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Mild Arming and Derivatization of Natural Products via an $In(OTf)_3$-Catalyzed Arene Iodination

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ABSTRACT

Iodination of arene-containing natural products employing *N*-iodosuccinimide catalyzed by $In(OTf)_3$ at ambient temperature is reported as a versatile and mild method for natural product derivatization amenable to small scale. This process facilitates natural product derivatization of arene moieties for SAR studies, homo- and heterodimerization of natural products, and also conjugation with reporters such as biotin via subsequent metal-mediated coupling reactions.

Natural products (NPs) form the basis of more than half of the drugs currently in clinical use due to the immense structural diversity, cellular target specificity, and cell permeability.[1] The efficient and mild tagging of NPs for isolation of putative cellular receptor(s) continues to be a bottleneck in mining the rich information content of NPs.[2] Selective derivatization and subsequent conjugation to reporter tags not only provide the necessary NP probes, but also allow the concurrent/simultaneous structure−activity relationship (SAR) studies of NPs to explore their full potential as drug leads. Thus, the development of new strategies for modifying NPs under mild conditions with good functional group tolerance is gaining interest.[3] We recently described one strategy to address this issue employing "chemosite" selective[4] Rh-catalyzed OH insertion for simultaneous arming and SAR studies of natural products bearing alcohol and amino functionalities, with the former being the most prevalent functional group in NPs.[5] Arenes including heterocyclic aromatics are also commonly observed in NP structures, thus we sought mild strategies for tagging such structures.

We considered iodination as a viable option for arene derivatization since not only would this provide precursors for a host of transition metal-catalyzed cross-coupling reactions,[6]

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(1) (a) Clardy, J.; Walsh, C. *Nature* **2004**, *432*, 829. (b) Feher, M.; Schmidt, J. M. *J. Chem. Inf. Comput. Sci.* **2003**, *43*, 218.

(2) For reviews, see: (a) Piggott, A. M.; Karuso, P. *Comb. Chem. High Throughput Screening* **2004**, *7*, 607. (b) Terstappen, G. C.; Schlüpen, C.; Raggiaschi, R.; Gaviraghi, G. *Nat. Rev. Drug Discovery* **2007**, *6*, 891.

(3) (a) Christmann, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 2740. (b) Lewis, C. A.; Miller, S. J. *Angew. Chem.* **2006**, *118*, 5744. (c) Thomas, C. J. *Curr. Top. Med. Chem.* **2006**, *6*, 1529. (d) Bureeva, S.; Andia-Pravdivy, J.; Kaplun, A. *Drug Discovery Today* **2005**, *10*, 1535. (e) Harris, C. R.; Thorarensen, A. *Curr. Med. Chem.* **2004**, *11*, 2213. (f) Yus, M. *Synlett* **2001**, 1197. (g) Riva, S. *Curr. Opin. Chem. Biol.* **2001**, *5*, 106. (h) Guthikonda, R. N.; Cama, L. D.; Quesada, M.; Woods, M. F.; Salzmann, T. N.; Christensen, B. G. *Pure Appl. Chem.* **1987**, *59*, 455.

(4) We previously proposed the term "chemosite selective" to describe a reaction that exhibits both chemoselectivity and site selectivity (see ref 5).

(5) (a) Peddibhotla, S.; Dang, Y.; Liu, J. O.; Romo, D. *J. Am. Chem. Soc.* **2007**, *129*, 12222. (b) Drahl, C. *Chem. Eng. News* **2007**, *85*, 18.

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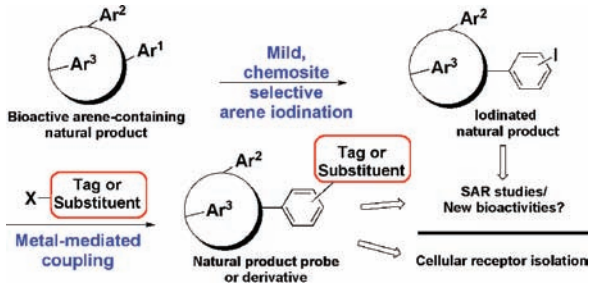
but this would also perturb the electronics and sterics of the substituted arene due to the large electronegative iodine atom enabling focused SAR studies (Scheme 1). Coupling reactions of the iodinated natural products would allow access to probes through attachment of various tags useful for biological studies.

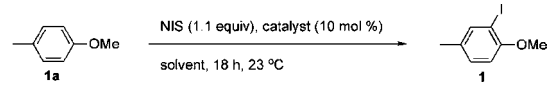
Scheme 1. Methods and Possible Outcomes for Derivatizing and Tagging Arene-Containing Natural Products



The direct arene iodination with molecular iodine is difficult to accomplish compared to the chlorination or bromination due to the low electrophilicity of iodine. Rather, iodide coupled with a strong oxidizing reagent is typically employed to generate an electrophilic I^+ species.[7] However, this reaction suffers from lack of generality due to the required strong oxidants which may react with sensitive functional groups in complex NPs. Recently, *N*-iodosuccinimide (NIS) was reported to be an efficient iodinating agent either at elevated temperature[8] or in conjunction with trifuoroacetic acid, triflic acid, $ZrCl_4$, or $BF_3{\cdot}H_2O$ as catalysts.[9] However, elevated temperatures or strong Bronsted/Lewis acids are likely incompatible with sensitive natural products. Thus, the paucity of mild methods for arene iodination led us to explore a mild Lewis acid-mediated iodination employing NIS. Herein, we demonstrate the development of such a process and describe its utility for derivatization of arene-containing NPs and subsequent metal-mediated couplings.

To identify a mild catalyst for iodination, we chose 4-methylanisole as a test substrate and screened various Lewis acids (10 mol %) with NIS in MeCN at ambient temperature (23 °C). An initial control experiment showed no reaction in the absence of catalyst after 18 h (Table 1, entry 1). We identified AgOTf, $Yb(OTf)_3$, $InBr_3$, $In(OTf)_3$, and TMSOTf as effective catalysts (Table 1, entries 2− 6). We focused further studies on $In(OTf)_3$ due to its mildness and lack of moisture sensitivity.[10] A brief survey of solvents indicated that CH_3CN was optimal; however, THF and CH_2Cl_2 gave lower but comparable yields (Table 1, entries 7 and 8), providing some flexibility for solvent choice based on NP solubility.[11]

Table 1. Screening of Catalysts and Solvents for Mild Iodination of 4-Methylanisole



entry	catalyst	solvent	% yield[a]
1	no catalyst	CH_3CN	NR[b]
2	AgOTf	CH_3CN	48
3	$Yb(OTf)_3$	CH_3CN	80
4	$In(OTf)_3$	CH_3CN	97
5	$InBr_3$	CH_3CN	97
6	TMSOTf	CH_3CN	98
7	$In(OTf)_3$	THF	>90[c]
8	$In(OTf)_3$	CH_2Cl_2	92

[a] Refers to isolated yields. [b] NR = no reaction. [c] Estimated conversion by ^{1}H NMR (300 MHz).

The iodination of various simple arenes was explored to determine generality and also to provide a profile for site selectivity when applying this method to NPs (Table 2). As expected, highest yields were obtained with electron-rich arenes[12] (Table 2, entries 1− 3, 6, 7, and 9−12). Although moderately electron-rich arenes required longer reaction time (up to 3 days), high yields were obtained under otherwise identical standard conditions (Table 2, entries 4 and 5). The regioselectivities observed with these substrates were as expected.

To study the applicability of the developed conditions in more complex settings, the iodination of several commercially available arene-containing NPs and derivatives was investigated (Scheme 2). Iodination of β-estradiol (**15**) under standard conditions gave monoiodination product **15a** in 80% yield along with 7% of diiodination product **15b** and 9% of recovered starting material. Compared with previously reported β-estradiol iodinations with $NaClO_2$/NaI/HCl,[13] chloramine-T/NaI,[14] and

(6) (a) Tsuji, J. *Transition Metal Reagents and Catalysts: Innovations in Organic Synthesis*; John Wiley & Sons: New York, 2000; (b) Diederich, F.; Stang, P. J. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: Weinheim, Germany, 1998.

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(8) Carreño, M. C.; Ruano, J. L. G.; Sanz, G.; Toledo, M. A.; Urbano, A. *Tetrahedron Lett.* **1996**, *37*, 4081.

(9) (a) Castanet, A.-S.; Colobert, F.; Broutin, P.-E. *Tetrahedron Lett.* **2002**, *43*, 5047. (b) Olah, G. A.; Wang, Q.; Sandford, G.; Surya Prakash, G. K. *J. Org. Chem.* **1993**, *58*, 3194. (c) Zhang, Y.; Shibatomi, K.; Yamamoto, H. *Synlett* **2005**, *18*, 2837. (d) Prakash, G. K. S.; Mathew, T.; Hoole, D.; Esteves, P. M.; Wang, Q.; Rasul, G.; Olah, G. A. *J. Am. Chem. Soc.* **2004**, *126*, 15770.

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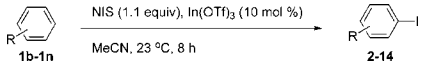
(11) Use of benzene as solvent gave <50% conversion.

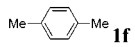
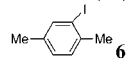
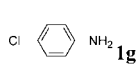
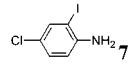
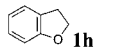
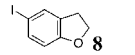
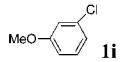
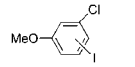
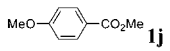
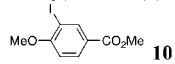
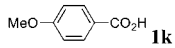
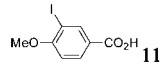
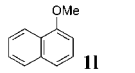
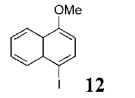
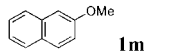
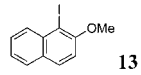
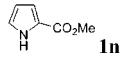
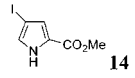
(12) Low conversions (<10%) were observed for electron poor arenes, such as chlorobenzene and methyl benzoate under standard conditions.

I_2/Cu(OAc)$_2$,[15] our procedure gave improved yield and regioselectivity. Iodination of the plant-derived isoflavone antioxidant, daidzein (**16**), was initially carried out under standard conditions with only 10% conversion after 24 h due to insolubility of daidzein in CH_3CN. Switching to DMF as solvent led to reaction completion within 8 h and afforded monoiodinated daidzein **16a** and diiodinated product **16b** in 66% and 20% yield, respectively. Iodination of the bacterial protein synthesis inhibitor, anisomycin (**17**),[16] under standard conditions produced a complex mixture demonstrating intolerance of the conditions to unprotected amines. However, following Boc-protection of the secondary amine, iodination could be achieved with good efficiency (83% yield). Iodination of the nonsteroidal anti-inflammatory agent, nabumetone (**18**), gave ortho-iodinated product **18a** in excellent yield (97%) with no detectable regioisomers (^{1}H NMR). The successful iodination of harmaline·HCl salt (**19**) demonstrated the tolerance of this method toward indole and iminium functionalities. Iodination of the anti-inflammatory agent resveratrol (**20**) was also successful, but given the high nucleophilicity of the bis-phenol, In(OTf)$_3$ was not required.

To determine whether In(OTf)$_3$ or TfOH was the actual catalyst in this process, the iodination with nabumetone (**18**) was carried out in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (0.6 equiv), which can serve as a Brønsted but not a Lewis base. Under these conditions, the rate of iodination was retarded dramatically (only 42% conversion after 16 h vs 97% after 8 h) although again the monoiodinated product **18a** was the only isolated product. In contrast, iodination with NIS and TfOH (0.1 equiv) was complete within 10 min, leading to the formation of the same iodinated product, **18a** (75% yield), but also two byproduct, α-iodinated adduct **18b** (3% yield) and bis-iodinated product **18c** (15% yield). These results suggest that while trace adventitious TfOH may increase the rate of the iodination, the site selectivity observed with In(OTf)$_3$ but not TfOH suggests that the former is likely the primary catalyst for activation of NIS in this process.

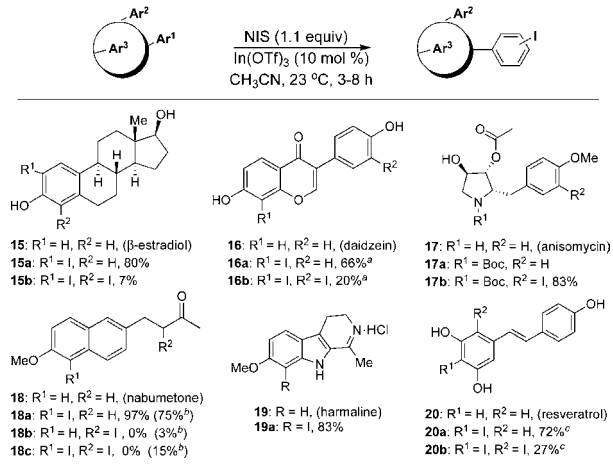
Table 2. In(OTf)$_3$-Catalyzed Monoiodination of Simple Arenes



entry	substrates	products	% yield[a]
1	R = OMe, **1b**	4-MeO-PhI, **2**	95
2	R = NH_2, **1c**	4-NH_2-PhI, **3**	94
3	R = OH, **1d**	4-HO-PhI, **4**	95
4	R = Me, **1e**	4-Me-PhI (**5a**) 2-Me-PhI (**5b**)	85[b] (**5a**:**5b**, 1:0.8)
5	 **1f**	 **6**	87[b]
6	 **1g**	 **7**	93
7	 **1h**	 **8**	92
8	 **1i**	 **9a** (*p*) and **9b** (*o*)	84 (**9a**:**9b**, 2:1)
9	 **1j**	 **10**	94[c]
10	 **1k**	 **11**	97[c]
11	 **1l**	 **12**	92
12	 **1m**	 **13**	93
13	 **1n**	 **14**	86[d]

[a] Refers to isolated yields. [b] The reaction required 3 days for completion. [c] The reaction required 36 h for completion. [d] This iodination was performed at 0 °C for 5 h and 23 °C for 1 h.

Scheme 2. Indium Triflate-Catalyzed Chemosite-Selective Iodination of Arene-Containing Natural Products



[a] DMF was employed as solvent. Use of H_2O or 50% CH_3CN/H_2O as solvent was successful but gave <30% conversion. [b] Reaction performed in the presence of 0.1 equiv of TfOH. [c] Reaction performed without In(OTf)$_3$.

To demonstrate the versatility of iodinated NPs for the syntheses of biological probes and derivatives for SAR studies, we explored various coupling reactions with iodonabumetone **18a** and iodo-*β*-estradiol **15a**. It is well-documented that iodoarenes are versatile synthetic intermediates for aromatic ring derivatization by a host of transition metal-catalyzed cross-coupling reactions.[6] In particular, Sonogashira coupling[17] was investigated and led to the formation of the protected amino

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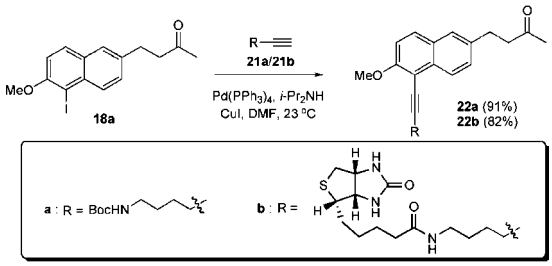
(14) Kometani, T.; Watt, D. S.; Ji, T. *Tetrahedron Lett.* **1985**, *26*, 2043.
(15) (a) Horiuchi, C. A.; Satoh, J. Y. *J. Chem. Soc., Chem. Commun.* **1982**, 671. (b) Horiuchi, C. A.; Haga, A.; Satoh, J. Y. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2459.
(16) For a lead reference to anisomycin derivative synthesis, see: Inverarity, I. A.; Viguier, R. F. H.; Cohen, P.; Hulme, A. N. *Bioconjugate Chem.* **2007**, *18*, 1593.
(17) (a) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874. (b) Crisp, G. T.; Gore, J. *Tetrahedron* **1997**, *53*, 1523.

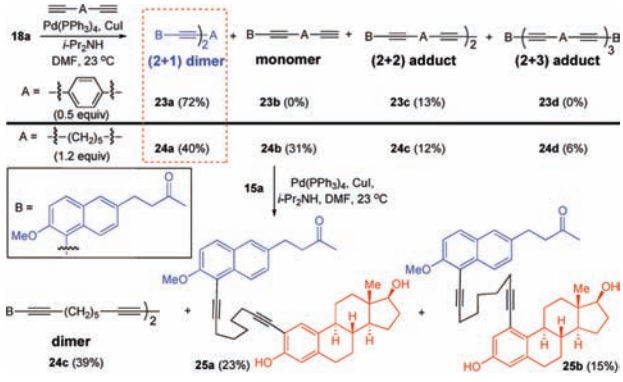
nabumetone derivative **22a** and the nabumetone-biotin conjugate **22b** in good yields (91% and 82%, respectively). (Scheme 3). It is noteworthy that in two steps, a biotin conjugate can be prepared efficiently in high yield from a novel, nonfunctionalized aryl site of a NP.

Scheme 3. Synthesis of Nabumetone Conjugates via Sonogashira Coupling with Iodonabumetone **18a**



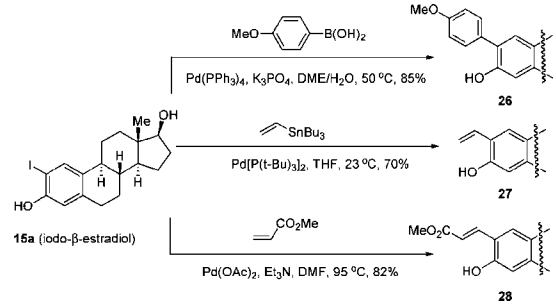
Other useful applications of iodinated NPs are homo- and heterodimerization with bis-alkyne linkers via double or sequential Sonogashira couplings (Scheme 4). Chemical inducers of dimerization (CIDs) have found great utility for inducing protein−protein interactions,[18] and dimeric small molecule protein ligands have been shown in some cases to be superior compared to the corresponding monomeric ligands.[19] Sonogashira couplings were successfully applied to form nabumetone dimers **23a** and **24a** in 72% and 40% yields, respectively, accompanied by monomer **24b** and higher order oligomers **23c**/**24c**,**d**. Monomer **24b** could be converted to regioisomeric heterodimers **25a**/**25b** by subsequent Sonogashira coupling with iodo-β-estradiol (**15a**). The observed scrambling of regioisomers is noteworthy and points to the intermediacy of a potential Pd(II)-stabilized benzyne intermediate.[20]

Scheme 4. Homo- (**23a**/**24a**) and Heterodimerization (**25a**/**25b**) of Iodinated NPs and Derviatives via Sonogashira Couplings



A common challenge with the use of NPs in drug discovery efforts is the inability to easily perform SAR studies once a hit has been identified due to the dearth of methods for direct derivatization of isolated NPs. The described strategy enables focused SAR studies involving modifications centered around arene moieties of NPs. To demonstrate this potential, other metal-catalyzed cross-couplings were explored with iodo β-estradiol **15a** (Scheme 5). Suzuki−Miyaura coupling with *p*-methoxyphenyl boronic acid afforded biaryl derivative **26** in excellent yield. Vinylation of β-estradiol was achieved in 70% yield via Stille coupling with $Pd[P(t\text{-}Bu)_3]_2$[21] to provide vinyl derivative **27**, and Heck coupling with methyl acrylate gave cinnamate derivative **28** in high yield.[22]

Scheme 5. Utility of Iodinated Natural Products for SAR Studies of Arene-Containing NP Derivatives



In summary, an efficient and mild iodination method employing NIS in conjunction with catalytic $In(OTf)_3$ was developed for arene-containing natural product derivatization. Both electron-rich arenes and arenes with weaker activating groups participate in this process and the reaction is tolerant of several functional groups but not unprotected amines. To demonstrate the utility of the resulting iodinated NPs, both homo- and heterodimers of NPs, and a biotin-nabumetone conjugate were prepared via Sonogashira couplings. In addition, several β-estradiol deriviatives were prepared by Suzuki, Stille, and Heck reactions to demonstrate how the described strategy enables SAR studies of natural products and derivatives at the periphery of arene moieties. The described strategy, in conjunction with our previously described NP OH insertion process,[5] will assist in the identification of unknown or poorly defined modes of action and SAR studies of novel natural products.

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Supporting Information Available: General procedures and characterization data (including selected ^1H and ^{13}C NMR spectra) for compound **1**−**28**. This material is available free of charge via the Internet at http://pubs.acs.org.

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