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SHORT COMMUNICATION

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First Enantioselective Catalytic Wittig Reaction

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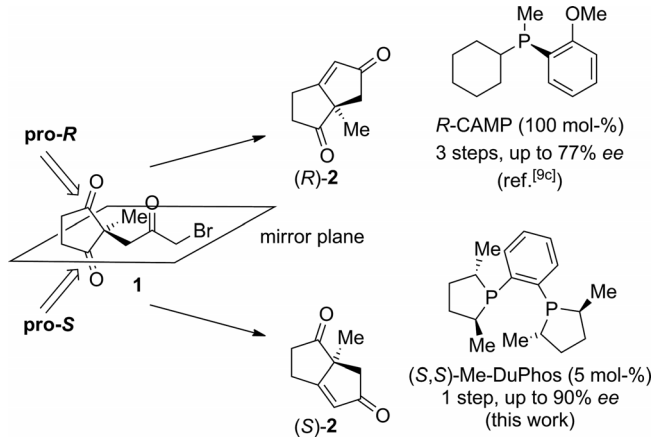
Herein we present the first catalytic enantioselective Wittig reaction. Chiral mono- and diphosphines were employed as catalysts for the desymmetrization of a prochiral ketone. The reaction was performed under microwave dielectric heating as well as under conventional heating. Selected catalysts led to moderate to good yields and enantioselectivities. In the presence of (+)-1,2-bis[(2*S*,5*S*)-2,5-dimethylphospholano]-benzene [(*S*,*S*)-Me-DuPhos], an enantiomeric excess of up to 90 % was obtained.

Introduction

In the beginning of this century, the award of the Nobel Prize to Knowles, Noyori, and Sharpless emphasized the advances and importance of enantioselective catalysis.[1] At the same time, asymmetric organocatalysis began to evolve as a fast-growing research area.[2] Even though great advances have been made in the synthesis of enantiomerically pure compounds, it still remains a fundamental research topic. Desymmetrization of *meso* compounds into derivatives with high optical purity is of particular interest, as the synthesis of the corresponding prochiral compounds is often straightforward.[3] Among others, this concept has been applied to the synthesis of chiral alkenes, for example, by asymmetric olefin metathesis.[4] An early example of the synthesis of a chiral alkene from a prochiral precursor is the proline-catalyzed intramolecular desymmetrization of *meso* dicarbonyl compounds known as the Hajos–Parrish–Eder–Sauer–Wiechert reaction.[5]

The Wittig reaction and related phosphorus-based transformations belong to fundamental methods for the chemo- and regioselective preparation of alkenes from carbonyl compounds.[6] In this context, there have been sporadic reports on asymmetric versions of the desymmetrization of suitable carbonyl substrates, mostly connected to the Horner–Wadsworth–Emmons reaction.[7] Those transformations usually require chiral auxiliaries attached either to the substrate or to the alkenylation reagent as a source of asymmetric induction.[8] In contrast, there have been only a few reports on asymmetric Wittig reactions.[9] Trost et al. reported the enantioselective synthesis of diketone **2** by differentiation of the two enantiotopic faces by utilizing stoichiometric amounts of the P-chiral phosphine *o*-anisylcyclohexylmethylphosphine [(*R*)-CAMP, Scheme 1].[9c,9d] Recently, the first catalytic Wittig reaction was reported by O'Brien et al., who employed an achiral phospholane as the catalyst and silanes as the reducing agents to regenerate the catalyst in situ from the corresponding phosphine oxide.[10] However, so far the challenge to develop a catalytic asymmetric procedure has remained unsolved. Herein, we report the first enantioselective catalytic Wittig reaction.



Scheme 1. Desymmetrization of prochiral ketone **1** by stoichiometric and catalytic Wittig reactions by utilizing chiral phosphines.

Results and Discussion

Bicyclic compounds such as **2** are versatile building blocks in pharmaceutical and natural product synthesis.[5,11] Hence, we chose the desymmetrization of prochiral diketone **1** as the model reaction to develop an enantioselective catalytic Wittig reaction. Substrate **1** can be easily prepared by allylation followed by bromo hydroxylation of **4** with *N*-bromosuccinimide (NBS) to afford bicyclic hemiketal **5** as a 2:1 mixture of diastereomers (Scheme 2). Oxidative ring

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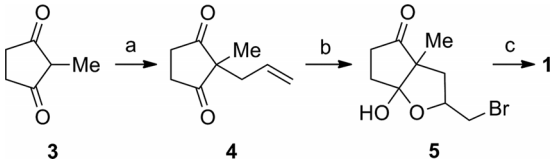
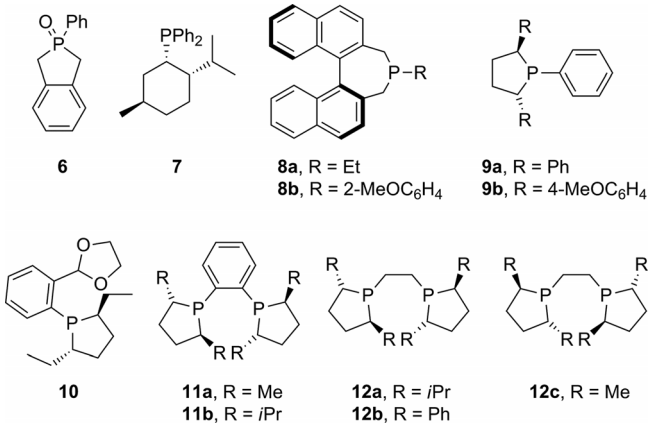
opening with Jones reagent gave desired α-halo ketone **1** as a precursor for the desymmetrization to the bis-nor-Wieland–Miescher ketone **2** in 79% yield.



Scheme 2. Synthesis of prochiral diketone **1**. Reagents and conditions: (a) Allyl bromide, KO*t*Bu, DMSO, 23 °C 16 h, 60%. (b) NBS, H_2O, acetone, 23 °C, 3 h, 85%. (c) CrO_3, aq. H_2SO_4 (6.3 M), acetone, 23 °C, 24 h, 79%.[12]

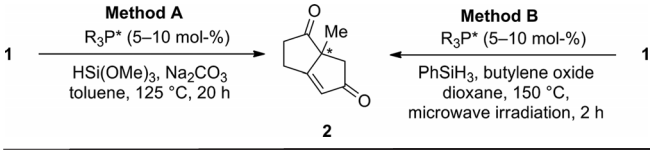
Given our interest in phosphorus-based organocatalysis and investigations toward catalytic Wittig-type reactions, we were engaged to develop an enantioselective catalytic Wittig reaction.[13] We identified several readily available chiral phosphines **7**–**12** as promising catalysts for this reaction (Scheme 3). We developed two novel methods for the performance of catalytic Wittig reactions.[14] Method A is based on conventional heating in toluene with sodium carbonate as the base and trimethoxysilane as the reducing agent by using 5–10 mol-% catalyst (Table 1). Method B is a microwave-assisted variant that is performed by utilizing dioxane as the solvent, phenylsilane as the reducing agent, and butylene oxide as the capped base.[15] Under the conditions of method A, employment of achiral phospholane **6** gave desired product *rac*-**2** in a good yield of 72% (Table 1, entry 1). To the best of our knowledge, this is also the first example of the conversion of a ketone in a catalytic Wittig reaction.



Scheme 3. Promising precatalyst **6** and chiral phosphines **7**–**12** for the (enantioselective) catalytic Wittig reaction.[17]

Encouraged by this result, we initially screened various structurally different chiral monophosphines **7**–**10**. Even though catalyst **7** led only to very low yields of (*S*)-**2**, the enantiomeric ratios under the reaction conditions of both methods A and B were promising (Table 1, entries 2 and 3). The utilization of 1,1′-bi-2-naphthol (BINOL) derivatives **8a** and **8b** proved for the first time the feasibility of an enantioselective catalytic Wittig reaction. Under the conditions of methods A and B, both catalysts gave moderate yields

Table 1. Screening of chiral (pre)catalysts for the enantioselective catalytic Wittig reaction.



Entry	Cat. (mol-%)	Cond.	Major product	Yield [%]	*ee*[a] [%]	*er*[a] (*R*/*S*)
1	**6** (10)	A	*rac*-**2**	72[b]	0	50:50
2	**7** (10)	A	(*S*)-**2**	<5[c]	40	30:70
3	**7** (10)	B	(*S*)-**2**	<5[c]	32	34:66
4	**8a** (10)	A	(*R*)-**2**	34[b]	34	67:33
5	**8a** (10)	A	(*R*)-**2**	62[b]	34	67:33
6	**8b** (10)	A	(*R*)-**2**	32[b]	74	87:13
7	**8b** (10)	B	(*R*)-**2**	10[b]	58	80:20
8	**9a** (10)	A	(*R*)-**2**	<20[c]	4	52:48
9	**9a** (10)	B	(*R*)-**2**	<20[c]	8	54:46
10	**9b** (10)	A	(*R*)-**2**	<20[c]	8	54:46
11	**9b** (10)	B	(*R*)-**2**	<20[c]	10	55:45
12	**10** (10)	A	(*R*)-**2**	<20[c]	8	54:46
13	**10** (10)	B	(*R*)-**2**	50[b]	8	54:46
14[d]	**11a** (5)	A	(*R*)-**2**	<10[c]	90	95:5
15	**11a** (5)	A	(*R*)-**2**	<10[c]	86	93:7
16	**11a** (5)	B	(*R*)-**2**	39[b]	62	81:19
17	**11b** (5)	A	(*S*)-**2**	<10[c]	54	23:77
18	**11b** (5)	B	(*S*)-**2**	<10[c]	44	28:72
19	**12a** (5)	A	(*S*)-**2**	<10[c]	28	36:64
20	**12a** (5)	B	(*S*)-**2**	42[b]	28	36:64
21	**12b** (5)	A	(*R*)-**2**	31[b]	20	60:40
22	**12b** (5)	B	(*R*)-**2**	29[b]	12	56:44
23	**12c** (5)	A	(*R*)-**2**	53[c]	36	68:32
24	**12c** (5)	B	(*R*)-**2**	63[b]	32	66:34

[a] The *ee* and *er* values were determined by chiral GC–MS. [b] Yield of isolated product after column chromatography. [c] Yield was determined by analysis of the reaction mixture by ^{1}H NMR spectroscopy. [d] The reaction time was reduced to 8 h.

of **2** with up to 74%*ee* (Table 1, entries 4–7). The absolute configuration of products **2** was assigned by comparison of the optical rotation values with those that were previously reported by Trost et al.[9d] As phospholane derivatives were expected to lead to improved yields, initially monophosphines **9** and **10** were employed (Table 1, entries 8–13).[10a,10b,16] However, only in the presence of catalyst **10** under microwave conditions was desired product **2** isolated in 50% yield (Table 1, entry 13). In all other cases, the conversion was low or complex reaction mixtures were obtained. Unfortunately, the obtained enantiomeric excess values with all three catalysts was ≤10%. We then turned our attention to readily available chiral diphosphines. The catalyst amount was reduced to 5 mol-% to allow a direct comparison with the monofunctional counterparts. At first, (*S*,*S*)-Me-DuPhos (**11a**) was employed as the catalyst, and to our delight, the enantiomeric excess increased up to 90% under thermal conditions (Table 1, entry 14). Although the yield was below 10% and, hence, the conversion seemed to be rather stoichiometric than catalytic, the enantiomeric excess was very encouraging. Moreover, under the conditions of method B desired product **2** was isolated in a good yield of 39% with 62%*ee* (Table 1, entry 16). The utilization

of sterically more demanding derivative **11b** did not lead to an improvement (Table 1, entries 17 and 18). Conversion of **1** in the presence of 1,2-bis[(2*R*,5*R*)-2,5-diisopropylphospholano]ethane [**12a**, (*R*,*R*)-*i*Pr-BPE] gave the desired product in up to 42% yield with 28%*ee* (Table 1, entries 19 and 20). (*R*,*R*)-Ph-BPE (**12b**) gave comparable results under both reaction conditions (Table 1, entries 21 and 22). However, utilization of (*R*,*R*)-Me-BPE (**12c**) proved once again the general feasibility of this method, which led to **2** in moderate yields and *ee* values (Table 1, entries 23 and 24).

Conclusions

In summary, we introduced the desymmetrization of prochiral ketone **1** into optically active olefin **2** by an asymmetric Wittig reaction under catalytic conditions. In the presence of catalytic amounts of chiral phosphine derivatives the desired product was obtained in very good enantiomeric excess up to 90% with yields up to 63%, which prove the general feasibility of an enantioselective catalytic Wittig reaction. Over 50 years after the discovery of the Wittig reaction[18] by Georg Wittig and co-workers, this is, to the best of our knowledge, the first example of a catalytic enantioselective version of this reaction.

Supporting Information (see footnote on the first page of this article): Experimental details, copies of the ^{1}H NMR and ^{13}C NMR spectra of all key intermediates **1**, **3**–**5** and final product **2**, as well as chiral GC chromatograms.

Acknowledgments

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[16] (*R*,*R*)-Me-BPE (Strem, > 98%), (*R*,*R*)-*i*Pr-BPE (ABCR, 97%), (*R*,*R*)-Ph-BPE (ABCR, 95%), (*S*,*S*)-Me-DuPhos (Strem, 98+%), (*S*,*S*)-*i*Pr-DuPhos (ABCR, 98%), (*S*)-Neomenthyldiphenylphosphane (Strem, 98%), 2-{2-[(2*S*,5*S*)-2,5-diethyl-1-phospholan]phenyl}-1,9-dioxolane (ABCR, 97%).

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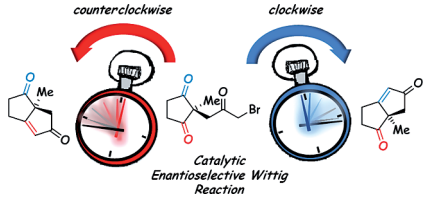
Desymmetrization

Over 50 years after the discovery of the Wittig reaction, the first example of a catalytic enantioselective version of this reaction is reported. Desymmetrization of a prochiral ketone leads to the so-called bisnor-Wieland–Miescher ketone in up to 90% *ee*.



Keywords: Asymmetric synthesis / Homogeneous catalysis / Olefination / Wittig reaction / Phosphanes

