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Ion-paired chiral ligands for asymmetric palladium catalysis

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Conventional chiral ligands rely on the use of a covalently constructed, single chiral molecule embedded with coordinative functional groups. Here, we report a new strategy for the design of a chiral ligand for asymmetric transition-metal catalysis; our approach is based on the development of an achiral cationic ammonium–phosphine hybrid ligand paired with a chiral binaphtholate anion. This ion-paired chiral ligand imparts a remarkable stereocontrolling ability to its palladium complex, which catalyses a highly enantioselective allylic alkylation of α-nitrocarboxylates. By exploiting the possible combinations of the achiral onium entities with suitable coordinative functionalities and readily available chiral acids, this approach should contribute to the development of a broad range of metal-catalysed, stereoselective chemical transformations.

Biomolecules exist almost exclusively as single enantiomers, and different enantiomers can exhibit markedly different biological activities. Thus, stereochemistry is of great importance in chemical interactions, such as in the natural molecular recognition events that occur within living organisms, and in interactions between drugs and their targets. Accordingly, there is enormous demand for methods that allow the preparation of chiral compounds in enantiomerically pure forms. Over the last few decades, enantioselective transformations mediated by chiral transition-metal catalysts have served as a powerful means to access chiral non-racemic compounds[1]. A chiral transition-metal catalyst typically comprises a central metal and a chiral ligand. The structural and electronic properties of the chiral ligand have a pivotal influence on catalytic activity and its ability to impart stereocontrol. The design and preparation of chiral ligands that can be used for a given transformation, with efficiency in both reactivity and stereoselectivity, is therefore a subject of central importance in the development of catalytic asymmetric reactions[2].

There remains, however, a formidable challenge associated with this endeavour. The synthesis of effective ligands built from single chiral molecules (Fig. 1a, top) can be complex, and this can hinder the iterative process of design, testing and optimization. This intrinsic problem has been addressed by the introduction of supramolecular coordination complexes, particularly the self-assembled, supramolecular bidentate ligands and their transition-metal complexes for combinatorial asymmetric catalysis[3–5]. Several seminal studies in this emerging field have demonstrated the advantages and potential of non-covalent bidentate ligand construction. With the exception of the recent independent contributions by the groups of Reek[6] and van Leeuwen[7], however, it has remained essential to use covalently constructed monodentate chiral ligands. On the other hand, the chiral anion strategy has opened up chiral ligand-free asymmetric catalysis, enabling enantioselective transformations via chiral metal salts (that is, cationic transition metals with chiral anions)[8–12]. This system, however, is applicable only to the reactions of metal-activated cationic intermediates with non-ionic nucleophiles.

We envisaged an essentially new strategy for the design of chiral ligands. Our approach is based on the use of readily modifiable achiral molecules bearing a coordinative functional group and quaternary onium moiety within appropriate proximity, which are linked with simple chiral molecules by means of electrostatic interaction (Fig. 1a, bottom). If this type of structurally flexible, ion-paired chiral ligand could impart notable activity and selectivity to the corresponding metal complex, it would provide unprecedented possibilities in designing and preparing structurally diverse chiral ligands for asymmetric transition-metal catalysis. Here, we report the successful implementation of this strategy through the development of achiral ammonium–phosphine hybrid ligands paired with chiral binaphtholate anions for asymmetric palladium catalysis. In particular, we developed a catalyst for the highly enantioselective allylic alkylation of α-nitrocarboxylates, thereby offering a reliable catalytic process for the asymmetric synthesis of α,α-disubstituted α-amino-acid derivatives.

Results and discussion

As the achiral component of an ion-paired ligand, we chose *ortho*-diphenylphosphinobenzyl-ammonium cation **1**, because the coordinative group (triarylphosphine) and the quaternary onium cation (tetraalkylammonium) are arranged in close proximity to one another[13–15]. The requisite triflate salt **1·OTf** was readily synthesized from commercially available *N*,*N*-dimethylbenzylamine in a two-step sequence and transformed into the corresponding ammonium hydroxide **1·OH** through an anion-exchange process using amberlyst A-26 (OH^-) in methanol (Fig. 1b, left). This intermediate was neutralized by treatment with (*R*)-3,3′-disubstituted BINOL (1,1′-bi-2-naphthol) derivatives **2a** and **2b** (1.0 equiv.). The resultant mixtures were co-evaporated with acetonitrile to afford yellow solids, which were washed with distilled water and dried under reduced pressure to give ion-paired chiral ligands **3a** and **3b** (Fig. 1b, right), respectively (see Supplementary Information for details). The three-dimensional molecular structure of **3b** was unambiguously determined by X-ray diffraction analysis of its racemic single crystal (Fig. 2). The chiral binaphtholate anion is located close to the ammonium cation, and an internal hydrogen-bonding interaction is observed between the remaining phenolic proton and the naphthoxide anion. In addition, the diphenyl substituents on the phosphorus centre and the trimethylammonium moiety are spaced apart from one another to minimize possible steric repulsion and thus the phosphine lone pair is oriented toward the ion-pairing site.

Our investigations then focused on the performance of **3a** and **3b** as chiral ligands. We chose palladium catalysis for the enantioselective

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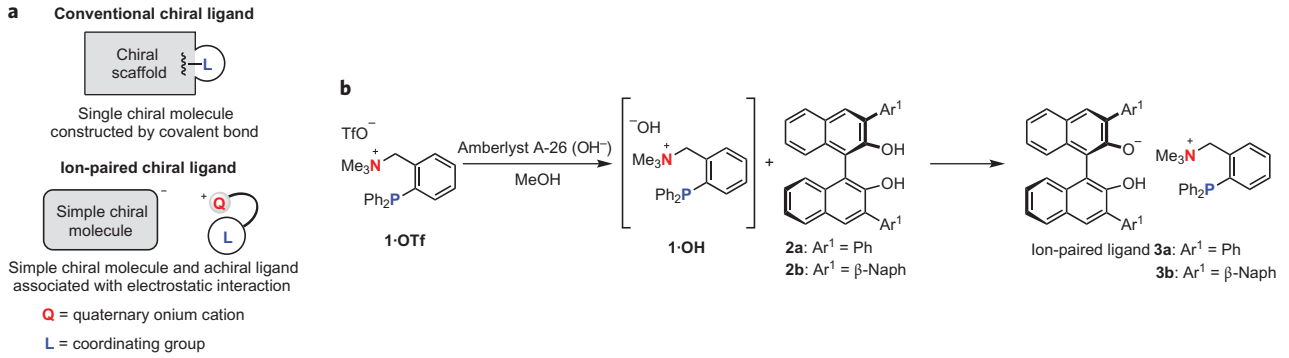


Figure 1 | Strategies for construction of a chiral environment around a metal catalyst. a, Conventional chiral ligand (top) and ion-paired chiral ligand (bottom). **b**, Preparation of ion-paired ligand **3**.

allylic alkylation of α-nitrocarboxylates[16] for the following reasons. (i) The advantage of using transition-metal catalysis is obvious due to the inherent difficulty of obtaining the C-alkylation product from the nitronate anions over O-alkylation[17]. (ii) Stereochemical control in the attack of a prochiral nucleophile (nitronate) on a π-allyl metal complex by a chiral ligand on the metal centre constitutes a general challenge[18–22]. (iii) Asymmetric reactions involving anionic nucleophiles are not controllable by the chiral anion strategy. (iv) This transformation, if successful, could provide a straightforward catalytic process for the asymmetric synthesis of non-coded α,α-disubstituted α-amino acids.[23]

Initial trials were carried out through the reaction of *tert*-butyl 2-nitropropionate (**4a**) with cinnamyl methyl carbonate (**5a**) in toluene at room temperature under the influence of the catalysts prepared *in situ* from tris(dibenzylideneacetone)dipalladium [$Pd_2(dba)_3$] and chiral ligand **3a** or **3b**. After 5 h of stirring, the desired alkylation product **6a** was obtained in good yields with moderate enantioselectivities. The palladium catalyst bearing **3b** as a ligand exerted higher catalytic and chiral efficiencies, demonstrating that the ion-paired chiral ligand **3** is indeed able to induce an appreciable enantiomeric excess (e.e.) on the prochiral nitronate generated from **4a** (Table 1, entries 1 and 2). In sharp contrast, however, the attempted use of either triphenylphosphine (PPh_3) as a ligand in the presence of benzyltrimethylammonium binaphthoxide **7** or achiral phosphinobenzylammonium bromide **1·Br** as a ligand in combination with the BINOL derivative **2b** under otherwise identical conditions led to the formation of racemic **6a** (entries 3 and 4). These results strongly suggest that ion-pairing between the ammonium–phosphine hybrid achiral ligand and the chiral binaphtholate anion is a prerequisite for achieving stereocontrol. Moreover, no asymmetric induction was detected in similar alkylations with catalysts prepared from ion-paired ligand **8** consisting of a *meta*-diphenylphosphinobenzylammonium cation[13] and ligand **9** having one carbon-elongated 2-(*ortho*-phosphinophenyl)ethylammonium cation, respectively (entries 5 and 6). These observations indicate the critical importance of the orientational precision and spatial arrangement of the coordinative phosphine functionality and the quaternary ammonium cation moiety pairing with an anion for inducing

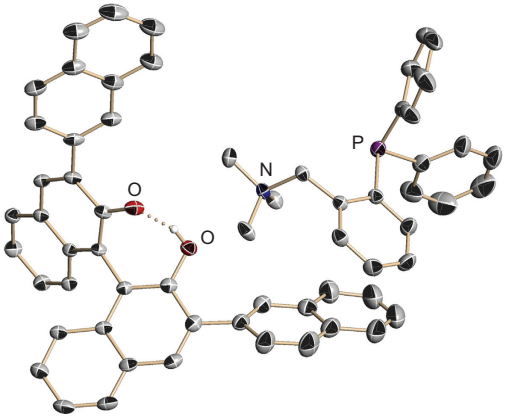
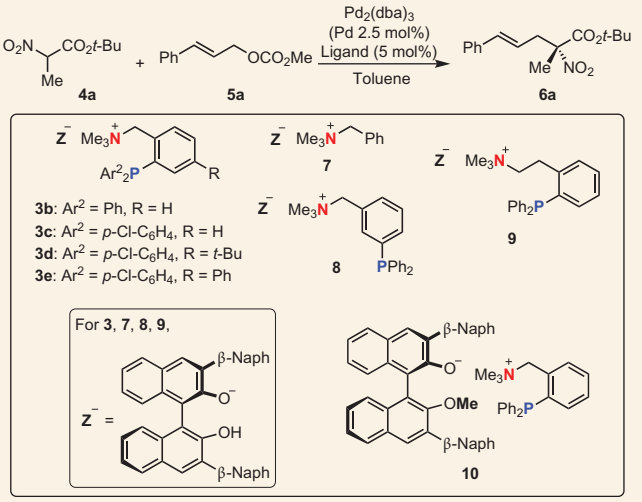


Figure 2 | ORTEP diagram of 3b. Calculated hydrogen atoms are omitted for clarity.

Table 1 | Enantioselective allylation of α-nitrocarboxylate 4a with cinnamyl carbonate 5a.



Entry	Ligand	Conditions	Yield (%)*	e.e. (%)†
1	**3a**	r.t., 5 h	56	38
2	**3b**	r.t., 5 h	78	68
3	PPh_3	With **7** (5 mol%), r.t., 5 h	99	<1
4	**1**·Br	With **2b** (5 mol%), r.t., 5 h	85	<1
5	**8**	r.t., 5 h	99	<1
6	**9**	r.t., 5 h	83	<1
7	**10**	r.t., 5 h	92	−3
8	**3c**	r.t., 5 h	99	73
9	**3d**	r.t., 5 h	99	75
10	**3e**	r.t., 5 h	99	83
11	**3e**	0 °C, 24 h	78	88
12	**3e**	Toluene/H_2O (20:1. v/v), 0 °C, 12 h	97	94

Reactions were performed with 0.2 mmol **4a** and 0.24 mmol **5a** in the presence of $Pd_2(dba)_3$ (Pd 2.5 mol%) and ligand (5 mol%) under the given reaction conditions. *Isolated yields. †Determined by chiral high-performance liquid chromatography (HPLC). ‡The absolute configuration of product **6a** was determined, after conversion to the known compound (see Supplementary Information for details). r.t., room temperature.

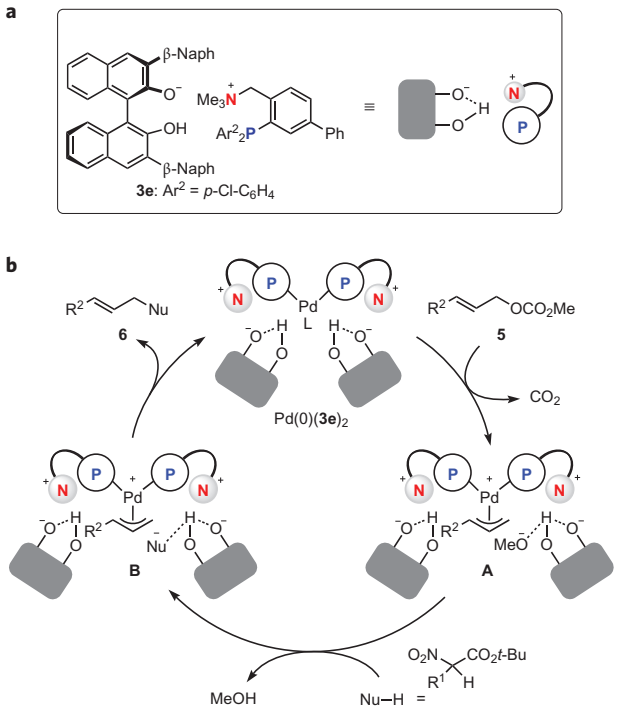


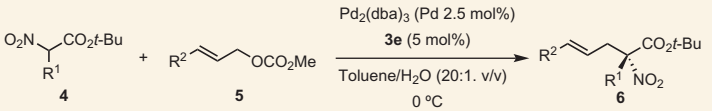
Figure 3 | Proposed catalytic cycle for enantioselective alkylation catalysed by an ion-paired chiral catalyst. The Pd(II)–**3e** (1:2) complex exists in the reaction mixture and functions as an active species.

enantiocontrol. This also provides compelling evidence that allows the possibility that the observed stereoselectivity can be delivered by the mere presence of the chiral binaphtholate anion as a counter-ion of the cationic π-allyl palladium intermediate to be ruled out. It is worth noting that an additional control experiment with the ion-paired chiral ligand **10** bearing a hydroxyl-protected binaphtholate anion under similar conditions furnished nearly racemic **6a** (entry 7), implying the crucial role of the free hydroxyl moiety of the anionic component of **3** in the present asymmetric catalysis.

Based on the experimental validation of the stereocontrolling ability of the ion-paired chiral ligand **3**, we further examined the relationship between the structure of **3** and its consequent reaction efficiency, with the electronic and steric manipulations of the readily modifiable achiral component emerging as key factors. As shown in Table 1, replacement of the phosphorus phenyl substituent (Ar^2) by the electron-withdrawing *para*-chlorophenyl group (**3c**) was beneficial in terms of reactivity and selectivity (entry 8). Interestingly, the introduction of additional substituents (R) such as *tert*-butyl (**3d**) and phenyl (**3e**) groups to the benzene linkage increased the enantioselectivity to 75% e.e. and 83% e.e., respectively (entries 9 and 10). Although the considerable rate retardation was inevitable when the reaction was performed at 0 °C, despite the expected selectivity enhancement (entry 11), the use of water as a co-solvent (toluene/H_2O = 20:1. v/v) improved both catalytic activity and enantioselectivity, and **6a** was isolated quantitatively with 94% e.e. (entry 12). To gain insight into the origin of the observed enhancement of reactivity and selectivity in the presence of water, we carried out ^{31}P NMR spectroscopic analysis of the catalysts. The ^{31}P NMR measurement of a mixture of $Pd_2(dba)_3$ and **3e** with a [Pd]/phosphine ratio of 1:2 in dry toluene at 0 °C showed two sharp peaks at $\delta = 30.6$ and -16.4 ppm, respectively. The signal at $\delta = -16.4$ ppm was assigned to the free ligand **3e**, and the other peak presumably corresponded to the palladium(0)–**3e** complex. However, only a single peak was detected at $\delta = 30.7$ ppm in the spectrum of the catalyst prepared in toluene/H_2O (20:1), suggesting that water would facilitate the ligand exchange process, and the resulting palladium(0) complex would probably be Pd(0)(**3e**)$_2$(dba).

To gain information about the structure of the palladium(II) complex, we initially monitored the reaction of **4a** with **5a** under optimized conditions using ^1H and ^{31}P NMR spectroscopy. The complete consumption of **4a** and the formation of **6a** were verified by the ^1H NMR analysis, but the signal appearing at $\delta = 30.7$ ppm in the ^{31}P NMR measurement after catalyst preparation was virtually unchanged throughout the reaction, and a signal from the palladium(II) complex could not be detected. This observation raised the possibility that the palladium(0) complex might be the resting state and oxidative addition would be a rate-determining step. We therefore performed kinetic experiments to elucidate the detailed reaction profiles, which revealed that the present palladium-catalysed allylic alkylation using **3e** as a chiral ligand had first-order dependence on **4a** and zero-order dependence on **5a**. These findings clearly indicate that the rate-determining step is carbon–carbon bond formation, and the *in situ* prepared palladium(0) complex is a non-reactive species from which reactive Pd(0)(**3e**)$_2$ would be generated in low concentration[24]. We then focused again on obtaining structural information about the palladium(II) complex. Because the continuous kinetic experiments showed first-order dependence of the reaction on the catalyst, a monomeric palladium complex is involved in the catalysis.

Table 2 | Substrate scope.



Entry	4	R^1	5	R^2	Product	Time (h)	Yield (%)*	e.e. (%)†
1	**4b**	Et	**5a**	Ph	**6b**	24	97	93
2	**4c**	CH_2CHMe_2	**5a**	Ph	**6c**	36	96	97
3	**4d**	*n*-Hex	**5a**	Ph	**6d**	30	97	95
4	**4e**	CH_2Ph	**5a**	Ph	**6e**	30	94	97
5	**4f**	$(CH_2)_2CO_2Me$	**5a**	Ph	**6f**	24	98	93
6	**4a**	Me	**5b**	*p*-Cl-C_6H_4	**6g**	18	90	90
7‡	**4a**	Me	**5c**	*p*-Br-C_6H_4	**6h**	24	99	90
8	**4a**	Me	**5d**	*p*-MeO-C_6H_4	**6i**	30	99	93
9‡	**4a**	Me	**5e**	2-naphthyl	**6j**	24	98	91
10	**4a**	Me	**5f**	2-thienyl	**6k**	48	94	91
11	**4a**	Me	**5g**	H	**6l**	12	91	<1

The reactions were performed with 0.2 mmol of **4** and 0.24 mmol of **5** in the presence of $Pd_2(dba)_3$ (Pd 2.5 mol%) and **3e** (5 mol%) under the given reaction conditions. *Isolated yields. †Determined by chiral HPLC. ‡Performed at −5 °C

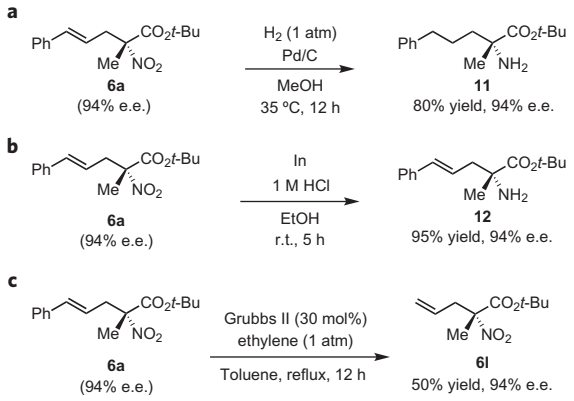


Figure 4 | Derivatization of alkylation product 6a. a, Usual hydrogenation reaction affords the saturated α-amino ester. **b**, Selective reduction of the nitro group using indium metal gives the unsaturated α-amino ester. **c**, Olefin metathesis with ethylene provides the same product of simple allylation **6l**.

In addition, we confirmed second-order dependence on the ligand **3e**, which was measured at constant concentration of $Pd_2(dba)_3$, and also observed modest yet positive nonlinear effects[25], strongly suggesting that a palladium(II) complex bearing two ion-paired ligands **3e** on the palladium metal acts as a reactive species in the bond-forming event (Supplementary Figs S6–S10). These results allowed us to postulate a plausible catalytic cycle (Fig. 3). The Pd(0)(**3e**)$_2$ adds to allylic carbonate **5** to give a cationic π-allyl palladium(II) complex **A**. This structure would be maintained after it reacts with nitroester **4** (Nu–H) to form **B**, incorporating a nucleophilic nitronate anion (Nu^-) that would probably have a hydrogen-bonding interaction with the phenolic proton of the binaphtholate anion. The organization of this intermediate through non-bonded interactions in the transition state would be essential in realizing the enantiofacial discrimination of the prochiral anionic nucleophile in its addition to the π-allyl palladium moiety, liberating product **6** and the parent palladium(0) complex. It should be emphasized that the results of a series of control experiments, particularly those supporting the importance of the mutual position of the ammonium cation and arylphosphine moieties of the achiral component of **3** (Table 1, entries 5 and 6) as well as the free hydroxyl moiety of the binaphtholate anion (entry 7), are consistent with the proposed reaction pathway.

Further experiments were conducted to explore the generality of the present enantioselective allylic alkylation protocol, and representative results are summarized in Table 2. A wide range of α-nitrocarboxylates **4** with different α-substituents, including a functionalized one, could be used as pronucleophiles, and excellent chemical yields and enantioselectivities were uniformly observed (entries 1–5). With respect to the electrophile component, variation in the electronic nature of the γ-substituents appears to have little influence on the asymmetric induction (entries 6–8), and the incorporation of fused aromatic and heteroaryl ring systems was also well tolerated (entries 9 and 10). In the reaction with simple allyl methyl carbonate, however, the product was obtained in an almost racemic form (entry 11).

Alkylation product **6** can be selectively derivatized into the corresponding saturated and unsaturated α,α-disubstituted α-amino esters in a facile manner through simple reduction processes (Fig. 4a,b). For example, exposure of **6a** to usual hydrogenation conditions (H_2, palladium on carbon in methanol) at 35 °C gave rise to the corresponding saturated α-amino ester **11** in 80% yield, while treatment of **6a** with indium metal and 1 M HCl in ethanol at room temperature left the double bond intact, affording **12** in 95% yield. In both transformations, no erosion of the enantiomeric purity was detected. In addition, olefin cross metathesis of **6a** with ethylene under the influence of Grubbs catalyst afforded the same product of simple allylation **6l**, without loss of e.e. (Fig. 4c). These illustrations clearly demonstrate the utility of the enantioselective nitroester alkylations as an expedient means to synthesize various optically active, non-proteinogenic α-amino acids and their derivatives.

Conclusion

We have introduced a chiral ligand assembled from an achiral quaternary ammonium–phosphine and a chiral binaphtholate anion through electrostatic interaction. We successfully demonstrated the remarkable ability of this ion-paired chiral ligand in inducing stereocontrol over a prochiral anionic nucleophile in the palladium catalysis by achieving a highly enantioselective allylic alkylation of α-nitrocarboxylates. This study provides a conceptually new approach to the design of chiral ligands for asymmetric transition-metal catalysis. On considering the multitude of combinations created by achiral onium cations with suitable coordinative functionalities at requisite positions and readily available chiral acids, we believe that this approach shows vast potential in the development of transition-metal-catalysed stereoselective bond-forming reactions, particularly those involving anionic species as a nucleophilic intermediate.

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Author contributions

K.O. and T.O. conceived and designed the study, and co-wrote the paper. K.O., M.I. and T.K. performed the experiments and analysed the data. All authors discussed the results and commented on the manuscript.

Additional information

The authors declare no competing financial interests. Supplementary information and chemical compound information accompany this paper at www.nature.com/naturechemistry. Reprints and permission information is available online at http://www.nature.com/reprints. Correspondence and requests for materials should be addressed to T.O.