

# A Short Review on Recent Advances and Applications of Bimane Chemistry

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## Abstract

1,5-diazabicyclo[3.3.0]octadienediones, also known as bimanes, are heterobicyclic compounds with generally high quantum yields, low toxicity, and low molecular weight. During the 1970s, the bimane fluorophore, which was synthesized from the reaction of a  $\beta$ -keto ester and hydrazine, was first reported by Kosower and co-workers. Since that time, significant effort has been invested in the introduction of functional groups at the  $\alpha$ -positions of *syn*-bimane, the bimane isomer in which both carbonyl groups are oriented in the same direction. In spite of these efforts, the successful attachment of high value functional groups at the  $\alpha$ -positions of *syn*-bimane remain scarce. A recent report from Prof. Flavio Grynspan's group using a solvent-free, environmentally friendly (i.e. "green") method allowed for a rapid, large-scale synthesis of bimane and the preparation and study of differently-substituted bimane derivatives. In this review, we describe the advantages of the current green synthesis of bimanes and the applications of the newly formed bimane derivatives as fluorescent and colorimetric sensors, with special attention paid to the relationship between the bimane structures, their photophysical characteristics, and their performance as chemical sensors.

**Keywords:** *Bimanes, Fluorescent Probes and Sensors*

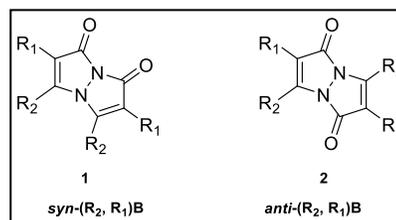
## 1. Introduction

Organic fluorescent dyes find applications as effective research tools, which enable the study of chemical, physical, and biological systems. Examples of popular classes of organic fluorescent dyes include BODIPYs, coumarins, squaraines, and fluoresceins. The relationship between their structures and photophysical properties has been established for all these fluorophores.<sup>1-6</sup> Examples of desirable photophysical properties that can be tuned via judicious structural modifications include significant Stokes' shifts, high relative and absolute quantum yields, and strong absorption coefficients. Therefore, it should come as no surprise that chromophores which have such desirable properties can be exploited in a broad range of applications, including as components of organic light-emitting diodes, light-harvesting materials, fluorescent tags and chemical sensors.

One particular high-impact application of organic fluorophores is in the imaging of biological systems.<sup>7</sup> Fluorophore-based imaging agents add to other commonly used bioimaging tools, including fluorescent metal systems as well as supramolecular organic and organometallic complexes used in bioimaging techniques such as positron emission tomography (PET), magnetic resonance imaging (MRI), and single-photon emission computerized tomography (SPECT).<sup>8-10</sup> Although the commonly used metal-based imaging agents have significant practical advantages due to the high fluorescence generated by metal-to-ligand charge transfer (MLCT),<sup>11</sup> such agents also suffer from high toxicity and high molecular weights. Supramolecular-based imaging agents also have notable disadvantages, particularly in their relative instability to biological environments that leads to

undesired complex dissociation.<sup>12</sup> Therefore, organic fluorophores with low toxicity, low molecular weight, and high stability in biological systems have significant appeal, with potentially broad-ranging applications in a variety of bioimaging scenarios.

Bimanes represent a promising option for a relatively unexplored class of organic fluorophores meeting the aforementioned criteria. Although these are generally low molecular weight, highly fluorescent molecules, they have been relatively under-explored by the scientific community to date. The heterobicyclic structural family bearing the bimane core, (formally named "1,5-diazabicyclo [3.3.0] octadienediones"), can be readily synthesized.<sup>13</sup> Bimanes are naturally found in two diastereomeric forms, *syn*- (with carbonyl groups oriented in the same direction) and *anti*- (with carbonyl groups oriented in opposite directions), which are



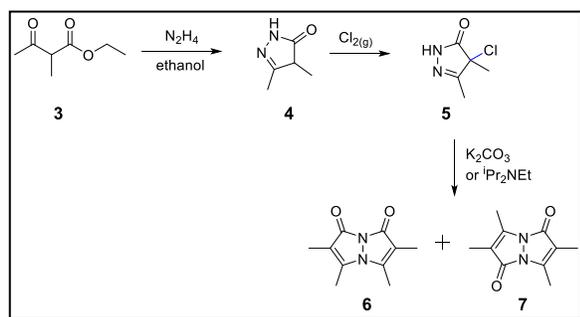
**Figure 1:** Core structure of bimane core

distinguished by markedly different photophysical properties. In particular, the generally high quantum yields of *syn*-bimanen stand in stark contrast to the lack of fluorescence of *anti*-bimanen. Recently, several novel bimane derivatives have been synthesized and used as components of both metal-containing and metal-free supramolecular complexes,

with applications of such bimanane-containing complexes in chemical sensing also described.<sup>14-18</sup>

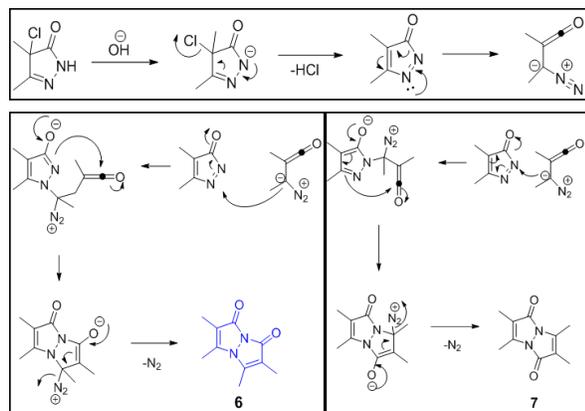
## 2. General synthesis of the bimanane core

The bimanane core is made up of two five-membered rings fused by a N-N single bond. The *syn*-bimane fluorophore has quasi-planar  $C_{2v}$  symmetry and has both  $\alpha$ - (adjacent to the carbonyl group) and  $\beta$ - (not adjacent to the carbonyl group) positions available for functionalization. The general synthesis of bimananes was first reported by Kosower *et al.*, who reacted a  $\beta$ -keto ester with hydrazine hydrate at 50 °C for one hour to form a pyrazolinone derivative, followed by chlorination with  $Cl_2(g)$ , and treatment under basic conditions to afford the *syn*-bimane (compound **6**) and *anti*-bimane (compound **7**) products (Scheme 1).<sup>19</sup>



**Scheme 1:** Kosower's synthetic route to *syn*- and *anti*-(Me,Me)bimane using a heterogeneous (solid  $K_2CO_3 \cdot 1.5 H_2O$ ) or homogeneous ( $Pr_2NEt$ ) base.

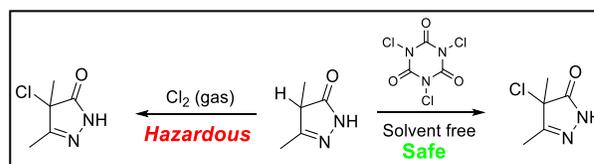
Mechanistically, Kosower and co-workers hypothesized that the synthesis of *syn* and *anti*-isomers takes place *via* the formation of a high-energy ketene intermediate (compound **8**; Scheme 2, top), and subsequent work by Tomioka and coworkers has generated tentative experimental evidence in support of this hypothesis.<sup>20</sup> From this intermediate, 1,4-addition or 1,6-addition, will lead to the formation of the *syn*- or *anti*- products, respectively (Scheme 2, bottom).<sup>20</sup>



**Scheme 2:** Proposed formation of the ketene intermediate **8**, as part of the synthesis of *syn*- and *anti*-(Me,Me)bimane (Top). The mechanism of *syn*- and *anti*-(Me,Me)bimane formation, as suggested by Kosower and coworkers (left: 1,4-addition and right: 1,6-addition).<sup>19</sup>

As mentioned previously (*vide supra*), the selection of base in the final step of Kosower's synthesis affects the isomeric distribution of products. In particular, the heterogeneous base  $K_2CO_3 \cdot 1.5 H_2O$  gives mostly the *syn*-isomer, determined to be the kinetic product, whereas homogeneous soluble bases such as *N,N*-diisopropylethylamine produce mainly the thermodynamically favored *anti*-isomer. Photophysical characterization of the two isomers revealed that the *syn*-(Me,Me)bimane (a bimane with Me groups in both  $\alpha$  and  $\beta$ -positions) exhibits three distinct absorbance band maxima ( $\lambda_{max}$ ) at 359 nm, 255 nm and 235 nm in dioxane, with extinction coefficients ( $\epsilon$ ) of 6500, 5200 and  $14,600 M^{-1} cm^{-1}$ , respectively. The band at 359 nm is the corresponding band of the bimane moiety in dioxane. The fluorescence quantum yield ( $\phi_F$ ) for this compound was found to be 72% in dioxane, with two fluorescence emission bands at 420 nm and 440 nm. On the other hand, the absorbance band for *anti*-(Me,Me)bimane is at 322 nm with molar extinction coefficient ( $\epsilon$ ) at  $15,100 M^{-1} cm^{-1}$ .<sup>19</sup>

Kosower's synthetic procedure for bimananes was modified by Grynszpan *et al.* using a "green chemistry" (i.e., environmentally friendly) approach (Scheme 3).<sup>21</sup> The use of dangerous  $Cl_2(g)$  during the chlorination of pyrazolinone was successfully avoided through the use of other chlorine ( $Cl^+$ ) sources, including sodium hypochlorite, *tert*-butyl hypochlorite, *N*-chlorosuccinimide (NCS), 1,3-dichloro-5,5-dimethylhydantoin (DCDMH), and trichloroisocyanuric acid (TCCA). This reaction proceeded effectively both in solution and under solvent-free conditions.

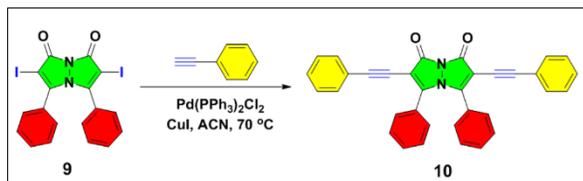


**Scheme 3:** Green chemistry approach for the synthesis of a halopyrazolinone using trichloroisocyanuric acid (TCCA), as reported by Grynszpan and co-workers.<sup>21</sup>

## 3. Synthesis of bimananes with $\alpha$ -extended $\pi$ -systems

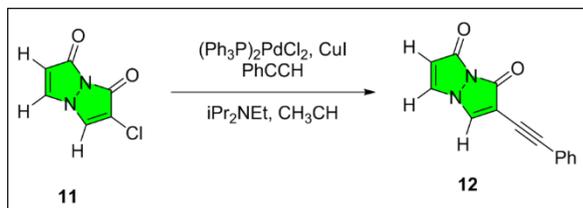
One notable class of bimane derivatives are those with extended  $\pi$ -conjugation, particularly at the  $\alpha$ -position. These derivatives are easily accessible *via* the metal-catalyzed cross-coupling of  $\alpha$ -iodinated bimanane derivatives (Scheme 4), which are in turn available *via* an improved synthetic approach developed by Grynszpan *et al.* Once synthesized, these  $\pi$ -extended bimananes have significant potential in the ability to use structural variations to tune the bimane's photophysical properties. For example, the bimane derivative with two alkyne-arene substituents at the  $\alpha$ -position (compound **10**, Scheme 4), has significantly red-shifted absorbance and emission spectra compared to the parent *syn*-(Me,Me)bimane. (Scheme 4)<sup>21</sup> In the rest of this section, we will discuss several recently reported  $\pi$ -extended bimananes, including both their syntheses and photophysical

investigations, with a particular focus on  $\pi$ -substitution at the  $\alpha$ -position.



**Scheme 4:** Synthesis of phenyl substituted bimane for extended  $\pi$ -system.<sup>21</sup>

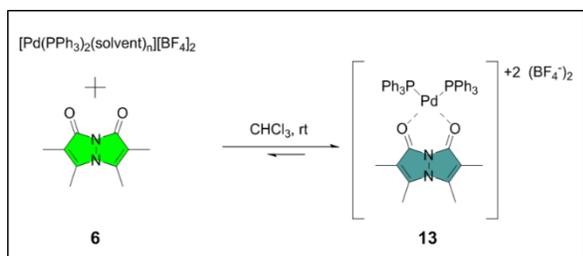
Extended  $\pi$ -conjugation at the  $\alpha$ -position was first reported by Kosower *et al.*, who described the synthesis and spectroscopic characterization of  $\alpha$ -substituted alkyne derivatives of bimane. Their synthetic procedure started from iodinated precursor **9** (Scheme 4) at the  $\alpha$ -position, with a metal-catalyzed Sonogashira coupling reaction affording the desired alkyne-containing products. Although other halogenated starting materials were also investigated, they were nearly unanimously unsuccessful, with the only exception being the reported cross-coupling of mono-chloro-substituted bimane (compound **11**), which afforded the mono-substituted alkynyl-arene product **12** in 15% yield (Scheme 5).



**Scheme 5:** Sonogashira C-C coupling reaction as reported by Kosower and Ben-Shoshan.<sup>22</sup>

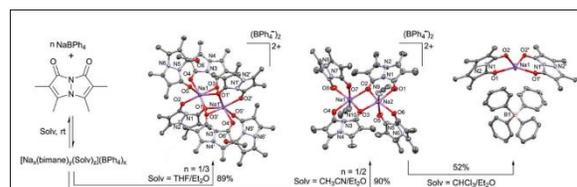
#### 4. Metal Complexes of Bimanes:

Despite the fact that bimanes have several structural features that lend themselves to complexation with metals, including both the O and N atoms as well as the sterically accessible  $\pi$ -system, their ability to complex metals was overlooked for several decades after their initial discovery. In the first report of a metal-bimane complex, Grynszpan and Montag reported that the highly luminescent *syn*-(Me,Me)bimane **6** forms a strong and non-fluorescent complex with Pd(II) (compound **13**, Scheme 6).<sup>23</sup> The complex's fluorescence quenching is a result of the heavy atom effect of palladium.



**Scheme 6:** First reported metal-bimane complex by Grynszpan, Montag and co-workers.<sup>23</sup>

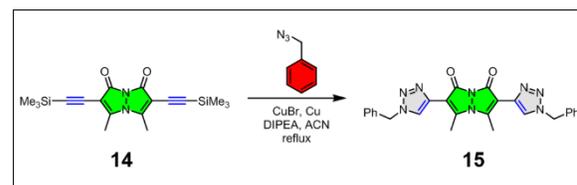
Since the initial report of Grynszpan and Montag in 2016, a number of other bimane-metal complexes have been reported, including with Ca(II), Na(I), K(I) and Li(I) metal centers. Many of these metals have significant relevance in biology, including sodium, which plays a critical intracellular role as part of sodium-potassium pumps.<sup>24,25</sup> Motivated in part by the significant biological relevance of sodium, researchers investigated the interaction of the sodium cation with *syn*-(Me,Me) bimane in a variety of organic solvents, revealing the existence of three unique crystal structures (Scheme 7). Within these crystal structures, there are several notable features, including the fact that bimane chelates to Na<sup>+</sup> in every structure *via* bidentate binding of the two O atoms (from the two carbonyl groups). In addition to this highly prevalent bidentate binding, both monodentate Na<sup>+</sup>-oxygen binding and chelating/bridging binding modes were also noted, albeit with lower frequencies. Moreover, photophysical investigations of the sodium-bimane complexes indicated a highly solvent-dependent decrease in fluorescence that occurred upon sodium binding, with mechanistic hypotheses presented to explain the observed fluorescence decreases. Even more recently, Grynszpan and Levine *et al.* reported the development of a bimane-cyclodextrin complex for cobalt detection, which relies on the



ability of bimane to bind cobalt with high efficiency.<sup>15</sup>

**Scheme 7:** Reversible formation of Na<sup>+</sup>-bimane complexes in solution (Solvent = CHCl<sub>3</sub>, THF, CH<sub>3</sub>CN, H<sub>2</sub>O), and crystal structures of the isolated complexes (with thermal ellipsoids at the 50% probability level).<sup>25</sup>

In further investigations of the possible metal-binding capabilities of bimane derivatives, Grynszpan and Levine *et al.* reported a novel bimane ditriazole compound (compound **15**, Scheme 8), available *via* a Huisgen-catalyzed click reaction between trimethylsilylacetylene-substituted bimane and benzyl azide.<sup>14</sup> The newly available compound **15** was able to bind two copper(II) atoms, with the 1:2 bimane:copper binding ratio determined *via* a variety of analytical techniques. Based on previously reported crystallographic data, and the MM2-calculated energy-minimized structure of compound **15**, an estimated structure for the final square

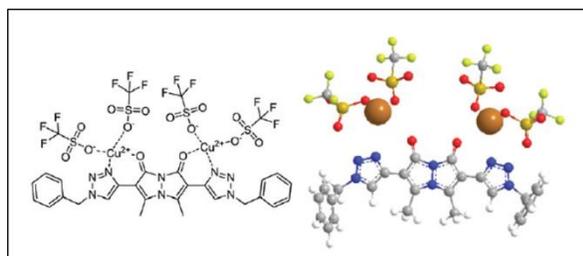


planar Cu(II)-containing complex was generated (Figure 2).

**Scheme 8:** CuBr catalyzed click reaction of **14** and benzylazide.<sup>14</sup>

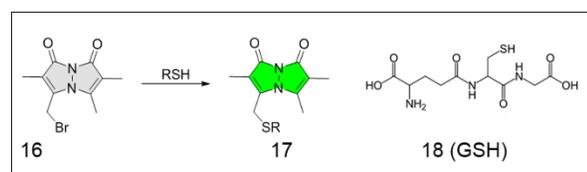
## 5. Recent Applications of bimanes

Since much of the appeal of bimanes resides in the high fluorescence of the *syn*-bimane isomer, it follows that the majority of applications of bimanes use precisely that property. For example, *syn*-bimane derivatives have been used as fluorescent tags for various enzymes, as well as fluorescent sensors for high-value analytes.



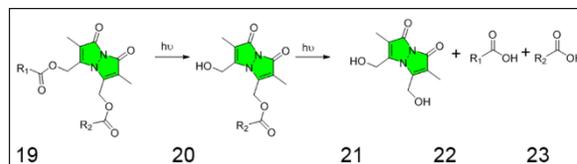
**Figure 2:** Non-minimized 2D and 3D depictions of the dipodal 15-diCu(II)triflate complex.<sup>14</sup>

In an early application of bimane as a fluorescent probe, Kosower and co-workers reported that the practically non-fluorescent bromobimane **16** could be used as a thiol sensor, *via* its conversion to the highly fluorescent, thiol-substituted products **17**, and that this sensor worked to detect the highly biologically relevant thiol, glutathione (compound **18**).<sup>26</sup>



**Scheme 9:** Reaction of glutathione with *syn*-(CH<sub>2</sub>Br,Me)(Me,Me)bimane **16**.

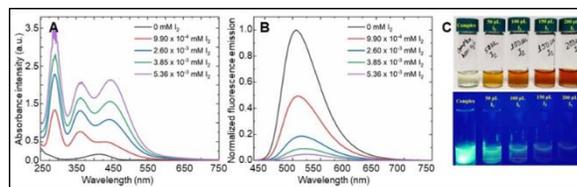
In a more recent example of bimane's utility as a fluorescent probe, in 2009 Zagotta and co-workers reported that *syn*-(CH<sub>2</sub>Br,Me)(Me,Me)bimane was able to fluorescently label cysteine residues.<sup>27</sup> Once the residues were successfully tagged with bimanes, the resulting proteins could undergo Förster Resonance Energy Transfer (FRET), both between tyrosine and bimane and between tryptophan and bimane. Such FRET studies provided critical information about the distance between the donor and acceptor, through using a sterically small fluorescent probe (bimane) that caused only minimal disruption to the native protein structure. Further work on FRET involving bimane fluorophores included the use of transition metal ions as part of the donor-acceptor pair, which enabled bimane tagging of proteins without covalent attachment to cysteine. Overall, the use of these systems to measure intra- and inter-protein distances resulted in relatively high accuracy in distance measurements, particularly for distances classified as "medium-range."



**Scheme 10:** Photorelease of bimane caged ester with two different carboxylic acids.

Additional examples of bimane applications include the work reported by Singh *et al.*, who developed a number of bimane-based caged esters for carboxylic acids and amino acids. Once synthesized, these compounds exhibited intriguing photophysical and photochemical characteristics.<sup>18</sup> In particular, exposure of the fluorescent photoremovable protecting groups (FPRPGs) to visible light (about 410 nm), resulted in the cleavage of both the carboxylic and amino acids, with the concomitant generation of a highly fluorescent bimane diol.

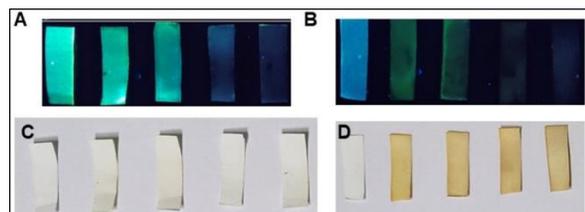
In another example, in 2019, Szilágyi *et al.* synthesized a range of bimanes decorated with various glycosyl residues. In particular, both monosaccharide and disaccharide residues were attached to both the *syn*-bimane and *anti*-bimane central cores *via* thio-, disulfido or seleno-glycosidic linkages, leading to the formation of novel glycoconjugates with a range of photophysical properties.<sup>17</sup> Subsequent Cu(I)-catalyzed Huisgen cycloaddition of glycosyl azides to a bimane diethynyl derivative furnished further bivalent glycoconjugates, with sugar residues linked to the central bimane core *via* 1,2,3-triazole rings.



**Figure 3.** Changes in the photophysical spectra of a bimane **15**:  $\beta$ -cyclodextrin complex with increasing concentrations of I<sub>2</sub>: (A) UV-visible absorption spectra; (B) Fluorescence emission spectra from excitation at 410 nm; and (C) Visible color changes in a solution of bimane **15**:  $\beta$ -cyclodextrin complex upon introduction of increasing concentrations of I<sub>2</sub> (top photograph) and the same solutions seen under 365 nm irradiation (bottom photograph). (left to right: 0  $\mu$ L I<sub>2</sub>, 50  $\mu$ L I<sub>2</sub>, 100  $\mu$ L I<sub>2</sub>, 150  $\mu$ L I<sub>2</sub>, 200  $\mu$ L I<sub>2</sub>; [I<sub>2</sub>]=0.1 M).<sup>16</sup>

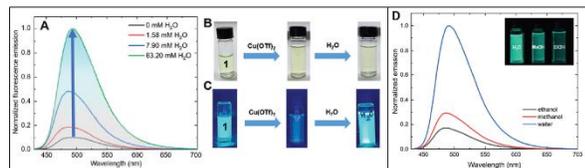
Moreover, Grynszpan and Levine *et al.* recently reported that an inclusion complex of **15** and  $\beta$ -cyclodextrin can be used for the effective detection of iodine.<sup>16</sup> Of note, the measured fluorescence emission of this compound significantly decreases in the presence of iodine, with sub-nanomolar detection limits found in solution. The comparison study between *syn*-(Me,Me)bimane and triazole bimane **15** interacting with iodine and facilitating the iodine detection via fluorescence quenching. Additional experiments demonstrated that the cyclodextrin-bimane complex could be effectively adsorbed onto filter paper, with the results demonstrating a distinct performance advantage of the

supramolecular cyclodextrin-bimane complex, particularly in the solid state.



**Figure 4.** Changes in the photophysical properties of functionalized filter papers upon exposure to increasing concentrations of  $I_2$ . (A) Changes in the fluorescence emission of free bimane **15** on filter paper from excitation at 365 nm; (B) Changes in the fluorescence emission of a  $\beta$ -cyclodextrin:bimane **15** complex on filter paper from excitation at 365 nm; (C) Changes in visible coloration of bimane **15** on filter paper after exposure to 2, 200  $\mu$ L  $I_2$ ;  $[I_2]=0.1$  M;  $[15]=2.00 \times 10^{-2}$  mM;  $[\beta\text{-cyclodextrin}]=4.56 \times 10^{-2}$  mM).<sup>16</sup>

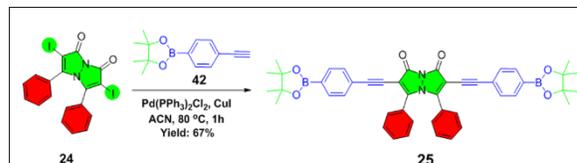
In 2022, Grynszpan and Levine *et al.* designed an ultrasensitive sensor for water detection with bimane **15** decorated with Cu(II) ions. The details of this bimane complex, including both its synthesis and characterization, were discussed in a previous section (“Metal Complexes of Bimanes”). Following the initial studies, researchers noted that the non-fluorescent copper complex turned highly fluorescent in the presence of extremely low concentrations of water (0.000786% v/v), *via* highly selective water-induced displacement of copper. Furthermore, the authors also demonstrated that this bimane-copper complex was moderately selective of water compared to other protic solvents like methanol and ethanol (Figure 5B), with a much stronger fluorescence response to water compared to other protic solvents.<sup>14</sup>



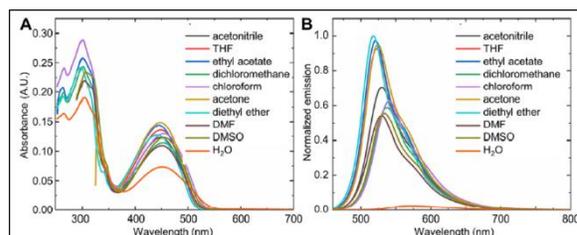
**Figure 5** (A) Fluorescence emission spectra of a compound **15**-copper(II) complex in dry acetonitrile after the addition of increasing amounts of water; (B) photographs of a solution of compound **15** in dry acetonitrile under ambient light with the sequential addition of copper(II) triflate and water; and (C) photographs of a solution of compound **15** in dry acetonitrile under  $\lambda_{ex} = 365$  nm irradiation with the sequential addition of copper(II) triflate and water ( $[15] = 25$  mM;  $[Cu(II)] = 1$  mM) (D) Inset shows a photograph of the solutions after solvent addition, under  $\lambda_{ex} = 365$  nm irradiation. ( $[15] = 25$  mM).<sup>14</sup>

Additional work in the development of water sensors from the groups of Grynszpan and Levine focused on the response of bimane **25** to water (Scheme 11). This structure, available from the Sonogashira-catalyzed cross-coupling of diiodo compound **24**, responded to water in both the liquid phase and as water vapor, resulting in fluorescence quenching in both cases.<sup>28</sup> This response can be seen both in the solution of bimane **25** and on filter papers to which bimane **25** was adsorbed, resulting in colorimetric and fluorometric changes. The addition of water induces the fluorescence quenching of bimane **25** is mostly via the water

induced hydrolysis of the boronate ester moieties on compound **25** to form the hydrolyzed boronic acid. The photophysical properties of compound **25** were fully characterized in acetonitrile, and the relative quantum yield ( $\phi$ ) of bimane **25** and its extinction coefficient ( $\epsilon$ ) were found to be 0.17 and  $1.23 \times 10^4$  L  $M^{-1}$   $cm^{-1}$ , respectively.



**Scheme 11.** Synthesis of ethynylphenylpinacol boronate functionalized bimane **25**.



**Figure 6** The (A) UV-visible and (B) fluorescence emission spectra of compound **25** in a variety of solvents, highlighting the marked difference in spectra observed in water (orange trace) compared to the organic solvents ( $[25] = 10$   $\mu$ M;  $\lambda_{ex} = 450$  nm).<sup>28</sup>

## 6. Conclusion and Future Perspective:

In this review, we have described several recent advances in bimane chemistry, with a particular focus on metal-containing and non-metal containing supramolecular bimane complexes, as well as applications of such complexes in chemical sensing. A variety of other new bimanes applications, including the use of bimanes in photo-cleavable esters and the use of bimanes as sensors in carbohydrate chemistry, have also been described. Due to the low molecular weight and straightforward synthetic accessibility of bimane derivatives, the field of bimane research is expanding at a rapid rate. While a variety of high-impact applications, particularly in biology and biological imaging, are conceivably available for novel bimane derivatives, more research is still needed to improve both the aqueous solubility and stability of bimanes under aqueous, biologically-relevant conditions.

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