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Tandem Inter [4 + 2]/Intra [3 + 2] Cycloadditions. 3. The Stereochemical Influence of the Lewis Acid

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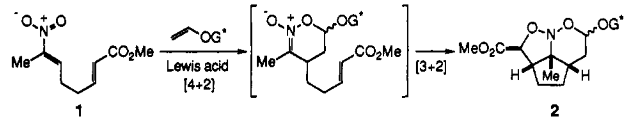
Summary: *trans*-2-Phenylcyclohexanol has been employed as a chiral auxiliary in the inter [4 + 2]/intra [3 + 2] tandem cycloaddition of nitroalkenes with chiral vinyl ethers. A novel reversal of selectivity between cycloadditions catalyzed by the Lewis acids Ti(O-*i*-Pr)$_2$Cl$_2$ and MAPh has been discovered.

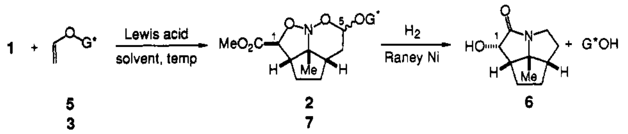
The application of chiral dienophiles, notably enol ethers and acrylates, in the Diels–Alder reaction provides a viable pathway for asymmetric induction leading to the stereoselective construction of cyclic frameworks.[1] This principle has been applied to the [4 + 2] cycloaddition of nitroalkene **1** with a chiral vinyl ether promoted by a Lewis acid, Ti(O-*i*-Pr)$_2$Cl$_2$, followed in tandem by a [3 + 2] cycloaddition of the intermediate nitronate with an intramolecularly tethered electron deficient olefin, Scheme I.[2] Overall, the tandem [4 + 2]/[3 + 2] cycloaddition allows for the construction of five stereogenic centers, three of which are controlled by the outcome of the initial [4 + 2] cycloaddition. Previously, we have described the high π-facial selectivity (98.3% ee) obtained using the vinyl ether derived from (+)-camphor (**3**).[2a] Although this chiral auxiliary has obvious utility and is recoverable after hydrogenolytic cleavage of the nitroso acetal, **2**, the construction of the auxiliary and corresponding vinyl ether **3** is a considerable undertaking. Therefore, a chiral auxiliary was sought that is available in a minimum number of synthetic steps and also provides comparable yields and asymmetric induction to that obtained from **3**.

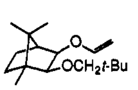
trans-2-Phenylcyclohexanol (**4**) has been applied as a chiral auxiliary in asymmetric Diels–Alder and [2 + 2] cycloadditions,[3] Bradsher cycloadditions,[4] Pauson–Khand bicyclizations,[5] and ene reactions[6] with successful results. It was therefore considered as a primary alternative to the camphor based auxiliary. Accordingly (−)-(1*R*,2*S*)-*trans*-2-phenylcyclohexanol[6a,7] (98.9% ee by chiral HPLC analysis[8] of the corresponding 3,5-dinitrophenyl carbamate derivative) was transformed to the vinyl ether **5** by a mercuric acetate catalyzed transetherification reaction.[9]

Scheme I



Scheme II





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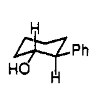

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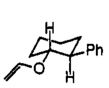

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Cycloadditions of nitroalkene substrate **1** with (−)-**5** promoted by Ti(O-*i*-Pr)$_2$Cl$_2$ at −90 °C resulted in a 73% yield of the nitroso acetal **2** as an 81:1 mixture of α and β anomers, Scheme II and Table I. In order to determine the extent of asymmetric induction, the mixture of nitroso acetals was cleaved to the tricyclic α-hydroxy lactam **6** in 76% yield by hydrogenation at atmospheric pressure over Raney nickel. The chiral auxiliary was recovered in 92% yield. Analysis of the corresponding 3,5-dinitrophenyl carbamate derivative by chiral HPLC[8] showed the lactam to be significantly enantiomerically enriched (97.7% ee). The major enantiomer possessed the 1*S* configuration as previously determined by comparison of the *O*-methylmandelate esters.[2a] On the basis of these results we note that vinyl ether (−)-**5** showed the same sense of asymmetric induction as the camphor auxiliary (+)-**3** with approximately the same magnitude, however, in reduced chemical yield. The stereochemical outcome is consistent with an endo attack of the vinyl ether in an s-trans conformation to the *re* face of the nitroalkene.[2a]

Concern over the reduced yield in the cycloaddition lead to the examination of other mild Lewis acids. The utility of bulky monomeric aluminum reagents as Lewis acids has recently been demonstrated in carbonyl activation,[10a] Claisen rearrangements,[10b] and intramolecular ene reactions,[10c] as well as in Diels–Alder reactions.[11] A survey of such reagents revealed that MAD (methyl aluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide)) and MAPh (methyl aluminum bis(2,6-diphenylphenoxide)) were capable of inducing the cycloaddition in high yields, Table I. The use of MAD as the Lewis acid afforded the nitroso acetal **2** in yields equivalent to those obtained with the camphor auxiliary and Ti(O-*i*-Pr)$_2$Cl$_2$ (88%). Unfortu-

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Table I. Lewis Acid Influence on Cycloadditions with Phenylcyclohexyl Vinyl Ether (5)

Lewis acid	equiv	5 (equiv)	temp (°C)	solvent	time (h)	2^a yield (%)	ratio 2^b	yield, (%)		% ee 6^c
							α_S:β_S:α_R:β_R	6	G*OH	(config)
$Ti(O-i-Pr)_2Cl_2$	3.0	1.5	−90, −78	CH_2Cl_2	0.5, 2.5	73	81.0:0.0:1.0:0.0	76	92	97.7 (1*S*)
MAD	3.0	1.5	−78	toluene	0.5	88	3.5:1.5:0.0:1.0	73	78	72.4 (1*S*)
MAPh	3.0	3.0	−78	CH_2Cl_2	3.0	85	1.0:2.0:0.0:38.7	76	97	79.2 (1*R*)

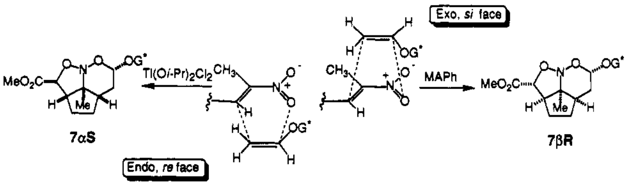
[a] Isolated as a mixture of diastereomers. [b] Determined by ^1H NMR; α/β refers to the configuration at C(5), *R*/*S* refers to the absolute configurational family defined at C(1) as established by cleavage to lactam **6**. [c] Determined by chiral HPLC.

Table II. Lewis Acid Influence on Cycloadditions with Camphor Vinyl Ether (3)

Lewis acid	equiv	3 (equiv)	temp (°C)	solvent	time (h)	7 yield, (%)	ratio 7^c	yield (%)		% ee 6^d
							α_S:β_S:α_R:β_R	6	G*OH	(config)
$Ti(O-i-Pr)_2Cl_2{}^a$	2.4	1.2	−78	CH_2Cl_2	24	82	4.1:1.0:0.0:0.0	86	92	98.3 (1*S*)
MAD	3.0	1.2	−78	toluene	0.5	86^b	1.0:0.0:0.0:1.1	67	81	2.3 (1*S*)
MAPh	6.0	1.2	−78	CH_2Cl_2	3.0	83	0.0:0.0:0.0:1.0	88	86	98.9 (1*R*)

[a] From ref 2a. [b] Isolated as a mixture of diastereomers. [c] Determined by ^1H NMR; α/β refers to the configuration at C(5), *R*/*S* refers to the absolute configurational family defined at C(1) as established by cleavage to lactam **6**. [d] Determined by chiral HPLC.

Scheme III



nately, the (1*S*)-hydroxy lactam was formed with lower selectivity (72.4% ee). An interesting observation, however, was made in that the cycloaddition catalyzed by MAPh resulted in the lactam enriched in the opposite enantiomeric series, 79.2% ee (*R*), to that found with $Ti(O-i-Pr)_2Cl_2$ or MAD.

The Lewis acid dependent reversal of selectivity was also verified in cycloadditions involving the camphor-derived vinyl ether **3** where even a stronger influence was observed, Table II. *In the cycloaddition promoted by MAPh, the same magnitude of asymmetric induction was observed as previously seen with $Ti(O\text{-}i\text{-}Pr)_2Cl_2$ but now in the opposite sense.* The resulting α-hydroxy lactam was enriched in the 1*R* configuration to the extent of 98.9% ee in contrast to 98.3% ee of the 1*S* enantiomer observed with $Ti(O-i-Pr)_2Cl_2$. These results are in contrast to the Lewis acid MAD which afforded essentially a racemic product.

The influence of an achiral Lewis acid on the stereochemical outcome of an asymmetric Diels–Alder reaction has been observed previously.[12] Helmchen et al.[12a] have described a reversal in the diastereoselectivity between aluminum- and titanium-based Lewis acid catalyzed Diels–Alder reactions involving the acrylate of (*S*)-ethyl lactate with cyclopentadiene. Likewise, Waldmann has observed the same effect in cycloadditions of *N*-acryloyl (*S*)-proline benzyl esters.[12b] In these cases the origin of reversal of selectivity is believed to be based on the prefered coordination of the Lewis acid to the acrylate where titanium is bidentate while aluminum is monodentate.[13] This explanation is not believed to be relevant here. Rather, our results can be explained simply by a reversal in the endo/exo selectivity of the [4 + 2] cycloaddition, Scheme III. The preference for the endo orientation of a vinyl ether in inverse electron demand Diels–Alder reactions has been documented in general[14] and in our own studies as well.[2] However, the introduction of an extemely bulky Lewis acid coordinated to the substrate could alter the selectivity. On the basis of the formation of a single β anomer and the comparison of possible transition structures, the high stereoselectivity obtained with MAPh and the camphor-derived vinyl ether **3** is consistent with a *si* face, exo approach of the vinyl ether in an s-trans conformation. The enhanced selectivity from the camphor-derived vinyl ether **3** compared to that from phenylcyclohexanol (**5**) arises from the greater bulk of the cyclic skeleton, isobornyl compared to cyclohexyl. Likewise, because of the steric requirements of the phenyl substituents of MAPh, it can more effectively block the endo approach of the vinyl ether, therefore allowing MAPh to have a higher exo selectivity than MAD. Note that in both cases the same diastereoface of the vinyl ether is involved.

In conclusion, we have demonstrated that *trans*-2-phenylcyclohexanol can act as an effective chiral auxiliary in nitroalkene cycloadditions limited, however, to $Ti(O-i-Pr)_2Cl_2$ as the Lewis acid. With the (+)-camphor-derived vinyl ether **3** it is possible to access both enantiomeric series of cycloadducts in high selectivity by simply changing the Lewis acid since excellent face selectivity is observed in both endo and exo modes. Other chiral auxiliaries are currently being explored to exploit this behavior and are under development for applications in total synthesis.

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Supplementary Material Available: Procedures for the cycloadditions of nitroalkene **1** along with subsequent cleavage and derivatization and full characterization of $2\alpha_S$, $2\beta_S$, $2\beta_R$, **5**, and $7\beta_R$ (12 pages). Ordering information is given on any current masthead page.

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