The Catalytic Enantioselective [1,2]-Wittig Rearrangement of Allylic Ethers

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Abstract

The catalytic enantioselective [1,2]-Wittig rearrangement of allylic ethers is currently unknown. This process constitutes a recognised challenge as it is traditionally considered to arise from a non-concerted reaction pathway *via* formation and recombination of radical pairs. This manuscript demonstrates a catalytic enantioselective solution to this challenge, and shows that [1,2]-Wittig products are generated *via* an alternative reaction cascade to traditional dogma. The developed process employs a chiral bifunctional iminophosphorane catalyst to promote an initial enantioselective [2,3]-sigmatropic rearrangement. A subsequent base promoted, stereoconvergent, ionic fragmentation-recombination that proceeds with high enantiospecificity and *retention of configuration*, formally equivalent to a Woodward-Hoffmann forbidden thermal [1,3]-sigmatropic rearrangement, generates [1,2]-Wittig products in up to 97:3 er. This unique chirality transfer process will have broad implications for fundamental stereocontrol in organic transformations.

Sigmatropic rearrangements are useful and reliable atom-economic reactions, with their ability to form carbon-carbon and carbon-heteroatom bonds through well-defined and predictable transition states [1] making these processes attractive for the synthesis of complex targets[2]. Among this broad set of reaction processes, [2,3]- and [1,2]-sigmatropic rearrangements are of synthetic and mechanistic significance [3,4]. The rearrangement of allylic ethers under basic reaction conditions typically leads to product mixtures proposed to arise from the thermally allowed concerted [2,3]-sigmatropic Wittig rearrangement, alongside a competitive non-concerted [1,2]-Wittig rearrangement generally thought to arise from homolytic fragmentation of the anionic intermediate to form a geminate radical pair and their subsequent recombination (Fig. 1A) [5,6]. As representative examples, both Rautenstrauch [7] and Baldwin [8] have shown that treatment of benzyl allyl ether **1** with *n*BuLi gives rise to a mixture of [2,3]- and [1,2]-products **2** and **3** respectively, with increased [1,2]-product observed at higher temperatures. Although not widely recognised, sporadic control reactions have demonstrated the feasibility of converting [2,3]-Wittig products to [1,2]-Wittig products (formally *via* a [1,3]-rearrangement), although the generality, mechanism and configurational consequence has not been established [9-14]. The concerted or dissociative (*via* ionic or radical intermediates) nature of both the [1,2]- and [1,3]-processes has been much debated. For example, Danheiser considered a concerted [1,3]-pathway to account for the inversion observed in the ring expansion of *cis*-cyclobutanol **4** [15]. However, Gajewski [16] and Cohen [17] both postulated a nonconcerted fragmentation pathway *via* an intermediate allylic anion that accounts for the observed *in situ* isomerism of *cis*-**4** to *trans*-**6**, and that use of enantiomerically pure *cis*-**4** or *trans*-**6** leads to racemic products (Fig. 1B) [18]. Applying the Woodward-Hoffmann rules indicates that a concerted [1,2]-rearrangement is forbidden, while a thermal [1,3]-rearrangement is symmetry allowed but geometrically challenging, with a suprafacial carbon shift expected to proceed with *inversion of configuration* at the oxygen bearing carbon [1]. Interestingly, Houk has previously shown that anionic Cope and amino-Cope reactions proceed through a stepwise dissociation-recombination process [19], consistent with competitive non-concerted [1,3]-rearrangements observed in related systems [20,21]. Given the mechanistic ambiguity surrounding these processes the enantioselective [1,2]-Wittig rearrangement of allylic ethers is a recognised challenge and is currently unknown despite its synthetic potential [22].

In this manuscript, the catalytic enantioselective [1,2]-Wittig rearrangement of allylic ethers is developed (up to 97:3 er) and is shown to proceed through a cascade process consisting of an initial enantioselective [2,3]-rearrangement (up to >99:1 er) promoted by a bifunctional iminophosphorane (BIMP) catalyst. The resultant tertiary carbinol bearing an α-branched allylic substituent is transformed to the linear [1,2]-Wittig isomeric product with *retention* of configuration at the oxygen bearing carbon (equivalent to a

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Woodward-Hoffmann forbidden [1,3]-sigmatropic rearrangement) through a dissociative intramolecular fragmentation-recombination event with high enantiospecificity (Fig. 1C). Substitution reactions that proceed with *retention* of configuration are rare, although recognised for alcohols *via* an S_Ni mechanism that proceed *via* contact ion-paired intermediates [23-25]. Traditionally the stereospecificity of nucleophilic substitution processes leads to *inversion of configuration* in S_N2 reaction processes at secondary centres and partial or complete racemisation in S_N1 processes at tertiary centres. However recent advances have showcased stereospecific substitution at tertiary and even quaternary centres in which stereochemical information is conferred despite ionization of a substrate [26-31]. In this context, the high enantiospecificity of the observed chirality transfer protocol that leads to [1,2]-products with *retention of configuration*, while proceeding through an ionic fragmentation and recombination process, is significant and holds promise for the elucidation of alternative reaction pathways for generating chiral products with high enantioselectivity.

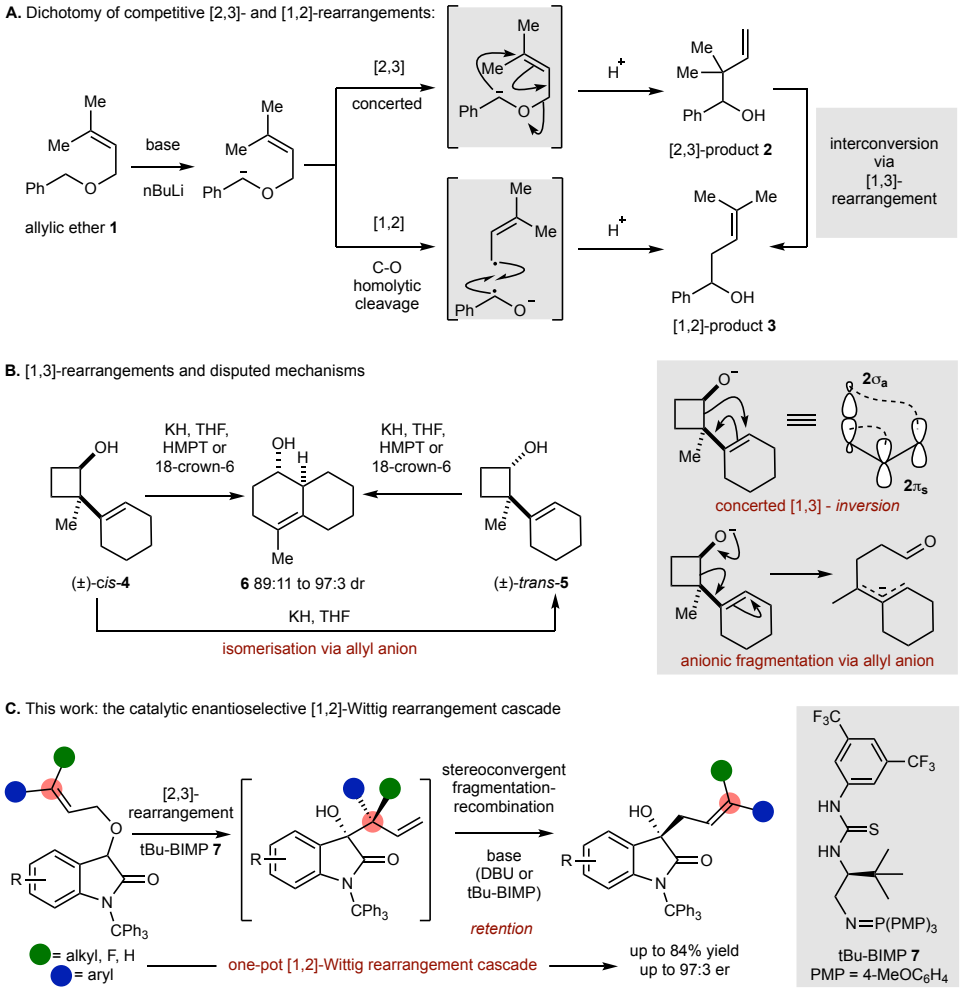

Fig 1: A. Traditional mechanism and dichotomy between [2,3]- and [1,2]-Wittig rearrangements. **B.** Stereochemical ambiguity of [1,3]-rearrangement reactions *via* concerted or fragmentary pathways. **C.** This work: the catalytic enantioselective [1,2]-Wittig rearrangement cascade.

Reaction Development

Building upon the observation that disubstitution at the allylic ether terminus typically leads to increased preference for [1,2]-rearrangement products [14], the use of bifunctional iminophosphoranes (BIMPs) as organocatalysts to promote the enantioselective [1,2]-rearrangement process was considered. Originally developed by Dixon, BIMPs have shown widespread use in a plethora of stereoselective transformations [32], possessing a Brønsted superbasic iminophosphorane with an H-bond donor to assert stereocontrol. Rearrangement upon an oxindole skeleton was chosen given the prevalence of this motif in natural products and bioactive molecules. Following initial screening of the effect of *N*-substituent, BIMP catalyst, solvent and temperature variation (see SI for information) using *N*-trityl substituted allylic ether **8** and *t*Bu-BIMP catalyst **7** showed that rearrangement to **9** in mesitylene led to selective formation of the [1,2]-product in excellent

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yield and promising enantioselectivity (Fig. 2A, 92:8 er). As [1,2]-Wittig products are traditionally expected to be generated *via* a radical recombination mechanism the effect of adding 20 mol% of 4-NHAc-TEMPO as an additive was probed. Formation of the [1,2]-product was not significantly inhibited, giving **9** in 73% yield and improved 95:5 er, with no 4-NHAc-TEMPO adducts observed [33]. The mass balance consisted of the aldol side product **10** (>95:5 dr, 75:25 er) that was isolated in 5% yield; addition of 1.0 equivalent of 4-NHAc-TEMPO was also tested, affording **9** in a further reduced 59% yield but enhanced 97:3 er. Control experiments indicated that taking a 1:1 mixture of allylic ether **8** and *N*-trityl isatin with *t*Bu-BIMP **7** gave aldol product **10** in 71% yield (>95:5 dr, 75:25 dr), consistent with *in situ* formation of an isatin derivative in the presence of 4-NHAc-TEMPO. Intrigued by these observations, *in situ* temporal reaction analysis monitored consumption of allylic ether **11** (40 mM) upon treatment with *t*Bu-BIMP **7** (20 mol%) to give [1,2]-Wittig product **13** in d_8-toluene using ^{1}H NMR spectroscopy (Fig. 2B). The rearrangement showed a first-order consumption in substrate **11** (that was racemic throughout the reaction process), with a transient mixture of diastereoisomeric [2,3]-rearrangement products **12** detected (δ_H = 5.15 and 4.87 ppm) that accumulated to a maximum concentration of ~15 mM and was subsequently transformed into the [1,2]-rearrangement product **13**, consistent with **12** being an intermediate in the generation of **13**. On a synthetic scale, stopping the reaction of allylic ether **8** after 1 h gave, at 75% conversion, a 63:37 mixture of [2,3]-products **14** and [1,2]-product **9** (96:4 er). Purification gave **14** (89:11 dr, both diastereoisomers 99:1 er) in 21% yield whose absolute configuration was determined by *N*-trityl deprotection and subsequent single crystal X-ray diffraction (see SI). The absolute configuration within **9** was confirmed by chemical synthesis (see SI for further information), indicating stereoconvergence and *retention of configuration* at C(3) in the rearrangement of diastereoisomers **14** to **9**. Separate control experiments validated the [2,3]-rearrangement products **14** as intermediates to the [1,2]-product **9** (Fig. 2C). Treating **14** (89:11 dr) under standard reaction conditions for 5 h gave the [1,2]-product **9** in 60% yield and 99:1 er, while treatment with *t*Bu-BIMP **7** alone gave **9** in 83% yield and 96:4 er. These experiments are consistent with the addition of 4-NHAc-TEMPO leading to enhanced enantiospecificity in the [1,3]-rearrangement although the precise origin of this enhanced selectivity has not been conclusively elucidated. Treatment of **14** with the achiral base DBU also promoted rearrangement, but with moderate conversion, giving **9** in 36% yield but with high enantioselectivity (96:4 er) consistent with DBU or *t*Bu-BIMP **7** acting as a base and not influencing enantiospecificity in this [1,3]-rearrangement process. Consistent with this observation, monitoring the conversion of **14** (89:11 dr) to **9** upon treatment with racemic or enantiopure BIMP derivatives did not lead to significant rate differences (see SI for further information) implying no matched and mismatched reactant combinations. The [2,3]-product **14** could also be transformed into the [1,2]-Wittig product **9** when heated at 100 °C without the addition of base, albeit with reduced yield (31%) and enantioselectivity (92:8 er). Crossover experiments (Fig. 2D) using a 50:50 mixture of ethers **15** and **16** either with *t*Bu-BIMP **7** alone, or with the addition of 4-NHAc-TEMPO, resulted in *only* [1,2]-products **17** and **18**, consistent with an *intramolecular* process in operation, with enhanced product enantioselectivity observed in the presence of 4-NHAc-TEMPO.

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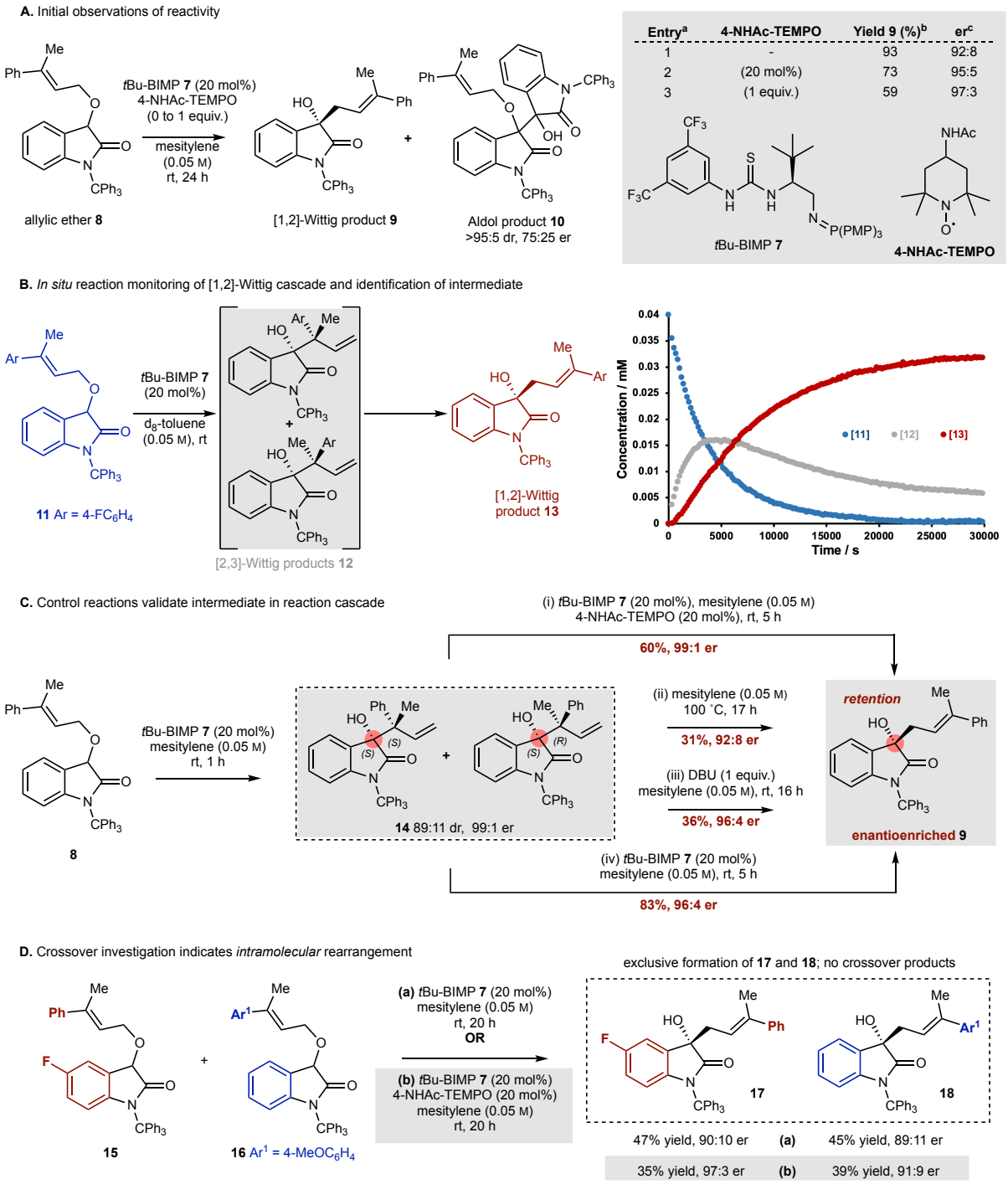

Fig. 2: A. Initial observations of [1,2]-Wittig reaction products. a Reaction performed on 0.1 mmol scale. b all yields are isolated. c Determined by HPLC analysis on a chiral stationary phase. **B.** Monitoring of the reaction by *in situ* ^{1}H NMR spectroscopy. [**12**] refers to combined concentration of two diastereoisomers. **C.** Preparation of enantioenriched [2,3]-intermediate and control experiments to validate intermediate. **D.** Crossover experiments indicate an *intramolecular* process.

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Having identified a viable reaction pathway, the scope of the enantioselective [1,2]-Wittig cascade was examined (Fig. 3). Changing the C(3')-alkyl substituent from methyl- to ethyl- was tolerated giving **19**, while using a C(3')-cyclopropyl substituted allylic ether as a radical probe generated only [1,2]-rearrangement product **20** (40% yield, 96:4 er) with the cyclopropyl ring intact[34]. Increasing the steric hindrance through incorporation of a C(3')-phenyl substituent resulted in moderate conversion, (see SI for further information), necessitating changing the *N*-trityl substituent to an *N*-benzyl for increased reactivity, giving **21** in 61% yield but reduced product enantioselectivity (73:27 er), consistent with screening studies that necessitated *N*-trityl substitution for optimal enantioselectivity (see SI for further information). A limitation of this process showed that both a (*Z*)-configured allylic ether and a dimethyl terminal allylic ether returned only starting material under the reaction conditions. Variation of the C(3')-aryl substituent showed that the incorporation of halogens (4-F-, 4-Cl- and 4-Br-), electron-donating (4-Ph-, 4-Me-, 4-MeO-) as well as electron withdrawing (4-CF_3-) substituents were tolerated, giving the [1,2]-rearrangement products **13**, **18**, **22-26** in high yields and enantioselectivity. The incorporation of 3-Me- and 2-Me substituents (**27**, **28**) was also tolerated, although with lower yields for the 2-Me-substituted example. In addition, 2-naphthyl-, thiophen-2-yl and thiazol-2-yl-substituted ethers all afforded the corresponding [1,2]-Wittig products **29-31** in 71% to 82% yields with 93:7 to 94:6 er. Substituent variation within the 4-, 5- and 6-positions of the oxindole included the incorporation of halogen (5-F-, 5-Cl-, 5-I, 6-Br, 6-Cl-), electron-donating (5-Me-, 5-MeO-) and electron-withdrawing (5-O_2N-) substituents that gave the corresponding products **17**, **32-39** in 67% to 80% yield and up to 96:4 er. While *N*-tritylation of 7-chloroisatin was unsuccessful, the *N*-benzyl analogue was prepared and tested, giving 7-Cl **40** in 81% yield but reduced enantioselectivity (73:27 er).

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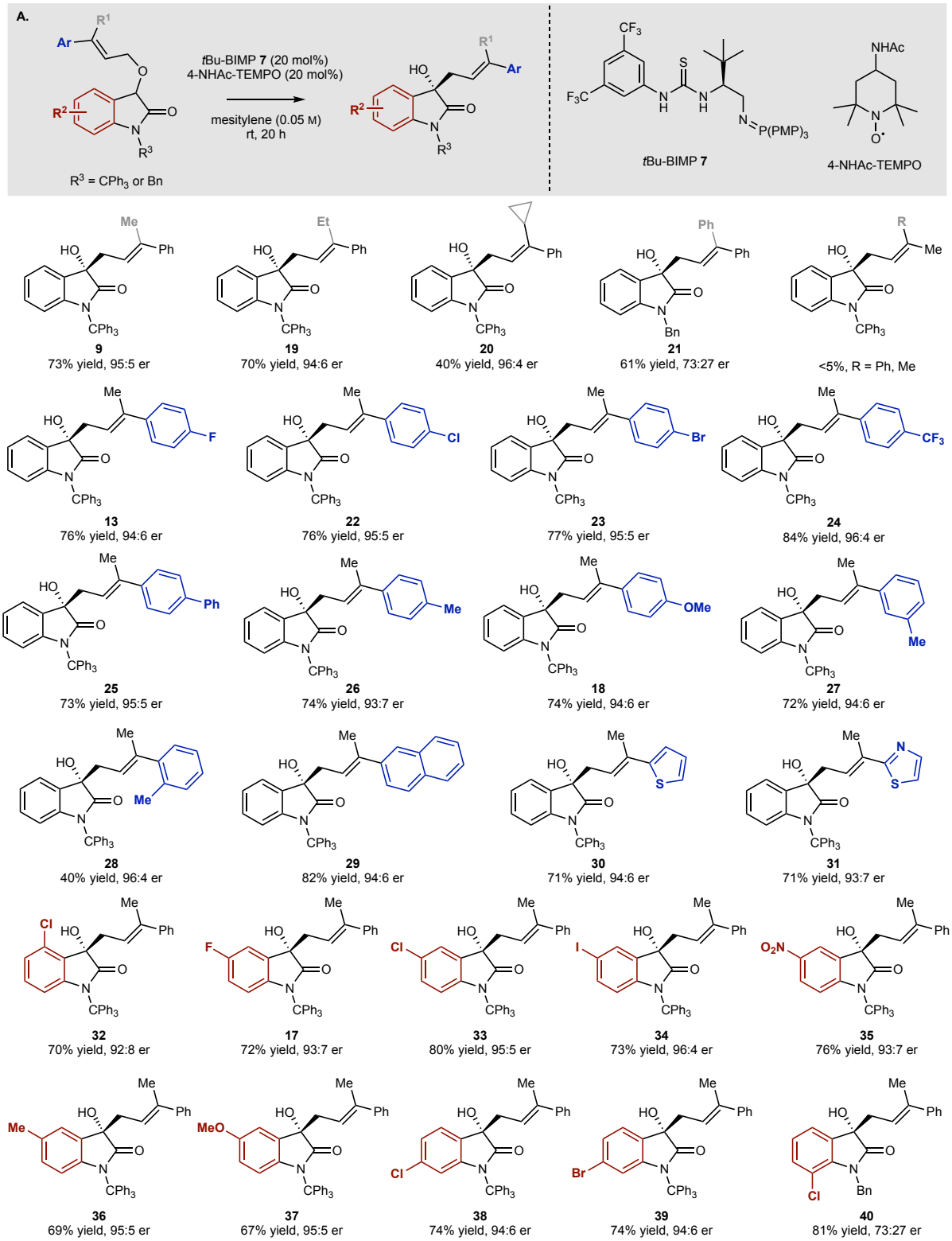

Fig. 3: Substrate scope and limitations of the [1,2]-Wittig rearrangement; all ers determined by HPLC analysis on a chiral stationary phase; all yields are isolated yields.

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To further probe the generality of this transformation, the effect of incorporating C(3')-F or C(3')-H substituents within the allylic ether terminus was investigated (Fig. 4A). In contrast to the parent C(3')-methyl series, treatment of **41** and **43** with *t*Bu-BIMP **7** at room temperature gave exclusively the corresponding [2,3]-rearrangement products **42** (91:9 dr, 98:2 er) and **44** (72:28 dr, 98:2 er) with no formation of the [1,2]-product. To convert these enantioenriched [2,3]-products to the corresponding [1,2]-Wittig products increased reaction temperatures (≥100 ˚C for **42** and **44**) and the addition of stoichiometric DBU (1 equiv.) was required. For example, stereoconvergence of the separable diastereoisomers (3*S*,1'*S*)- and (3*S*,1'*R*)-**44** upon treatment with DBU in mesitylene at 120 ˚C was observed, with both giving (*E*,*S*)-[1,2]-Wittig product **45** in 94:6 and 93:7 er respectively. Solvent polarity has a significant effect upon the enantiospecificity of the [1,3]-rearrangement at these increased reaction temperatures (see SI for further information) with highest product enantioselectivity observed in solvents of low polarity (toluene and mesitylene) rather than polar solvents (DMF or MeCN). Rearrangement with *retention of configuration* is still observed, although addition of 4-NHAc-TEMPO does not lead to increased product er in this series (see SI for further information). Having demonstrated that high temperatures are required to promote the [1,3]-rearrangement of the initially formed [2,3]-products, a telescoped process to allow one-pot access to [1,2]-Wittig products was developed that utilised toluene as a solvent (Fig. 4B). Treatment of a range of allylic ethers with *t*Bu-BIMP **7** promoted enantioselective [2,3]-rearrangement, that was followed by the addition of DBU (1 equiv.) and heating to between 60 ˚C and 100 ˚C. Following this procedure, in the C(3')-F series, inclusion of Ph, 4-MeC_6H_4-, 4-$MeOC_6H_4$ and 4-$F_3CC_6H_4$-substituted allylic ethers, as well as 4-Cl, 5-F, 5-NO_2, 5-MeO and 6-Cl substituents within the oxindole were tolerated, giving the corresponding [1,2]-Wittig products (**46-54**) with good to excellent enantioselectivity (91:9 to 97:3 er). In the C(3')-H series, variation of the aryl substituent within the allylic ether showed that Ph, 4-$MeOC_6H_4$, 4-$F_3CC_6H_4$, 4-FC_6H_4, 2-$MeOC_6H_4$, 1-naphthyl and 2-naphthyl-substitution, heteroaromatic 3-thienyl and C(2')-methyl substitution, alongside 4-Cl, 5-OMe and 6-Br substituents within the oxindole were tolerated, allowing the formation of enantioenriched [1,2]-Wittig rearrangement products **45, 55-65** (87:13 to 95:5 er). Notably, lower product yields (41% to 73%) were observed in this one-pot process than noted in Fig. 3, reflecting the propensity for competitive decomposition at the elevated reaction temperatures required to promote the [1,3]-rearrangement.

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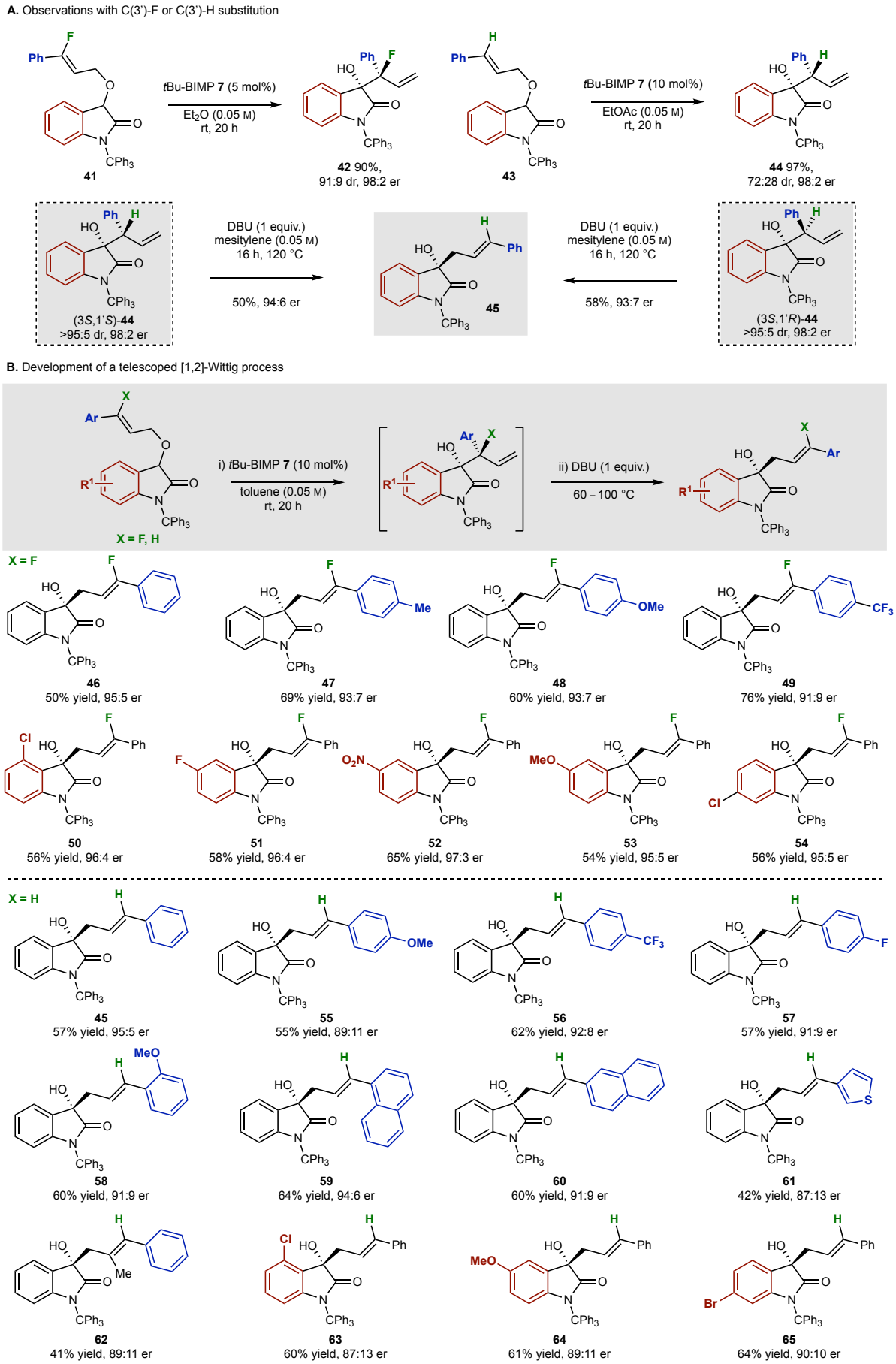

Fig. 4: A. Observations with C(3')-F or C(3')-H substitution; selective formation of [2,3]-rearrangement product and temperature required to promote [1,3]-rearrangement. **B.** Substrate scope and limitations of the telescoped [1,2]-Wittig process; all ers determined by HPLC analysis on a chiral stationary phase; all yields are isolated yields; *t*Bu-BIMP **7** (20 mol %) used to prepare **62**.

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Mechanistic Considerations

Having demonstrated the scope of this process, consideration to the mechanism of this cascade was given. Initial association of *t*Bu-BIMP **7** to the oxindole carbonyl of substrate **I** by hydrogen-bonding is assumed to direct deprotonation of the allylic ether-BIMP complex **II** to give **III**, with subsequent concerted [2,3]-sigmatropic rearrangement giving **IV** with high enantioselectivity. Subsequent protonation and catalyst release gives isolable **V**. A subsequent base (*t*Bu-BIMP or DBU) catalysed anion-accelerated [1,3]-rearrangement that proceeds with *retention of configuration* at the carbinol centre generates [1,2]-Wittig product **VI** (Fig. 5A). Building on this framework, DFT analyses were used to probe three mechanistic possibilities for the unconventional [1,3]-rearrangement from either the neutral alcohol or anionic alkoxide; concerted [1,3]-sigmatropic rearrangement, homolytic fragmentation followed by recombination, or anionic fragmentation and recombination (Fig. 5B) [35,36]. In these initial calculations the *N*-trityl group was truncated to an *N*-methyl and the ammonium counterion was omitted to reduce the complexity of the calculations; DFT calculations in both diastereoisomeric series were considered and showed similar energetic trends (see SI for further information), although for simplicity only those for the major diastereoisomer are illustrated. Extensive modelling was unable to locate a cyclic transition state without constraining the bond-forming and bond-breaking distances, thus only an approximation to the cyclic process could be obtained *via* a constrained cyclic transition state. Although examples of [1,3]-sigmatropic rearrangements exist in the literature, most exhibit high activation barriers or occur with smaller, more flexible, or more sterically accessible systems than **I** [37-43]. Consideration of the reaction barriers/intermediate energy differences (see SI for further information) for the homolytic and ionic pathways from either the neutral alcohol or alkoxide revealed that those proceeding *via* the alkoxide **66** are significantly favoured, consistent with an anion-accelerated fragmentation process[12,16,44]. Furthermore, comparison of bond lengths of the breaking C-C bond within the neutral (1.6 Å) and deprotonated (1.7 Å) species indicate that significant bond lengthening is observed upon deprotonation, consistent with weakening of this bond as proposed by Evans[45]. Overall, both the constrained cyclic transition state ($\Delta G^{\ddagger} = 56.9$ kcal·mol^{-1}) and the homolytic diradical fragmentation/recombination pathway ($\Delta G^{\ddagger} = 63.2$ kcal·mol^{-1}) were significantly disfavoured compared to an ionic fragmentation/recombination pathway ($\Delta G^{\ddagger} = 2.0$ kcal·mol^{-1}). Fig 5B shows a free energy surface for the ionic fragmentation/recombination pathway from deprotonated intermediate **66** to product **67**[46,47]. This stepwise dissociative process proceeds through bond cleavage *via* TS^{A} that generates a delocalised allylic anion and isatin, that recombines in an effectively barrierless process to generate **67**. The calculated low barrier to C-C cleavage was postulated to be a consequence of the computational omission of the assumed ammonium counterion ([*t*Bu-BIMP-H]$^{+}$ or [DBU-H]$^{+}$) that would be expected to raise this barrier[16]. Indeed, when this ionic fragmentation pathway was explored with [*t*Bu-BIMP-H]$^{+}$ included as the ammonium counterion the barrier to C-C bond cleavage *via* ionic fragmentation was raised to 7.8 kcal·mol^{-1} (see Fig. 5C). This barrier is consistent with that calculated in a stepwise dissociation-recombination process in an anion-accelerated amino-Cope rearrangement (8.6 kcal·mol^{-1}) by Houk and Njardarson[19]. The observed *retention of configuration* with high enantiospecificity within the products is consistent with the bond-breaking process to generate the allylic anion and isatin, followed by recombination upon the *re*-face of the isatin, occurring at a faster rate than conformational change and bond rotation to allow *si*-face addition of the isatin that leads to reduced enantioselectivity. Further evidence for an anionic pathway can be taken from the known reversibility of crotyl and allylic Grignard additions to aldehydes and ketones[48,49]. To experimentally probe the validity of this proposed anionic fragmentation pathway, taking isolated racemic [2,3]-rearrangement products that differed in the electronic effect of C(1')-aryl substituents with *t*Bu-BIMP **7** showed that inclusion of electron withdrawing substituents led to enhanced reaction rates[50]. Hammett analysis (Fig. 5D) revealed a ρ value of +0.76 when plotted against the substituent constant σ−, consistent with the build-up of negative charge within the rate limiting transition state of the reaction and the proposed anionic fragmentation. Given the importance of understanding fundamental stereochemical chemical processes the enantiospecificity observed in this pathway will have broader implications for a plethora of other synthetic transformations.

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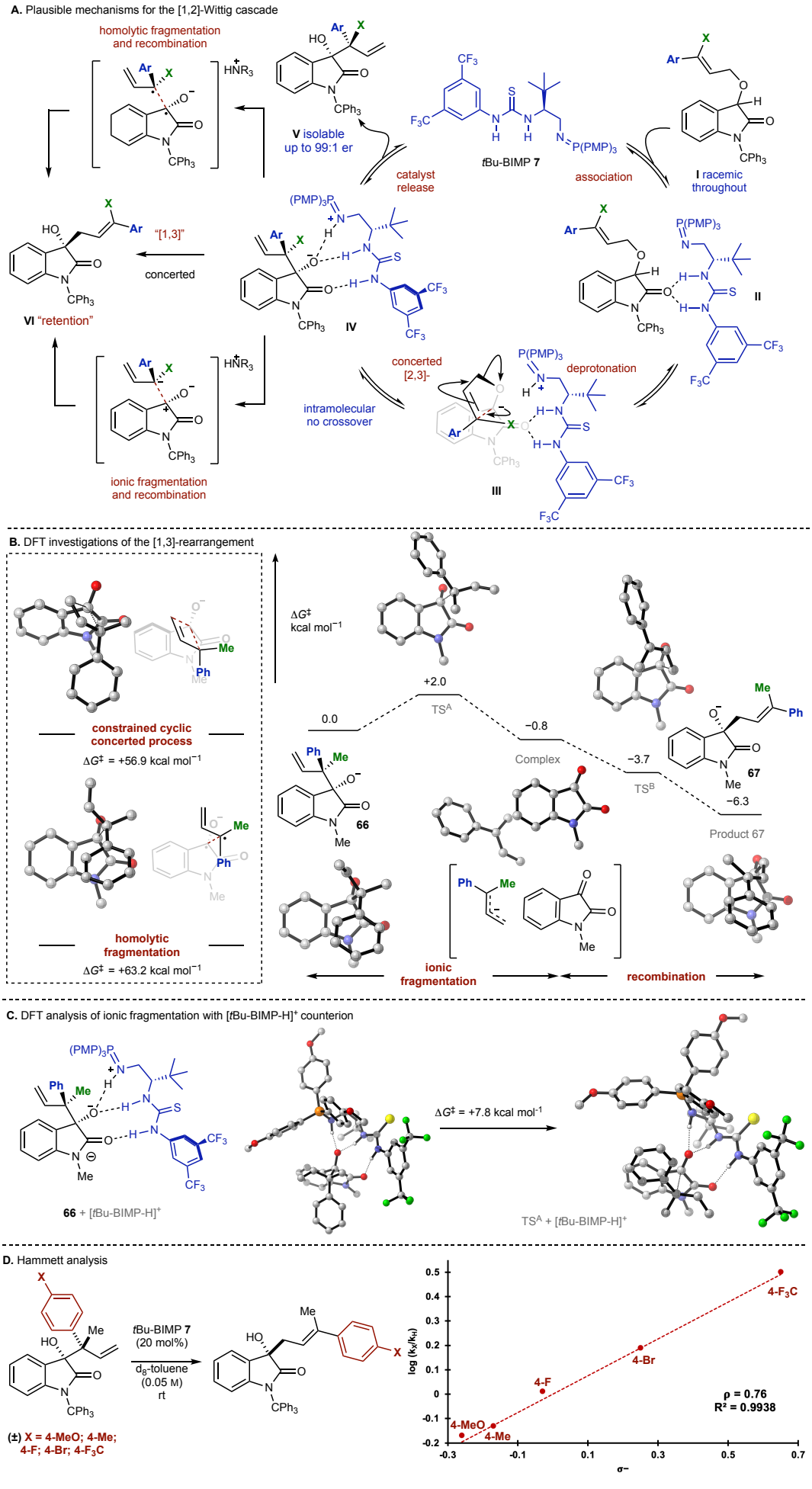

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Fig. 5: A. Plausible mechanisms for the [1,2]-Wittig cascade. **B.** DFT free energy pathway (B3LYP-D3(BJ)/Def2-TZVP/IEFPCM(mesitylene)//B3LYP/6-31G(d)/IEFPCM(mesitylene)) for the ionic fragmentation/recombination of the deprotonated alcohol (*S*,*S*)-**66** as well as the lowest energy transition states for the concerted cyclic process (constrained at the bond-forming and bond-breaking interactions) and the homolytic fragmentation. **C.** Pre-reaction complex and transition state for the ionic fragmentation of deprotonated alcohol (*S*,*S*)-**66** catalysed by [*t*Bu-BIMP-H]$^+$ (B3LYP-D3(BJ)/Def2-TZVP/IEFPCM(mesitylene)//B3LYP/6-31G(d)/IEFPCM(mesitylene)). **D.** Hammett analysis of the [1,3]-rearrangement.

Data availability:

Data are available in the manuscript and supplementary materials. The research data supporting this publication can be accessed at https://doi.org/10.17630/5b5778a0-f337-4cbe-b336-c2afac22693b: data underpinning "The Catalytic Enantioselective [1,2]-Wittig Rearrangement of Allylic Ethers". University of St Andrews Research Portal; PURE ID: 295983644. All Gaussian16 output files for all computed structures are openly available in Dataset for "The Catalytic Enantioselective [1,2]-Wittig Rearrangement of Allylic Ethers" in the University of Bath Research Data Archive at https://doi.org/10.15125/BATH-01337. Temporary link to the dataset for reviewers: https://researchdata.bath.ac.uk/preview/1337, access code (active 90 days from 1st November): GUcnSVEKkZBkA8VmBU30QyKibKoosegS (This line will be removed upon publication). The supplementary crystallographic data for this paper are available free of charge from the Cambridge Crystallographic Data Centre (CCDC) under accession numbers 2305636 and 2305637.

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Acknowledgements
The research leading to these results has received funding from the Royal Society (Newton Fellowship to TK), EPSRC (TK, KK, EP/T023643/1; EHEF, EP/R513155/1; EHEF, MNG, EP/W003724/1), The Carlsberg Foundation (MJ) and the EaSI-CAT centre for Doctoral Training (JOY). The authors gratefully acknowledge the University of Bath's Research Computing Group (doi.org/10.15125/b6cd-s854) for their support in this work.

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Ethics Declaration:
Competing interests:
The authors declare no competing interests.

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