Organic LETTERS

Letter

pubs.acs.org/OrgLett

Divergent Synthesis of Dihydroxanthene-Hemicyanine Fused Near-Infrared Fluorophores through the Late-Stage Amination of a Bifunctional Precursor

Michelle Jui Hsien Ong,[†] Rajavel Srinivasan,[*,∥,†] Anthony Romieu,[*,‡,§] and Jean-Alexandre Richard[*,†]

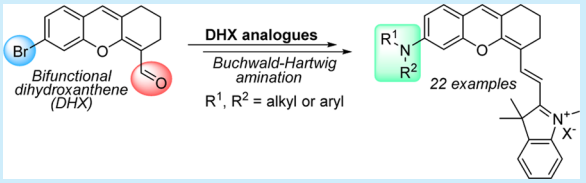
[†]Organic Chemistry, Institute of Chemical and Engineering Sciences (ICES), Agency for Science, Technology and Research (A*STAR), 8 Biomedical Grove, Neuros, #07-01, Singapore, Singapore 138665

[‡]ICMUB, UMR 6302, CNRS, Univ. Bourgogne Franche-Comté, 9, Avenue Alain Savary, 21078 Dijon cedex, France

[§]Institut Universitaire de France, 103 Boulevard Saint-Michel, 75005 Paris, France

Supporting Information

ABSTRACT: A late-stage amination of a bifunctional dihydroxanthene (DHX) scaffold is reported to access a wide variety of new near-infrared (NIR) chromophores/fluorophores. The divergent approach allows the coupling of aliphatic and aromatic amines and readily provides molecular diversity shedding light on the structure–fluorescence relationship of this emerging class of NIR fluorophores.



In the absence of intelligence predicting the properties of small organic molecules, chemists need to rely on the development of robust synthetic strategies to access the chemical space of molecules of interest. A powerful approach streamlining this process is the late-stage functionalization of structurally advanced intermediates because it provides a time-efficient access to molecular diversity and/or short-lived intermediates. Medicinal[1] and radiochemists[2] for instance have embraced this approach, and the development of powerful synthetic methodologies to build and derivatize molecular scaffolds are necessary to maximize its efficiency. Such a strategy applied to organic-based fluorophores[3] has been thoroughly performed on the xanthene skeleton through the addition of organometallic and hetero nucleophiles to the C9 position of xanthone derivatives to provide pyronins,[4] rosamines,[5] and fluorescein analogues.[6] Likewise, the C3′ and C6′ phenolic positions of fluorescein have been converted through Pd-catalyzed amination cross-coupling to access nonconventional rhodamine[7] and rhodol fluorophores (Figure 1A).[8] Near-infrared (NIR) fluorophores are of particular interest for imaging because they alleviate the need for multiphoton excitation[9] and provide benefits in terms of gain of sensitivity and use of wavelengths that are less damaging for living tissues.[10] The most relevant example illustrating the late-stage diversification of NIR dyes and modulation of their fluorescence properties is the modification of the *meso* position of heptacarbocyanine dyes through $S_{NR}1$ or Pd-catalyzed cross-coupling reactions (Figure 1A).[11] Aiming at the development of alternative NIR dye scaffolds with high potential for postsynthetic functionalization and fluorescence tunability we became interested in the promising but so far understudied *N,N*-dialkylamino-dihydroxanthene-hemicyanine fused fluorophores.[12] Our investigations[13] and the recent work of Yuan and co-workers[14] identified 1,3,3-trimethyl-2-methyl-eneindoline (Fischer's base) as being the optimum electron-pulling moiety to obtain high fluorescence brightness with an

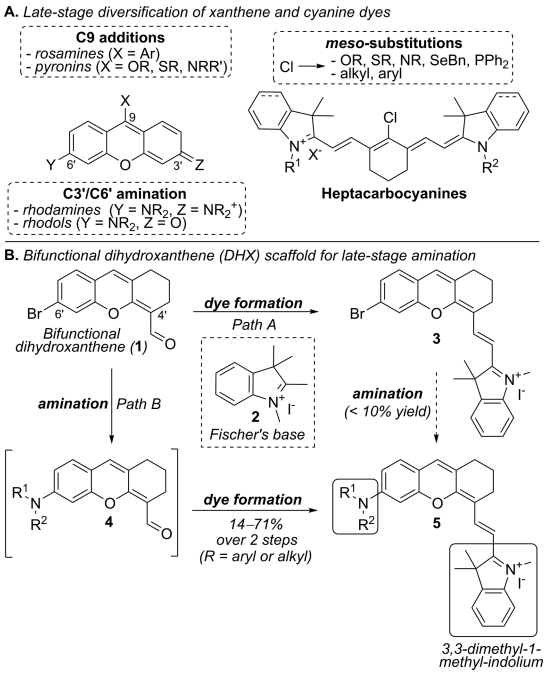


Figure 1. (A) Late-stage diversification of organic-based fluorophores. (B) A bifunctional scaffold for the late-stage amination leading to *N,N*-disubstituted-amino DHX-hemicyanine fused NIR dyes.

emission maximum above 730 nm. However, no systematic variation of the nature of the amino electron-donating moiety of dihydroxanthene scaffold has been reported yet. By analogy with the significant changes in fluorescence emission between

Received: August 27, 2016

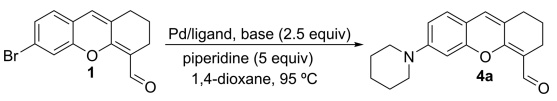
© XXXX American Chemical Society

DOI: 10.1021/acs.orglett.6b02564
Org. Lett. XXXX, XXX, XXX–XXX

rhodamine 110, tetramethylrhodamine (TMR), and rhodamine B (*i.e.*, Y = NH_2, NMe_2, and NEt_2; Z = NH_2^+, NMe_2^+, and NEt_2^+, Figure 1A)[15] we anticipated that the variation of the nature of the *N*-substituent(s) would have a dramatic effect on the fluorescence and shed light on the structure−fluorescence relationship (SFR) of this emerging and promising class of NIR fluorophores. In order to test that hypothesis, we designed the bifunctional dihydroxanthene scaffold **1** featuring two orthogonal chemical handles for late-stage diversification: (1) a C6′-substituted aryl bromide to perform transition metal-catalyzed reactions such as Buchwald−Hartwig amination and Pd-catalyzed C−C bond cross-coupling (*i.e.*, Heck, Sonogashira, or Suzuki coupling); (2) a formyl moiety at C4′ to provide flexibility regarding the extension of the π-conjugated system (Figure 1B). Our initial investigations using bifunctional scaffold **1** aimed at the formation of bromo-substituted DHX-hemicyanine fused dye **3** in order to perform the Buchwald−Hartwig amination at the very last step. However, under a variety of conditions tested the desired amination could only be observed in low yields, most likely the result of partial degradation of the dimethine bridge of **3** in the presence of excess base at high temperature (Figure 1B, Path A). Alternatively, the amination of bifunctional precursor **1** immediately followed by a Knoevenagel condensation with Fischer's base provided the desired dyes in good yields over two steps (Figure 1B, Path B). We report here the details of our investigations following that strategy which culminated in the synthesis of a broad range (22 different compounds) of *N*-substituted dihydroxanthene-hemicyanine fused dyes featuring unique optical properties either in simulated physiological conditions or in organic media.

The S_NAr amination of aryl halides has already been reported for other chromophores/fluorophores (*e.g.*, coumarins, xanthenes),[16] but at the outset of this study we were not aware of any Buchwald−Hartwig amination using aryl bromides for the synthesis of libraries of arylamine-based fluorophores.[16a,17] By choosing aryl bromides over aryl triflates as starting materials, our objective was to avoid the competitive detriflation which is usually circumvented by using a high catalyst loading (*i.e.*, respectively 10 and 15 mol % of metal and ligand for each triflate function).[7a,8] Hoping to improve those conditions with a minimum catalyst loading, we performed an optimization study using bromide **1** with piperidine as a coupling partner, and a selection of the conditions tested is presented in Table 1 (for the full details of the optimization, see the Supporting Information (SI)). The combined use of a 10 mol % palladium loading and XPhos as ligand[18] was efficient to cleanly provide the amination product, but less metal and ligand amounts (*i.e.*, 2.5 mol %) resulted in a dramatic decrease of the reaction conversion (Table 1, entries 1−2). The same loading using the DavePhos ligand (Table 1, entry 3)[19] was successful to sustain the same level of activity while a change of base (*i.e.*, LiO*t*-Bu), palladium source (*i.e.*, Pd(0) to Pd(II) and further reduction of the catalyst loading (*i.e.*, 1 mol %) resulted in a less efficient catalytic system (Table 1, entries 4−6).

Table 1. Optimization of the Late-Stage Buchwald−Hartwig Amination



entry	Pd source (mol %)	ligand (mol %)	base	conversion[a] (%)
1	Pd_2dba_3 (10)	XPhos (10)	Cs_2CO_3	95
2	Pd_2dba_3 (2.5)	XPhos (2.5)	Cs_2CO_3	40
3	Pd_2dba_3 (2.5)	DavePhos (2.5)	Cs_2CO_3	89−95
4	Pd_2dba_3 (2.5)	DavePhos (2.5)	LiO*t*-Bu	11
5	$Pd(OAc)_2$ (2.5)	DavePhos (2.5)	Cs_2CO_3	48
6	Pd_2dba_3 (1)	DavePhos (1)	Cs_2CO_3	63

[a]Determined by ^1H integration of the NMR of the crude product.

With these optimum conditions in hand, we then explored the scope of the reaction by first expanding the range of heterocyclic amines introduced on the DHX core. 1,2,3,4-Tetrahydroisoquinoline, substituted piperazines, and morpholine could be coupled in 39−71% overall yield to provide the corresponding dyes **5b−f**. In addition to the 6-membered ring namely piperidine, the methodology also proved to be suitable for the introduction of 4-, 5-, and 7-membered azacyclic rings (Scheme 1, dyes **5g−j**). Finally, the reaction with a range of noncyclic *N*,*N*-dialkylamines was also successful (Scheme 1, dyes **5k−o**). It was then interesting to assess the effectiveness of this synthetic transformation with less reactive *N*-monoalkyl arylamine coupling partners. *N*-Methylaniline and 1,2,3,4-tetrahydroquinoline provided the desired dyes **5p** and **5r** in 47% and 51% yield respectively while indoline was less reactive and dye **5q** was isolated in a moderate 29% yield. Pushing further the difficulty of the coupling through lowering the nucleophilic reactivity of amine coupling partners, we were pleased to observe that reactions conducted with *N*,*N*-diarylamines and even 3,6-di-*tert*-butylcarbazole were also successful and provided dyes **5s−5u** in 14% to 43% yield.

Having demonstrated the large scope of amines which could be introduced on the DHX scaffold, we then determined their photophysical properties in different media including phosphate-buffered saline (PBS) with 5% (w/v) bovine serum albumin (BSA) as simulated body fluid,[21] EtOH, and $CHCl_3$ (Table 2 and SI for selected examples of Abs/Ex/Em spectra). As designed, compounds **5a−5s** display both absorption and emission peaks well into the NIR region at 691−736 nm and 726−768 nm respectively, depending on the substitution pattern of the amino group and solvent. However, no significant solvatochromism effect was observed for this class of DHX−hemicyanine hybrids. The presence of BSA, an additive known to disrupt interaction/aggregation between fluorophore molecules, in PBS provides NIR emitters with satisfying fluorescence quantum yields under physiological conditions (4−11%) sufficient for considering their further use in biosensing/bioimaging applications. The superiority of the fully carbocyclic amines (Table 2, entries 1, 2, 7−10) over the heteroyclic ones (Table 2, entries 3−6) should be noted, probably because of the reductive photoinduced electron transfer (PeT) quenching mechanism[22] favored by the presence of donor moieties including *N*-substituted piperazinyl and morpholinyl in DHX-hemicyanine hybrids **5c−5f**. By analogy with the *N*,*N*′-diarylrhodamines developed by the Molecular Probes company and currently used as fluorescence quenching compounds (QSY dyes),[23] the *N*-aryl/*N*,*N*-diaryl derivatives **5p−5u** exhibited a dramatic decrease in fluorescence or even a complete extinction of their NIR emission. That feature could be an asset for the development of reaction-based "turn-on" fluorogenic probes targeting analytes capable of causing selective desarylation reactions. It is worth noting that the structure of *N*,*N*-diaryl derivatives **5s−5u** closely resembles that of the donor moieties used for organic electronics[24] so that the methodology could open a range of applications beyond fluorescence imaging. Finally, as a preliminary demonstration of the utility of bifunctional precursor **1** we prepared NIR fluorophore **5v** featuring a NO2AtBu (a precursor of NOTA chelating agent), with the aim of developing multimodal probes for nuclear/NIR fluorescence imaging (Scheme 2).[25]

DOI: 10.1021/acs.orglett.6b02564
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 1. Synthesis of *N,N-Bis*-amino-Substituted Dihydroxanthene Dyes Featuring Alkyl−Alkyl, Alkyl−Aryl, and Aryl−Aryl Substituents

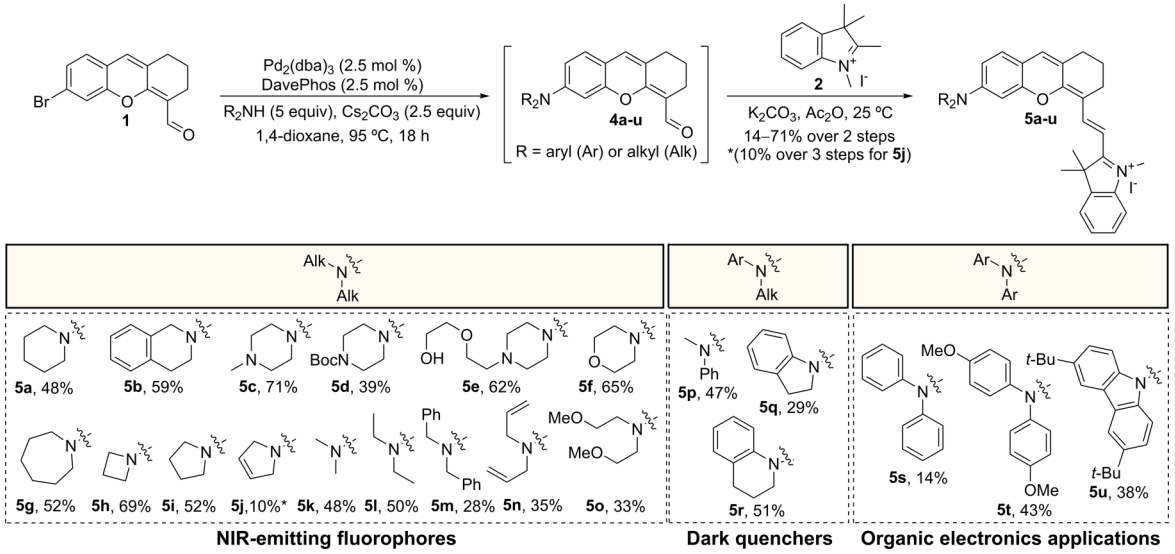
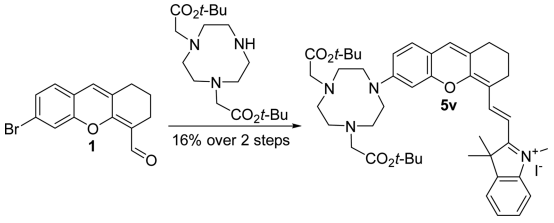


Table 2. Optical Properties of DHX-Hemicyanine Fused NIR Dyes 5a−u

		Abs λ_{max} (nm)[a]			Em λ_{max} (nm)[c]			ε (M^{-1} cm^{-1})			Stokes' shift (nm)			QY (%)[d]		
entry	dye	PBS[b]	EtOH	$CHCl_3$	PBS[b]	EtOH	$CHCl_3$	PBS[b]	EtOH	$CHCl_3$	PBS[b]	EtOH	$CHCl_3$	PBS[b]	EtOH	$CHCl_3$
1	**5a**	717	713	723	737	739	740	75 415	93 490	111 730	20	26	17	8	12	20
2	**5b**	715	710	719	731	731	733	58 280	73 200	80 350	16	21	14	9	11	19
3	**5c**	691	699	709	726	731	733	48 450	63 670	70 000	35	32	24	6	7	19
4	**5d**	–[e]	700	710	–[e]	731	729	–[e]	36 765	41 240	–[e]	31	19	–[e]	9	16
5	**5e**	701	702	713	730	731	735	44 850	60 330	68 620	29	29	22	7	8	20
6	**5f**	703	696	706	730	731	730	46 370	59 330	62 230	27	35	24	7	7	15
7	**5g**	724	718	727	738	738	740	52 780	65 080	78 800	14	20	13	10	17	26
8	**5h**	719	711	721	737	738	736	70 260	86 630	99 100	18	27	15	9	15	25
9	**5i**	723	717	725	735	739	738	53 040	62 290	75 805	12	22	13	10	15	25
10	**5j**	717	710	719	731	732	731	77 480	87 820	101 140	14	22	22	11	14	25
11	**5k**	720	710	718	734	732	732	74 260	87 000	100 600	14	22	14	10	14	25
12	**5l**	724	717	724	738	736	738	131 840	163 560	194 080	14	19	14	10	17	30
13	**5m**	–[e]	709	715	–[e]	728	730	–[e]	59 550	72 450	–[e]	19	15	–[e]	12	25
14	**5n**	715	709	717	729	729	729	63 410	77 840	94 430	14	20	12	9	13	28
15	**5o**	715	712	719	732	732	733	52 890	66 780	76 370	17	20	14	9	12	25
16	**5p**	715	708	717	735	732	735	55 240	69 800	33 270	20	24	18	7	6	22
17	**5q**	727	721	736	750	–[f]	768	39 160	44 450	51 410	23	–[f]	32	4	–[f]	3
18	**5r**	722	715	730	743	–[f]	750	46 045	55 840	66 050	11	–[f]	20	4	–[f]	2
19	**5s**	–[e]	708	722	–[e]	745	757	–[e]	46 440	55 470	–[e]	37	35	–[e]	4	12
20	**5t**	–[e]	717	729	–[e]	–[f]	–[f]	–[e]	75 365	76 910	–[e]	–[f]	–[f]	–[e]	–[f]	–[f]
21	**5u**	–[e]	608	624[g]	–[e]	–[f]	736	–[e]	32 900	34 450	–[e]	–[f]	112	–[e]	–[f]	2

[a]Assigned to S0−S1 transition but vibronic and S0−S2 transitions are also observed (see Supporting Information for the corresponding Abs spectra). [b]PBS buffer containing 5% BSA. [c]Excitation at 650 nm. [d]Determined at 25 °C using indocyanine green (ICG, ϕ_F = 10.6% in DMSO, λ_{ex} = 650 nm) as standard.[20] [e]Solubility in aqueous medium was insufficient for accurate measurements. [f]No fluorescence detected. [g]Very broad absorption band.

Scheme 2. Synthesis of a NO2AtBu-Substituted DHX-Hemicyanine Fused NIR Dye 5v



In summary, we have developed a divergent access to a small library of NIR-emitting dihydroxanthene-hemicyanine fused dyes. We designed an expedient synthesis of a bifunctional DHX-based precursor featuring an aryl bromide and aldehyde moieties suitable for late-stage diversifications. We identified reaction conditions allowing a Buchwald−Hartwig amination at only a 2.5 mol % catalyst loading, a significant improvement over the 10−15 mol % loading routinely used for aryl triflates. The scope of the reaction includes the introduction of aliphatic secondary amines, *N*-alkylanilines, and *N,N*-biaryl amines and provides a simple, efficient way to tune the electron-donating

DOI: 10.1021/acs.orglett.6b02564
Org. Lett. XXXX, XXX, XXX−XXX

ability of the *N*-substituted amino group and, ultimately, the fluorescence properties of the resulting DHX-hemicyanine fused NIR fluorophores. The simplicity and conciseness of this two-step synthetic sequence allow an easy exploration of new chemical space and provide a convenient starting point for the development of reaction-based small-molecule fluorescent probes,[26] NIR dark quencher molecules,[27] and NIR organic electronic materials.[28]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02564.

Experimental procedures, analytical data including ^{1}H and ^{13}C NMR spectra and selected absorption/excitation/emission spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: rajavels@tju.edu.cn (R.S.).
*E-mail: anthony.romieu@u-bourgogne.fr (A.R.).
*E-mail: jean_alexandre@ices.a-star.edu.sg (J.-A.R.).

Present Address

[‖]School of Pharmaceutical Science and Technology, Tianjin University, Building 24, 92 Weijin Road, Nankai District, Tianjin, 300072 P. R. China.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support for this work was provided by ICES, A*STAR (Singapore), Institut Universitaire de France (IUF), the Burgundy region ("FABER" programme, PARI Action 6, SSTIC 6 "Imagerie, instrumentation, chimie et applications biomédicales"), and a PHC Merlion grant (2015, 5.04.15). A.R. thanks the "Plateforme d'Analyse Chimique et de Synthèse Moléculaire de l'Université de Bourgogne" (PACSMUB, http://www.wpcm.fr) for access to spectroscopy instrumentation. Chematech company (Dijon, France) is warmly thanked for providing NO2AtBu.

■ REFERENCES

(1) Cernak, T.; Dykstra, K. D.; Tyagarajan, S.; Vachal, P.; Krska, S. W. *Chem. Soc. Rev.* **2016**, *45*, 546.
(2) Neumann, C. N.; Ritter, T. *Angew. Chem., Int. Ed.* **2015**, *54*, 3216.
(3) Vendrell, M.; Zhai, D.; Er, J. C.; Chang, Y.-T. *Chem. Rev.* **2012**, *112*, 4391.
(4) (a) Wu, L.; Burgess, K. *Org. Lett.* **2008**, *10*, 1779. (b) Horváth, P.; Šebej, P.; Šolomek, T.; Klán, P. *J. Org. Chem.* **2015**, *80*, 1299.
(5) (a) Ahn, Y.-H.; Lee, J.-S.; Chang, Y.-T. *J. Am. Chem. Soc.* **2007**, *129*, 4510. (b) Wu, L.; Burgess, K. *J. Org. Chem.* **2008**, *73*, 8711. (c) Im, C.-N.; Kang, N.-Y.; Ha, H.-H.; Bi, X.; Lee, J. J.; Park, S.-J.; Lee, S. Y.; Vendrell, M.; Kim, Y. K.; Lee, J.-S.; Li, J.; Ahn, Y.-H.; Feng, B.; Ng, H.-H.; Yun, S.-W.; Chang, Y.-T. *Angew. Chem., Int. Ed.* **2010**, *49*, 7497. (d) Kraus, G. A.; Guney, T.; Kempema, A.; Hyman, J. M.; Parvin, B. *Tetrahedron Lett.* **2014**, *55*, 1549.
(6) (a) Urano, Y.; Kamiya, M.; Kanda, K.; Ueno, T.; Hirose, K.; Nagano, T. *J. Am. Chem. Soc.* **2005**, *127*, 4888. (b) Mineno, T.; Ueno, T.; Urano, Y.; Kojima, H.; Nagano, T. *Org. Lett.* **2006**, *8*, 5963. (c) Martínez-Peragón, Á.; Miguel, D.; Jurado, R.; Justicia, J.; Álvarez-Pez, J. M.; Cuerva, J. M.; Crovetto, L. *Chem. - Eur. J.* **2014**, *20*, 447.
(7) (a) Grimm, J. B.; Lavis, L. D. *Org. Lett.* **2011**, *13*, 6354. (b) Grimm, J. B.; Sung, A. J.; Legant, W. R.; Hulamm, P.; Matlosz, S. M.; Betzig, E.; Lavis, L. D. *ACS Chem. Biol.* **2013**, *8*, 1303. (c) Grimm, J. B.; English, B. P.; Chen, J.; Slaughter, J. P.; Zhang, Z.; Revyakin, A.; Patel, R.; Macklin, J. J.; Normanno, D.; Singer, R. H.; Lionnet, T.; Lavis, L. D. *Nat. Methods* **2015**, *12*, 244.
(8) Peng, T.; Yang, D. *Org. Lett.* **2010**, *12*, 496.
(9) (a) Pawlicki, M.; Collins, H. A.; Denning, R. G.; Anderson, H. L. *Angew. Chem., Int. Ed.* **2009**, *48*, 3244. (b) Kim, H. M.; Cho, B. R. *Chem. Rev.* **2015**, *115*, 5014.
(10) (a) Weissleder, R.; Mahmood, U. *Radiology* **2001**, *219*, 316. (b) Frangioni, J. V. *Curr. Opin. Chem. Biol.* **2003**, *7*, 626.
(11) For selected examples, see: (a) Li, P.; Tang, B.; Xing, Y.; Li, P.; Yang, G.; Zhang, L. *Analyst* **2008**, *133*, 1409. (b) Kiyose, K.; Aizawa, S.; Sasaki, E.; Kojima, H.; Hanaoka, K.; Terai, T.; Urano, Y.; Nagano, T. *Chem. - Eur. J.* **2009**, *15*, 9191. (c) Samanta, A.; Vendrell, M.; Das, R.; Chang, Y.-T. *Chem. Commun.* **2010**, *46*, 7406. (d) Ornelas, C.; Lodescar, R.; Durandin, A.; Canary, J. W.; Pennell, R.; Liebes, L. F.; Weck, M. *Chem. - Eur. J.* **2011**, *17*, 3619. (e) Xu, K.; Chen, H.; Tian, J.; Ding, B.; Xie, Y.; Qiang, M.; Tang, B. *Chem. Commun.* **2011**, *47*, 9468. (f) Pascal, S.; Haefele, A.; Monnereau, C.; Charaf-Eddin, A.; Jacquemin, D.; Le Guennic, B.; Andraud, C.; Maury, O. *J. Phys. Chem. A* **2014**, *118*, 4038. (g) Wang, X.; Lv, J.; Yao, X.; Li, Y.; Huang, F.; Li, M.; Yang, J.; Ruan, X.; Tang, B. *Chem. Commun.* **2014**, *50*, 15439. (h) Njiojob, C. N.; Owens, E. A.; Narayana, L.; Hyun, H.; Choi, H. S.; Henary, M. *J. Med. Chem.* **2015**, *58*, 2845. (i) Zheng, L.; Wang, L.; Wang, P.; Sun, Q.; Liu, X.; Zhang, X.; Qiu, S. *Tetrahedron Lett.* **2016**, *57*, 932.
(12) (a) Czerney, P.; Grummt, U.-W. *J. Chem. Res., Synop.* **1996**, *4*, 173. (b) Yuan, L.; Lin, W.; Yang, Y.; Chen, H. *J. Am. Chem. Soc.* **2012**, *134*, 1200. (c) Yuan, L.; Lin, W.; Zhao, S.; Gao, W.; Chen, B.; He, L.; Zhu, S. *J. Am. Chem. Soc.* **2012**, *134*, 13510. (d) Richard, J.-A. *Org. Biomol. Chem.* **2015**, *13*, 8169.
(13) Romieu, A.; Richard, J.-A. *Tetrahedron Lett.* **2016**, *57*, 317.
(14) Wei, Y.; Cheng, D.; Ren, T.; Li, Y.; Zeng, Z.; Yuan, L. *Anal. Chem.* **2016**, *88*, 1842.
(15) Beija, M.; Afonso, C. A. M.; Martinho, J. M. G. *Chem. Soc. Rev.* **2009**, *38*, 2410.
(16) (a) Woodroofe, C. C.; Lim, M. H.; Bu, W.; Lippard, S. J. *Tetrahedron* **2005**, *61*, 3097. (b) Song, X.; Johnson, A.; Foley, J. *J. Am. Chem. Soc.* **2008**, *130*, 17652. (c) Lee, J.; Lee, K. H.; Jeon, J.; Dragulescu-Andrasi, A.; Xiao, F.; Rao, J. *ACS Chem. Biol.* **2010**, *5*, 1065. (d) Yun, S.-W.; Leong, C.; Bi, X.; Ha, H.-H.; Yu, Y. H.; Tan, Y. L.; Narayanan, G.; Sankaran, S.; Kim, J.-Y.; Hariharan, S.; Ahmed, S.; Chang, Y.-T. *Chem. Commun.* **2014**, *50*, 7492. (e) Chevalier, A.; Renault, K.; Boschetti, F.; Renard, P.-Y.; Romieu, A. *Eur. J. Org. Chem.* **2015**, *2015*, 152.
(17) For isolated examples, see ref 16a and: Wysocki, L. M.; Grimm, J. B.; Tkachuk, A. N.; Brown, T. A.; Betzig, E.; Lavis, L. D. *Angew. Chem., Int. Ed.* **2011**, *50*, 11206.
(18) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653.
(19) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338.
(20) Brouwer, A. M. *Pure Appl. Chem.* **2011**, *83*, 2213.
(21) Pauli, J.; Grabolle, M.; Brehm, R.; Spieles, M.; Hamann, F. M.; Wenzel, M.; Hilger, I.; Resch-Genger, U. *Bioconjugate Chem.* **2011**, *22*, 1298.
(22) Zhang, W.; Ma, Z.; Du, L.; Li, M. *Analyst* **2014**, *139*, 2641.
(23) Haugland, R. P.; Singer, V. L.; Yue, S. T. PCT Int. Appl. WO 2000064988, 2000.
(24) Qi, J.; Qiao, W.; Wang, Z. Y. *Chem. Rec.* **2016**, *16*, 1531.
(25) For reviews, see: (a) Azhdarinia, A.; Ghosh, P.; Ghosh, S.; Wilganowski, N.; Sevick-Muraca, E. M. *Mol. Imaging Biol.* **2012**, *14*, 261. (b) Ghosh, S. C.; Azhdarinia, A. *Curr. Med. Chem.* **2015**, *22*, 3390.
(26) Sun, W.; Guo, S.; Hu, C.; Fan, J.; Peng, X. *Chem. Rev.* **2016**, *116*, 7768.
(27) Myochin, T.; Hanaoka, K.; Iwaki, S.; Ueno, T.; Komatsu, T.; Terai, T.; Nagano, T.; Urano, Y. *J. Am. Chem. Soc.* **2015**, *137*, 4759.
(28) (a) Qian, G.; Wang, Z. Y. *Chem. - Asian J.* **2010**, *5*, 1006. (b) Dou, L.; Liu, Y.; Hong, Z.; Li, G.; Yang, Y. *Chem. Rev.* **2015**, *115*, 12633.

DOI: 10.1021/acs.orglett.6b02564
Org. Lett. XXXX, XXX, XXX−XXX