Asymmetric Synthesis

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Asymmetric Aza-Wittig Reactions: Enantioselective Synthesis of β-Quaternary Azacycles**

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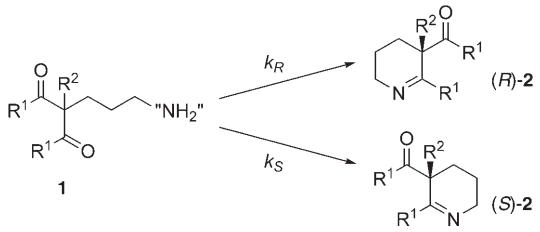
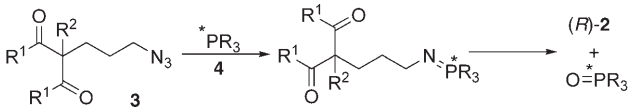
Polysubstituted nitrogen heterocycles are prevalent in pharmaceuticals and biologically important natural product targets, and new approaches to these systems are in constant demand. A frequently occurring motif is the presence of an asymmetric all-carbon quaternary center in the 3-position of pyrrolidines, piperidines, and their polycyclic derivatives. All-carbon quaternary stereocenters are amongst the most challenging constructs in modern synthesis,[1] and a new approach to such functionality would be of considerable utility. It occurred to us that this moiety could potentially be introduced from simple prochiral 1,3-dicarbonyl precursors **1** bearing an amine equivalent by the desymmetrizing formation of a keto imine **2** (Scheme 1).[2]



Scheme 1. Desymmetrizing imine formation by amine equivalent "NH_2" for the construction of quaternary asymmetric centers.

Bonjoch and co-workers have demonstrated that a diastereoselective variant of this strategy is possible by using α-chiral amines in their studies on reductive amination of 2-(2-oxooethyl)cycloalkyl 1,3-diones.[3,4] A conceptually much more powerful and general strategy would employ external chiral reagents in place of nonrecyclable chiral amines and further would leave the imine intact for subsequent derivatization. Given the rapid and reversible nature of imine formation, the potential for reagent-based acceleration of the reaction and/or retention of the stereochemical integrity of the products that are formed seems low. The aza-Wittig reaction of iminophosphoranes with carbonyl compounds,[5,6] however, is an irreversible imine-forming reaction and also allows for the introduction of external chirality through the use of chiral ligands on phosphorus. Thus, the Staudinger reaction of azidodiketones **3** with an appropriate chiral phosphorus reagent **4** would generate a chiral iminophosphorane, which undergoes selective metathesis with one of the two (now diastereotopic) carbonyl groups to yield, irreversibly, enantioenriched **2** and the corresponding phosphorus(V) oxide (Scheme 2). The analogies with asymmetric variants of the carbon-based Wittig reaction are clear,[7,8] but to our knowledge there have been no reports of asymmetric variants of the aza-Wittig reaction. Herein we outline the successful demonstration of the first examples of this process.



Scheme 2. Asymmetric aza-Wittig reactions mediated by chiral phosphorus(III) reagents **4**.

The azido-1,3-diketone substrates **3a–d** were prepared in four steps commencing from either pentane-1,3-dione or cyclohexane-1,3-dione as shown in Scheme 3. For the chiral phosphorus(III) reagents, we chose the known and readily available proline-derived diazaphospholidine **4a**[9] and oxazaphospholidine **4b**,[10] and the cyclohexyldiamine-derived diazaphospholidine **4c** (Scheme 3).[11]

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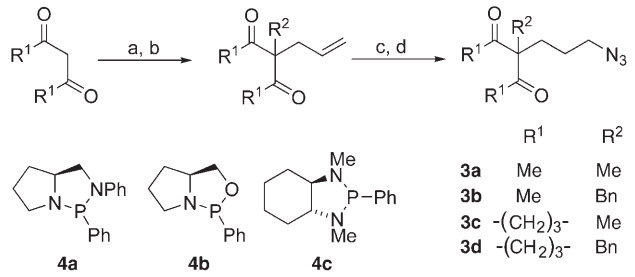
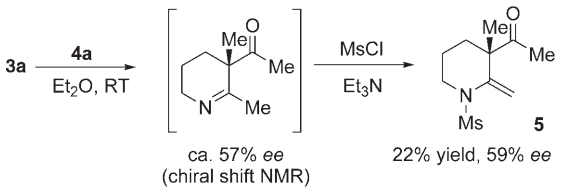


Scheme 3. Synthesis of substrates **3a–d**. Reagents and conditions: a) aqueous NaOH, MeI or BnBr; b) 1 M NaOH, allyl bromide, Bu_4NI, room temperature; c) Cy_2BH, THF, 0 °C, then NaOAc, I_2; d) NaN_3, Bu_4NI, aqueous acetone, room temperature. Overall yields: **3a** 44%, **3b** 41%, **3c** 29%, **3d** 18%. Bn = benzyl; Cy = cyclohexyl.

Initial studies with diketo azide **3a** and diazaphospholidine **4a** showed that the reaction proceeded to conversion after about 56 hours at room temperature. Initially we attempted to assay the enantiomeric purity of the keto imine product from the crude reaction mixture by chiral shift NMR spectroscopic studies using BINOL as an additive. These studies showed that significant asymmetric induction was occurring (up to ca. 57% *ee*), but the values were found not to be reproducible between runs of identical experiments. We suspected that trace moisture was catalyzing racemization through imine hydrolysis to the achiral aminodiketone, and the viability of this pathway was verified by monitoring the *ee* value of a sample of the crude imine which was left exposed to atmospheric moisture. The enantiomeric purity decreased steadily from 50–60% to 0% over a period of three days. We therefore repeated the experiments with rigorous exclusion of water and further trapped the crude keto imine product as the stable *N*-methanesulfonyl enamine **5** by treatment with methanesulfonyl chloride and triethylamine (Scheme 4).



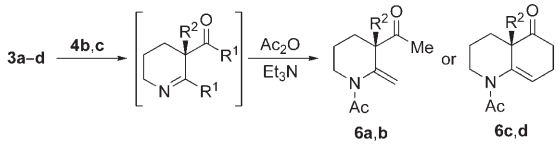
Scheme 4. Trapping of the initially formed keto imines leads to preservation of the enantiomeric integrity of the reaction. Ms = methanesulfonyl.

Upon chiral GC analysis of **5** we were delighted to find that the enantiomeric purity of the crude imine had been retained in the isolated product. It should be noted that the trapping strategy not only safeguards the enantiomeric integrity of the products but also further differentiates the two desymmetrized functional groups—the remaining ketone is electrophilic whereas the newly formed enamine is nucleophilic.

Encouraged by these results, we further optimized the reaction by a) utilizing the more reactive phosphorus(III) reagents **4b** and **4c** to shorten the reaction times and b) changing the trapping regime from mesylation to the higher-yielding and more reliable N-acetylation. These optimized conditions were applied to the range of substrates **3a–d**, and the results are shown in Table 1.

The reproducibility of the reaction was verified by carrying out duplicate runs—the *ee* values shown are the

Table 1: Desymmetrization of diketo azides **3a–d** to yield **6a–d**.[a]

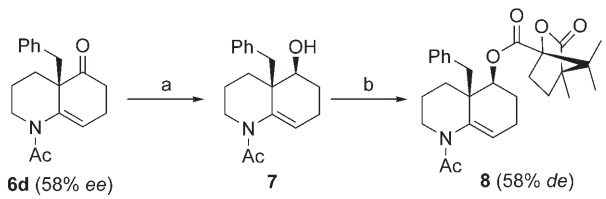


Entry	Azide	Reagent	Yield [%][b]	*ee* [%][c]
1	**3a**	**4b**	67	43.0
2	**3a**	**4c**	74	29.5
3	**3b**	**4b**	69	60.5
4	**3b**	**4c**	71	24.5
5	**3c**	**4b**	75	29.0
6	**3c**	**4c**	78	43.0
7	**3d**	**4b**	92	38.5
8	**3d**	**4c**	95	57.0

[a] Reactions carried out in Et_2O or THF, at room temperature or elevated temperature; for individual reaction conditions, see the Supporting Information. [b] Yield of isolated purified product (average of two runs). [c] Average of two runs (all values ±2%) as determined by chiral HPLC analysis on Chiralcel OD or OJ columns. Ac = acetyl.

average of the two runs with a maximum variance of ±2%. In all cases the yields of the isolated products were good to excellent. In general the oxazaphospholidine **4b** gave higher asymmetric induction for the acyclic substrates whereas the diazaphospholidine **4c** gave higher asymmetric induction for the cyclic substrates. The maximum levels of asymmetric induction were around 60% *ee*. Though this value is not yet at the high levels observed in many modern asymmetric transformations, this result represents the first successful demonstration that the asymmetric aza-Wittig reaction is a viable process. We anticipate that further tuning of the reagents and/or substrates will lead to enhanced enantioselectivity.

The absolute sense of asymmetric induction was determined for keto enamide **6d**. We exploited the differentiated reactivity of the ketone and enamine by carrying out chemoselective reduction of the ketone with sodium borohydride to afford **7** (Scheme 5). Derivatization of the resulting equatorial alcohol with (1*S*)-camphanic chloride gave ester **8** (Scheme 5). The material that was formed had 58% *de* by ^{1}H NMR spectroscopy and HPLC, thus confirming the



Scheme 5. Chemoselective manipulation of keto enamides and proof of absolute stereochemistry. Reagents and conditions: a) $NaBH_4$, room temperature (93% yield); b) (1*S*)-camphanic chloride, DMAP, DCE, reflux (98% yield). DMAP = 4-(dimethylamino)pyridine; DCE = 1,2-dichloroethane.

measured asymmetric induction. The major diastereoisomer was isolated by preparative HPLC, and crystals were grown for X-ray diffraction analysis.[12] The obtained crystal structure confirmed that the iminophosphorane had attacked the pro-*R* carbonyl group of **3d**.

In summary, we have disclosed the first example of a new class of asymmetric transformation, the asymmetric aza-Wittig reaction, in the context of the desymmetrization of prochiral azido-1,3-diketones. Further work to improve the levels of enantioselectivity, to extend the range of substrates for desymmetrization, and to apply this reaction in target synthesis is in progress.

Experimental Section

A thoroughly flame-dried two-necked flask, fitted with a dry reflux condenser and connected to a Schlenk line through a rotaflo stopcock, was charged with an azidodiketone substrate **3a–d** (0.5 mmol, 1.0 equiv), and the apparatus was evacuated and then purged with a positive pressure of nitrogen. Freshly distilled dry solvent (see the Supporting Information for individual experimental details) was added to the flask by a septum, and a solution of the phosphane **4b** or **4c** (0.6 mmol, 1.2 equiv) was added, the total volume of solvent being 5 mL. The septum was replaced with a glass stopper, and the reaction was allowed to proceed either at room temperature or with heating (see the Supporting Information). At the end of the reaction, solvent was removed in vacuo to give the crude imine. The apparatus was then purged with a positive pressure of nitrogen, the glass stopper was replaced with a rubber septum, and DCE (5 mL), NEt_3 (4.0 equiv), Ac_2O (2 equiv), and DMAP (0.1 equiv) were successively added to the flask. The septum was replaced with a glass stopper, and the mixture was heated in an oil bath at 85–90 °C for 5–9 h. The mixture was then cooled to room temperature, diluted with dichloromethane (40 mL), washed with water (50 mL) and brine (50 mL), and dried with $MgSO_4$. The solvent was evaporated to give a residue, which was preadsorbed on silica gel and purified by flash column chromatography.

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[12] CCDC-603132 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

