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Hypervalent Iodine(III)-Promoted Intermolecular C−C Coupling of Vindoline with β-Ketoesters and Related Substrates

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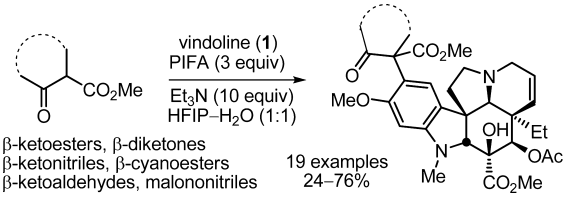
ABSTRACT



The regioselective intermolecular coupling reaction of vindoline with a wide range of substrates including β-ketoesters, β-diketones, β-ketoaldehydes, β-ketonitriles, malononitriles, and β-cyanoesters provides an opportunity for the synthesis of vinblastine analogues containing deep-seated changes in the upper velbanamine subunit. The transition-metal-free hypervalent iodine(III)-promoted intermolecular sp^3/sp^2 coupling, representing a special class of selective C−H activation with direct carbon−carbon bond formation, proceeds with generation of a quaternary center capable of incorporation of the vinblastine C16′ methyl ester and functionalized for subsequent divergent heterocycle introduction.

A central component in the current synthesis of the bisindole alkaloids including vinblastine[1] has been the development of methods that permit the generation of the key C15−C16′ bond that links the upper velbanamine subunit with vindoline by conducting a challenging sp^3/sp^2 coupling reaction with generation of a quaternary center (Figure 1). To date and because of their structural complexity, this has largely focused on approaches that permit the synthesis of the natural products[2−12] with little consideration for the extension of the efforts to key analogues containing deep-seated changes in the upper velbanamine subunit.[13−17] In efforts focused on the potential replacement of the velbanamine indole, we became interested in the development of a coupling reaction with vindoline that would permit the late stage, divergent[18] introduction of a range of alternative heterocycles. Herein, we report the development of a powerful and effective intermolecular coupling reaction of vindoline with substituted acidic methylene compounds typified by β-ketoesters, enlisting

(1) (a) Noble, R. L.; Beer, C. T.; Cutts, J. H. *Ann. N.Y. Acad. Sci.* **1958**, *76*, 882. (b) Svoboda, G. H.; Nuess, N.; Gorman, M. *J. Am. Pharm. Assoc. Sci. Ed.* **1959**, *48*, 659.

(2) (a) Potier, P.; Langlois, N.; Langlois, Y.; Gueritte, F. *J. Chem. Soc., Chem. Commun.* **1975**, 670. (b) Langlois, N.; Gueritte, F.; Langlois, Y.; Potier, P. *J. Am. Chem. Soc.* **1976**, *98*, 7017. (c) Mangeney, P.; Andriamialisoa, R. Z.; Langlois, N.; Langlois, Y.; Potier, P. *J. Am. Chem. Soc.* **1979**, *101*, 2243.

(3) (a) Kutney, J. P.; Ratcliffe, A. H.; Treasurywala, A. M.; Wunderly, S. *Heterocycles* **1975**, *3*, 639. (b) Kutney, J. P.; Hibino, T.; Jahngen, E.; Okutani, T.; Ratcliffe, A. H.; Treasurywala, A. M.; Wunderly, S. *Helv. Chim. Acta* **1976**, *59*, 2858.

(4) Bornmann, W. G.; Kuehne, M. E. *J. Org. Chem.* **1992**, *57*, 1752.

(5) Schill, G.; Priester, C. U.; Windhovel, U. F.; Fritz, H. *Tetrahedron* **1987**, *43*, 3765.

(6) Magnus, P.; Mendoza, J. S.; Stamford, A.; Ladlow, M.; Willis, P. *J. Am. Chem. Soc.* **1992**, *114*, 10232.

(7) Gunic, E.; Tabakovic, I.; Gasic, M. J. *J. Chem. Soc., Chem. Commun.* **1993**, 1496.

(8) Yokoshima, S.; Ueda, T.; Kobayashi, S.; Sato, A.; Kuboyama, T.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 2137.

(9) Vukovic, J.; Goodbody, A. E.; Kutney, J. P.; Misawa, M. *Tetrahedron* **1988**, *44*, 325.

(10) Sagui, F.; Chirivi, C.; Fontana, G.; Nicotra, S.; Passarella, D.; Riva, S.; Danieli, B. *Tetrahedron* **2009**, *65*, 312.

(11) Ishikawa, H.; Colby, D. A.; Boger, D. L. *J. Am. Chem. Soc.* **2008**, *130*, 420.

(12) Ishikawa, H.; Colby, D. A.; Seto, S.; Va, P.; Tam, A.; Kakei, H.; Rayl, T. J.; Hwang, I.; Boger, D. L. *J. Am. Chem. Soc.* **2009**, *131*, 4904.

(13) Gotoh, H.; Sears, J. E.; Eschenmoser, A.; Boger, D. L. *J. Am. Chem. Soc.* **2012**, *134*, 13240.

(14) Harvey, M. J.; Banwell, M. G.; Lupton, D. W. *Tetrahedron Lett.* **2008**, *49*, 4780.

(15) For representative Pd(0)-catalyzed couplings of 15-halovindoline, see: (a) Fekete, M.; Kalonits, P.; Novak, L. *Heterocycles* **2005**, *65*, 165. (b) Johnson, P. D.; Sohn, J.; Rawal, V. H. *J. Org. Chem.* **2006**, *71*, 7899.

(16) Fahy, J.; du Boullay, V. T.; Bigg, D. C. H. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 505.

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hypervalent iodine(III) reagents. Central to the design of the studies, the coupling substrates permit the incorporation of the C16′ methyl ester as well as functionality (a ketone) that should permit the late-stage, divergent heterocycle introduction.

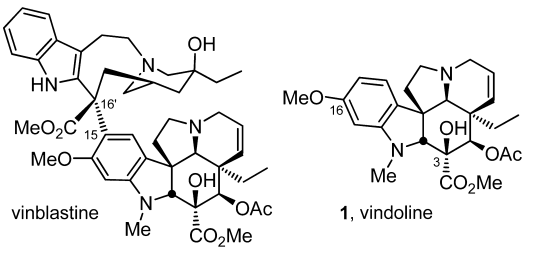
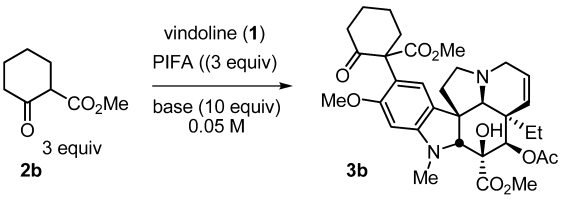


Figure 1. Structure of vinblastine and vindoline.

With 2-carbomethoxycyclopentanone (**2a**) and 2-carbomethoxycyclohexanone (**2b**) as model substrates, a range of oxidants were examined for their ability to promote their coupling with vindoline (**1**) including ceric ammonium nitrate ($Ce(NH_4)_2(NO_3)_6$), $Mn(OAc)_3$, VOF_3, $FeCl_3$, or $Fe(phen)_3(PF_6)_3$ and a full set of alternative Fe(III) complexes,[9,11−13] $CuCl_2$ and $Cu(acac)_2$, and DDQ in a range of solvents with a variety of recommended additives, as well as Koser's reagent (PhI(OTs)OH). Although small amounts of coupling were occasionally observed with the Fe(III)-based reagents,[13] only the iodine(III)-based reagents consistently provided the coupling product in modest conversions (**2a**, 33−29%; **2b**, 0%, in 0.05 M in HFIP,[19] 25 °C, 5−10 min). In a survey of readily available iodine(III)-based reagents including Koser's reagent (PhI(OTs)OH), phenyliodine(III) diacetate (PIDA), and phenyliodine(III) bis(trifluoroacetate) (PIFA) and several aryl substituted variants, PIFA[19] emerged as the most effective reagent for further optimization studies. With the more challenging of the two model substrates (**2b**), the choice of solvent (1:1 HIPA−H_2O, 0.05 M) with the inclusion of H_2O and addition of a tertiary amine additive (Et_3N, 10 equiv) resulted in effective room temperature coupling to provide **3b** in good yields (Figure 2). Clear from the representative optimization efforts summarized in Figure 2 are the key roles played by the combined elements of the mixed aqueous solvent system (1:1 HFIP−H_2O vs HFIP, HFIP with H_2O (5 equiv), or 1:1 HFIP−MeOH; entry 5 vs entries 2, 8, or 9), the use of hexafluoroisopropanol (HFIP) relative to other potential related cosolvents (TFE, entry 5 vs 7), the importance of the added base (entry 5 vs 4), and the nature of the base (entry 5 vs 6).

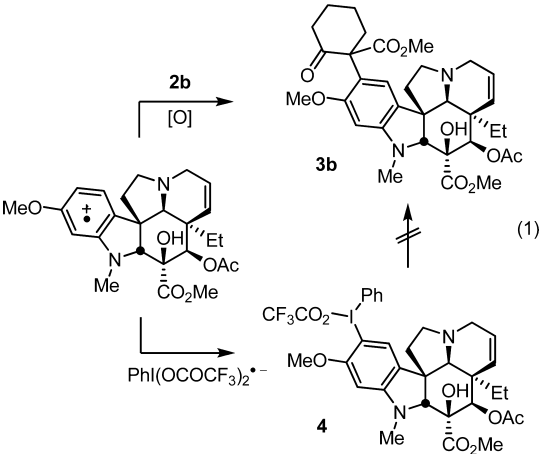


entry	base	solvent[a]	temp	yield
1	K_2CO_3	TFE or HFIP	25 °C	0%
2	Et_3N	HFIP	25 °C	0%
3	Et_3N	CH_2Cl_2	−78 to 25 °C	0%
4	none	HFIP–H_2O (1:1)	25 °C	0%
5	Et_3N	HFIP–H_2O (1:1)	25 °C	67%
6	K_2CO_3	HFIP–H_2O (1:1)	25 °C	34%
7	Et_3N	TFE–H_2O (1:1)	25 °C	8%
8	Et_3N	HFIP, H_2O (5 equiv)	25 °C	0%
9	Et_3N	HFIP–MeOH (1:1)	25 °C	0%
10	DBU	TFE–H_2O (1:1)	25 °C	0%
11[b]	none	TFE or HFIP	25 °C	0%

[a]HFIP = hexafluoroisopropanol, TFE = trifluoroethanol
[b]Conditions reported in reference 19

Figure 2. Representative initial optimization studies.

In instances where the reaction failed to produce the coupling product or provided it in more modest conversions, the PIFA electrophilic substitution of vindoline was observed and provided **4**. Efforts to convert **4** to the product **3b** under a variety of conditions were not successful, resulting in no reaction with **2b** or, on occasion, expectedly transferring instead the less electron-rich phenyl group to the substrate **2b**. Mechanistically and in line with the proposals of Kita,[19] this suggests the reaction may proceed by an initial single electron oxidation of vindoline to generate the corresponding radical cation that either reacts with the deprotonated β-ketoester nucleophile **2b** to provide **3b** after subsequent oxidation of the addition product radical or competitively recombines with the reagent-derived radical anion to nonproductively provide **4** (eq 1).

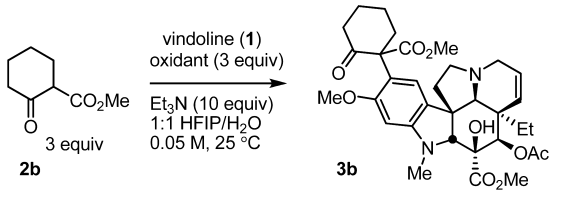


(17) (a) Va, P.; Campbell, E. L.; Robertson, W. M.; Boger, D. L. *J. Am. Chem. Soc.* **2010**, *132*, 8489. (b) Tam, A.; Gotoh, H.; Robertson, W. M.; Boger, D. L. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6408. (c) Gotoh, H.; Duncan, K. K.; Robertson, W. M.; Boger, D. L. *ACS Med. Chem. Lett.* **2011**, *2*, 948. (d) Leggans, E. K.; Barker, T. J.; Duncan, K. K.; Boger, D. L. *Org. Lett.* **2012**, *14*, 1428. (e) Leggans, E. K.; Duncan, K. K.; Barker, T. J.; Schleicher, K. D.; Boger, D. L. *J. Med. Chem.* **2013**, *56*, 628. (f) Schleicher, K. D.; Sasaki, Y.; Tam, A.; Kato, D.; Duncan, K. K.; Boger, D. L. *J. Med. Chem.* **2013**, *56*, 483.

(18) Boger, D. L.; Brotherton, C. E. *J. Org. Chem.* **1984**, *49*, 4050.

(19) (a) Kita, Y.; Tohma, H.; Hatanaka, K.; Takada, T.; Fujita, S.; Mitoh, S.; Sakurai, H.; Oka, S. *J. Am. Chem. Soc.* **1994**, *116*, 3684. (b) Arisawa, M.; Ramesh, N. G.; Nakajima, M.; Tohma, H.; Kita, Y. *J. Org. Chem.* **2001**, *66*, 59.

With these parameters defined, the reexamination of the oxidant (PIFA vs PIDA or Koser's reagent) and the amount of reagent employed revealed the superior behavior of PIFA (3 equiv) under these reaction conditions (Figure 3). Aside from defining a productive stoichiometry range for the use of PIFA (2−3 equiv), the studies further revealed that use of excess PIFA (6 equiv) can result in the subsequent consumption of the desired product **3b**.



entry	oxidant	yield
1	$PhI(OCOCF_3)_2$ (PIFA)	67%
2	PhI(OTs)OH (Koser)	43%
3	$PhI(OAc)_2$ (PIDA)	31%
4	PIFA (1 equiv)	29%
5	PIFA (1.5 equiv)	40%
6	PIFA (3 equiv)	67%
7	PIFA (6 equiv)	0%

Figure 3. Final optimization studies.

With these conditions defined, the scope of the reaction was examined with a range of substituted acidic methylene compounds (Figure 4).

A range of substituted β-ketoesters (**2a**−**2d**, **2j**, and **2m**, but not **2e** and **2f**), β-diketones (**2h**, **2i**, and **2l**), β-ketonitriles (**2g**, **2k**, and **2n**), the malononitrile **2p**, and the β-cyanoester **2o** participated effectively in the coupling reaction to provide the corresponding products **3** as a mixture of diastereomers (ca. 1:1), whereas the less acidic dimethyl methylmalonate **2q** did not. It is likely that in HFIP (pK_a = 9.3), insufficient amounts of the less acidic substrates such as **2q** are deprotonated (vs solvent) under the reaction conditions to permit coupling with the vindoline-derived intermediate radical cation competitive with generation of **4**. Even the initially unexpected behavior of **2a**−**f** appears to be related to the relative acidity of the β-ketoesters, which display a trend correlating precisely with the coupling capabilities (**2a** > **2b** > **2d** > **2c** > **2e** > **2f**),[20] with the pK_a cutoff for observation of the coupling reaction lying between **2c** (not **2d**) and **2e** (Supporting Information Figure S1). By simply converting the β-ketoester **2f** to the more acidic β-ketonitrile **2g**, the substrate now participates effectively in the coupling reaction. Finally, the coupling reaction failed to provide identifiable coupling products if the substrates were unsubstituted (secondary vs tertiary centers), potentially producing a nonquaternary center.

An additional and special case of coupling substrates proved to be β-ketoaldehydes (Figure 5). Here, the reaction

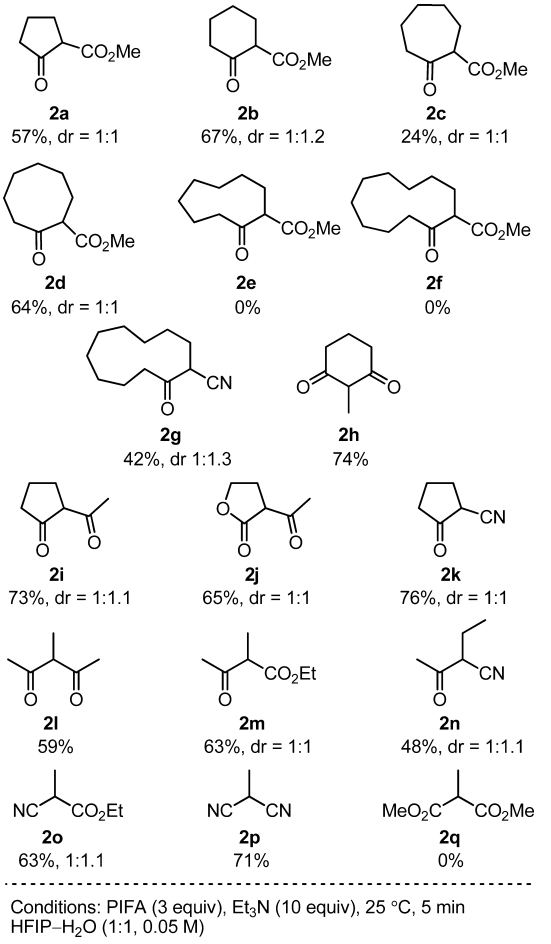
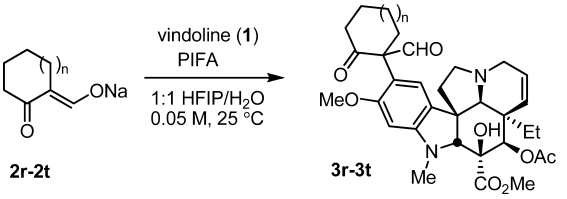


Figure 4. Scope of the PIFA-promoted coupling reaction.



n	oxidant	yield
1, **2r**	PIFA (1 equiv)	21%, **3r**
1, **2r**	PIFA (2 equiv)	50%, **3r**
1, **2r**	PIFA (3 equiv)	44%, **3r**
1, **2r**	PIFA (4 equiv)	28%, **3r**
4, **2s**	PIFA (3 equiv)	58%, **3s**
6, **2t**	PIFA (3 equiv)	63%, **3t**

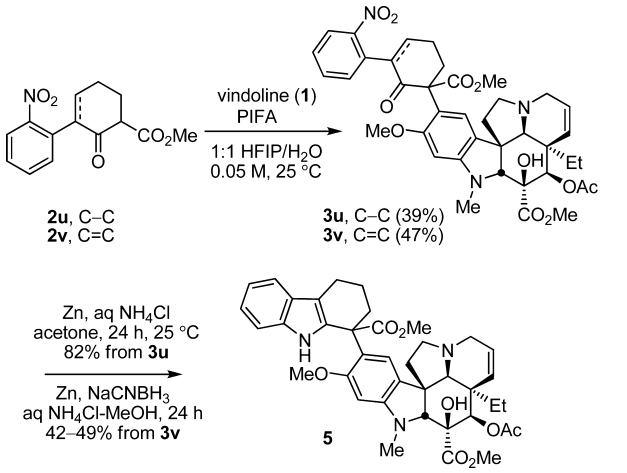
Figure 5. β-Ketoaldehyde coupling reaction.

could be conducted best without the addition of Et_3N, but using the sodium enolates directly with PIFA (2−3 equiv) in HFIP−H_2O (25 °C, 0.05 M, 30 min).

In addition to providing access to velbanamine-derived analogues of vinblastine incorporating alternatives to the

(20) Rhoads, S. J.; Decora, A. W. *Tetrahedron* **1963**, *19*, 1645.

Scheme 1



key indole, the approach also offers the opportunity to access those containing the indole as well. Representative of such opportunities and without optimization, the PIFA-promoted coupling of **2u** or **2v** with (−)-vindoline provided the coupling products **3u** (39%) and **3v** (47%) that, upon reduction to the saturated aniline (Zn, aq NH_4Cl−acetone, 25 °C, 24 h), undergo condensation with the proximal ketone to provide the indole **5**[13] as a 1:1 mixture of diastereomers (Scheme 1).

The intermolecular coupling of a wide range of substrates with vindoline provides an opportunity for the synthesis of vinblastine analogues with deep-seated changes in the upper velbanamine subunit, including those possessing heterocyclic substitutions for the indole. Notably, the transition-metal-free hypervalent iodine(III)-promoted intermolecular sp^3/sp^2 coupling, representing a special class of selective C−H activation with carbon−carbon bond formation, proceeds with generation of a quaternary center capable of direct incorporation of the vinblastine C16′ methyl ester and functionalized for subsequent divergent heterocycle introduction.

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Supporting Information Available. Full experimental details, compound characterizations, and spectra are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.