Diastereoselective intramolecular photochemical [2 + 2] cycloaddition reactions of tethered L-(+)-valinol derived tetrahydrophthalimides

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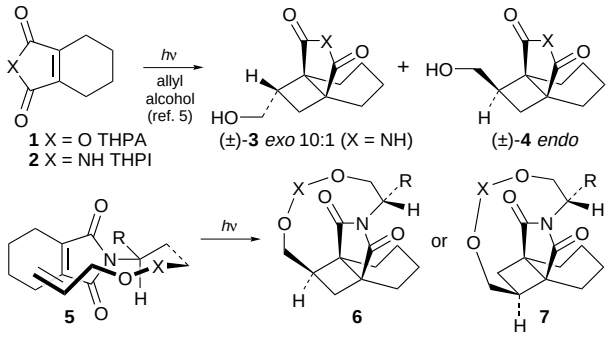
Intramolecular photochemical [2 + 2] cycloaddition of allyl alcohol linked to amino acid derived 3,4,5,6-tetrahydrophthalimides, either *via* a carbonate or silicon tether, gives the corresponding cyclobutanes in excellent yield with diastereoselectivities as high as 8 : 1.

Asymmetric [2 + 2] photocycloaddition using chiral auxiliaries and chiral additives is far less developed than other areas of asymmetric synthesis. Although a number of systems have been studied,[1] there exist very few methods for the preparation of enantiomerically pure cyclobutanes compared to the corresponding thermal [4 + 2] and [3 + 2] cycloaddition reactions. Both Fleming[2] and Crimmins[3] have reported the use of silicon tethers in controlling regio- and stereo-selectivity in [2 + 2] photocycloadditions. Very recently Piva and Pete[4] reported some promising results using chiral hydroxy acids as spacers for controlling asymmetric intramolecular [2 + 2] photocycloadditions. We now disclose our own results in this area involving the diastereoselective intramolecular [2 + 2] cycloaddition reactions of alkenols tethered to L-(+)-valinol derived tetrahydrophthalimides.

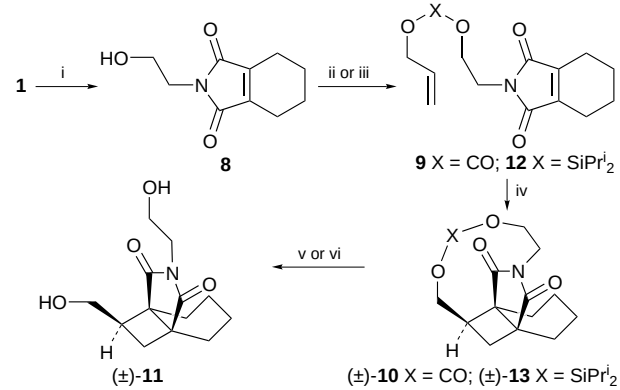
We recently reported[5] that 3,4,5,6-tetrahydrophthalic anhydride (THPA, **1**) and the corresponding imide (THPI, **2**) underwent efficient intermolecular photocycloaddition with alkenols to give the corresponding cyclobutanes in excellent yields with diastereoselectivities as high as 10 : 1. The major isomer in all cases was the *exo* isomer **3** which, due to the absence of any absolute stereochemical control, was formed as a racemic mixture (only one enantiomer drawn for clarity). We then elected to study the cycloaddition reactions of alkenols linked to THPI derivatives in order to achieve two goals: (i) the selective formation of the *endo* isomer **4** and (ii) by the use of chiral linkers, control the absolute stereochemistry of **4**. If the cycloadducts **6** or **7** could be formed selectively from **5** then cleavage of the tether (X) would lead to the synthesis of enantiopure *endo* cycloadducts (Scheme 1).

Initially we investigated the use of ethanolamine as a linker and found that heating THPA with ethanolamine in toluene gave the tetrahydrophthalimide derivative **8** in 96% yield. Reaction of **8** with allyl chloroformate gave the carbonate tethered tetrahydrophthalimide **9** in good yield (84%). Irradiation† of **9** in MeCN for just 90 min resulted in the exclusive formation of the (±)-*endo* cycloadduct **10** in excellent yield (95%, only one enantiomer drawn for clarity). Hydrolysis to the diol **11**, followed by NOE studies, confirmed the highly selective *endo* mode of cycloaddition obtained by use of a carbonate tether. Synthesis of the silicon tethered[2] variant **12** (X = $SiPr^i_2$) was achieved by treatment of **8** with 2 equiv. of $Cl_2SiPr^i_2$ followed by an excess of allyl alcohol (53% overall). Irradiation of **12** again gave the (±)-*endo* cycloadduct **13** as the sole product in 74% yield. Treatment of **13** with Bu_4NF yielded the diol **11** in excellent yield (82%) (Scheme 2).



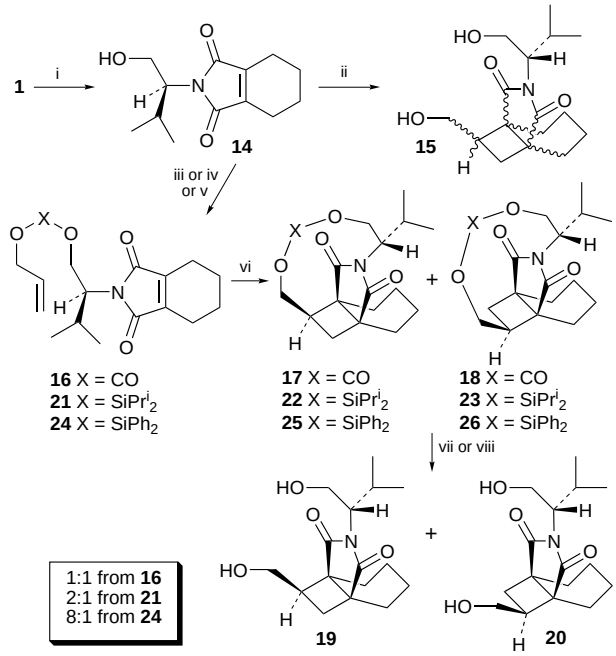
Scheme 1

With the *exo*/*endo* selectivity problem solved we then turned our attention to the use of tethered chiral ethanolamines to control the diastereoselectivity of the *endo* selective cycloadditions and ultimately the enantioselectivity upon removal of the chiral ethanolamine. Treatment of **1** with L-(+)-valinol gave the tetrahydrophthalimide **14** in excellent yield (95%). Irradiation of **14** with allyl alcohol gave rise to a complex mixture (75%) of four cycloadducts which by NMR spectroscopy appeared to be the various possible *exo* and *endo* diastereoisomers of **15**. This was not too surprising as it would be expected that there would be little stereochemical control exerted by the valinol unit during an intermolecular photocycloaddition. Reaction of **14** with allyl chloroformate as before gave the carbonate **16** in moderate yield (61%). Irradiation of **16** gave two cycloadducts (**17** and **18**) which upon hydrolysis (74%) were shown by ^{1}H NMR spectroscopy to be an inseparable 1 : 1 mixture‡ of the diastereomeric diols **19** and **20**. Although this result was disappointing in terms of asymmetric induction, the overall yield in the photocycloaddition step was high (90%) and the irradiation times were short (60 min), thus indicating that the basic photocycloaddition was not hampered by the introduction of a chiral centre in the linker. Synthesis of the $SiPr^i_2$ tethered variant was carried out as before to give **21** in 71% yield. Irradiation (90 min) of **21** gave a mixture of the cycloadducts **22** and **23** (74%) which, upon treatment with Bu_4NF, gave the diols **19** and **20** as an inseparable mixture of diastereoisomers (87%) in a ratio of 2 : 1 although it was not possible to assign which was the major isomer. Encouraged by these results we decided

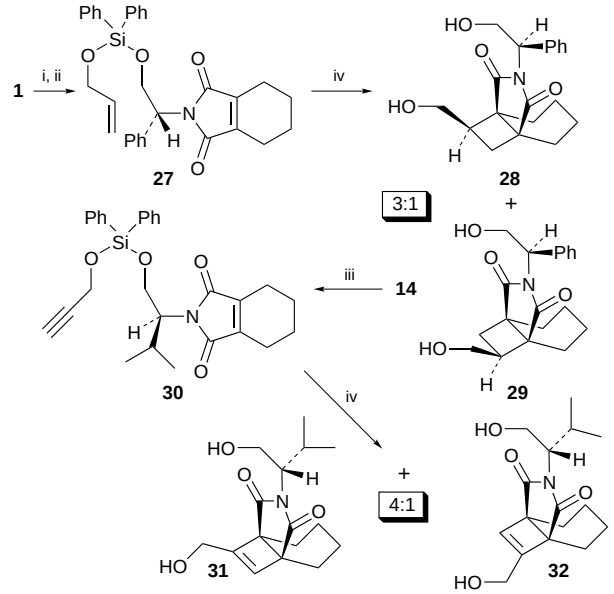


Scheme 2 *Reagents and conditions*: i, ethanolamine, toluene, heat, 96%; ii, allyl chloroformate, pyridine, THF, 0 °C, 84% for **9**; iii, $Cl_2SiPr^i_2$ (2 equiv.), Et_3N, CH_2Cl_2, then allyl alcohol (4 equiv.), 53% for **12**; iv, *h*ν, MeCN, 95% for **10**, 74% for **13**; v, KOH (1.2 equiv.), EtOH–H_2O (1 : 1), 64% from **10**; vi, Bu_4NF, THF, 82% from **13**

to try and increase the diastereoselectivity of the cycloaddition by changing the nature of the groups on silicon. Thus treatment of **14** with Cl_2SiPh_2 in DMF followed by treatment with an excess of allyl alcohol gave the $SiPh_2$ tethered variant **24** in 60% overall yield. Irradiation (60 min) of **24** gave an excellent yield (82%) of the two cycloadducts **25** and **26** which, upon treatment with Bu_4NF, gave the diastereomeric diols **19** and **20** in 97% yield and in a very pleasing ratio of 8 : 1. Again it was not possible to assign which was the major diastereoisomer, although it was the same as that obtained with the diisopropyl tether (Scheme 3).



Scheme 3 *Reagents and conditions*: i, L-(+)-valinol, toluene, heat, 95%; ii, *h*ν, allyl alcohol, MeCN, 6 h, 75%; iii, allyl chloroformate, pyridine, THF, 3 h, 0 °C, 61% for **16**; iv, $Cl_2SiPr^i_2$, Et_3N, CH_2Cl_2, then allyl alcohol (4 equiv.), 71% for **21**; v, Cl_2SiPh_2 (2 equiv.), Et_3N, DMF, then allyl alcohol (4 equiv.), 60% for **24**; vi, *h*ν, MeCN, 60–90 min, 90% for **17**/**18**, 74% for **22**/**23**, 82% for **25**/**26**; vii, KOH (1.2 equiv.), EtOH–H_2O (1 : 1), 74% from **17**/**18**; viii, Bu_4NF, THF, 87% from **22**/**23**, 97% from **25**/**26**



Scheme 4 *Reagents and conditions*: i, (*R*)-(−)-2-phenylglycinol, toluene, heat, 97%; ii, Cl_2SiPh_2 (2 equiv.), Et_3N, MeCN, then allyl alcohol (4 equiv.), 46%; iii, Cl_2SiPh_2 (2 equiv.), Et_3N, MeCN, then prop-2-yn-1-ol (4 equiv.), 58%; iv, *h*ν, MeCN, 5–6 h, then Bu_4NF, THF, 83% overall for **28**/**29** and 38% overall for **31**/**32**

In order to study the effects of other chiral ethanolamines, **1** was treated with (*R*)-(−)-2-phenylglycinol to give the corresponding tetrahydrophthalimide (97%). Treatment of this with Cl_2SiPh_2 in DMF followed by an excess of allyl alcohol gave the $SiPh_2$ tethered phthalimide **27** in 46% overall yield. Irradiation gave a high yield of cycloaddition products (89%) which, upon cleavage with Bu_4NF (93%), afforded the diastereoisomeric diols **28** and **29** in a ratio of 3 : 1. This clearly demonstrates that the valinol unit is superior to phenylglycinol in controlling diastereoselectivity during photocycloaddition. Finally, treatment of the valinol derivative **14** with Cl_2SiPh_2 followed by treatment with an excess of prop-2-ynyl alcohol gave the $SiPh_2$ tethered alkynol variant **30** in moderate overall yield (58%). Irradiation of **30** gave a 46% yield of the corresponding cyclobutenes which, upon desilylation with Bu_4NF (81%), gave the diastereoisomeric diols **31** and **32** in a ratio of 4 : 1. Although the ratio was not as good as in the allyl alcohol case (**24**) this is, to the best of our knowledge, the first example of this type of diastereoselective cyclobutene formation (Scheme 4).

In summary, L-(+)-valinol derived tetrahydrophthalimides containing silicon tethered alkenol and alkynol units have been shown to undergo efficient, diastereoselective intramolecular [2 + 2] photocycloadditions. Present studies are concerned with the assignment of the absolute configuration of the major diastereoisomer from these cycloadditions in order gain some information about the transition state, and hopefully increase the diastereoselectivity by investigating different reaction conditions. We are also investigating the efficient hydrolytic removal of the valinol linker so that ultimately it can be used as a true chiral auxiliary in the enantioselective, photochemical synthesis of highly substituted cyclo-butanes and -butenes.

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Footnotes

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† Glassware consisted of a standard, water cooled, pyrex immersion well photochemical apparatus of 100 ml reaction volume. All reactions were carried out in dry, degassed MeCN (100 ml) with concentrations of between 0.01–0.036 M in substrate. Irradiations were performed using a 125 W medium-pressure mercury vapour lamp obtained from Osram HQL (MBF-U) bulbs. All new compounds were fully characterised by IR, ^{1}H NMR and ^{13}C NMR spectroscopy, and either elemental analysis or HRMS.

‡ The diastereoisomeric ratio was readily ascertained by ^{1}H NMR spectroscopy from comparison of the integrals of the two pairs of diastereotopic Me groups present in the various mixtures of **19** and **20**.

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