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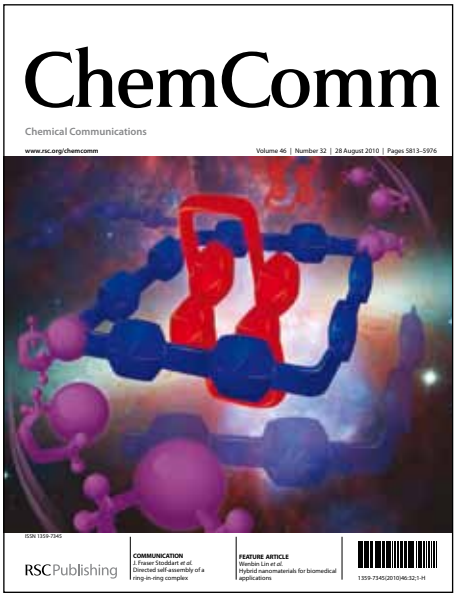

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Thiourea-Phosphonium Salts From Amino Acids: Cooperative Phase-Transfer Catalysis in Enantioselective aza-Henry Reaction

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New chiral bifunctional thiourea-phosphonium salts have been developed based on natural amino acids as highly efficient phase-transfer catalysts in the enantioselective aza-Henry reaction.

Asymmetric phase-transfer catalysis has evolved into one of the most versatile and powerful tools for the syntheses of chiral organic compounds at both academic and industrial levels.[1] As a key factor in fuelling the rapid progress in this field, the development of new chiral phase-transfer catalysts has inarguably been one of the research focuses.[2] So far, the most reported successful phase-transfer catalysts are based on the skeletons of cinchona alkaloids,[1a-b] chiral binaphthyls[1c-e] and most of these catalysts have a quaternary tetraalkylammonium center surrounded by large steric hindrance. On the other hand, examples with alternative onium centers like phosphonium were rather limited,[3] which might be due to the ready elimination of phosphoniums under the basic conditions that usually required in phase transfer catalysis.[4] Recent impressive progress in this area includes the binaphthyl-modified quaternary phosphonium catalysts developed by Maruoka,[5a,5b] Lectka[5c] and Ma[5d] groups (Figure 1, **I**), and the *P*-spiro tetraaminophosphonium catalysts developed by Ooi and coworkers (Figure 1, **II**).[6] These new chiral phosphonium-centered catalysts have significantly

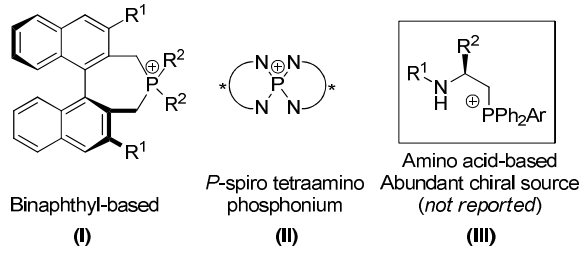

Figure 1. Chiral quaternary phosphonium catalysts (Anions are omitted)

expanded the application scope of phase transfer catalysis.

Amino acids are privileged scaffolds for the development of new chiral organocatalysts due to their facile tunings of the catalytic efficiency through structural modifications.[7] The recently developed organocatalysts based on amino acids such as primary-secondary amines, tertiary amine-thioureas, aminophosphines in our group[7f,8] have demonstrated high efficiency in a variety of asymmetric reactions. The excellent asymmetric catalysis demonstrated by these bifunctional/multifunctional catalysts is usually ascribed to the cooperative catalysis of the different functionalities present in these catalysts. Although the concept of cooperative catalysis has been widely employed in the design of various new catalysts, its application to phase-transfer catalysts is still very limited.[9] We now describe novel bifunctional thiourea-aromatic phosphonium catalysts synthesized from amino acids (Figure 2), which are highly efficient in catalyzing asymmetric aza-Henry reactions through cooperative phase transfer catalysis. These novel bifunctional phosphonium phase-transfer catalysts are easily accessible (see the †ESI for details), and air- and moisture-stable for routine handling.

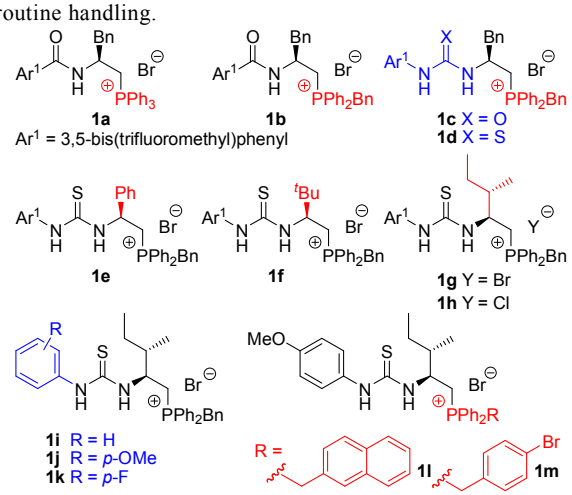

Figure 2. Chiral thiourea-phosphonium salts.

Using the N-Boc imine *in situ* generated from amidosulfone **2a**,[10] and nitromethane **3a**, we first examined the catalytic efficiency of a series of bifunctional aromatic phosphonium salts in this aza-Henry reaction (Table 1). The

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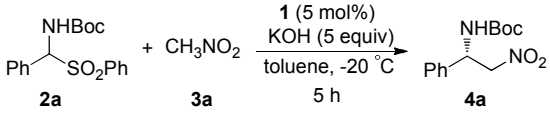
modular structures of these catalysts include three basic components: the acidic amine moiety, the amino acid skeleton and the phosphonium centre, and each would allow facile modifications for better catalytic efficiency. As for the acidic amine moiety, the thiourea structure with two hydrogen-bonding donors has obvious advantages over other structures such as acyl amines and urea in terms of enantioselectivity when L-phenylalanine-derived catalysts **1b-1d** were used (entries 2-4). These results, together with other results,[8f, 11] suggest the important role of dual hydrogen-bonding interaction in this type of catalytic system. Then catalysts **1e-1h** derived from other amino acids were screened, and the L-isoleucine-derived **1g** was selected for further investigation in view of the total results (entries 5-7). Notably, changing the counteranion from bromide to chloride did not affect the reaction (entry 8). To our delight, the 3,5-bis(trifluoromethyl)phenyl of the thiourea could be replaced by more common and cheaper aryl groups to give comparable catalytic efficiency (entries 9-11). Increasing the volume of the phosphonium centre by using larger benzylic groups (**1l-1m**) brought little influence on the results (entries 12-13) while the use of triphenylphosphine (**1a**) was detrimental to the reaction (entry 1).[12] Also of note is the high catalytic efficiency of these novel catalysts in that the reaction were usually completed in 5 h, which is a remarkable improvement over previously used chiral ammonium salt catalysts.[13,9f] As a compromise of factors like the cost and accessibility, catalyst **1j** was selected for further optimisation of other reaction parameters such as solvent, base, catalyst loading amount and reaction temperature and no better results was obtained (see the †ESI for details). Thus, the optimum reaction condition was determined as follows: 5 equiv of KOH and 5 mol% of **1j** in toluene were used at -20 ºC (entry 10).

Table 1. Screen of catalysts[a]



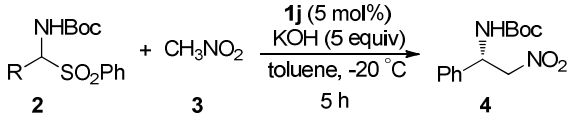
2a **3a** **4a**

Entry	Catalyst	Yield (%)[b]	ee (%)[c]
1	**1a**	75	-16
2	**1b**	64	43
3	**1c**	98	74
4	**1d**	71	89
5	**1e**	83	92
6	**1f**	68	96
7	**1g**	75	95
8	**1h**	75	95
9	**1i**	83	93
10	**1j**	79	96
11	**1k**	68	95
12	**1l**	71	96
13	**1m**	75	96

[a] Reaction conditions: **2a** (0.1 mmol), **3a** (0.5 mmol) and base (0.5 mmol) in the presence of **1** (5 mol%) in various solvents (1.0 mL). [b] Isolated yields. [c] Determined by chiral stationary phase HPLC.

Next, a series of amidosulfones **2** were tested under the optimized reaction conditions and a broad substrate scope was observed (Table 2). Specifically, when R was an aromatic group, high to excellent yields, and excellent ee values were generally obtained, irrespective of the electronic nature and positions of the substituents on the benzene ring (Table 2, entries 1-11). Heteroaromatic substrates **2l** and **2m** also participated in the reaction well (Table 2, entries 12-13). Moreover, the more challenging aliphatic substrates were also well tolerated in the reaction, albeit with a slight drop in the enantioselectivity (Table 2, entries 14-15).

Table 2. Scope study with different amidosulfones **2**. [a]



2 **3** **4**

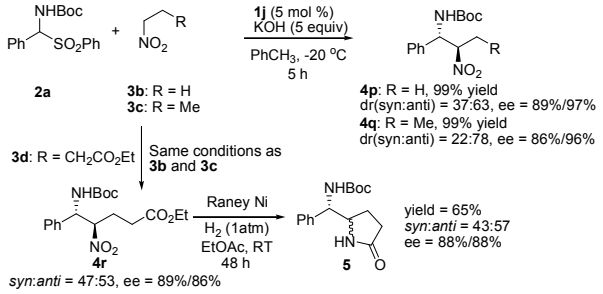
Entry	2	R	4	Yield (%)[b]	Ee (%)[c]
1	**2a**	Ph	**4a**	79	96
2	**2b**	*p*-FC_6H_4	**4b**	77	97
3	**2c**	*p* -ClC_6H_4	**4c**	80	97
4	**2d**	*p* -BrC_6H_4	**4d**	78	97
5	**2e**	*p* -MeC_6H_4	**4e**	82	96
6	**2f**	*p* -$MeOC_6H_4$	**4f**	81	97
7	**2g**	*p* -$CF_3C_6H_4$	**4g**	84	98
8	**2h**	*p* -$NO_2C_6H_4$	**4h**	68	95
9	**2i**	α-Naphthyl	**4i**	92	96
10	**2j**	*m*-ClC_6H_4	**4j**	83	97
11	**2k**	*o*-FC_6H_4	**4k**	95	91
12	**2l**	*o* -furyl	**4l**	98	93
13	**2m**	*o* -thienyl	**4m**	92	92
14[d]	**2n**	cyclohexyl	**4n**	88	88
15[d]	**2o**	phenyl ethyl	**4o**	88	88

[a] Reaction conditions: **2** (0.1 mmol), **3a** (0.5 mmol) and KOH (0.5 mmol) in the presence of **1j** (5 mol%) in toluene (1.0 mL). [b] Isolated yields.[c] Determined by chiral stationary phase HPLC. The absolute configurations of **4** were determined by comparison of the specific optical rotation values with literature data. [d] 5 mol% of catalyst **1g** was used at -30 ℃.

To further explore the scope of the reaction, several substituted nitroalkanes were then evaluated with amidosulfone **2a** (Scheme 1). With the simple nitroalkanes **3b** and **3c** used, a mixture of *syn*- and *anti*-products was obtained in quantitative yields, with high enantioselectivities for both products. The reaction with functionalized nitroalkane **3c** also proceeded smoothly to give the two diastereomers of the product **4r** with nearly the same high enantioselectivity. As an illustration of the utility of the reaction, the product **4r** was transformed to a chiral aminio-substituted γ-lactam **5**, which represents an important structural motif found in many physiologically active substances.[14] The stereochemical integrity of **4r** was basically maintained in the one-step hydrogenation using Raney Ni.

In order to gain insight into the cooperative catalysis of

these bifunctional thiourea-phosphonium salts in the catalytic process, two control experiments were run in the presence of catalyst **1n** with a single hydrogen-bond N-Methylthiourea and **1o** without the phosphonium center under the conditions used in table 1 (Figure 1). Compared to the results obtained with **1d** (71% yield and 89% ee in table 1, entry 4), with these two modified catalysts, both the yield and the enantioselecitivity of the product were significantly lower. These results indicated that both the dual hydrogen-bond sites of the thiourea moiety and the phosphonium centre of this bifunctional phase-transfer catalysts were crucial to achieve excellent enantiocontrol in the aza-Henry reaction.[15]



Scheme 1. Reactions with nitroalkanes **3** and a useful transformation of the product **4r**.

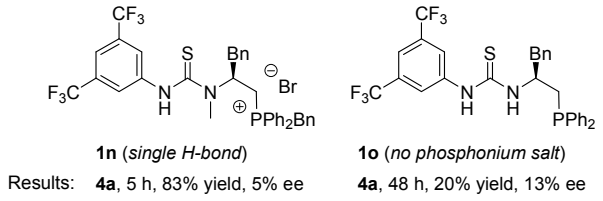


Figure 3. Control experiment results in support of cooperative catalysis for the bifunctional catalysts .

In summary, we have developed novel chiral bifunctional quaternary phosphonium salts as highly efficient phase-transfer catalysts in the aza-Henry reaction from readily available and inexpensive chiral amino acids. The easy tunability of catalytic activities enabled by their modular structures as well as their ready accessibility hold a great promise for extensive applications in phase-transfer catalysis. Efforts towards the application of these new phase-transfer catalysts to other reactions as well as a deeper mechanistic understanding of the catalytic process are underway in our laboratory.

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