A powerful synergistic effect for highly efficient diastereo- and enantioselective phase-transfer catalyzed conjugate additions†

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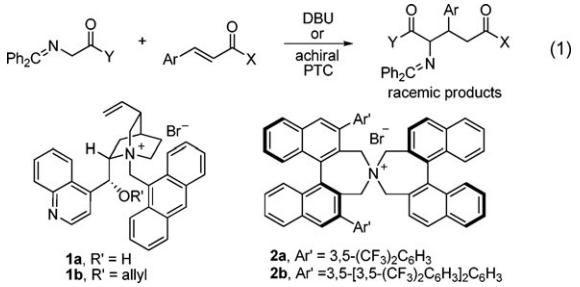
An efficient, catalytic, diastereo- and enantioselective conjugate addition of *N*-(diphenylmethylene)glycine *tert*-butyl ester to β-aryl substituted enones was realized in the presence of 1 mol% of newly desired dinuclear *N*-spiro-ammonium salts, affording functionalized α-amino acid derivatives in 57–98% yields with high diastereoselectivity (up to 99 : 1 dr) and enantioselectivity (up to 96.5 : 3.5 er).

Catalytic asymmetric carbon–carbon bond forming reactions using glycine imine esters as nucleophiles have been intensively studied and have evolved into a powerful tool for the synthesis of various natural and non-natural amino acids following the seminal work of O'Donnell.[1] Among them, catalytic asymmetric conjugate addition of glycine imine esters to α,β-unsaturated carbonyl compounds provides expedient access to useful multi-functional chiral building blocks.[2] Despite recent impressive progress in organo- and metal-catalyzed asymmetric 1,4-additions of glycine imine esters to many α,β-unsaturated carbonyl compounds,[3,4] the use of β-aryl substituted α,β-unsaturated carbonyl compounds as the Michael acceptors of glycine imine esters is extremely rare. DBU and achiral phase-transfer catalyst promoted conjugate addition of glycine imines to cinnamate derivatives have been recently reported (eqn (1)).[5] However, to date there are no successful examples of direct catalytic asymmetric conjugate additions of glycine imines to β-aryl substituted Michael acceptors. This is probably due to the fact that such as a reaction would be kinetically slow as it involves two bulky reactants to give an adduct possessing vicinal tertiary centers, and simultaneous control of diastereo- and enantioselectivity could be extremely challenging. Attempts to use several well documented and highly reactive phase-transfer catalysts such as **1**[1b] and **2**[1c] were unsuccessful in the reaction of *N*-(diphenylmethylene)glycine *tert*-butyl ester to chalcone and low ee's and/or yields were observed.[6]



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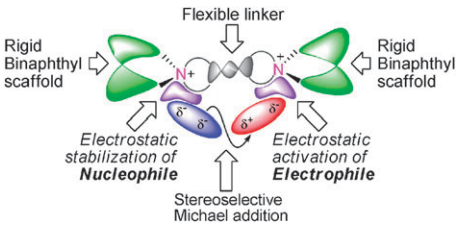
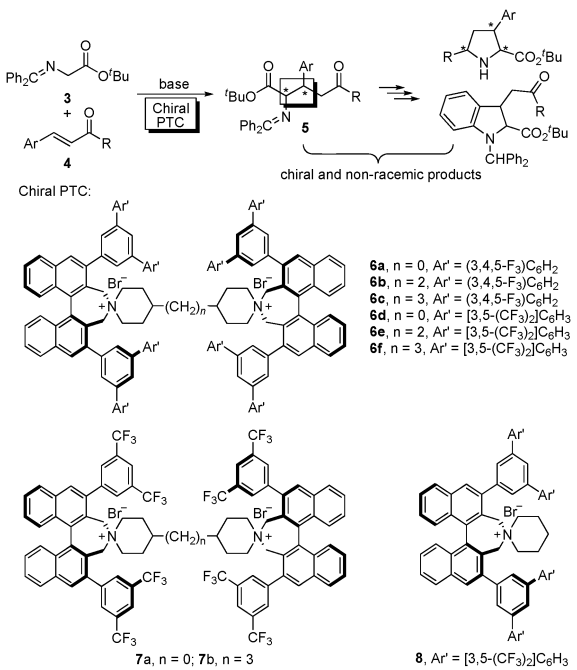


Fig. 1 Designing principle for synergistic asymmetric bifunctional phase-transfer catalysis of conjugate addition by dinuclear chiral *N*-spiro-ammonium salts.

We surmised that a simultaneous, ideally synergetic, activation of both the nucleophile and the electrophile is necessary for this particularly challenging reaction. Therefore, a chiral dinuclear phase-transfer catalyst containing two quaternary ammonium units could provide a potential solution.[7] As depicted in Fig. 1, one quaternary ammonium moiety in the dinuclear phase-transfer catalyst stabilizes the anionic enolate nucleophile, while the second ammonium unit, if judiciously annexed by means of a flexible linker, would simultaneously activate the chalcone *via* electrostatic interaction with its carbonyl group. It is further anticipated that the chiral bifunctional catalyst would facilitate the reaction in a synergistic manner by bringing the two reaction partners in close proximity and coaxing them into favorable orientations. In this communication, we establish that chiral



Scheme 1 Dinuclear *N*-spiro-ammonium salts **6** as chiral catalysts for the conjugate addition of **3** to β-aryl substituted enones **4**.

Table 1 Conjugate addition of **3** to chalcone **4a** catalyzed by **6**

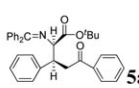
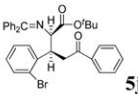
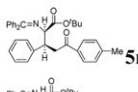
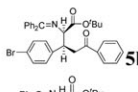
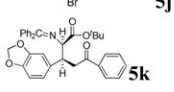
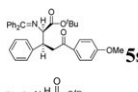
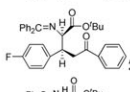
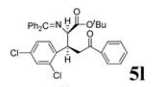
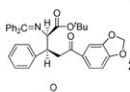
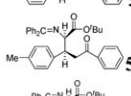
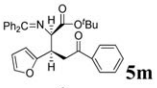
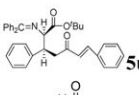
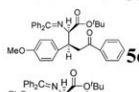
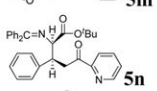
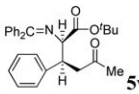
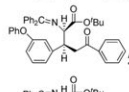
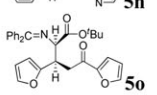
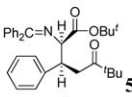
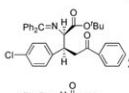
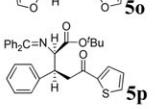
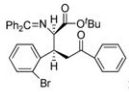
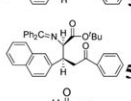
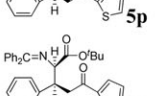
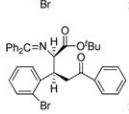
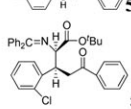
Entry	PTC	T/°C	Solvent	Yield[a] (%)	Dr[b]	Er[c]
1	**6a**	10	Toluene	98	97 : 3	69 : 31
2	**6b**	10	Toluene	98	97 : 3	90 : 10
3	**6c**	10	Toluene	98	97 : 3	85 : 15
4	**6d**	10	Toluene	95	97 : 3	86 : 14
5	**6e**	10	Toluene	96	97 : 3	84 : 16
6	**6f**	10	Toluene	98	96 : 4	94 : 6
7	**6f**	10	CH_2Cl_2	96	96 : 4	70 : 30
8	**6f**	10	THF	90	96 : 4	79 : 21
9	**6f**	10	Et_2O	93	98 : 2	91 : 9
10	**6f**	10	Benzene	98	97 : 3	86 : 14
11	**6f**	10	Xylene	98	98 : 2	95 : 5
12[d]	**6f**	0	Xylene	72	98 : 2	91 : 9
13[e]	**6f**	25	Xylene	98	97 : 3	95.5 : 4.5
14[f]	**6f**	30	Xylene	98	97 : 3	96.5 : 3.5
15[f]	**6f**	40	Xylene	98	95 : 5	95 : 5

[a] Isolated yield. [b] Enantiomeric excess was determined by chiral HPLC analysis. [c] Determined by NMR for crude product. [d] Reaction time: 96 h. [e] Reaction time: 24 h. [f] Reaction time: 12 h.

BINOL-derived *N*-spiro-ammonium structures can be engineered into powerful bifunctional catalysts which synergistically stabilize/activate both the nucleophile and the electrophile for highly efficient, diastereo- and enantioselective conjugate addition of a glycine imine ester to β-aryl substituted enones. Specifically, we have found that modification on the 3,3′-positions of the chiral binaphthyl skeleton with a phenyl group that further bears two substituents at its own 3,5-positions is a prerequisite for high stereoselectivity in the conjugate addition of **3** to **4** (Scheme 1) and the dimeric architecture of the quaternary ammonium salts **6** is necessary to maintain high reactivity for the addition reaction. The synthetic versatility of the resulting adducts **5** was demonstrated by their conversion to a number of enantiomerically enriched proline and indoline-2-carboxylic acid derivatives possessing multiple stereocenters.

Our quest for a new catalytic system suitable for asymmetric addition of **3** to **4** began with the examination of our previously reported dinuclear *N*-spiro-ammonium salts such as **7a** and **7b**[8] in the addition of *N*-(diphenylmethylene)glycine *tert*-butyl ester **3** to chalcone **4a**. The reaction proceeded well with both catalysts to afford the desired product **5a** in excellent yield and diastereoselectivity (up to 98%, 98 : 2 dr), but with only moderate enantioselectivities (< 75 : 25 er). This finding does indeed represent a significant improvement as Maruoka's mono-quaternary ammonium salts such as **2a** and **2b** gave very low yield and/or poor stereoselectivity (*supra infra*),[6] and we believe that the bifunctional nature of **7** must be responsible for the enhancement in reaction rate as well as in providing good control of diastereoselectivity. This quickly directed us to the screening of catalysts **6a–f** whose aryl groups at the 3,3′-positions of the chiral binaphthyl scaffold are amenable for further modifications with bulky aryl groups with the anticipation that this specific modification would bring about an improvement in enantioselectivity. To our delight, this modification does lead to the improvement in enantioselectivity (Table 1, entries 1–6), with 1 mol% of catalyst **6f** giving the best performance in terms of both the diastereoselectivity and the enantioselectivity (96 : 4 dr, 94 : 6 er, entry 6). A mono-cationic analog of **6f** derived from piperidine, the quaternary ammonium salt **8**, was found to perform poorly in nearly all aspects (52% yield, 80 : 20 dr, and

Table 2 Conjugated addition of glycine ester **3** to enones **4** with **6f**

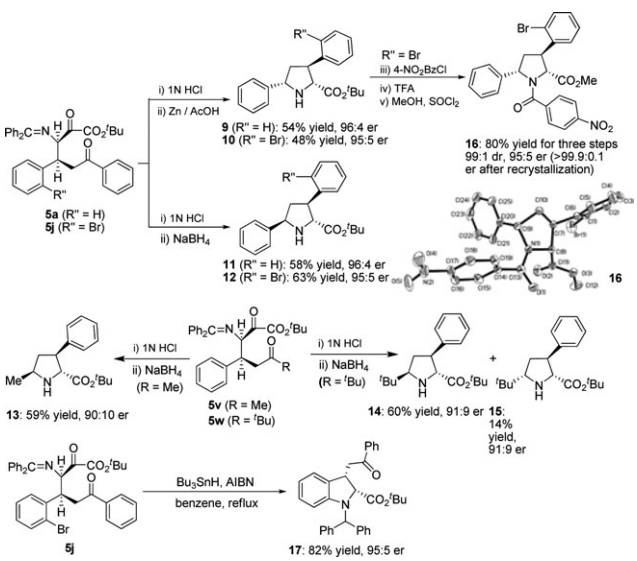
Entry	Product	Yield[a] (%)	Dr[b]	Er[c]	Entry	Product	Yield[a] (%)	Dr[b]	Er[c]	Entry	Product	Yield[a] (%)	Dr[b]	Er[c]
1	 **5a**	98	97:3	96.5:3.5	10	 **5j**	96	98:2	95:5	18	 **5r**	98	94:6	94:6
2	 **5b**	98	95:5	94:6	11	 **5k**	94	95:5	96:4	19	 **5s**	98	97:3	93.5:6.5
3[d]	 **5c**	98	96:4	95:5	12	 **5l**	98	98:2	95:5	20	 **5t**	97	98:2	96.5:3.5
4	 **5d**	98	95:5	94:6	13	 **5m**	98	97:3	95:5	21	 **5u**	98	97:3	91:9
5	 **5e**	92	97:3	96:4	14	 **5n**	92	94:6	94:6	22	 **5v**	84	93:7	90.5:9.5
6[d]	 **5f**	98	95:5	92.5:7.5	15	 **5o**	91	98:2	94.5:5.5	23	 **5w**	57	99:1	91:9
7	 **5g**	94	95:5	92:8	16	 **5p**	98	96:4	95:5	24[e]	 **5j**	92	98:2	95:5
8	 **5h**	98	93:7	93:7	17	 **5q**	95	98:2	93.5:6.5	25[f]	 **5j**	94	98:2	95:5
9	 **5i**	92	99:1	95.5:4.5										

[a] Isolated yield. [b] Enantiomeric excess was determined by NMR or HPLC analysis. [c] Determined by NMR for crude product. [d] At −15 °C. [e] The reaction was run with 10 g of **4j**. [f] In the presence of 1 mol% of the recovered catalyst **6f**.

73 : 27 er) for the addition of **3** to **4a**, corroborating the notion that peripheral modification of the binaphthyl units alone is not enough and the linker-based conjoining of two quaternary centers are necessary in order to achieve synergistic dual activation of the reactants. Subsequent optimization on the reaction conditions (entries 7–15) led to the discovery that the best results were obtained when xylene was used as the solvent and the reactions run at 30 °C (98% yield, 97 : 3 dr, 96.5 : 3.5 er, entry 14).

A series of β-aryl substituted enones were examined in the diastereo- and enantioselective conjugate additions of glycine imine ester **3** using **6f** as the catalyst under the optimized conditions (Table 2). Catalyst **6f** exhibited a remarkably broad substrate scope, and the corresponding products (**5a–t**) were obtained in excellent isolated yields (91–98%) with high diastereoselectivities (93 : 7–99 : 1 dr) and enantioselectivities (91 : 9–96.5 : 3.5 er) (entries 1–21). It is noteworthy that **6f** performed well not only with substituted chalcones (entries 1–12, 18–20), similarly high stereoselection was also observed for substrates derived from heteroaromatic aldehydes and/or ketones (entries 13–17). Application of this reaction to the diastereo- and enantioselective disymmetrization of 1,5-diphenyl-1,4-pentadien-3-one also proved successful (entry 21). In addition, enones with an aliphatic ketone group also gave high stereoselection albeit with diminished yields (entries 22 and 23). To test the feasibility of potential large scale application of this asymmetric process, the reaction of 2-bromochalcone was repeated at a 10 g scale and product **5j** was isolated in 92% yield, 98 : 2 dr and 95 : 5 er (entry 24). The chiral organocatalyst can be readily recycled with one simple regenerating process (see ESI†), and the recovered catalyst could be reused without an appreciable loss of reactivity and stereoselectivity (entry 25).

Adducts **5** are versatile synthetic intermediates and can be readily transformed into highly functionalized α-amino acid derivatives that are otherwise difficult to access. For example, the hydrolysis of the adducts **5a**, **5j**, **5v** and **5w**, followed by intramolecular reductive amination, gave 3,5-disubstituted D-proline derivatives (**9–15**). Further transformation of **12** furnished the crystalline derivative **16** whose absolute stereochemistry was determined to be (2*R*,3*S*,5*S*) from single-crystal X-ray structural analysis (Scheme 2) (ESI†). In addition, free radical-mediated aryl amination[5] of **5j** gave indoline-2-carboxylic acid derivative **17** without any erosion of its enantiopurity. These promising results indicate that the present protocol provides a reliable and rapid approach for the synthesis of chiral proline and indoline-2-carboxylic acid derivatives.



Scheme 2 Synthetic transformations of the adducts **5**.

In summary, we have developed an efficient diastereo- and enantioselective conjugate addition of *N*-(diphenylmethylene) glycine *tert*-butyl ester to chalcones and their analogs. In the presence of catalytic amount of dinuclear *N*-spiro-ammonium salt **6f** (1 mol%), the reaction proceeded smoothly for a broad variety of β-aryl substituted enones. Moreover, mild reaction conditions and applicability for large-scale preparations make compound **6f** a practical catalyst for the synthesis of highly functionalized α-amino acid derivatives. Further mechanistic investigation and extension of the reaction scope are underway in our laboratory.

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Notes and references

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