined relative to fluoresceine in NaOH 0.1 M as standard ($\Phi_F$ = 0.92).
- Fluorescence quantum yields of **5a-5c** and **6a** were determined relative to rhodamine 6G in as standard ($\Phi_F$ = 0.94 in EtOH).

Bathochromic shift

**6a 5a 5c 5b**

# Conclusions

1) Palladium-catalyzed cross-coupling reactions using indium organometallics ($R_3In$) with 2,6-dihalogenated BODIPYs afforded the dicoupling products with atom economy in moderate yields.

2) Indium(III)-catalyzed intermolecular double hydroarylation reactions of arylalkynes with *meso*-substituted BODIPYs provide branched 2,6-dialkenyl BODIPYs with Markovnikov regioselectivity in excellent yields.

3) The resulting BODIPYs displayed fluorescence emissions from 538 to 565 nm and high quantum yields (up to $\Phi_F$ = 0.96).