Organocatalytic Asymmetric Wittig Reactions: Generation of Enantioenriched Axially Chiral Olefins Breaking a Symmetry Plane

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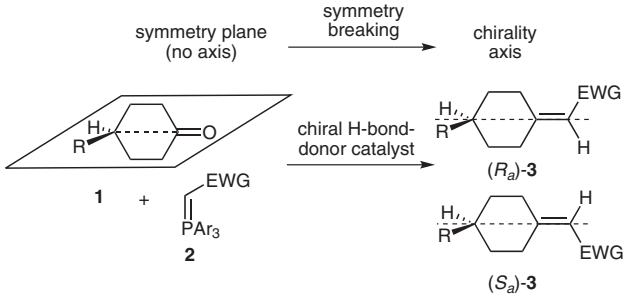
Abstract: The first catalytic asymmetric Wittig reaction is presented. Hydrogen-bond donors catalyze the [2+2] cycloaddition reaction between stabilized phosphorus ylides and 4-substituted cyclohexanones, breaking their symmetry plane and furnishing axially chiral olefins with moderate stereoselectivities.

Key words: asymmetric catalysis, chirality, olefination, Wittig reaction, ylides

Asymmetric organocatalysis has witnessed spectacular advances over the last few years.[1] Transmission of the chiral information from catalyst to substrate has been achieved with high fidelity in an impressive range of chemical transformations. In most cases, the result of these efficient asymmetric protocols is the stereocontrolled formation of a chiral center, typically a tetrahedral carbon atom bearing four different substituents. Also kinetic resolutions, wherein the catalyst distinguishes two enantiomeric substrates and desymmetrization processes, wherein the catalyst recognizes local asymmetry, discriminating two enantiotopic moieties, have been studied in detail. In these latter cases, substrate/product asymmetry is again mostly due to tetrahedral carbon atoms. However, chirality is not restricted to the presence of a chiral center.[2] Compounds featuring a chirality axis or plane are in fact of tremendous importance. Axial/planar chirality is showcased in many natural compounds,[3] ligands or catalysts for asymmetric synthesis,[4] synthetic intermediates,[5] and molecular switches/motors.[6] Use of organocatalysis for the stereocontrolled generation of chiral axes or planes has, however, been largely ignored.[7]

Herein, we present the first example of a catalytic asymmetric Wittig reaction (Scheme 1). The reaction furnishes enantioenriched axially chiral olefins **3** and is catalyzed by hydrogen-bond donors. The Wittig[8] olefination between carbonyl compounds and phosphorus ylides, together with its related counterparts (Horner[9] involving phosphine oxides and Horner–Wadsworth–Emmons[10] involving phosphonates), is amongst the most venerable transformations of organic chemistry. These powerful methods for C=C bond formation have found ubiquitous applications in organic synthesis,[11] including preparations of axially chiral olefins.[12]



Scheme 1 Asymmetric olefination of ketones **1**

Olefination of a ketone featuring a symmetry plane but lacking a symmetry axis leads in fact to an axially chiral alkene, as exemplified in Scheme 1 for the benchmark reaction for asymmetric Wittig-type processes, with 4-substituted cyclohexanones **1**.[13] Stereoselectivity in this class of symmetry-breaking transformations has been achieved in the past using Wittig and related olefinations, exploiting stoichiometric chiral auxiliaries and reagents.[13,14] A single example instead made use of a chiral catalyst.[15,16] Horner–Wadsworth–Emmons olefination of 4-*tert*-butylcyclohexanone (**1a**), performed under phase-transfer-catalysis conditions, gave the corresponding olefin in only moderate enantioselectivity (<57% ee). We tentatively ascribed this moderate stereocontrol to the reversibility of the first step in Horner–Wadsworth–Emmons reactions.[11a] We thus set our focus on the Wittig reaction with stabilized phosphorus ylides **2**, which is known to proceed irreversibly through an asynchronous [2+2]-cycloaddition pathway.[17] To achieve enantioenrichment in the resulting alkenes **3**, we envisioned the use of chiral hydrogen-bond donors[18] as catalysts, to coordinate the cyclohexanone carbonyl which bears a partial negative charge during the cycloaddition (Scheme 2). Applying a simplified working model, selectivity in the prochiral face of the ylide **2** attacking in the [2+2]-cycloaddition step results in the predominant formation of one of the two enantiomeric products (S_a)-**3** and (R_a)-**3**. Stereospecificity in the elimination of phosphine oxide should in fact ensure full central-to-axial chirality transfer. This model assumed a high

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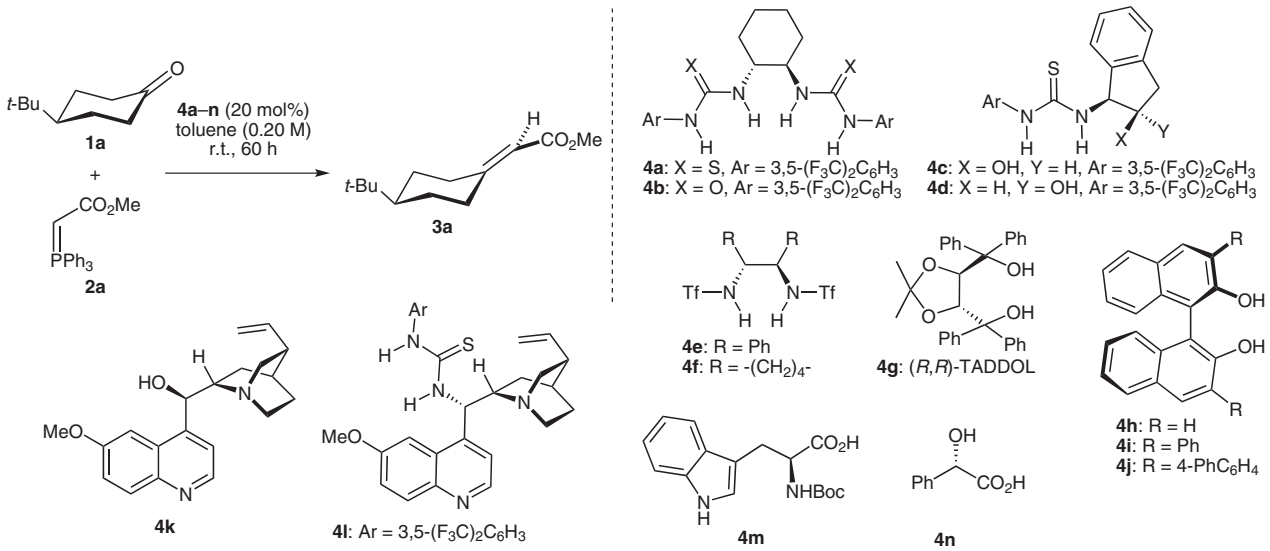
prevalence of the equatorial conformer in the parent cyclohexanone **1**, as well as exclusive attack at the equatorial face of the ketone[19] by the bulky ylide **2** nucleophile. However, competing reaction pathways cannot be excluded.

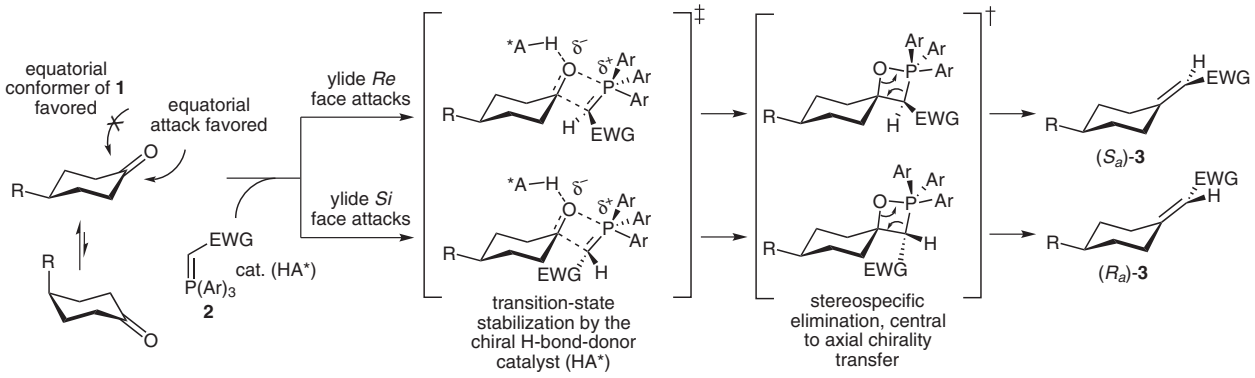
We started our investigations studying the asymmetric Wittig reaction between 4-*tert*-butylcyclohexanone (**1a**) and phosphorus ylide **2a**, bearing a methyl ester as stabilizing group (Table 1). Confident in that weak hydrogen-bond donors, such as alcohols, phenols, (thio)ureas, and aliphatic carboxylic acids, would not protonate the ylide leading to catalyst deactivation,[20,21] we screened a number of such compounds[18] in the reaction. As shown in Table 1 for a representative set of results, there is not a clear correlation between catalyst acidity and activity. Amongst the (thio)urea catalysts **4a**–**d** tested, **4a** seemed to be the most efficient (Table 1, entries 1–4). Bifunctional catalysts **4k**,**l** bearing a basic tertiary amino group were instead found to be unsuitable (Table 1, entries 11 and 12). The same holds for the rather acidic triflimide catalysts **4e**,**f**, as well as for the binaphthols **4h**–**j** (Table 1, entries 5, 6, 8–10). In contrast, α-amino and α-hydroxy acid derivatives **4m**,**n** catalyzed the reaction to some extent; stereoselectivity was, however, very poor (Table 1, entries 13 and 14). The most efficient catalyst in terms of enantioinduction was found to be the (*R*,*R*)-TADDOL (**4g**),

Table 1 Representative Results from the Screening of the Different Catalysts **4a**–**n** in the Wittig Reaction between **1a** and **2a**[a]



Entry	Catalyst	Conversion (%)[b]	ee (%)[c]
1	**4a**	20	45
2	**4b**	11	25
3	**4c**	7	20
4	**4d**	10	17
5	**4e**	<5	–
6	**4f**	<5	–
7	**4g**	6	53
8	**4h**	15	2
9	**4i**	4	11
10	**4j**	5	0
11	**4k**	<5	–
12	**4l**	7	3
13	**4m**	11	16
14	**4n**	14	14

[a] Conditions: ketone **1a** (0.05 mmol), catalyst **4a**–**n** (0.010 mmol, 20 mol%), ylide **2a** (0.0625 mmol, 1.25 equiv), toluene (0.25 mL), 60 h, r.t.
[b] Determined by ^{1}H NMR spectroscopy.
[c] Determined by chiral stationary phase HPLC.



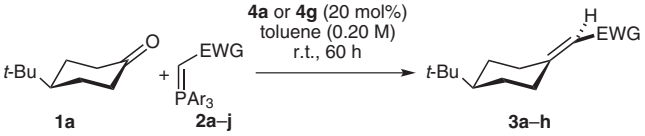
Scheme 2 Simplified working model for the asymmetric Wittig reaction catalyzed by hydrogen-bond donors (HA*)

which produced the axially chiral alkene **3a** with a promising 53% ee, despite the very low conversion (Table 1, entry 7).

The effect of stereoelectronic variations at the ylide **2** was studied next, using the most promising catalysts **4a**[22] and **4g**[23] (Table 2). Whereas the steric bulk of the ester group did not influence the enantioinduction to a great extent, increasing electron density at the ester did improve the conversion, with both **4a** and **4g** as catalysts (Table 2, entries 1–6). The *tert*-butyl derivative **2c** gave the best results in terms of conversion. Enantioselectivity was instead slightly better with the benzyl ester ylide **2b**, but only when **4g** was used (Table 2, entry 4). We somehow expected ketone-, cyano-, and thioester-derived ylides **2d–f** to be less reactive, due to the strong electron-withdrawing properties of these stabilizing groups suppressing nucleophilicity. Indeed, only the cyano-derived ylide **2f** furnished the corresponding olefin **3f** (Table 2, entries 7–10). Stereoselectivity was similar or lower compared to the ester-derived ylides **2a–c** (Table 2, entries 1–6). This stabilizing group was thus discarded. The lack of reactivity displayed by *p*-nitrophenyl[24] and amide-derived ylides **2g**,**h** was instead much more surprising (Table 2, entries 11 and 12). At this point, an extensive screening of solvents and reaction dilutions was undertaken, without giving notable improvements. Similarly, variation of the catalyst structure, using TADDOL derivatives bearing different aromatic groups (1-naphthyl and 2-naphthyl), and a series of 1,2-cyclohexanediamine-derived thioureas, did not improve the results obtained with the lead catalysts **4a** and **4g**.

Therefore we turned again our attention to a fine tuning of the ylide structure, with the aim of increasing its nucleophilicity in order to perform the reaction at lower temperatures. To this end, **2i** and **2j** – bearing electron-rich aryl groups at phosphorus[25] – were prepared and tested in the reaction. Indeed, these species showed enhanced reactivity (Table 2, entries 13–15). Enantioselectivity was, however, not compromised only when TADDOL **4g** was used as catalyst. Using these electron-rich ylides **2i** and **2j**, and swapping reaction stoichiometry, it was finally possible to cool the reaction to 0 °C, with a beneficial effect on the enantioselectivity (Table 2, entries 16 and 17). Good lev-

Table 2 Representative Results from the Screening of the Different Ylides **2a–j** in the Wittig Reaction[a]



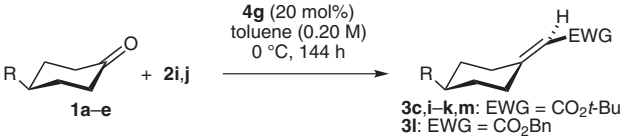
Entry	Cat. **4**	Ylide **2**	EWG	Ar	Conv. of **3** (%)[b]	ee (%)[c]
1	**4a**	**2a**	CO_2Me	Ph	**3a** 20	45
2	**4g**	**2a**	CO_2Me	Ph	**3a** 6	53
3	**4a**	**2b**	CO_2Bn	Ph	**3b** 30	37
4	**4g**	**2b**	CO_2Bn	Ph	**3b** 10	68
5	**4a**	**2c**	CO_2t-Bu	Ph	**3c** 52	48
6	**4g**	**2c**	CO_2t-Bu	Ph	**3c** 22	64
7	**4a**	**2d**	COMe	Ph	**3d** <5[d]	–
8	**4a**	**2e**	COSBn	Ph	**3e** <5[d]	–
9	**4a**	**2f**	CN	Ph	**3f** 32	48
10	**4g**	**2f**	CN	Ph	**3f** 18	27
11	**4a**	**2g**	4-$O_2NC_6H_5$	Ph	**3g** <5[d]	–
12	**4a**	**2h**	$CONMe_2$	Ph	**3h** <5[d]	–
13	**4a**	**2i**	CO_2t-Bu	4-$MeOC_6H_4$	**3c** 82	22
14	**4g**	**2i**	CO_2t-Bu	4-$MeOC_6H_4$	**3c** 55	60
15	**4g**	**2j**	CO_2Bn	4-$MeOC_6H_4$	**3b** 41	68
16[e]	**4g**	**2i**	CO_2t-Bu	4-$MeOC_6H_4$	**3c** 72	70
17[e]	**4g**	**2j**	CO_2Bn	4-$MeOC_6H_4$	**3c** 50	75

[a] Conditions: ketone **1a** (0.05 mmol), catalyst **4a** or **4g** (0.010 mmol, 20 mol%), ylide **2a–j** (0.0625 mmol, 1.25 equiv), toluene (0.25 mL), 60 h, r.t.
[b] Determined by ^{1}H NMR spectroscopy.
[c] Determined by chiral stationary phase HPLC.
[d] Same result with catalyst **4g**.
[e] Reaction performed at 0 °C, using 3 equiv of **1a**.

els of conversion were obtained, even at this reduced temperature, with the more electron-rich *tert*-butyl ester derived ylide **2i**.

Using these latter reaction conditions, and prolonging reaction time to 144 hours, the effect of variations in the cyclohexanone 4-substituent was briefly explored. As shown in Table 3, results comparable with the parent 4-*tert*-butyl-substituted cyclohexanone **1a** were obtained using a range of 4-alkyl-substituted cyclohexanones **1b–d** (Table 3, entries 1–4), as well as 4-phenyl-substituted **1e** (Table 3, entry 6), using ylide **2i**. As we were not able to determine the enantiomeric excess of the olefin **3k** derived from 4-methyl cyclohexanone **1d**, the reaction was also performed with the corresponding benzyl ester ylide **2j** (Table 3, entry 5). Lower yield of the olefin **3l** was obtained, as expected.

Table 3 Variation of the Cyclohexanone **1**[a]



Entry	1	R	3	Yield (%)[b]	ee (%)[c]
1	**1a**	*t*-Bu	**3c**	74	70
2	**1b**	*i*-Pr	**3i**	76	59
3	**1c**	*n*-Pr	**3j**	76	64
4	**1d**	Me	**3k**	83	n.d.
5[d]	**1d**	Me	**3l**	41	56
6	**1e**	Ph	**3m**	93	67

[a] Conditions: ketone **1a–e** (0.45 mmol), catalyst **4g** (0.030 mmol), ylide **2i** (0.15 mmol), toluene (0.75 mL), 0 °C, 144 h.
[b] Isolated yield after chromatography on silica gel.
[c] Determined by chiral stationary phase HPLC.
[d] Ylide **2j** was used, in a toluene–*n*-hexane (1:3) solvent mixture.

In conclusion, the present work unequivocally demonstrates that absolute stereochemistry in asymmetric Wittig reactions can be controlled using hydrogen-bond donors as catalysts. Coordination and stabilization of the transition state in the [2+2] cycloaddition leading to an oxaphosphoethane intermediate carrying the chiral information is considered to be responsible for the observed stereocontrol. Although currently restricted to the benchmark reaction with 4-substituted cyclohexanone derivatives **1** leading to axially chiral olefins **3**,[26] these findings might open the way to the development of other classes of asymmetric Wittig-type transformations.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(26) We tested 3-phenylcyclobutanone and a 3,4-*cis*-disubstituted cyclopentanone, using both catalyst **4a** and **4g** under different reaction conditions. Whereas the cyclopentanone was found to be much less reactive than 4-substituted cyclohexanones, giving the corresponding olefins only in low yields (<20%), the cyclobutanone showed good reactivity, but the alkene was obtained with rather poor enantioselectivity (<36% ee). See the Supporting Information for details.