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Phosphine-Catalyzed Synthesis of Chiral *N*-Heterocycles *via* (Asymmetric) P(III)/P(V) Redox Cycling

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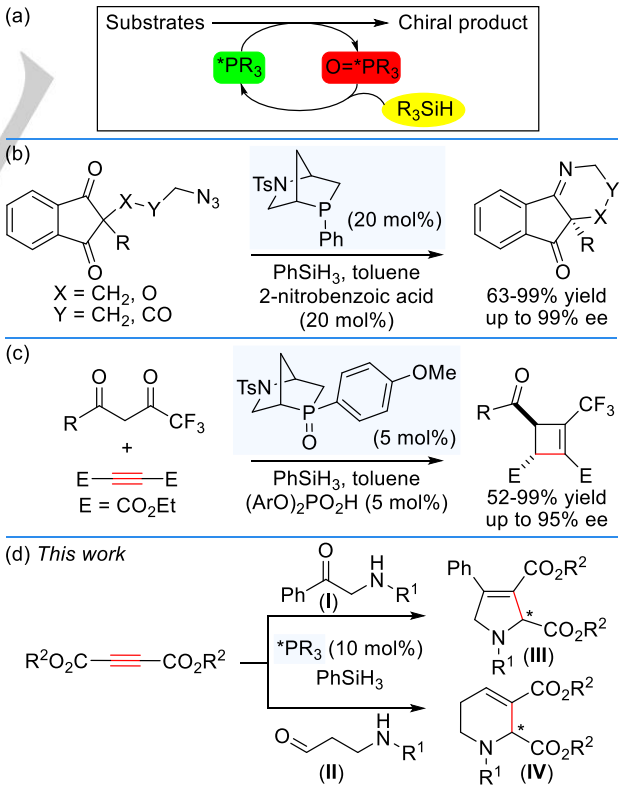
Abstract: Phosphine-catalyzed tandem Michael addition/intramolecular Wittig reactions have been developed for the synthesis of chiral 2,5-dihydro-1*H*-pyrrole and tetrahydropyridine derivatives. These processes have been rendered catalytic in phosphine, thanks to the *in situ* reduction of phosphine oxide by phenylsilane. Furthermore, catalytic and asymmetric P(III)/P(V) processes were implemented using enantiopure chiral phosphines.

In the last decade, a great effort has been invested to develop catalytic processes involving phosphines, *via in situ* reduction of the phosphine oxide formed during the reaction.[1] Indeed, the use of organosilane as reducing agent allows the chemoselective reduction of the phosphine oxide byproduct and therefore the regeneration of the trivalent phosphine, the “active” catalyst. Based on this strategy, several different reactions were made more sustainable, such as the Wittig,[2] Staudinger,[3] Mitsunobu,[4] Appel[5] and Cadogan[6] reactions, among others.[7] Interestingly, different tandem catalytic processes have also been developed. Alongside with tandem transformations such as the Staudinger/aza-Wittig reaction,[8] we designed a catalytic tandem Michael addition/intramolecular Wittig reaction, for the synthesis of *N*-heterocycles and polysubstituted cyclopentenones.[9] The purification step of these processes is significantly simplified because the silanol/siloxane waste (coming from the phosphine oxide reduction with silane) is easily separated from the crude mixture with a simple liquid-liquid extraction. Furthermore, in cases involving the formation of stereogenic centers, these catalytic processes could also unlock the development of asymmetric transformations (Scheme 1a). While it was previously not conceivable to use stoichiometric quantities of expensive chiral phosphines for these transformations, it is now possible to consider the use of substoichiometric amounts of chiral phosphines. The generation of such P^{III}/P^{V} enantioselective processes has been considered for a long time as an arduous task, as it is very difficult to find an enantiopure chiral phosphine which could be at the same time nucleophilic enough at the P^{III} oxidation state, and with an easily reductible phosphine oxide $O=P^{V}$ under mild reaction conditions. Furthermore, in the context of enantioselective catalysis, the product has to be isolated with high stereoselectivity. All these prerequisites explain the difficulty of the present task for the development of new P^{III}/P^{V} catalytic and asymmetric redox transformations. In 2014, Werner described the first enantioselective catalytic Wittig transformation, *via* the desymmetrization of prochiral diketones.[10] After these initial results, it was not until 2019 that Kwon and our group simultaneously developed highly efficient catalytic and asymmetric tandem processes. Indeed, the desymmetrization of prochiral azido-1,3-diketones *via* a P^{III}/P^{V} process was established with the use of chiral phosphine *endo*-phenyl-HypPhos, phenylsilane as reducing agent and 2-nitrobenzoic acid as additive (Scheme 1b).[11] Different heterocycles were isolated in good yields and excellent enantioselectivities. The same year, we developed the first catalytic and asymmetric tandem Michael addition/Wittig reaction.[12] Excellent yields and up to 95% ee have been obtained for the synthesis of fluorinated cyclobutene and spiro[3.4]octanone derivatives (Scheme 1c). In recent years, we also developed a straightforward phosphine-catalyzed methodology for the synthesis of many nitrogen-containing heterocycles, including 2,3-dihydro-1,3,4-oxadiazole, 9*H*-pyrrolo[1,2-*a*]indoles, pyrrolizines, 1,2-dihydroquinolines and others, with preliminary results in asymmetric catalysis.[9b]



Scheme 1. (a) General strategy for a catalytic and asymmetric P^{III}/P^{V} process. (b) and (c) Representative examples. (d) Proposed work for the synthesis of dihydropyrrole and tetrahydropyridine derivatives.

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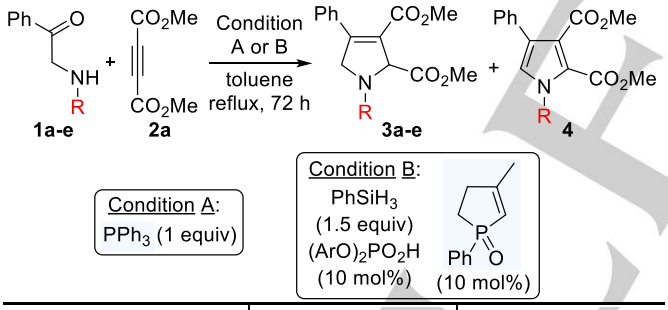
Following our previous studies, we propose in the present work to use *N*-substituted 2-amino-1-phenylethan-1-one (**I**) and 3-aminopropanal (**II**) derivatives as substrates, in the presence of dialkyl acetylenedicarboxylate (DAAD) and trivalent phosphine, to furnish the corresponding 2,5-dihydro-1*H*-pyrrole (**III**)[13a-c] and tetrahydropyridine (**IV**)[9b, 13d] backbones (Scheme 1d). These *N*-heterocycles are present in numerous natural products and bioactive compounds, and can also be useful as synthetic intermediates in more complex scaffolds.[14] After validation of the proposed syntheses using stoichiometric amounts of triphenylphosphine, the catalytic processes have been implemented. Finally, the use of enantiopure chiral phosphines, in line with an optimized reducing system, allowed to achieve honorable levels of enantioselectivity in the targeted reactions.

At the outset of this study, we first tested the reactivity of five different *N*-substituted 2-amino-1-phenylethan-1-one substrates **1a-e**, in the presence of dimethyl but-2-ynedioate **2a** and stoichiometric amounts of triphenylphosphine (Condition A in Table 1). The reaction produced the desired 1,4-diphenyl-2,5-dihydro-1*H*-pyrrole product **3a** in 62% yield, with the simultaneous formation of the corresponding pyrrole derivative **4a** (entry 1). Surprisingly, the *N*-*para*-chloro-phenyl substrate furnished mostly the achiral pyrrole product **4b** (entry 2). Fortunately, the desired dihydro-1*H*-pyrrole products **3c-e** were formed in 75-85% yields, with *para*-methoxyphenyl,[13b] tosyl and carboxybenzyl substituents (entries 3-5). We next attempted to develop a catalytic version of this tandem transformation (Table 1, Condition B).

Table 1. Variation of the nitrogen-substituent for selective formation of dihydropyrroles **3**.

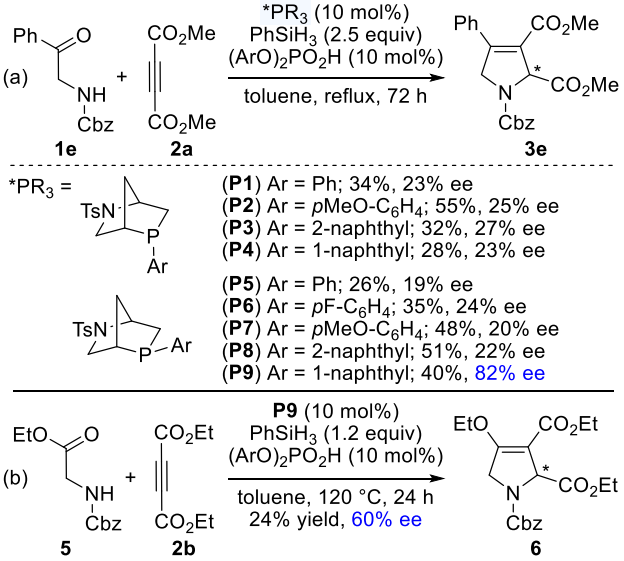


Entry	R	Condition A		Condition B	
		3/4 *ratio*[a]	Yield **3** [%][b]	**3/4** *ratio*[a]	Yield **3** [%][b]
1	**1a**, Ph	3/1	**3a**, 62	1/3	**3a**, 6
2	**1b**, *p*Cl-C_6H_4	1/4	**3b**, <5	3/1	<5
3	**1c**, *p*MeO-C_6H_4	8/1	**3c**, 85	<1/20	<5
4	**1d**,Ts	5/1	**3d**, 75	>20/1	**3d**, 34
5	**1e**,Cbz	>20/1	**3e**, 84	>20/1	**3e**, 35
6	**1e**,Cbz	-	-	>20/1	**3e**, 99[c]
7	**1e**,Cbz	-	-	>20/1	**3e**, 80[d]

[a] Determined according to ^{1}H NMR of the crude mixture. [b] Isolated yield. [c] 2.5 equiv of $PhSiH_3$ instead of 1.5 equiv. [d] $PhSiH_3$ (2 equiv), 120 °C, microwave heating, 2 h.

The initial protocol for this reaction was the use of 4-methyl-1-phenyl-2,3-dihydrophosphole 1-oxide as precatalyst (10 mol%) and *bis*(*p*-nitrophenyl)phosphate (10 mol%) as additive, in the presence of phenylsilane (1.5 equivalents), in refluxing toluene. Previous results have already proved the chemoselectivity of this system combining phenylsilane and phosphate, to efficiently reduce the phosphine oxide.[15] Unfortunately, the first attempts failed (entries 1-3, right column). Indeed, either the conversion was not good, or the isolated major product was the pyrrole derivative **4a** and **4c**. It is noteworthy that with the use of *N*-tosyl substrate, **3d** was isolated in 34% yield (entry 4). The modification of the reaction conditions did not improve this result. Finally, using 2.5 equivalents of silane with the same reaction conditions resulted in a 99% yield with *N*-Cbz substrate **1e** (entry 6), thereby validating the development of efficient catalytic P^{III}/P^{V} process for the synthesis of *N*-Cbz-phenyl-2,5-dihydro-1*H*-pyrrole-2,3-dicarboxylate **3e**. Microwave heating condition can be used in this transformation, decreasing the reaction time to only two hours (80% yield, entry 7).

Having shown that the reaction can be made catalytic in phosphine, we then used enantiopure chiral phosphines to develop the first asymmetric synthesis of such molecules (Scheme 2a). The really important point in this study is to find the right balance between reactivity, enantioselectivity and facility to reduce the corresponding phosphine oxide. First, we screened HypPhos phosphines **P1**-**P9**, which have previously demonstrated their effectiveness in phosphine organocatalysis.[11, 12, 16] If as a general trend, the isolated yields were moderate (up to 55% yield in **3e** with the use of **P2**), the enantioselectivity reached 82% ee with chiral phosphine *exo*-1-naphthyl-**P9**. This catalytic reaction condition was also used with *N*-Cbz ethyl glycinate substrate **5**, in the presence of DAAD **2b** (Scheme 2b). Results remained moderate in terms of conversion and enantioselectivity (up to 60% ee). This result however outperforms our previous endeavours on the same reaction (30% ee).[9b]



Scheme 2. Screening of chiral phosphines for the formation of dihydropyrrole derivatives **3e** and **6**.

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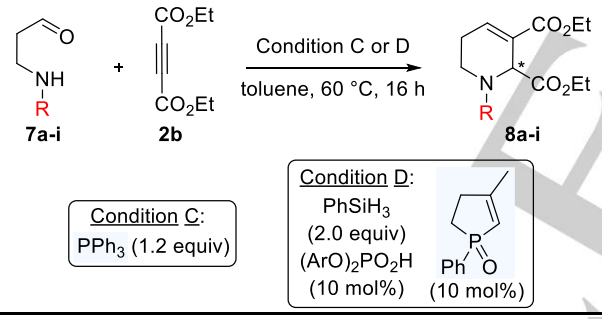
We next turned our attention to the synthesis of chiral tetrahydropyridines **8** from 3-aminopropanal substrates **7a-i** (Table 2). First, five carbamate derivatives (N-CO_2-R') were prepared with R' = benzyl, *tert*-butyl, allyl, 9-fluorenylmethyl and 2,2,2-trichloroethyl substituents (substrates **7a-e**). 2,2,2-trifluoro-*N*-(3-oxopropyl)acetamide **7f** was also prepared, featuring a strong electron-withdrawing group. Finally, three sulfonamides **7g-i** were synthesized in good yield (see SI for the procedures). Using 1.2 equivalents of triphenylphosphine in toluene, 16 h at 60 °C (condition C), all *N*-protected 1,2,3,6-tetrahydropyridines were isolated in moderate to good yields (56-94% yields), with the exception of *N*-Boc- and *m*-Tosyl-substrates (entries 2 and 8, Table 2) leading to low conversions. Before screening different chiral phosphines, we verified that optimized conditions for the development of phosphine-catalyzed transformations, i.e. Condition D, Table 2 (10 mol% of phospholene oxide and *bis*(*p*-nitrophenyl)phosphate, with 2.0 equivalents of phenylsilane in toluene at 60°C) gave isolated yields similar to those obtained with stoichiometric amounts of phosphine. Indeed, products **8a**, **8c-e** and **8g-i** were obtained in 57-92% yields (Table 2, right column). Again, Boc-protected **8b** has not been isolated though. Similarly, "Conditions D" did not give the expected cyclized product **8f** either (entry 6). As previously demonstrated,[9c] in this case a diethyl 2-(3-aminopropylidene)succinate product was instead isolated as an *E*/*Z* isomeric mixture. Next, the use of enantiopure HypPhos phosphine **P9** gave products **8a**, **8c-e** and **8g-i** in up to 62% ee (Table 3, entries 1 and 3).

Table 2. Synthesis of different *N*-substituted tetrahydropyridines **8a-i**.

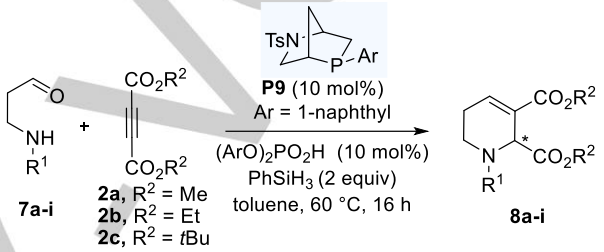


Entry	R	Condition C yield [%][a]	Condition D yield [%][a]
1	**7a**, CO_2Bn (Cbz)	**8a**, 64	90[b]
2	**7b**, CO_2tBu (Boc)	**8b**, <5	<5
3	**7c**, $CO_2CH_2CHCH_2$ (Alloc)	**8c**, 83	60
4	**7d**, Fluorenylmethoxycarbonyl (Fmoc)	**8d**, 68	67
5	**7e**, $CO_2CH_2CCl_3$ (Troc)	**8e**, 94	92
6	**7f**, $COCF_3$ (TFA)	**8f**, 91	<5
7	**7g**, SO_2-*p*Me-C_6H_4 (*p*Ts)	**8g**, 72	79[b]
8	**7h**, SO_2-*m*Me-C_6H_4 (*m*Ts)	**8h**, 18	70
9	**7i**, SO_2-*p*OMe-C_6H_4	**8i**, 56	57

[a] Isolated yield. [b] Result from ref. [9b]

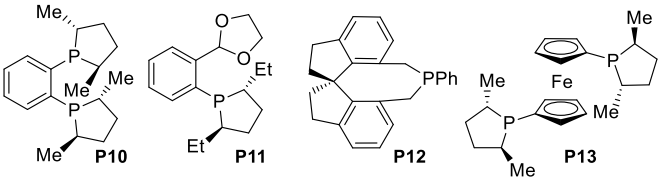
As a general trend, these first results showcased the difficulty to obtain both decent yields and enantiomeric excesses. The best compromise between yield and enantioselectivity was obtained with substrate **7e** (R^1 = Troc = 2,2,2-trichloroethyl, 73% yield, 41% ee, entry 4). Other chiral phosphines **P10**-**P12** were screened with this substrate. The enantioselectivity of **8e** increased to 63% ee, at the expense of a lower yield (entries 5-7). Variation of the DAAD substrate has been then studied, with the use of dimethyl and di-*tert*-butyl acetylenedicarboxylates **2b-c**. Yields remained acceptable, but enantiomeric excesses have not increased significantly (up to 48% ee, entries 8-9). Finally, for sulfonamide-derived substrates **7g-i**, better results were reached using of Me-Ferrocelane phosphine **P13** (up to 48% ee, entries 10-12).

Table 3. Towards a catalytic and asymmetric synthesis of tetrahydropyridines **8**.



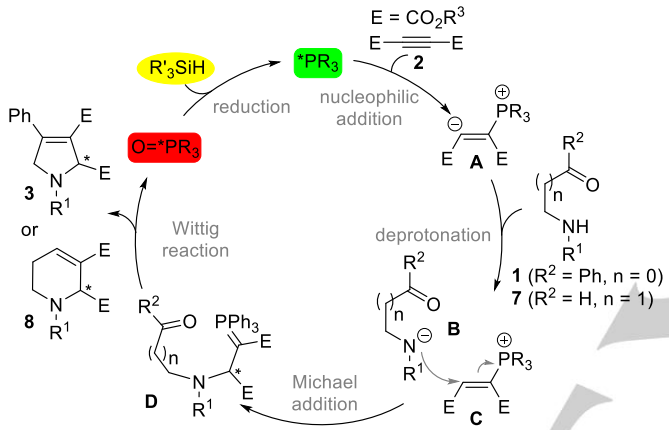
Entry	R^1	R^2	*PR_3	yield [%][a]	ee [%][b]
1	**7a**, Cbz	Et	**P9**	**8a**, 11 (23)[c]	62 (63)[c]
2	**7c**, Alloc	Et	**P9**	**8c**, <5	24
3	**7d**, Fmoc	Et	**P9**	**8d**, 5	62
4	**7e**, Troc	Et	**P9**	**8e**, 73	41
5	**7e**, Troc	Et	**P10**	**8e**, 7	63
6	**7e**, Troc	Et	**P11**	**8e**, 18	50
7	**7e**, Troc	Et	**P12**	**8e**, 20	38
8	**7e**, Troc	Me	**P9**	**8ea**, 56	48
9	**7e**, Troc	*t*Bu	**P9**	**8ec**, 58	31
10	**7g**, *p*Ts	Et	**P13**	**8g**, 27	41
11	**7h**, *m*Ts	Et	**P13**	**8h**, 30	33
12	**7i**, SO_2-*p*OMe-C_6H_4	Et	**P13**	**8i**, 32	48

[a] Isolated yield. [b] Determined by HPLC on a chiral stationary phase. [c] **P9** (20 mol%).



A postulated mechanism is presented in Scheme 3. The reaction starts with the formation of zwitterionic species **A**, after the addition of the trivalent phosphine to DAAD substrate **2**. With its protonation by substrates **1** or **7**, the resulting nitrogen nucleophile

B adds on the vinylphosphonium salt **C** to generate ylide **D**. This is the enantiodetermining step of this transformation. Following the intramolecular Wittig reaction, chiral *N*-heterocycles **3** or **8** are delivered and the phosphine oxide is reduced *in situ* by the phenylsilane to regenerate the trivalent phosphine catalyst. To facilitate this reduction, both the addition of catalytic amounts of phosphate and the use of cyclic phosphines have a positive impact on the reaction outcome. Indeed, chiral bicyclic phosphines often represent the ideal balance between nucleophilicity and facility of performing the P^{III}/P^{V} redox cycling, while having a congested chiral structure that can achieve good stereoselectivity.[8b] The direct formation of *N*-aryl-pyrroles **4a-c** can be explained by the direct addition of the nitrogen atom of **1** to DAAD substrate **2**, following a cyclization/dehydration process, without the use of phosphine.[17a-c,18] Indeed, with more nucleophilic substrate **1c** and using "Condition B" without phosphine, pyrrole **4c** was isolated. Fortunately, with *N*-Cbz substrate **1e**, this non-desired reactivity was suppressed.



Scheme 3. Proposed mechanism for the formation of **3** and **8**.

In conclusion, we have demonstrated that the two catalytic approaches described in this study provided a facile and efficient route for the isolation of substitued dihydropyrroles and tetrahydropyridines. The use of enantiopure bicyclic HypPhos phosphines furnished five- and six-membered nitrogen heterocyles in moderate yields and promising enantioselectivities. Further studies will be oriented toward the development of other transformations *via* P(III)/P(V) redox cycling and the development of specifically designed chiral phosphines.

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Keywords: Phosphine • organocatalysis • asymmetric • dihydro-1*H*-pyrrole • tetrahydropyridine

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[18] Another possible mechanism for pyrrole formation would first involve the addition of zwitterion **A** directly on the ketone function of substrate **1**. After an intramolecular aza-Michael addition and elimination of the phosphine, a dehydration step may also lead to the pyrrole product **4**.

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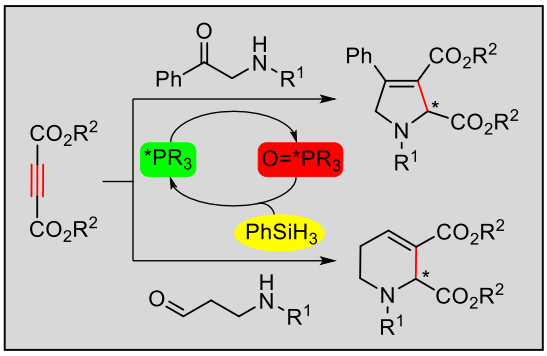

An access to chiral 2,5-dihydro-1*H*-pyrroles and tetrahydropyridines has been elaborated through a phosphine-catalyzed Michael addition/Wittig reaction. The use of catalytic amounts of chiral phosphines affords these nitrogen heterocycles with promising enantioselectivities.

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