Pericyclic Cascades

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Pericyclic Cascade with Chirality Transfer: Reaction Pathway and Origin of Enantioselectivity of the Hetero-Claisen Approach to Oxindoles**

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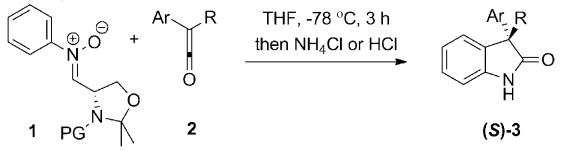
Cascade reactions[1] are of increasing value in organic synthesis due to their potential for expedient generation of molecular complexity. Pericyclic cascades[1,2] are especially appealing by virtue of their often predictable and exquisite stereochemical control. The diverse pericyclic cascades devised for target-oriented syntheses often act on substrates bearing well-recognized structural motifs with amply documented reactivity requirements and stereochemical properties. Nevertheless, the interplay between theory and experiment continues to uncover novel cascade mechanisms with new or underexplored reactivity patterns. Indeed, for the 2+2 cycloadditions of ketenes with 1,3-dienes[3] and imines,[4] the pericyclic mechanisms once formulated have recently been revised to cascades of more than one elementary mechanistic step. Other more elaborate pericyclic cascades of synthetic interest have also been elucidated by computations.[5] We recently developed an efficient enantioselective route to 3,3-disubstituted oxindoles from chiral nitrones and disubstituted ketenes, but the origin of the asymmetric induction remained unclear from existing mechanistic proposals.[6] We now propose a novel pericyclic cascade composed of a 3+2 cycloaddition and a hetero-[3,3]-sigmatropic rearrangement, featuring chirality transfer in each of the two constituent steps, which proves crucial in engendering impressive enantioselectivity.

The reactions of *N*-phenylnitrones with diphenylketene to form oxindoles were first investigated by Staudinger[7] and subsequently by Lippmann[8] and Taylor.[9] Building upon this precedent, and the utility of 3-alkyl-3-aryloxindoles (**3**) as valuable synthetic intermediates that can be derivatized to numerous natural products and medicinal targets,[10] we reported[6] that treatment of nitrone **1a**, derived from Garner's aldehyde,[11] with an alkylarylketene (**2**) afforded, after aqueous workup, oxindoles (*S*)-**3a–c** in 80–88% yield and 81–90% *ee* (Table 1, entries 1–3). Further experimental optimization of this process showed that nitrones derived from Garner's aldehyde are critical to achieve high asymmetric induction, with increasing size of the oxazolidine *N*-substituent (**1b–c**) consistently leading to improved enantioselectivities. For example, nitrone **1c** incorporating the bulky 2,4,6-triisopropylbenzenesulfonyl group led to excellent stereoinduction in its reaction with alkylarylketenes **2a–d** (entries 4–8), giving *ee* values of up to 98%.

Table 1: Enantioselective oxindole synthesis from homochiral nitrones **1** and alkylarylketenes **2**.



Entry	PG[d]	R/Ar	Product	Yield [%][a]	*ee* [%][b]
1[c]	Boc[d] (**1a**)	Me/Ph (**2a**)	**3a**	85	87
2[c]	Boc[d] (**1a**)	Et/Ph (**2b**)	**3b**	80	81
3[c]	Boc[d] (**1a**)	Et/*p*-(MeO)C_6H_4 (**2c**)	**3c**	88	90
4	Ts[d] (**1b**)	Et/Ph (**2b**)	**3b**	75	91
5	TIPBS[d] (**1c**)	Et/Ph (**2b**)	**3b**	84	96
6	TIPBS[d] (**1c**)	Et/*p*-(MeO)C_6H_4 (**2c**)	**3c**	81	98
7	TIPBS[d] (**1c**)	Et/*p*-FC_6H_4 (**2d**)	**3d**	79	98
8	TIPBS[d] (**1c**)	Me/Ph (**2a**)	**3a**	60	98

[a] Yield of isolated **3**. [b] Determined by HPLC on a purified sample of **3**. [c] Ref. [6]. [d] PG = protecting group. Boc = *tert*-butoxycarbonyl. Ts = *para*-toluenesulfonyl. TIPBS = 2,4,6-triisopropylbenzenesulfonyl.

The initially proposed reaction pathways for this process (pathway I, Scheme 1),[6–9] involved the ketene (shown here as **2a**) reacting as an electrophile towards the nitrone (shown here as **4**), giving, after rearomatization, the experimentally isolable imino acids **5** bearing a quaternary carbon. Subsequent hydrolysis and cyclization afford the oxindole products **3**.

We computationally explored possible reaction pathways in this system, using **4** and **2a** as model reactants (Scheme 1). Intriguingly, although the pericyclic step in pathway I is analogous[12] to the proposed mechanisms of the Brunner oxindole[13] and Fischer indole syntheses,[14] all our attempts in

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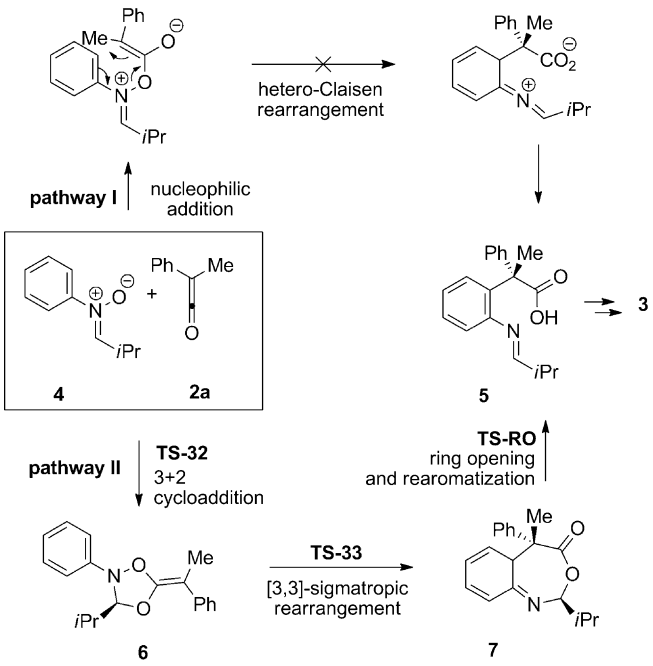


Scheme 1. Nucleophilic addition/hetero-Claisen rearrangement pathway proposed previously (pathway I) and novel pericyclic cascade mechanism (pathway II).

locating the transition structure (TS) for this step failed.[15] Instead, we have identified a new mechanism for the formation of **5**. The key imino acid **5** arises from **4** and **2a** through a pericyclic cascade composed of a 1,3-dipolar cycloaddition and a hetero-[3,3]-sigmatropic rearrangement (Scheme 1, pathway II). A novel mode of chirality transfer through the pericyclic steps explains the origin of the asymmetric induction.

Ketenes are versatile compounds known to undergo nucleophilic attack, but can also react as 2π components in cycloadditions.[16] We studied the TSs for the 3+2 cycloaddition of **4** and **2a** (pathway II) and the subsequent fate of the intermediates (Figure 1). Remarkably, the most favorable mode of the cycloaddition was predicted to be across the C=O bond of **2a** forming the substituted 1,4,2-dioxazolidine **6**, with an activation free energy of only 11.8 kcal mol^{-1} (**TS-32**, Figure 1). The cycloaddition across the C=C bond has a considerably higher activation free energy (22.4 kcal mol^{-1}). The ketene C=O group has been shown to participate in 4+2,[3,17] 2+2,[18] and 3+2 cycloadditions.[19] **TS-32** has a very short partial C–O bond (d_{CO} = 1.57 Å), which causes further polarization of the C=N bond of the nitrone. At the transition state, the carbon of the 1,3-dipole possesses electrophilic character (0.1e), and there is substantial negative charge building up on the ketene oxygen (−0.6 e). The total charge transfer in **TS-32** is 0.2 e. The cycloaddition is concerted; the intrinsic reaction coordinate (IRC) path connected reactants **4** and **2a** to **6**.[20,21]

The cycloadduct **6** features an exocyclic alkylidene group suitably positioned with respect to the nitrogen-bound phenyl ring for an aromatic hetero-[3,3]-rearrangement to proceed.

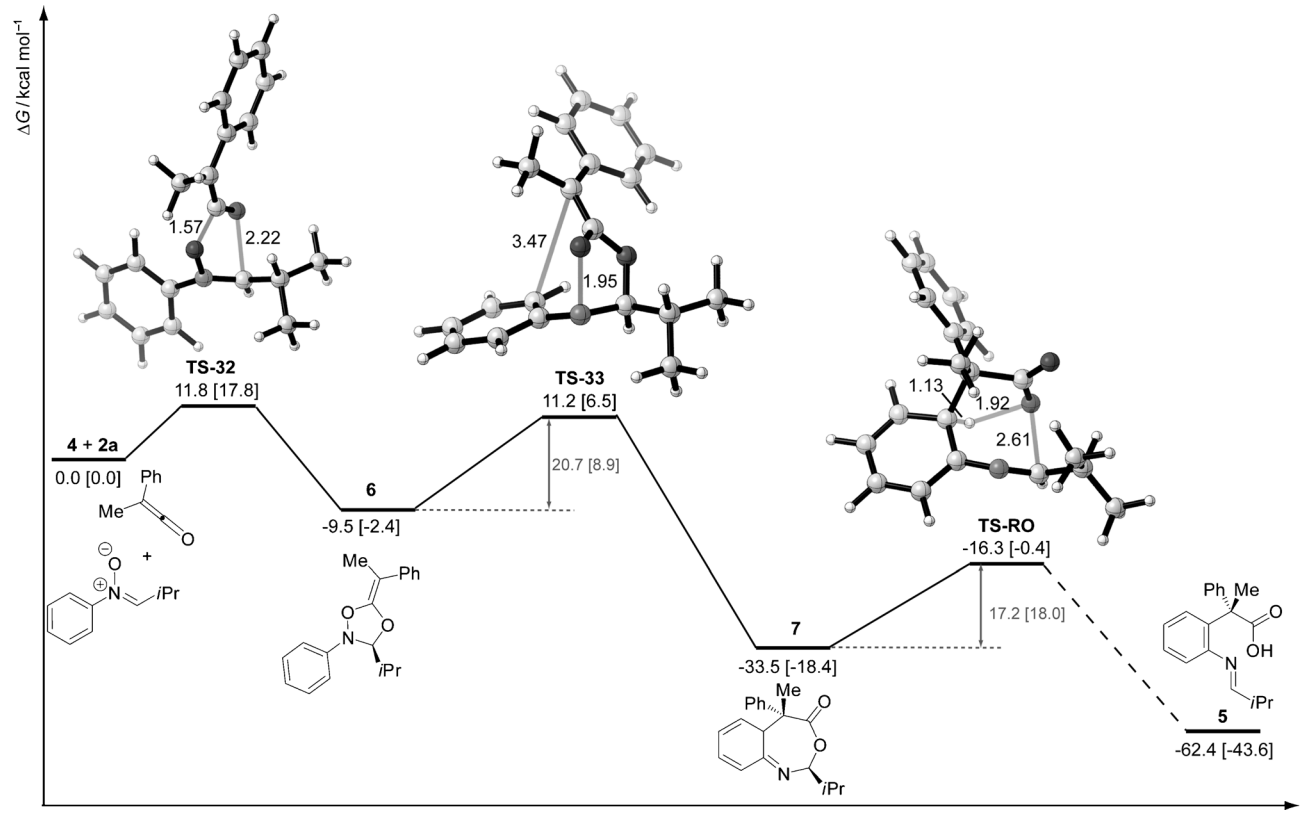


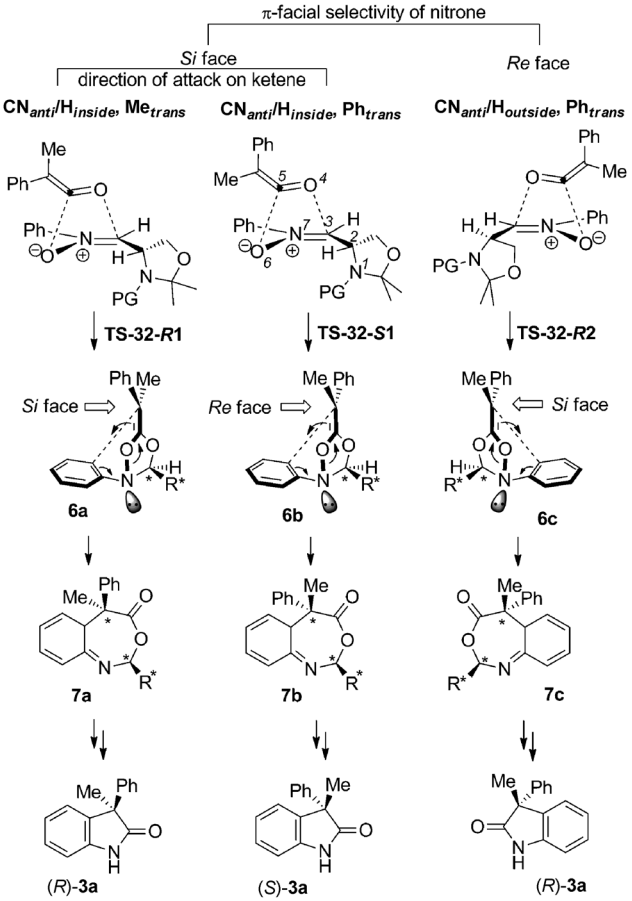
Figure 1. Energy profile for the pericyclic cascade mechanism of **4** and **2a**. **TS-32**, **TS-33,** and **TS-RO** refer to the transition structures for the 3+2 cycloaddition, the hetero-Claisen rearrangement, and the rearomatization with concomitant ring opening, respectively. (M06-2X/6-311+G(d,p)(THF)//B3LYP/6-31G(d), gas-phase B3LYP/6-31G(d) energies are given in brackets).

This process (**TS-33**) is predicted to be facile, with an activation free energy of 11.2 kcal mol^{-1} from **4** and **2a**, giving the intermediate **7** with the quaternary stereocenter installed, with an exergonicity of 33.5 kcal mol^{-1}. The transition state is highly asynchronous; an excessively long forming C–C bond (d_{CC} = 3.47 Å) predicts almost no bonding between the interacting orbitals at the TS. However, both the IRC calculations and the potential energy surface (PES) scan in the gas phase and in solvent reveal no intermediates between **TS-33** and **7**.[21] The PES also shows that the transition state is mainly associated with the breaking of the N–O bond. The formation of the C–C bond is found to be a spontaneous downhill process, presumably driven by the high exergonicity of the transformation. Intermediate **7** then undergoes cleavage of the hemiaminal linkage and aromatization via **TS-RO** to give the aromatic imino acid **5**. The free-energy barrier is calculated to be 17.2 kcal mol^{-1} for this step. However, **TS-RO** involves an intramolecular proton transfer, which is more likely to be a catalyzed process under experimental conditions.[21]

These calculations establish that pathway II, composed of tandem 3+2 cycloaddition/hetero-[3,3]-sigmatropic rearrangement is energetically viable under the experimental conditions, while the hetero-Claisen rearrangement of the ketene–nitrone adduct in pathway I is prohibitively high in energy.

The stereochemical aspects of pathway II were then considered. The reaction of **1a** and **2a** gave oxindole (*S*)-**3a** in 87 % *ee* (Table 1, entry 1).[6] As illustrated in Scheme 2, the cycloaddition installs a stereogenic center at C3 and an unsymmetrically substituted C=C double bond in the diastereomeric intermediates **6a–c**, the stereochemical information of which is transferred to the intermediate **7a–c** through the stereospecific [3,3]-rearrangement. Ring opening and rearomatization will destroy the stereocenter at C3 but the quaternary stereocenter will remain intact. The configuration of the quaternary stereocenter in the imino acid and the oxindole is, therefore, determined at the 3+2 cycloaddition step simultaneously by two factors: the face of the nitrone exposed for cycloaddition, and the direction of attack of the ketene, where the phenyl group can be oriented *trans* or *cis* to the incipient O6–C5 bond. The transition state **TS32-S1** corresponds to the cycloaddition involving the *Si* face of the nitrone and the ketene with a *trans*-oriented phenyl group. This will give rise to cycloadduct **6b** featuring an *E*-configured C=C double bond. Subsequent [3,3]-sigmatropic rearrangement through the *Re* face of the alkene will install the *S* stereocenter. On the other hand, the *R* enantiomer will be obtained by reversing either the orientation of the ketene (**TS32-R1**) or the face of the nitrone attacked (**TS32-R2**) during the cycloaddition.

The optimized TSs are illustrated in Figure 2. **TS-32-S1** leading to (*S*)-**3a** is lowest in energy, while **TS-32-R1** and **TS-32-R2** are less stable by 1.5 and 3.6 kcal mol^{-1}, respectively.[22] The free-energy difference between **TS-32-S1** and **TS-32-R1** corresponds to an *ee* value of 84 %, in good agreement with experiment. The steric contact of the ketene *cis* substituent with the *tert*-butoxycarbonyl (Boc) group is more unfavorable for the bulkier phenyl group (**TS-32-R1**) than for a methyl



Scheme 2. Chirality transfer between the pericyclic steps. R* = Boc-protected chiral auxiliary.

group (**TS-32-S1**). This predicts the further improvement in enantioselectivity with increasing size of the *N*-protecting group, which was indeed observed experimentally (Table 1). The *trans* preference of the aryl group of ketenes observed here is in accord to our previous findings about reactions with chiral alcohol nucleophiles.[23]

The other stereodetermining factor, the π-facial selectivity induced by the chiral auxiliary on the nitrone,[24] can be understood by examining the conformation of the nitrone about the C2–C3 bond in **TS-32-S1** and **TS-32-R2** (Figure 2). When the nitrone reacts through its *Si* face (**TS-32-S1**), the ketene approaches the nitrone, *anti* to the oxazolidine C–N bond (τ(1234) = −177.1°), and, thus, away from the steric bulk of the Boc group. The hydrogen atom and the ring methylene group adopt the *inside* and the *outside* positions, respectively. Garner's aldehyde,[11] from which **1a** is derived, often obeys Felkin–Anh stereochemical control in nucleophilic additions.[25] A feature shared by this model and the cycloaddition TSs here is the preference for the C–N bond on the stereocenter to be *anti* to the forming bond. In our cycloaddition TSs, however, the *inside* position, instead of the *outside* position, is sterically the more demanding site because of 1,3-allylic strain[26] of any substituent with the nitrone oxygen. The *outside* position is also sterically favored in the cycloaddition TSs than in the Felkin–Anh model because of

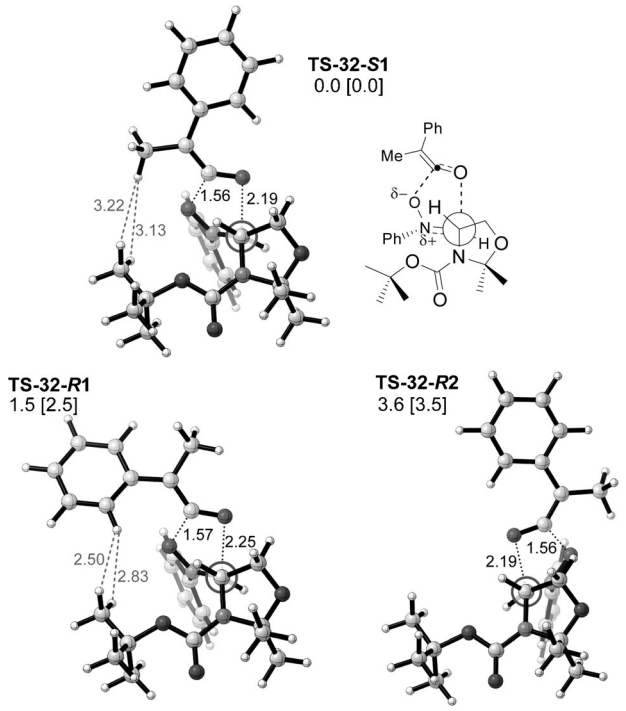


Figure 2. Stereoisomeric transition structures and their relative free energies. (M06-2X/6-311 + G(d,p) (THF)//B3LYP/6-31G(d), gas-phase B3LYP/6-31G(d) energies are given in brackets).

the nearly perpendicular angle of attack from the ketene oxygen (O4-C3-N7 = 84.5°), rather than the obtuse, Bürgi–Dunitz angle in carbonyl additions.[27] Thus, although the *anti* relationship between the forming C–O bond and the C–N bond is maintained in both **TS-32-R2** and **TS-32-S1, TS-32-R2** is destabilized by steric crowding because of the ring methylene group occupying the *inside* position.

In summary, for the chiral auxiliary-controlled synthesis of oxindoles from nitrones and ketenes, the enantioselectivity of this process has been optimized (up to 98 % *ee*) through the use of an oxazolidine *N*-2,4,6-triisopropylbenzenesulfonyl substituent. We delineated a new pericyclic cascade composed of a 3+2 cycloaddition involving the ketene carbonyl group and a hetero-[3,3]-sigmatropic rearrangement. The high enantioselectivity is attained by both effective π-facial control from the chiral auxiliary of the nitrone and the high propensity of the ketene to adopt the aryl-*trans* orientation during the cycloaddition. The stereochemical information embedded in the cycloadduct formed is then transferred, through the sigmatropic rearrangement, to the imino acid (*S*)-**5b**, which is converted in situ to oxindole (*S*)-**3a**, thus achieving an overall acyclic 1,6-stereochemical induction from the chiral auxiliary to the final product. Computational data on reactants with different *N*-protecting groups and substituents on the nitrone C=N bond and the nitrone aromatic ring are consistent with our model and will be disclosed in a full article. The findings described here demonstrate the power of modern, accurate quantum mechanical computations in the discovery of novel asymmetric pericyclic cascades of synthetic interest.

Experimental Section

Representative procedure: To a solution of nitrone **1c** (0.070 g, 0.144 mmol) in dry tetrahydrofuran (THF) (2 mL) under nitrogen at −78 °C was added dropwise a solution of ketene **2c** (0.043 g, 0.288 mmol) in dry THF (1 mL). The mixture was stirred at −78 °C overnight. The reaction was then quenched with 2 M HCl (aq) (0.5 mL) and stirred for 30 min, allowing to warm to RT before extraction with Et_2O (3 × 10 mL). The combined organic phases were washed with $NaHCO_3$ (aq), dried over Na_2SO_4, filtered, and concentrated in vacuo to give a crude oil which was purified by column chromatography over silica (0–30 % EtOAc in petroleum ether) to yield **3c** (0.031 g, 81 %) as an off-white solid.

All calculations were carried out at the M06-2X/6-311 + G(d,p)-(THF)//B3LYP/6-31G(d) level of theory with Gaussian 09.[28] Computational details are given in the Supporting Information. In the text, M06-2X free energies including solvation corrections are reported.

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[15] Attempts to locate the TS for this step by constraining the forming C–C and the breaking N–O bonds at various partial bond distances in the gas phase and in solution yielded highly unstable TSs with a free energy of at least 44.1 kcal mol^{-1} relative to the separated reactants.

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[20] Computations in solvent models located a shallow intermediate ($d_{CO} = 1.71$ Å) with a very similar optimized geometry to that of **TS-32** and only 0.2 kcal mol^{-1} below it, and with an enthalpy barrier of 2.6 kcal mol^{-1} for cyclization.

[21] See the Supporting Information for the PES scan and IRC paths.

[22] **TS-32-S2**, in which both the face of nitrone attacked and the orientation of the ketene are reversed, is over 5 kcal mol^{-1} higher in energy than **TS-32-S1**.

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