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Origin of the *E*/*Z* Selectivity in the Synthesis of Tetrasubstituted Olefins by Wittig Reaction of α-Fluorophosphonium Ylides: An Explanation for the Low Stereoselectivity Observed in Reactions of α-Alkoxy Aldehydes

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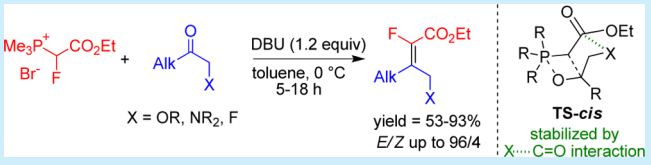
Supporting Information

ABSTRACT: A series of tetrasubstituted fluoroalkenes were synthesized in good yield and high *E*/*Z* selectivity (up to 96/4) by Wittig reaction between α-heterosubstituted ketones and α-fluorophosphonium ylides. A detailed study of factors that control stereoselectivity in these reactions shows that stereoselectivity is the result of stabilizing CH···F and N···C═O interactions in the addition TS leading to the *E* isomer. This analysis provides a rationale for the observed decrease in selectivity for reactions of stabilized ylides with α-alkoxy aldehydes.



The Wittig reaction occupies a central role in organic synthesis as it is one of the most widely used methods for the synthesis of alkenes.[1,2] The stereoselectivity of the Wittig reaction depends on the substrates: nonstabilized phosphonium ylides (R_3P=CHR′, R′ = alkyl) react with aldehydes to yield alkenes with a high *Z* selectivity, whereas stabilized ylides (R_3P=CHR′, R′ = EWG) furnish high *E* selectivity. Comprehensive experimental studies, supported by recent computational results, allowed for the elucidation of the mechanism and the rationalization of the observed stereoselectivity in the Wittig reaction.[2,3] The first step of the process is oxaphosphetane formation[4,5] and is recognized as determining the stereoselectivity. The transition-state models developed by Vedejs et al.[2] account for the *Z* selectivity observed in reaction of nonstabilized ylides by preferential addition of these latter to aldehydes through an early puckered *cis* TS, which minimizes 1,2 and 1,3 steric interactions (Figure 1). For stabilized ylides, computational studies showed that TS structures and *E*/*Z* selectivity are controlled by a dipole−dipole interaction as well as 1,2 and 1,3 steric interactions.[3]

Reactions of phosphonium ylides with ketones are scarcely described, probably due to the fact that tri- and tetrasubstituted alkenes are generally obtained in poor yield with a low *E*/*Z* selectivity.[1,6] In the course of the synthesis development of a drug candidate, we investigated the Wittig reaction between the stabilized ylide formed by deprotonation of α-fluorophosphonium salt **1a** and *N*-benzylpiperidin-3-one (**2a**) (Scheme 1). Much to our surprise, the desired tetrasubstituted olefin was obtained in good yield with a high stereoselectivity for the *E* isomer (**3a**).[7] Here, we report the synthesis of a series of fluorinated tetrasubstituted olefins in good yield and with a high stereocontrol. A detailed study of the observed stereoselectivity shows that it is the result of stabilizing CH···F

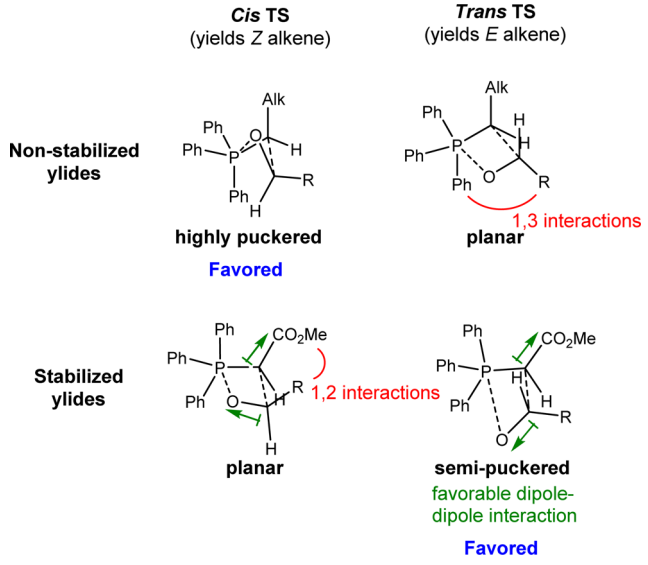


Figure 1. TS structure model and rationale of selectivity for the Wittig reaction.

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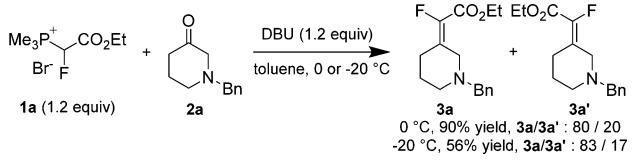
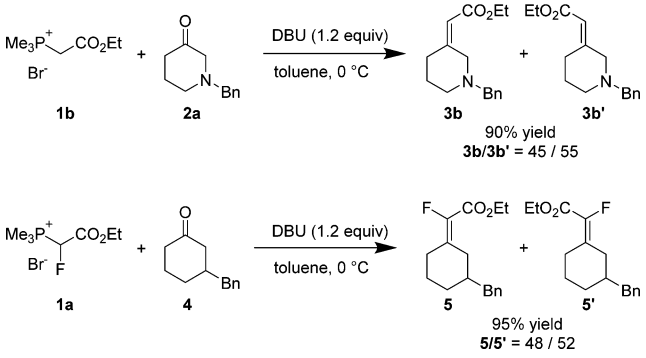
Scheme 1. Wittig Reaction of Ylide Formed from α-Fluorophosphonium Salt (1a) and *N*-Benzylpiperidin-3-one (2a)



hydrogen bonds and N···C=O interactions in the addition TS leading to the *E* isomer (**3a**).

To understand factors that govern the selectivity in reaction of **1a** and **2a**, we first investigated the importance of the fluoride substituent in the ylide and of the amine group of the piperidin-3-one derivative. This was done by performing the reaction with nonfluorinated phosphonium salt **1b** and with cyclohexanone derivative **4** (Scheme 2). These experiments

Scheme 2. Reaction of Non-fluorinated Phosphonium Salt (1b) and of 3-Benzylcyclohexanone (4)



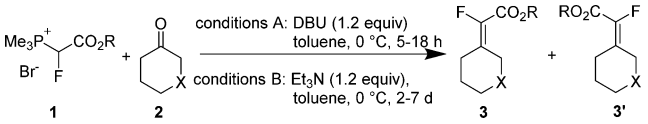
showed that neither of these two structural motives can, alone, account for the observed *E* selectivity in the reaction of **1a** and **2a**. Indeed, deletion of either one of them leads to a loss of stereoselectivity, as the olefins are obtained in essentially equal ratios. The observed selectivity is thus the result of a synergistic effect between these two structural features.

Next, we studied the influence of the nature of the *N*-protecting group in the piperidinone derivative and of the alkyl ester moiety in the ylide (X and R, respectively; Table 1). Increasing the steric hindrance of any of these groups leads to an erosion of the preference for **3** (entries 1−7, Table 1). Steric interactions favor formation of **3′**; electronic factors must be responsible for the observed selectivity in favor of isomer **3**.

We also performed the reaction of **2a** with the triphenylphosphonium analogue of **1a**. This reaction was, however, very slow and low-yielding (<3% olefin **3a** obtained after 24 h; see the Supporting Information for details). The nature of the phosphonium group (trimethylphosphonium) in **1** is thus a key factor for allowing the synthesis of tetrasubstituted olefins.

The predominant role of electronic interactions in determining stereoselectivity could be further demonstrated by investigating the reaction of *N*-aryl derivatives **2f−h**.[8] Indeed, these experiments show that the **3**/**3′** ratio increases (from 59/41 to 80/20) with the electron density on the nitrogen atom of **2** as modulated by the nature of the *N*-aryl group (entries 9−11, Table 1). These observations suggest the involvement of the lone pair of the piperidin-3-one nitrogen

Table 1. Influence of Structural Modifications on the Stereoselectivity (3/3′)



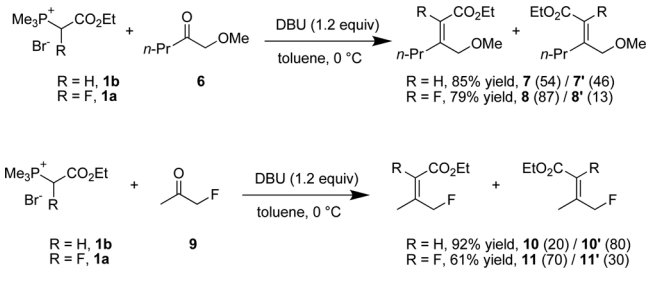
entry	X	R	conditions	yield[a] (%)	3/3′[b]
1	NMe (**2b**)	Et (**1a**)	A	53 (**3c**)	96/4
2	NEt (**2c**)	Et (**1a**)	A	65 (**3d**)	84/16
3	NAllyl (**2d**)	Et (**1a**)	A	51 (**3e**)	93/7
4	NBn (**2a**)	Et (**1a**)	A	90 (**3a**)	80/20
5	$NCHPh_2$ (**2e**)	Et (**1a**)	A	85 (**3f**)	67/33
6	NBn (**2a**)	Me (**1c**)	A	76 (**3g**)	86/14
7	NBn (**2a**)	*t*-Bu (**1d**)	A	57 (**3h**)	58/42
8	N-*p*-NO_2Ph (**2f**)	Et (**1a**)	A	0[c]	
9			B	52 (**3i**)	59/41
10	NPh (**2g**)	Et (**1a**)	B	86 (**3j**)	72/28
11	N-*p*-MeOPh (**2h**)	Et (**1a**)	B	76 (**3k**)	80/20
12	O (**2i**)	Et (**1a**)	A	93 (**3l**)	96/4

[a]Yield in isolated product after flash column chromatography. [b]Ratio determined by GC, HPLC, or ^{1}H NMR on the crude mixture. Configuration determined by NMR (^{19}F−^{1}H heteroNOESY; see the Supporting Information). [c]The product of self-condensation of the ketone was the main product (see the Supporting Information).

atom in a specific interaction in the TS. A similar interaction must also be present in the case of an oxygen atom as demonstrated by the high selectivity (96/4) observed with pyran-3-one **2i** (entry 12, Table 1).

Interestingly, this stereoselective synthesis of tetrasubstituted olefins can be extended to acyclic derivatives and other α-heterosubstituents: deprotonation of **1a** and reaction of the ylide with ketones **6** and **9** leads to olefins **8** and **11**, respectively, with a moderate to good stereoselectivity (Scheme 3). Again, the crucial role of both the fluoride atom in the ylide

Scheme 3. Wittig Reaction with Acyclic Ketones



and the α-heterosubstituent in the ketone in determining stereoselectivity was demonstrated. Indeed, reaction of **1b**, the nonfluorinated equivalent of **1a** provides olefins **7** and **10** with no significant (46/54) or a reversed stereoselectivity (20/80), respectively.

In order to gain deeper insights into the origin of observed stereoselectivity between fluorophosphonium ylides and α-heterosubstituted ketones, we investigated the Wittig reaction of ylides formed from **1a** and **1b** with *N*-methylpiperidin-3-one **2b** and cyclohexanone by computational means. Calculations were performed at the B3LYP-D3(toluene)/6-31+G**//B3LYP/6-31G*(toluene) level of theory.[9] In our calculations, as observed in Wittig reactions of aldehydes,[3] we find significant barriers to formation of the oxaphosphetane,

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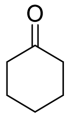
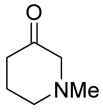
followed by much lower barriers to cleavage of the latter (see the Supporting Information). This confirms that initial cycloaddition is nonreversible. The relative energies of the *cis* and *trans* cycloaddition TSs thereby determine *E*/*Z* selectivity.

Obtained relative free energies for cycloaddition TSs reproduce observed trends for stereoselectivity (Table 2). In each case, two TSs involving, respectively, an axial and an equatorial approach of the ylide were found. In reactions of cyclohexanone, the equatorial approach is thoroughly favored, probably due to steric factors (1,3-diaxial interactions). One can observe, however, that this preference for equatorial positioning of the ylide carbon decreases slightly with fluoro substitution (compare reaction of cyclohexanone with **1a** and with **1b**, Table 2). Analysis of TS structures reveals that this can be accounted for by the presence of stronger CH···F hydrogen bonds (with hydrogen atoms in α and β position of the ketone) in the axial case (Figure 2).[10,11]

Table 2. Relative Free Energy of Cycloaddition TSs (kcal/mol Relative to Reactants)

carbonyl cmpd	ylide	approach	TS-3'[a]	TS-3[a]	exp. 3/3' selectivity
	**1b**	axial		47.8	/
		equatorial		44.9	/
	1a	axial		37.9	/
		equatorial		35.3	/
 **2b**	**1b**	axial	39.3	37.7	45/55
		equatorial	37.9	38.3	
	1a	axial	29.5	27.6	96/4
		equatorial	28.6	31.6	

[a]TS-**3** and TS-**3**′ are the TSs leading to **3** and **3**′, respectively.

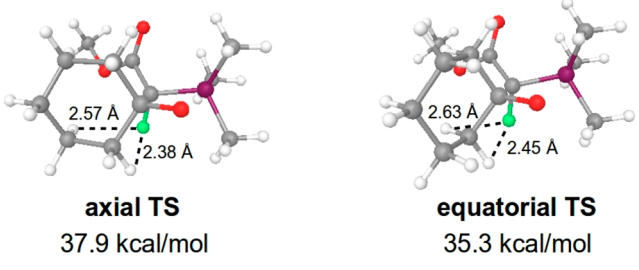


Figure 2. Structure and relative free energy of axial and equatorial TSs for the addition of ylide **1a** onto cyclohexanone.

The same is true for *trans* TSs-**3**′ in reactions of *N*-methylpiperidin-3-one **2b**. In contrast, for TS-**3**s the axial approach is now favored over the equatorial one, indicating that another effect is in play. Indeed, analysis of the electronic structure of the axial TS-**3**s reveals the presence of a stabilizing interaction between the nitrogen lone pair and the ester carbonyl group (Figure 3).[12] Stabilization arising from this interaction is estimated at 2.5 kcal/mol using NBO second-order perturbation theory. The observed high *E* selectivity in reaction of **1a** with piperidin-3-one derivatives can thus be accounted for by stabilizing N···C═O and CH···F hydrogen-bond interactions in axial TS-**3**. For geometrical reasons, TS-**3**′s involve only one CH···F hydrogen bond and no N···C═O interactions.

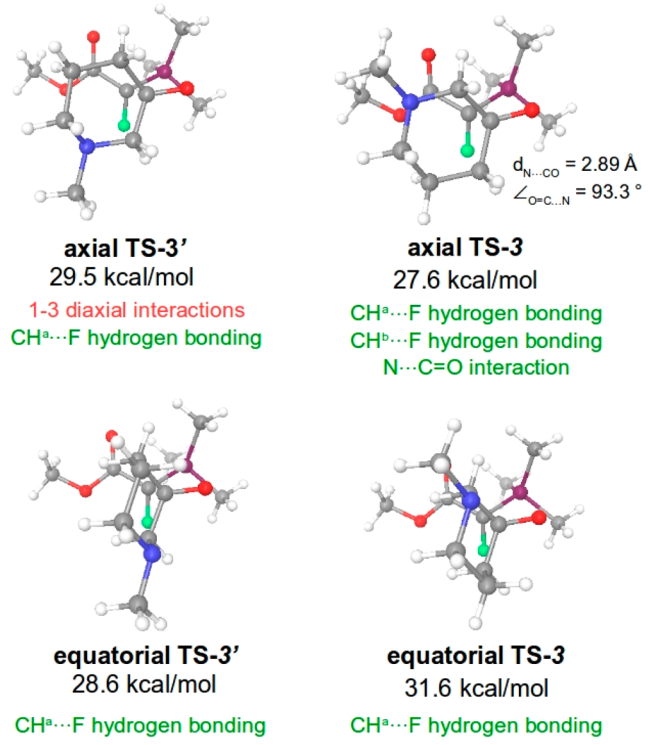
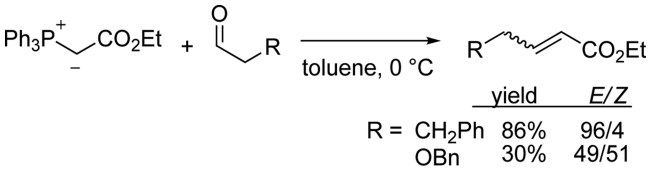


Figure 3. Structure and relative free energy of TSs for the addition of ylide **1a** onto **2b**.

This analysis provides an explanation for the sometimes quite-low *E* selectivity (or even preferential formation of *Z* product) observed in reactions of α-alkoxy aldehydes (Scheme 4).[1f,2] This observed decrease in selectivity is also nicely reproduced by calculations: *trans* addition TS is computed to be more stable than the *cis* one by 0.7 and 2.0 kcal/mol for reaction of ylide **12** with methoxyacetaldehyde and butyraldehyde, respectively (Figure 4). Previously, one of us proposed that a destabilizing interaction between the dipole of the ylide and the C−OR bond dipole in TS-*trans* was responsible for this low selectivity (see Figure 4).[3a,b] This study shows that it can better be accounted for by the presence of a stabilizing O···C═O interaction in TS-*cis* which counterbalances the stabilizing dipole−dipole interaction present in TS-*trans* (vide supra).[12]

Scheme 4. Decrease in *E*/*Z* Selectivity with α-Alkoxy Substitution of Aldehydes



In summary, we have shown that the Wittig reaction between stabilized α-fluorophosphonium ylide **1** and *N*-protected piperidin-3-one derivatives yields the corresponding tetrasubstituted alkenes with a high *E* selectivity. This high selectivity

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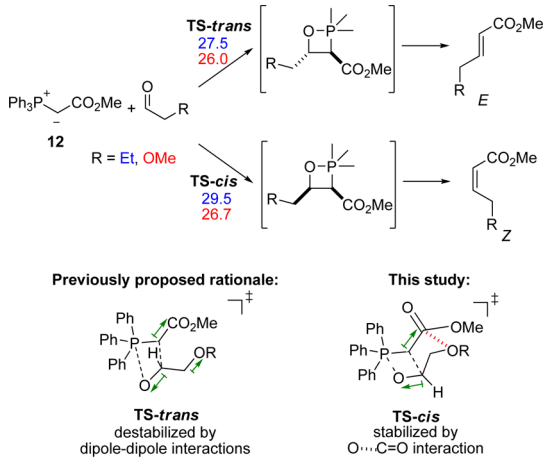

Figure 4. Computed free energy of addition TSs and rationale for the decrease in *E* selectivity observed in Wittig reaction of stabilized ylides when the aldehyde is α-substituted by an alkoxy group (free energies in kcal/mol relative to reactants).

could be extended to other cyclic and acyclic α-heterosubstituted ketones. A detailed investigation showed that observed stereoselectivity can be accounted for by CH···F hydrogen bonds and a stabilizing N···C=O interaction in the *cis* addition TS (TS-**3**) leading to **3a**. Identification of this latter interaction now allows us to rationalize the observed decrease in selectivity for reactions of stabilized ylides with α-alkoxy aldehydes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00344.

Experimental procedures, characterization data, NMR spectra, computational details, other computational data, and Cartesian coordinates for all optimized structures (PDF)

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Notes

The authors declare no competing financial interest.

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(4) In the presence of strongly coordinating ions such as lithium, betaine intermediates may sometimes be formed, and in these cases selectivities are different. In this work, we focus on salt-free reactions.

(5) For a recent in-depth experimental, computational, and dynamic trajectory study on the mechanism of oxaphosphetane formation, see: Chen, Z.; Nieves-Quinones, Y.; Waas, J. R.; Singleton, D. A. *J. Am. Chem. Soc.* **2014**, *136*, 13122−13125.

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(8) Due to the increased acidity of α-protons in **2f**, self-condensation of the ketone was the main reaction in the presence of DBU in this case (entry 8, Table 1). The use of a weaker base such as triethylamine and another solvent (in which ketones were better soluble) allowed, however, the formation of the desired alkenes as the main product, albeit after longer reaction times (entries 9−11, Table 1).

(9) Calculations were carried out at the B3LYP-D3/aug′-cc-pVTZ(toluene)//B3LYP/6-31G*(toluene) level of theory using the Jaguar 8.0 program package (*Jaguar 8.0*; Schrodinger, LLC, New York, NY, 2011). Thermal and entropic contributions to free energy were computed by performing frequency calculations at the B3LYP/6-31G(d) level of theory. See the Supporting Information for full computational details and data.

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(11) See the Supporting Information for full geometrical parameters of these hydrogen bonds, NCI plots, and test calculations for estimating the stabilization energy associated with these CH···F interactions.

(12) A stabilizing O···C=O interaction in TS-**3′** is not possible for geometrical reasons.

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