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Intramolecular [3 + 2]-Cycloaddition Reaction of Push–Pull Dipoles Across Heteroaromatic π-Systems

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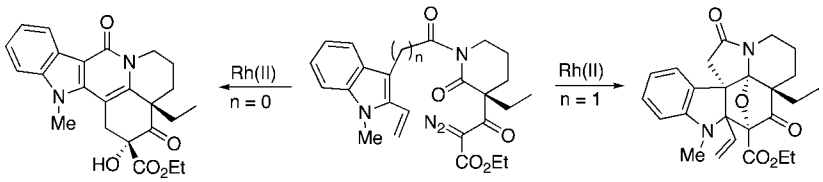
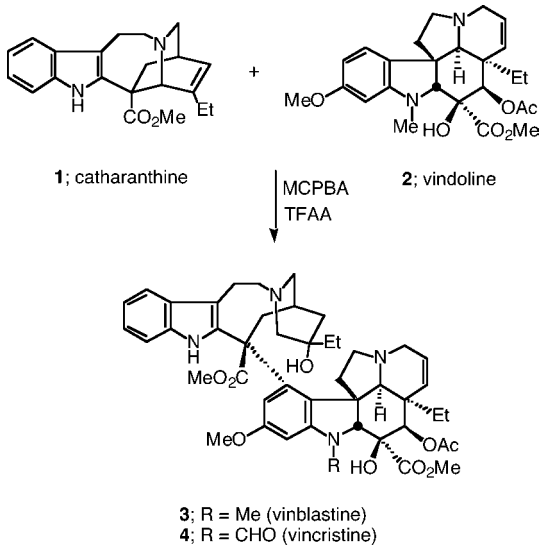
ABSTRACT



Push–pull dipoles generated from the Rh(II)-catalyzed reaction of diazo imides containing tethered heteroaromatic rings undergo successful [3 + 2]-cycloaddition across the 2,3-π-bond to provide novel pentacyclic compounds in good to excellent yields in a stereocontrolled fashion. The facility of the cycloaddition is critically dependent on conformational factors in the transition state.

The dimeric *Catharanthus* alkaloids vinblastine (**3**) and vincristine (**4**)[1] are clinically useful anticancer agents that are routinely used for the treatment of a number of human cancers.[2−3] These two natural products have been isolated from the leaves of the Madagascan periwinkle plant *Catharanthus roseus*[4] but are present in only very low concentration. Consequently, numerous research groups have been actively engaged in developing methods for the synthesis of the upper (catharanthine (**1**)) and lower (vindoline (**2**))[5−7] halves as well as the critical coupling reaction.[8−10] Although vindoline (**2**) is the major alkaloid in *Catharanthus roseus* and is readily isolated and purified, catharanthine (**1**) is only a minor constituent and is substantially more difficult to obtain and purify.[11] An attractive solution to the supply problem would involve the coupling of synthetic catharanthine (**1**) with readily available vindoline (**2**). This approach would also permit the synthesis of a variety of dimeric analogues.



(±)-Catharanthine (**1**) has been the target of numerous successful and formal total syntheses.[12] The previous routes to **1** generally make use of a preexisting indolyl framework

(1) Noble, R. L.; Beer, C. T.; Cutts, J. H. *Ann. N. Y. Acad. Sci.* **1958**, *76*, 882.
(2) Neus, N.; Neus, M. N. The Therapeutic Use of Bisindole Alkaloids from Catharanthus. In *The Alkaloids*; Brossi, A., Suffness, M., Eds.; Academic Press: New York, 1990; Vol. 37, p 232.
(3) Cordell, G. A.; Saxton, J. E. Bisindole Alkaloids. In *The Alkaloids*; Rodrigo, R. G. A., Ed.; Academic Press, Inc.: San Diego, 1981; Vol. 20.
(4) Blasko, G.; Cordell, G. A. Isolation, Structure Elucidation and Biosynthesis of the Bisindole Catharanthus. In *The Alkaloids*; Brossi, A., Suffness, M., Eds.; Academic Press: New York, 1990; Vol. 37, p 12.
(5) For a review on synthetic studies of vinblastine, see: Antitumor Bisindole Alkaloids from *Catharanthus roseus* (L.). In *The Alkaloids*; Brossi, A., Suffness, M., Eds.; Academic Press: New York, 1990; Vol. 37, Chapter 2, pp 77−131.
(6) Kuehne, M. E.; Matson, P. A.; Bornmann, W. G. *J. Org. Chem.* **1991**, *56*, 513.

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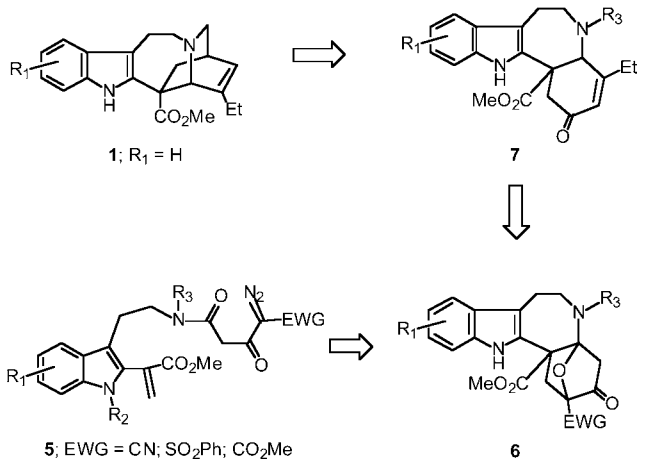
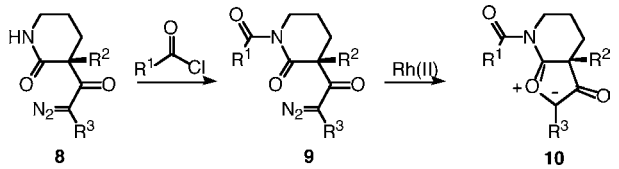
Scheme 1



and do not allow for the ready construction of analogues substituted on the aromatic ring.[12] In earlier work from our laboratory we had described a synthetic route to 4-oxo-6,7-dihydrovindorosine that involved an intramolecular [3 + 2]-cycloaddition of a carbonyl ylide dipole across a tethered indole ring.[13] The sequence of reactions used is part of our general approach to the total synthesis of various azaspirocyclic natural products based on the *tandem cyclization−cycloaddition* reaction of rhodium carbenoids as the key strategic element.[14] Prompted by our earlier studies, we became interested in using a related Rh(II)-catalyzed cascade sequence for the eventual synthesis of catharanthine and its modified analogues. Our synthetic plan is shown in antithetic format in Scheme 1 and is centered on the construction of the key oxabicyclic intermediate **6**, which, by analogy with our previous work should be available by the tandem rhodium(II)-catalyzed cyclization−cycloaddition of diazo amide **5**.[15]

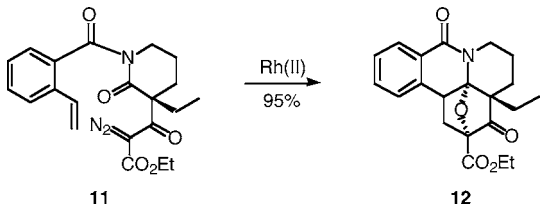
The potential of this methodology for the synthesis of catharanthine and related iboga alkaloids prompted us to first carry out some model studies to probe the likelihood of the key [3 + 2]-cycloaddition across a tethered vinyl group. The starting diazo imido substrates (i.e., **9**) were easily prepared by treating the stable N−H diazo amides **8** with an appropriate acid chloride in the presence of 4 Å molecular sieves (Scheme 2). Formation of the push−pull 1,3-dipole

Scheme 2

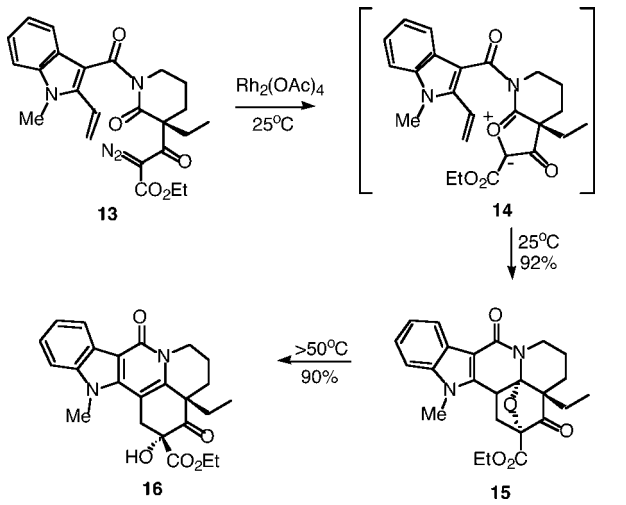


10 was achieved by reaction of **9** with $Rh_2(OAc)_4$, which afforded a rhodium carbenoid species that underwent ready cyclization onto the neighboring imido carbonyl to form the carbonyl ylide dipole. Subsequent intramolecular cycloaddition across the tethered vinyl group in the model system **11** furnished cycloadduct **12** in 95% isolated yield, thereby demonstrating the facility of the cascade sequence (Scheme 3). We were pleased to find that the analogous vinyl-indolyl-substituted diazo imide **13** underwent a related Rh(II)-catalyzed cyclization to give the azapolycyclic cycloadduct **15** in 92% yield. The cascade sequence was extremely facile and took place at room temperature. When the Rh(II)-catalyzed reaction was carried out at 50 °C or higher, the only product isolated corresponded to the ring-opened pyridone **16**. Control experiments demonstrated that heating a pure sample of **15** in ether provided **16** in 90% yield (Scheme 4).

Scheme 3



Scheme 4



Armed with these promising results, we set out to explore the cycloaddition chemistry of the homologous indolyl diazo imide **17**, which is a more suitable model for an eventual

(7) Magnus, P.; Mendoza, J. S.; Stamford, A.; Ladlow, M.; Willis, P. *J. Am. Chem. Soc.* **1992**, *114*, 10232.
(8) (a) Potier, P.; Langlois, N.; Langlois, Y.; Gueritte, F. *J. Chem. Soc., Chem. Commun.* **1975**, 670. (b) Mangeney, P.; Andriamialisoa, R. Z.; Langlois, N.; Langlois, Y.; Potier, P. *J. Am. Chem. Soc.* **1979**, *101*, 2243.
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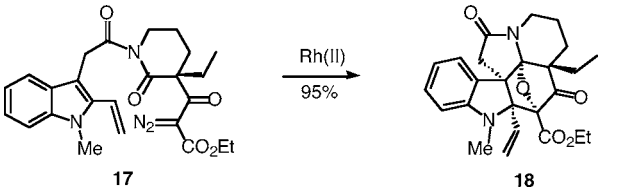
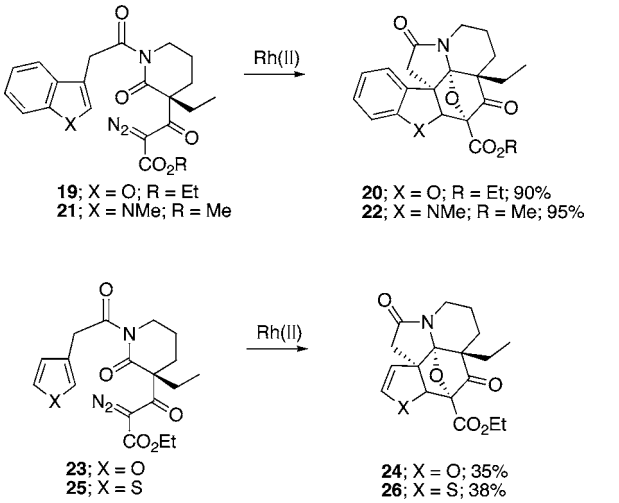
Scheme 5



Scheme 6



synthesis of catharanthine. *Most surprisingly*, subjection of **17** to Rh(II) catalysis led exclusively to cycloadduct **18** (95%) where cycloaddition of the 1,3-dipole occurred preferentially across the indole π-bond rather than with the tethered vinyl group (Scheme 5). Although there are examples in the literature where the 2,3-double bond of indole participates in [4 + 2]-cycloaddition chemistry,[16−18] the indole ring generally shows only a low tendency to act as a dienophile with electron-rich dienes.[19,20] In bimolecular Diels−Alder reactions that occur with normal electron demand, indole acts as a 2π-substrate only if electron-withdrawing groups are present in the 1- and 3-positions.[15,16] Intramolecular cycloaddition reactions, however, benefit from higher reactivity and greater control of stereoselectivity relative to their intermolecular counterparts. More than likely, the initially formed dipole derived from **17** resides in a conformation where the 4π-array of the carbonyl ylide dipole is able to better overlap in the traditional two-plane orientation approach with the indolyl π-bond than with the vinyl group, thereby controlling the periselectivity of the cycloaddition.

In the context of extending the above cycloaddition reaction to other ring systems, we wondered whether the push−pull dipole found in **10** might also undergo intramolecular dipolar cycloaddition with different heteroaromatic π-bonds. Five-membered-ring heteroaromatics such as furan, thiophene, and benzofurans have, despite their aromaticity, frontier orbital energies and shapes similar to those of cyclopentadiene.[21] The reactivity of these heteroaromatic dipolarophiles is, however, sharply decreased because of the loss of aromaticity in the cycloaddition transition states. A vast amount of information is available concerning the reactivity of heteroaromatics in cycloadditions where the heteroaromatics function as 4$_\pi$s components,[22] but a study of their dipolarophilic reactivity has not been extensively examined to date.[20,23] Consequently, we initiated a study to determine whether push−pull dipoles of type **10** would undergo cycloaddition with several other heteroaromatic π-systems.

Our initial efforts focused on the Rh(II)-catalyzed reaction of the benzofuranyl-substituted diazo imide **19**. Gratifyingly, treatment of **19** with rhodium(II) pivalate at 100 °C in benzene using a microwave reactor afforded the polyheterocyclic adduct **20** in 90% yield and with complete diastereospecificity. The regio- and relative stereochemistry of **20** was assigned by ^{1}H NMR and confirmed by single-crystal X-ray analysis. A similar product (i.e., **22**) was obtained in 95% yield using the related indolyl-substituted diazo imide **21** (Scheme 6).[24]

Bolstered by these positive results, we next examined the Rh(II)-catalyzed behavior of the cyclic diazo imide containing a tethered furan ring. Treatment of **23** with rhodium(II) pivalate at 90 °C in benzene furnished cycloadduct **24** but only in 35% yield. The lower yield encountered with this system is probably related to its greater aromaticity relative to the benzo-fused systems. Thiophene has a lower lying HOMO level than does furan, which increases the energy gap between the interacting FMOs.[19] This is probably why so little is known about dipolar cycloadditions across thiophene rings. We found, however, that no significant

(11) Svoboda, G. H.; Neuss, N.; Gorman, M. *J. Am. Pharm. Assoc., Sci. Ed.* **1959**, *48*, 659.

(12) For some leading references, see those cited in: Reding, M. T.; Fukuyama, T. *Org. Lett.* **1999**, *1*, 973.

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(14) (a) Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223. (b) Padwa, A.; Hornbuckle, S. F. *Chem. Rev.* **1991**, *91*, 263.

(15) Antithetical conversion of **6** into **7** would require a number of additional steps including an oxabicyclic ring-opening reaction followed by a subsequent elimination of the EWG group (i.e., SO_2Ph, CN, etc.) as well as an eventual intramolecular nucleophilic N−C bond formation.

(16) (a) Wenkert, E.; Piettre, S. R. *J. Am. Chem. Soc.* **1988**, *53*, 5850. (b) Wenkert, E.; Moeller, P. D. R.; Piettre, S. R. *J. Am. Chem. Soc.* **1988**, *110*, 7188.

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(18) For a similar approach to the Vinca alkaloids using a tandem intramolecular Diels−Alder/dipolar cycloaddition sequence of a 1,3,4-oxadiazole across the indole double bond, see: Wilkie, G. D.; Elliott, G. I.; Blagg, B. S.; Wolkenberg, S. E.; Soenen, D. R.; Miller, M. M.; Pollack, S.; Boger, D. L. *J. Am. Chem. Soc.* **2002**, *124*, 11292.

(19) (a) Biolatto, B.; Kneeteman, M.; Paredes, E.; Mancini, P. M. E. *J. Org. Chem.* **2001**, *66*, 3906. (b) Magnus, P.; Gallagher, T.; Brown, P.; Pappalardo, P. *Acc. Chem. Res.* **1984**, *17*, 35.

(20) Indole is quite a good dienophile in inverse electron demand Diels−Alder cycloadditions; see: Lee, L.; Snyder, J. K. *Advances in Cycloaddition Chemistry*; Harmata, M., Ed.; JAI Press: 1999; Vol. 6, p 119.

(21) Del Bene, J.; Jaffe, H. H. *J. Chem. Phys.* **1968**, *48*, 4050.

(22) (a) Sauer, J. *Angew Chem., Int. Ed. Engl.* **1967**, *6*, 16. (b) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1990. Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795. (c) Woo, S.; Keay, B. A. *Synthesis* **1996**, 669.

(23) For some leading references, see: (a) Padwa, A.; Hertzog, D. L.; Nadler, W. R. *J. Org. Chem.* **1994**, *59*, 7072.

(24) Conversion of **21** to **22** was previously described in ref 13.

difference in yield occurred when the related thiophenyl-substituted diazo imide **25** was treated with the Rh(II) catalyst. The major product formed in 38% yield corresponded to cycloadduct **26**. This result stands in contrast to other literature reports, where it is known that the greater aromatic character of thiophene considerably limits its ability to undergo cycloaddition chemistry.[15] The above example also represents the first instance of an intramolecular [3 + 2]-cycloaddition of a 1,3-dipole across the thiophene 2,3-π-bond.

In conclusion, we have demonstrated that push−pull dipoles generated from the Rh(II)-catalyzed reaction of diazo imides undergo successful 1,3-dipolar cycloaddition across heteroaromatic π-bonds to provide novel pentacyclic compounds in good to excellent yield and in a stereocontrolled fashion. The facility of the cycloaddition is critically dependent on conformational factors in the transition state. We are currently investigating the scope and limitations of the intramolecular cycloaddition of these push−pull dipoles as a potential method for the synthesis of various alkaloidal targets. The results of this investigation will be reported in due course.

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Supporting Information Available: Spectroscopic data and experimental details for the preparation of all new compounds together with an ORTEP drawing for cycloadduct **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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