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Triarylaminium Radical Cation Promoted Coupling of Catharanthine with Vindoline: Diastereospecific Synthesis of Anhydrovinblastine and Reaction Scope

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Abstract. A new triarylaminium radical cation promoted coupling of catharanthine with vindoline is disclosed, enlisting tris(4-bromophenyl)aminium hexachlororantimonate (BAHA, 1.1 equiv) in aqueous 0.05 N HCl/trifluoroethanol (1–10:1) at room temperature (25 °C), that provides anhydrovinblastine in superb yield (85%) with complete control of the newly formed quaternary C16' stereochemistry. A definition of the scope of aromatic substrates that participate with catharanthine in the BAHA-mediated diastereoselective coupling reaction and simplified indole substrates other than catharanthine that participate in the reaction are disclosed that identify key structural features required for participation in the reaction, providing a generalized indole functionalization reaction that bears little structural relationship to catharanthine or vindoline.

INTRODUCTION

As a result of their clinical use as antitumor drugs, vinblastine (**1**) and vincristine (**2**) are the most widely recognized members of the bis-indole Vinca alkaloids (Figure 1).[1,2] They were originally isolated in trace quantities from *Cantharanthus roseus*[1] and their biological activity was among the first to be shown to arise from targeting tubulin, resulting in disruption of microtubulin dynamics, inhibition of microtubule formation, and mitotic block that is still regarded today as one of the more successful oncology drug targets.[3] We reported the total synthesis of vinblastine and its unnatural enantiomer in studies that are complementary to earlier pioneering efforts.[4-11] Our approach enlisted a powerful biomimetic Fe(III)-promoted coupling of vindoline (**3**) with catharanthine (**4**) as a key step.[12] When combined with a subsequent in situ Fe(III)-promoted hydrogen atom transfer (HAT) oxidation reaction that we developed for the introduction of the C20' tertiary alcohol,[11,13,14] this provided a remarkable two-step, one-pot procedure for use in the synthesis of vinblastine that we additionally utilized in the total synthesis of a series of related natural products, including vincristine (**2**),[11] and in the preparation of an extensive series of analogs (Figure 1).[4d]

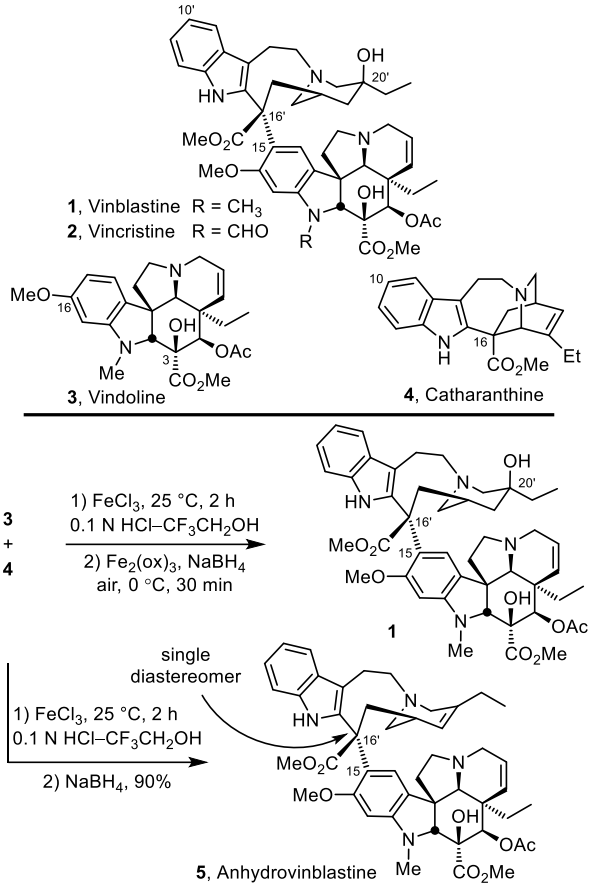


Figure 1. Natural products and Fe(III)-promoted coupling.

Since its discovery by Kutney,[12] insights into this coupling reaction have been disclosed although there are mechanistic features of this reaction that are still not completely defined. The Fe(III)-promoted coupling reaction is conducted in acidic aqueous solvent and exhibits a remarkable stereochemical selectivity for formation of a quaternary center that produces exclusively the natural C16' diastereomer at 25 °C in yields as high as 90% (Figure 1). This stands in contrast to the alternative Polonovski fragmentation[5,6] (Figure 2), which is not nearly as diastereoselective. Although this reaction favors formation of the natural C16' stereochemistry at –40 °C (5:1), it provides mainly the opposite unnatural C16' stereochemistry at 0 or 25 °C (1:3).[15] Moreover, solvent (H_2O) or nucleophile (Cl^-) trap of putative reactive intermediates are not observed under the acidic aqueous conditions of the Fe(III)-promoted reaction and catharanthine is recovered unchanged when subjected to the reaction conditions in the absence of vindoline (2 h, $NaBH_4$ workup).[15,16] This indicates that the azabenzfulvene intermediate central to the Polonovski fragmentation and related couplings may not be a subsequent (further

oxidized) participant in the Fe(III)-promoted coupling reaction. We have suggested that the Fe(III)-mediated coupling reaction itself is radical mediated, involving reversible generation and subsequent reaction of a persistent, charge-separated cation radical (Figure 2).[16] Consistent with this proposal, we were able to demonstrate that simple electron-deficient radicals cleanly and regioselectively add to vindoline at the same C15 site. An intramolecular one-electron two-center bonding interaction between the radical site alpha to the methyl ester and the iminium carbon in the fragmented radical cation **B** or an electrophilic fully delocalized radical cation best formulated as **C** may impose a mechanistic as well as conformational stereochemical control over the reaction in which the upper face of the radical is not only sterically disfavored, but that requires the reaction to proceed with exclusive inversion of the catharanthine C16' stereochemistry, thus accounting for the diastereospecific nature of the coupling reaction. Combined, this proposal suggests that the initial indole radical cation **A** and its fragmented cation radical **B** or the delocalized radical cation **C** may possess a unique blend of stability, persistence, electrophilic character, and conformational properties at room temperature to effectively react selectively with vindoline.

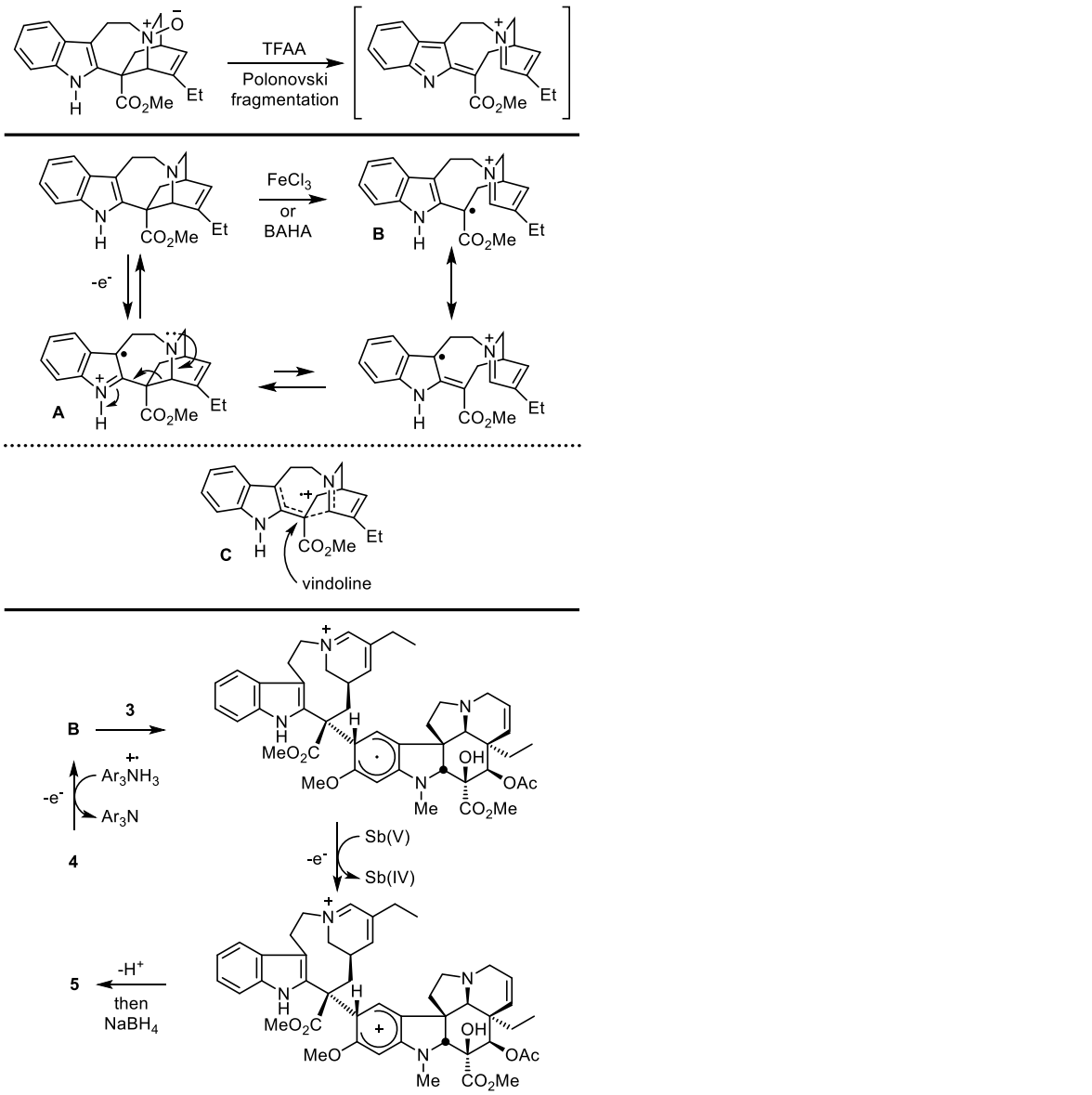


Figure 2. BAHA-promoted single-electron oxidative coupling.

In addition to other Fe(III) salts ($FeCl_3$, 90% > $Fe_2(SO_4)_3$, 71% > $Fe_2(ox)_3$, 0%), we have shown that additional oxidants ($Mn(OAc)_3$, 79% and $Ce(NH_4)_2(NO_3)_6$, 51%) under near identical reaction conditions also promote the coupling of catharanthine and vindoline to provide **5**.[16] In addition, electrochemical,[17] photochemical,[18] and enzymatic[19] coupling reactions have been described, and a photoredox-catalyzed fragmentation of catharanthine has been reported.[20] Herein, we disclose studies on a new complementary triarylaminium radical cation promoted coupling reaction of catharanthine and vindoline and initial studies on the scope of the reaction.

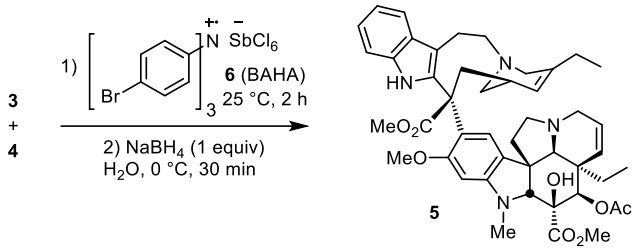
Triarylaminium radical cation salts have found use in a variety of transformations, including protecting group manipulations (PMB ether, dithioacetal, and dithioketal deprotections), glycosidation

reactions of phenylseleno- and ethylthioglycosides, radical rearrangements, as well as a number of radical cation mediated pericyclic reactions including [4+2],[21] [2+2],[22] and [3+2][23] cycloaddition reactions.[24] In addition, triarylaminium radical cation salts have been shown to oxidize a variety of tertiary amines and electron rich aromatics.[25] Based on this precedent, we anticipated that triarylaminium radical cation salts might also promote the coupling of catharanthine and vindoline, leading to the generation of anhydrovinblastine (**5**). If successful, this would constitute the first example of the use of an organic oxidant for promoting the vindoline/catharanthine coupling reaction, provide a useful alternative to inorganic oxidants, further clarify key elements of the reaction mechanism, potentially expand the scope of such reactions, permit the use of more carefully tuned oxidants, and further extend the synthetic utility of organic single-electron oxidants like BAHA.

RESULTS AND DISCUSSION

Initial studies were directed at promoting the oxidative coupling of catharanthine with vindoline using tris(4-bromophenyl)aminium hexachloroantimonate (BAHA, **6**) as a stochiometric radical cation oxidant. The use of organic solvents such as CH_2Cl_2, MeCN, EtOAc, $CHCl_3$, and hexafluoroisopropanol (HFIP) did not lead to productive coupling reactions in the presence of BAHA (Figure 3, entries 1-5). However, the formation of anhydrovinblastine (**5**) was observed in a modest 18% yield in 2,2,2-trifluoroethanol (TFE, entry 6). This notable discovery represented the first use of an organic single-electron oxidant for promoting the coupling of catharanthine and vindoline, providing an alternative to inorganic oxidants. Reactions conducted in water gave low yields of coupling product (7%, entry 7), but the reaction yield improved to 45% in aqueous TFE (entry 8). Appreciable yields of **5** (46%) were obtained when the reaction was conducted in aqueous 0.05 N HCl (entry 9) where it is thought protonation of the tertiary amines protect their competitive oxidation. Significantly, a combined 0.05 N aqueous HCl/TFE solvent system (10:1) afforded anhydrovinblastine in 83% yield, likely due to increased solubility of the starting materials in the acidic, aqueous reaction media (entry 10). Mixed solvent systems with higher ratios of HFIP or TFE to aqueous 0.05 N HCl provided similar reaction

yields (entries 11 and 12). Although not extensively investigated, use of alternative acids (H_2SO_4, TFA vs HCl), while supporting the reaction, did not further improve the coupling reaction (entries 13 and 14).



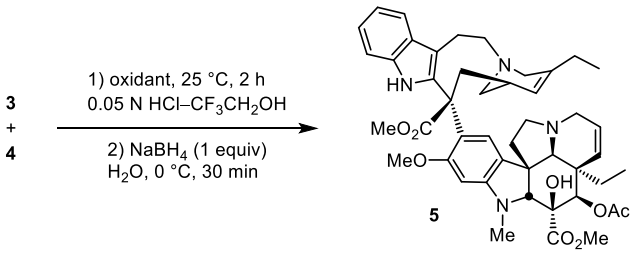
entry[a]	solvent	% yield
1	CH_2Cl_2	0%
2	MeCN	0%
3	EtOAc	0%
4	$CHCl_3$	0%
5	HFIP	0%
6	TFE	18%
7	H_2O	7%
8[b]	H_2O-TFE	45%
9	0.05 N HCl	46%
10[c]	0.05 N HCl–TFE	83%
11[b]	0.05 N HCl–TFE	85%
12[b]	0.05 N HCl–HFIP	84%
13[b]	0.05 N H_2SO_4–TFE	62%
14[b]	0.05 N TFA–TFE	50%

[a]1 equiv of each substrate (**3** and **4**), 1.1 equiv **6**.
[b]2:1 solvent ratio.[c]10:1 solvent ratio.

Figure 3. Examination of reaction solvent.

Based on a proposed mechanism, we had anticipated the reaction to require 2 equiv of oxidant for full conversion to product (Figure 2). Yet, the reaction of catharanthine with vindoline in the presence of 1.1 equiv of BAHA (**6**) provided **5** in 85% yield (Figure 4, entry 1). With this observation, we came to appreciate that the counterion $SbCl_6^-$, for which a variety of oxidation reactions are known,[26] was acting as a second milder oxidant responsible for the presumed oxidation of the subsequent vindoline addition product that leads to the final aromatization. To confirm the effect of counterion and to further examine alternative triarylaminium radical cations, we prepared a series of triarylaminium radical cation salts. Salts **7** and **8** differ from BAHA in that they contain non-oxidizing BF_4^- and PF_6^- counterions.[27] Reactions conducted with 1.1 equiv of **7** or **8** gave low yields of coupling product, reflecting the integral participation of the $SbCl_6^-$ counterion (entries 3 and 5). In contrast to BAHA, yields nearly doubled when 2 equiv of oxidants **7** or **8** were employed (entries 4 and 6). These results are consistent with the presumption that the BF_4^- and PF_6^- counterions are non-participatory counterions, whereas the $SbCl_6^-$

counterion found in BAHA serves as a second mild oxidant to support the coupling reaction. Reaction with 1.1 equiv of the less powerful oxidant **9**, differing from BAHA (**6**) in the substitution of the aryl group (Me vs Br) gave low yields of anhydrovinblastine (34%, entry 7), whereas increasing this oxidants loading to 2 equiv increased the yield to 74% (entry 8). The efficient reactivity of BAHA (**6**) relative to oxidant **9** may be attributed to the difference in oxidation potential of the tris(4-bromophenyl)aminium radical cation in BAHA (**6**, $E°'$ = +1.10 V vs SCE in MeCN) versus the tris(4-methylphenyl)aminium group in oxidant **9** ($E°'$ = +0.78 V vs SCE in MeCN).[28] The combination of effective oxidation potential and counterion established BAHA as the oxidant of choice for the remainder of the study.



entry[a]	oxidant	equiv	% yield
1	**6**	1.1	85%
2	**6**	2	65%
3	**7**	1.1	25%
4	**7**	2	60%
5	**8**	1.1	12%
6	**8**	2	20%
7	**9**	1.1	34%
8	**9**	2	74%

[a]1 equiv of each substrate (**3** and **4**), 2:1 solvent ratio.

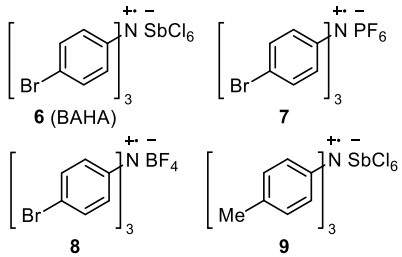
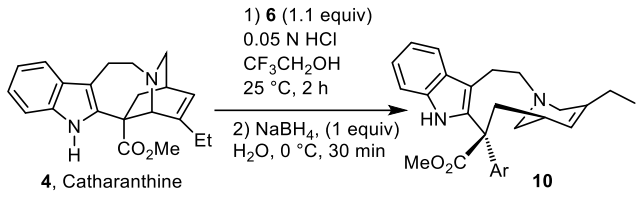
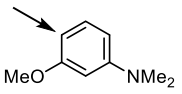
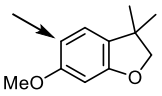
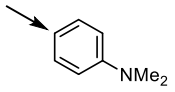
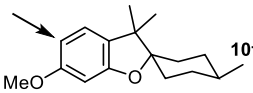
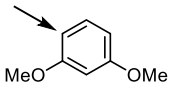
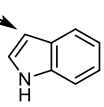
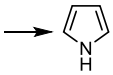
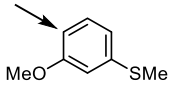
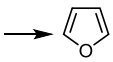


Figure 4. Examination of the triarylaminium radical cation.

We turned our attention to the coupling reaction of catharanthine with substrates other than vindoline. A variety of electron-rich aryl and heteroaromatic coupling partners were found to participate in effective coupling reactions with catharanthine promoted by BAHA (Figure 5). Remarkably, each reaction provided a single diastereomer (diastereospecific), matching the natural C16' stereochemistry of vinblastine. Each reaction is also regioselective favoring the site anticipated for electrophilic radical addition or aromatic substitution of the catharanthine coupling partner. These results indicate that the

stereochemistry of the coupling reaction is controlled by catharanthine alone and that it is independent of the structure of its reaction partner (e.g.; vindoline). Moreover and because BAHA and especially the related reagents **7** and **8** produce the single-electron oxidation product as a free discrete radical cation (i.e., **C**), there is no need to invoke an inner shell electron transfer or metal-bound intermediate in the analogous reactions mediated by inorganic oxidants (e.g.; Fe(III), Mn(III), Ce(IV)) to account for the remarkable stereochemical outcome of the reactions.[16] The scope of the Polonovski fragmentation-based coupling and related reactions that proceed through an azabenzfulvene has not been examined. The limited examples that are reported display an analogous regioselectivity and a similar requirement for electron-rich aromatic substrates, but the reactions exhibit a temperature-dependent stereochemical outcome, producing predominately (e.g., 5:1) but not exclusively the natural C16' stereochemistry at low temperatures (e.g.; –40 °C) and the opposite unnatural C16' stereochemistry at higher temperatures (e.g.; 1:>3 at 0–25 ^{o}C °C).[15] The diastereospecific nature of now both the BAHA as well as the $FeCl_3$ promoted reactions are analogous and involves exclusive inversion of the catharanthine C16' stereochemistry that we now can more confidently suggest occurs through requisite backside attack on the electrophilic delocalized radical cation **C**. These reactions are now even more clearly mechanistically distinguishable from the Polonovski fragmentation and related couplings where temperature-dependent conformational features of the catharanthine-derived azabenfulvene controls the variable reaction diastereoselectivity.[15] Coupling reactions conducted with BAHA with the electron-rich aromatics *N*,*N*-dimethylaniline (**10b**), 1,3-dimethoxybenzene (**10c**), and indole (**10g**) gave a single product in high yield. Sterically hindered electron-rich aryl substrates also gave reaction products **10e** and **10f** in excellent yield and diastereoselectivity. Moderate yields were observed with the coupling of pyrrole (**10h**) and furan (**10i**). Highly electron-rich substrates such as **10a** gave low yields due to competing oxidative oligomerization reactions of the aryl substrate. Whereas strongly electron-rich aromatic substrates were found to participate in the coupling reaction effectively, less electron-rich substrates (e.g.; anisole), neutral aromatic substrates (benzene and thiophene), and electron-deficient aromatic substrates (e.g.; methyl benzoate) failed to couple with catharanthine.



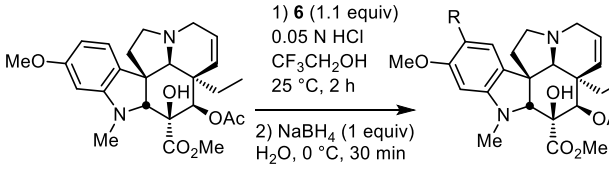
aromatic substrate[a]	% yield	aromatic substrate[a]	% yield
	**10a**, 15%		**10e**, 74%
	**10b**, 92%[b]		**10f**, 68%[b]
	**10c**, 84%		**10g**, 69%[b]
			**10h**, 47%
	**10d**, trace		**10i**, 40%[c]

[a]Unless indicated otherwise, 1 equiv of substrate. [b]$(CF_3)_2CHOH$ used in place of CF_3CH_2OH, 2 equiv of substrate. [c]3 equiv substrate.

Figure 5. Catharanthine coupling with aromatic substrates.

A variety of substrates other than catharanthine were also examined for their coupling with vindoline (Figure 6). Synthetic modification of the catharanthine C16 substituent provided a series of substrates with alternative C16 electron-withdrawing groups (**11a-c**) as well the compound **11d** with simple C16 hydrogen substitution.[29] Catharanthine derivatives with electron-withdrawing C16 substituents participated in effective BAHA-promoted coupling reactions with vindoline to provide **14a-c** (58-76%).[29] In contrast, compound **11d**, bearing no C16 substituent, provided a low yield (8%) of coupling product **14d**, indicating that electron-withdrawing C16 substituents are required to support the coupling reaction, presumably stabilizing the radical cation intermediate (Figure 2). Like catharanthine, each of these modified C16 catharanthine derivatives underwent coupling with vindoline with complete diastereoselectivity. Substantially expanding the scope of the reactions, simplified indole derivatives **12** and **13**, lacking the catharanthine bicyclic structure and tertiary amine, also underwent successful coupling reactions with vindoline. With **12** and **13**, the reaction products were formed as a mixture of diastereomers, highlighting the role catharanthine plays in the substrate controlled diastereoselectivity. Significantly, these results indicate that a single-electron indole oxidation is sufficient for the coupling

reaction to occur and that the oxidation reaction does not require the presence or participation of the catharanthine tertiary amino group.[16,30] In fact, it is thought that the use of the aqueous acidic reaction conditions for the coupling reaction serves to protect the substrate tertiary amines from oxidation by virtue of their protonation. Like catharanthine, the reactions of **12** and **13** are conducted at room temperature in acidic aqueous solution (0.05 N aq HCl/CF_3CH_2OH) without competitive nucleophilic solvent (H_2O) or counter anion (Cl^-) participation, suggesting that the reactions are also unlikely to proceed through an indole-derived azabenzfulvene derived from a second single-electron oxidation. Since the reaction no longer requires the reduction of the catharanthine-derived iminium ion in the reaction product, $NaBH_4$ is no longer required for reductive workup of the reactions.[31]



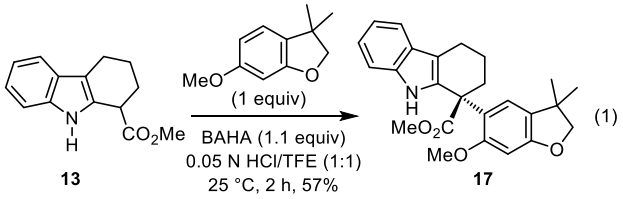
3, Vindoline **14-16**

substrate[a]	reaction product
R' = CO_2Et (**11a**) $CONH_2$ (**11b**) CN (**11c**) H (**11d**)	R' = CO_2Et (**14a**), 61% $CONH_2$ (**14b**), 58%[b,c] CN (**14c**), 76%[c] H (**14d**), 12%[c]
n = 1 (**12**) n = 2 (**13**)	n = 1 (**15**), 50%, 1.5:1 dr[d,f] n = 2 (**16**), 55%, 1.2:1 dr[e,f]

[a]Unless indicated otherwise, 1 equiv of each substrate. [b]3 equiv **3**. [c]$(CF_3)_2CHOH$ used in place of CF_3CH_2OH. [d]2 equiv **6**, 2 equiv **12**. [e]2 equiv **13**. [f]No $NaBH_4$ reduction.

Figure 6. BAHA-promoted coupling of vindoline with catharanthine derivatives and simpler indoles.

Finally, we examined the reaction of a simplified substrate (**13**) other than catharanthine with a coupling partner other than vindoline (eq 1). The simplified indole **13** displayed the identical reactivity observed with catharanthine itself, coupling with an electron-rich aromatic substrate (1 equiv) and providing **17** as the only observed product in good yield (57%) under mild reaction conditions (1.1 equiv BAHA, 2 h, 25 ^{o}C) in the mixed reaction solvent system (1:1 aq 0.05 N HCl/TFE). Interestingly and although not optimized or investigated in detail, this coupling also proceeded effectively (40%) in TFE alone. Presumably this reflects in part the role aqueous acid plays in protonation protection of oxidizable amines, which is not needed for this set of substrates. More broadly, it suggests this generalized coupling reaction using BAHA as an organic oxidant, unlike the analogous $FeCl_3$ mediated reactions, can be utilized in the organic media alone where the latter is solubility limited. Significantly, these combined studies define a generalization of the reaction to substrates that bear no close structural resemblance to either catharanthine or vindoline, providing powerful new methodology for the synthesis of indole-containing products structurally unrelated to vinblastine. Notably, the methodology represents quaternary center generation adjacent to indole by a reaction mediated by BAHA and conducted at room temperature.



(1)

CONCLUSIONS

A powerful new triarylaminium radical cation promoted coupling of catharanthine with vindoline is disclosed that is conducted in aqueous 0.05 N HCl/TFE (2–10:1) at room temperature, enlisting BAHA (1.1 equiv). The reaction provides anhydrovinblastine in excellent yield (85%) with complete regioselectivity and diastereoselectivity for formation of the newly generated quaternary C16' stereochemistry. The diastereospecific nature of now both the BAHA as well as the analogous $FeCl_3$ promoted reactions, which proceed with exclusive inversion of the catharanthine C16' stereochemistry, is such that we can now more confidently conclude that they are mechanistically distinguishable from

and do not involve the same intermediates observed in the Polonovski fragmentation and related couplings. Moreover, whereas temperature-dependent conformational features of the intermediate catharanthine-derived azabenfulvene controls the condition-dependent diastereoselectivity of the latter, the former displays characteristics of a diastereospecific reaction in which we suggest the stereochemical outcome is mechanistically imposed by the requisite backside attack of vindoline on the electrophilic delocalized radical cation **C**. An examination of alternative aromatic substrates other than vindoline and simplified indole substrates other than catharanthine defined the scope of this organoradical cation promoted reaction, identifying key structural features required for participation in the reaction. This provided a generalized indole functionalization reaction and powerful new methodology for the synthesis of indole-containing natural products as well expanded opportunities for the preparation of previously inaccessible vinblastine analogs. Such extensions of the studies are in progress and will be disclosed in due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:10.1021/jacs.xxxxxxx.

Detailed experimental procedures and characterization data for all compounds. All new compounds include ^{1}H NMR, ^{13}C NMR, HRMS, and optical rotation characterization. Details of the X-ray structure determinations for 3'*S*-**15** and 3'*R*-**16.** Copies of ^{1}H NMR spectra provided (PDF).

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Notes

The authors declare no competing financial interest.

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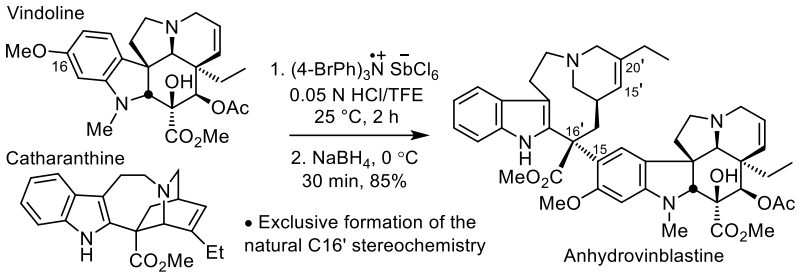
TOC graphic


Vindoline
MeO
16
N
OH
OAc
Me
CO2Me
Catharanthine
N
H
CO2Me
Et
1. (4-BrPh)3N+ SbCl6−
0.05 N HCl/TFE
25 °C, 2 h
2. NaBH4, 0 °C
30 min, 85%
• Exclusive formation of the
natural C16' stereochemistry
N
20'
15'
16'
15
N
H
MeO2C
MeO
OH
OAc
N
Me
CO2Me
Anhydrovinblastine