# A new method for the generation of indole-2,3-quinodimethanes and 2-(*N*-alkoxycarbonylamino)-1,3-dienes. Intramolecular Heck/Diels–Alder cycloaddition cascade starting from acyclic α-phosphono enecarbamates†

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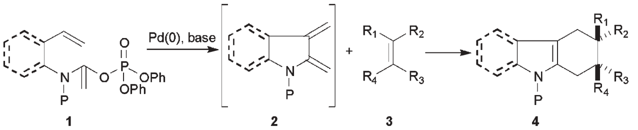
***Received (in Cambridge, UK) 22nd March 2007, Accepted 17th April 2007***
***First published as an Advance Article on the web 1st May 2007***
**DOI: 10.1039/b704374k**

**An intramolecular Heck/Diels–Alder cycloaddition cascade starting from acyclic α-phosphono enecarbamates has been developed to prepare nitrogen heterocycles *via* indole-2,3-quinodimethanes and 2-(*N*-alkoxycarbonylamino)-1,3-dienes.**

As exemplified by Heck, Stille and Suzuki–Miyaura reactions, Pd(0)-catalysed reactions play significant roles in organic synthesis by virtue of their exceptional chemo- and stereoselectivity, mild reaction conditions and tolerance of sensitive functional groups. Organic chemists have put much effort into the development of strategies and tactics employing Pd(0)-catalysed reactions to synthesise structurally complex molecules, including natural products and pharmaceuticals.[1] However, the utilisation of phosphate as a leaving group in Pd(0)-catalysed reactions has been limited to date.[2–4] We have recently discovered that Suzuki–Miyaura coupling using cyclic α-phosphono enol ethers is a powerful process for convergent synthesis of marine polycyclic ether natural products.[5] In the course of our study, we noticed that there is no example of the preparation of acyclic α-phosphono enamides and enecarbamates despite their potential utility in the Pd(0)-catalysed synthesis of nitrogen heterocycles. We describe herein an intramolecular Heck/Diels–Alder (IHDA) cycloaddition cascade starting from acyclic α-phosphono enecarbamates; this cascade efficiently provides a variety of nitrogen heterocycles *via* indole-2,3-quinodimethanes and 2-(*N*-alkoxycarbonylamino)-1,3-dienes.

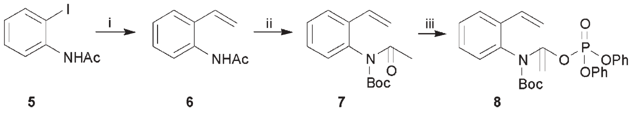
Recently, several reports have appeared[6–8] on the synthesis of heterocyclic skeletons by means of a cascade process implementing an intramolecular Heck reaction.[9] Such cascade processes are ideal organic transformations with respect to atom economy and overall efficiency. We envisioned that indole-2,3-quinodimethane (*i.e.*, **2**) could be generated from acyclic α-phosphono enecarbamate **1** by means of an intramolecular Heck reaction, which in turn could be trapped *in situ* by an appropriate dienophile **3** to provide tetrahydrocarbazole (*i.e.*, **4**) (Scheme 1). This approach is clearly different from the reported methods for indole-2,3-quinodimethanes,[10] which generally rely on either 1,4-elimination of 2,3-disubstituted indole or thermal degradation of thieno[3,4-*b*]indole dioxide.[11] Furthermore, we envisioned that our strategy could be extended to a general synthesis of exocyclic 2-acylamino-1,3-dienes.



**Scheme 1** Concept of the present work.

We first prepared α-phosphono enecarbamate **8** as a model precursor for the generation of indole-2,3-quinodimethane (Scheme 2). Thus, *N*-(2-iodophenyl)acetamide **5** was cross-coupled with tri-*n*-butylvinyltin in the presence of $PdCl_2(PPh_3)_2$ to give **6**.[12] After protection of the amide with $Boc_2O$/DMAP, treatment of the resultant imide **7** with KHMDS and $(PhO)_2P(O)Cl$ afforded **8**, which was used without purification. The results of IHDA using **8** and a variety of dienophiles are summarised in Table 1. Treatment of **8** with 10 mol% of $Pd(PPh_3)_4$ in the presence of $K_2CO_3$ and methyl acrylate in DMF at 80 °C provided an approximately 2 : 1 mixture of tetrahydrocarbazoles **9a,b**[13] in 75% yield from **7**. Utilisation of other dienophiles such as acrylonitrile, methyl vinyl ketone, dimethyl fumarate and *N*-methylmaleimide also gave good yields of the corresponding tetrahydrocarbazoles. The IHDA was effectively carried out in polar solvents such as DMF, 1,4-dioxane and $CH_3CN$, while THF and toluene were less effective. The regioselectivity of the cycloaddition did not depend on the solvent or the reaction temperature. In the absence of a dienophile, the known dimerised product **14**[13] was obtained in 49% yield, which provides experimental evidence for the generation of transparent indole-2,3-quinodimethane (Scheme 3).

A variety of substituted tetrahydrocarbazoles were synthesised based on the IHDA cascade (Table 2). A diverse set of acyclic α-phosphono enecarbamates **15–21** were prepared from the respective 2-iodoaniline derivatives as described for **8**. Exposure



**Scheme 2** *Reagents and conditions*: i, tri-*n*-butylvinyltin, $PdCl_2(PPh_3)_2$, THF, reflux, 94%; ii, $Boc_2O$, DMAP, THF, rt, 100%; iii, KHMDS, $(PhO)_2P(O)Cl$, HMPA, THF, −78 °C.

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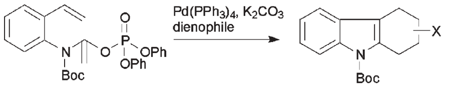
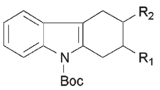
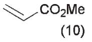
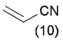
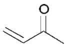
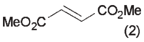
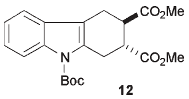
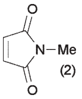
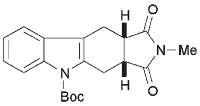
† Electronic supplementary information (ESI) available: Representative experimental procedures and spectroscopic data for new compounds. See DOI: 10.1039/b704374k

**Table 1** Synthesis of tetrahydrocarbazole derivatives

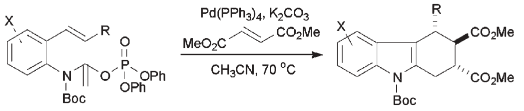


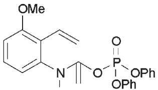
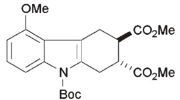
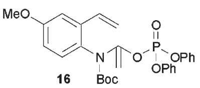
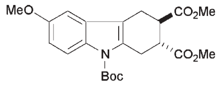
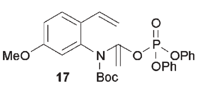
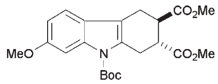
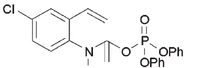
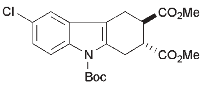
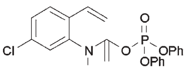
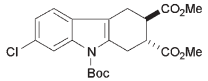
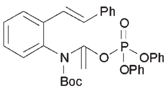
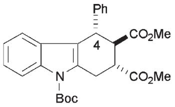
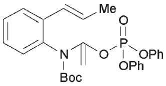
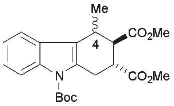
**8** → **9-13**

| Dienophile (eq.) | Conditions | Products | Yield (%) |
|---|---|---|---|
| | |  | |
|  (10) | DMF, 80 °C | **9a**: $R_1$ = $CO_2Me$; $R_2$ = H<br>**9b**: $R_1$ = H; $R_2$ = $CO_2Me$ | 75 (**9a** : **9b** = *ca.* 2 : 1) |
| | Dioxane, 80 °C | | 75 (**9a** : **9b** = *ca.* 2 : 1) |
| | THF, reflux | | 59 (**9a** : **9b** = *ca.* 2 : 1) |
| | Toluene, 100 °C | | 32 (**9a** : **9b** = *ca.* 2 : 1) |
|  (10) | DMF, 80 °C | **10a**: $R_1$ = CN; $R_2$ = H<br>**10b**: $R_1$ = H; $R_2$ = CN | 61 (**10a** : **10b** = *ca.* 2 : 1) |
|  (10) | DMF, 80 °C | **11a**: $R_1$ = $COCH_3$; $R_2$ = H<br>**11b**: $R_1$ = H; $R_2$ = $COCH_3$ | 85 (**11a** : **11b** = *ca.* 2 : 1) |
|  (2) | $CH_3CN$, 70 °C |  **12** | 83 |
|  (2) | $CH_3CN$, 70 °C |  **13** | 64 |

[a] All reactions were performed using 10 mol% of $Pd(PPh_3)_4$, 1.2–2.0 eq. of $K_2CO_3$ and 2–10 eq. of dienophile. Yields are overall from imide **7**.

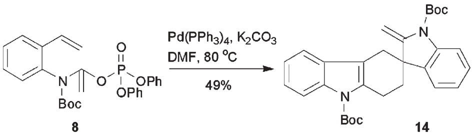
**Table 2** Synthesis of a variety of substituted tetrahydrocarbazoles[a]



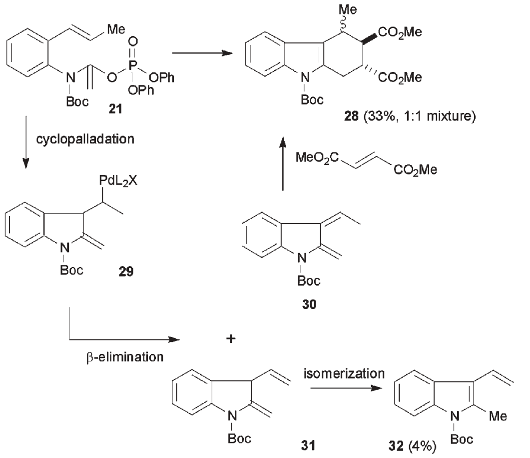
| α-Phosphono enecarbamate | Product | Yield (%) |
|---|---|---|
|  **15** |  **22** | 75 |
|  **16** |  **23** | 76 |
|  **17** |  **24** | 85 |
|  **18** |  **25** | 93 |
|  **19** |  **26** | 91 |
|  **20** |  **27**: ca. 12:1 mixture of diastereomers at C4 | 76 |
|  **21** |  **28**: ca. 1:1 mixture of diastereomers at C4 | 33 |

[a] 10 mol% of $Pd(PPh_3)_4$, 1.2 eq. of $K_2CO_3$ and 2 eq. of dimethyl fumarate in $CH_3CN$ at 70 °C. Yields are overall from the respective Boc imides.

of **15–20** to $Pd(PPh_3)_4$, $K_2CO_3$ and dimethyl fumarate in $CH_3CN$ at 70 °C afforded the desired tetrahydrocarbazoles **22–27** in good to excellent yields. In contrast, under the same conditions, **21** gave **28** as a 1 : 1 mixture of diastereomers in only moderate yield (33% along with 9% of recovered **21**). Careful inspection of the reaction mixture resulted in isolation of a small amount (4%) of **32** as a byproduct, suggesting that an undesired mode of β-elimination of the cyclopalladation intermediate (**29** to **31**) might account for the low yield of **28** (Scheme 4).

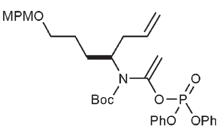
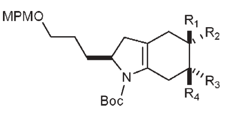
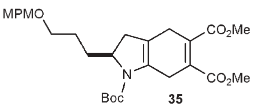
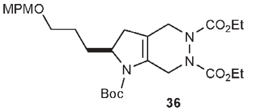
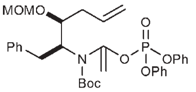
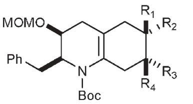
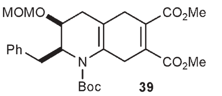


**Scheme 3** Intramolecular Heck reaction of **8** in the absence of dienophile.



**Scheme 4** Two competitive modes of β-elimination of **29**.

**Table 3** Synthesis of non-benzofused nitrogen heterocycles by IHDA

| α-Phosphono enecarbamate | Product | Yield (%) |
|---|---|---|
| <br>**33** | <br>**34a**: $R_1 = R_3 = CO_2Me$, $R_2 = R_4 = H$<br>**34b**: $R_1 = R_3 = H$, $R_2 = R_4 = CO_2Me$ | 73[a]<br>(**34a** : **34b** = 1 : 1) |
|  | <br>**35** | 62[a] |
|  | <br>**36** | 81[a] |
| <br>**37** | <br>**38a**: $R_1 = R_3 = CO_2Me$, $R_2 = R_4 = H$<br>**38b**: $R_1 = R_3 = H$, $R_2 = R_4 = CO_2Me$ | 53[a]<br>(**38a** : **38b** = 1 : 1) |
|  | <br>**39** | 51[b] |

[a] 10 mol% of $Pd(PPh_3)_4$, 1.2 eq. of $K_2CO_3$, DMF, 80 °C, then add 2–5 eq. of dienophile (dimethyl fumarate, DMAD, DEAD), 50–80 °C. [b] 1.2 eq. of $Ag_2CO_3$ was used as a base. Yields are overall from the respective Boc imides.

Finally, we exploited the IHDA of α-phosphono enecarbamates in the synthesis of non-benzofused heterocyclic compounds (Table 3). Treatment of **33** with $Pd(PPh_3)_4$ and $K_2CO_3$ smoothly generated an exocyclic diene (not shown), which was reacted with appropriate dienophiles to give 5/6-bicyclic compounds **34a,b** (1 : 1 mixture of diastereomers), **35** and **36**, respectively. The IHDA cascade could also be applied to the synthesis of 6/6-bicyclic compounds **38a,b** and **39**. The lack of diastereocontrol in the case of **34a,b** and **38a,b** was disappointing but these data are in accordance with the previous reports on 2-(*N*-acylamino)-1,3-dienes.[14] Overall, the IHDA strategy is not limited to the generation of indole-2,3-quinodimethanes; it is generally applicable to the generation of exocyclic 2-(*N*-alkoxycarbonylamino)-1,3-dienes that readily undergo DA cycloaddition with an appropriate dienophile to provide nitrogen heterocycles.

In conclusion, we have developed an IHDA cascade starting from acyclic α-phosphono enecarbamates. The chemistry demonstrated here highlights the synthetic utility of acyclic α-phosphono enecarbamates in the Heck reaction and provides a new strategy for the generation of indole-2,3-quinodimethanes and related 2-(*N*-alkoxycarbonylamino)-1,3-dienes, useful compounds for the rapid synthesis of nitrogen heterocycles. Further exploitation of α-phosphono enecarbamates in the context of palladium chemistry is currently under investigation, as is the application of the IHDA strategy to the synthesis of natural products.[15]

This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan.

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