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Ligand-enabled multiple absolute stereocontrol in metal-catalysed cycloaddition for construction of contiguous all-carbon quaternary stereocentres

Kohsuke Ohmatsu[1,2], Naomichi Imagawa[2] and Takashi Ooi[1,2]*

The development of a general catalytic method for the direct and stereoselective construction of contiguous all-carbon quaternary stereocentres remains a formidable challenge in chemical synthesis. Here, we report a highly enantio- and diastereoselective [3+2] annulation reaction of 5-vinyloxazolidinones and activated trisubstituted alkenes catalysed by a palladium complex bearing a newly devised phosphine ligand with a chiral ammonium salt component, which enables the single-step construction of three contiguous stereocentres, including vicinal all-carbon quaternary stereocentres, in a five-membered heterocyclic framework. This stereoselective cycloaddition protocol relies on the remarkable ability of the chiral ligand to rigorously control the absolute stereochemistry of each chiral centre associated with the multiple bond-forming events, and provides a reliable catalytic process for the asymmetric synthesis of densely functionalized pyrrolidines.

A contiguous array of all-carbon quaternary stereocentres is found in many complex natural products, and it is often crucial for the expression of their biological activities. Accordingly, the establishment of reliable methodologies for the efficient stereoselective construction of this structural motif represents a significant and highly important task, but is among the most challenging objectives in organic synthesis[1–6]. In principle, the prospective molecular transformations for the construction of a contiguous array of chiral quaternary carbons can be classified into two general schemes. One is asymmetric addition to tetrasubstituted alkenes (Fig. 1a), wherein regiochemical control is indispensable to ensure the structural integrity of the product, and the relative stereochemistry of the two resulting chiral centres is highly dependent on the geometry of the starting alkenes. As such, the development of this mode of reaction requires geometrically pure alkenes in order to achieve rigorous stereocontrol. This approach is thus hindered by the difficulty associated with selective preparation of tetrasubstituted alkenes[7]. The other scheme is the asymmetric coupling of trisubstituted carbon nucleophiles and electrophiles (Fig. 1b). Although the complicated stereochemical presetting of substrates is not essential, bond formation between the sterically congested, prochiral carbons of these species is inherently unfavourable, and achievement of the requisite high level of absolute and relative stereocontrol through the simultaneous yet precise recognition of their intricate stereochemistries poses a formidable challenge. As a means of addressing this long-standing problem, intramolecular processes are considered to be advantageous, particularly in terms of circumventing the steric constraints on the reactivity by exploiting the enforced proximity of the two reactive sites. In fact, as previously reported, a limited number of approaches mostly rely on intramolecular reactions such as polyene cyclization[8,9], sigmatropic rearrangement[10–14] and intramolecular cycloadditions[15]. However, although substrate-directed diastereoselective methods have been well documented, the development of catalytic asymmetric protocols for the direct and selective generation of vicinal all-carbon quaternary stereocentres in a single synthetic operation remains largely unexplored[14,16–21].

Transition-metal-catalysed intermolecular cycloadditions for the rapid assembly of cyclic molecular frameworks have been studied extensively[22,23]. Among the wide range of useful variations, catalytic annulation mediated by a zwitterionic π-allylpalladium intermediate is one of the most powerful tools for the stereoselective synthesis of highly substituted cyclic compounds from relatively simple materials[24–29]. The overall bond connection in this system is believed to take place in a stepwise manner. When a readily accessible trisubstituted alkene is used as an electrophilic coupling partner, the initial intermolecular addition of the allylpalladium species affords the zwitterionic intermediate possessing a trisubstituted carbanionic site (Fig. 1c). If the subsequent ring closure is fast enough to allow retention of the stereochemical information from the parent alkene geometry in the generated carbanion, enantiofacial discrimination of the alkene in the intermolecular addition step would enable the stereoselective construction of not only the trisubstituted chiral centre, but also the adjacent quaternary carbon stereocentre. Moreover, employment of a precursor with a tetrasubstituted chiral carbon for the generation of the 1,1-disubstituted allylpalladium species allows for the introduction of an additional quaternary stereocentre in the second ring-closing event. Importantly, control of the isomerization of the planar chiral π-allylpalladium via π–σ–π interconversion is necessary to accomplish the stereoselective construction of this chiral carbon centre[29–31]. To achieve such double absolute stereocontrol, that is, the discrimination of the prochiral trisubstituted alkene and control of the planar chirality of the π-allylpalladium, in a single cycloaddition process, we devised a new type of phosphine ligand with a pendant chiral ammonium salt (Fig. 1d)[32,33]. It was hypothesized that each structural component of this onium–phosphine hybrid ligand (arylphosphine, chiral ammonium ion and counterion) would play a pivotal role in a cooperative manner through the generation of a doubly ion-pairing intermediate, in which the remote anionic site of the

[1]Institute of Transformative Bio-Molecules (WPI-ITbM), Nagoya University, Nagoya 464-8602, Japan, [2]Department of Applied Chemistry, Graduate School of Engineering, Nagoya University, Nagoya 464-8603, Japan. *e-mail: tooi@apchem.nagoya-u.ac.jp

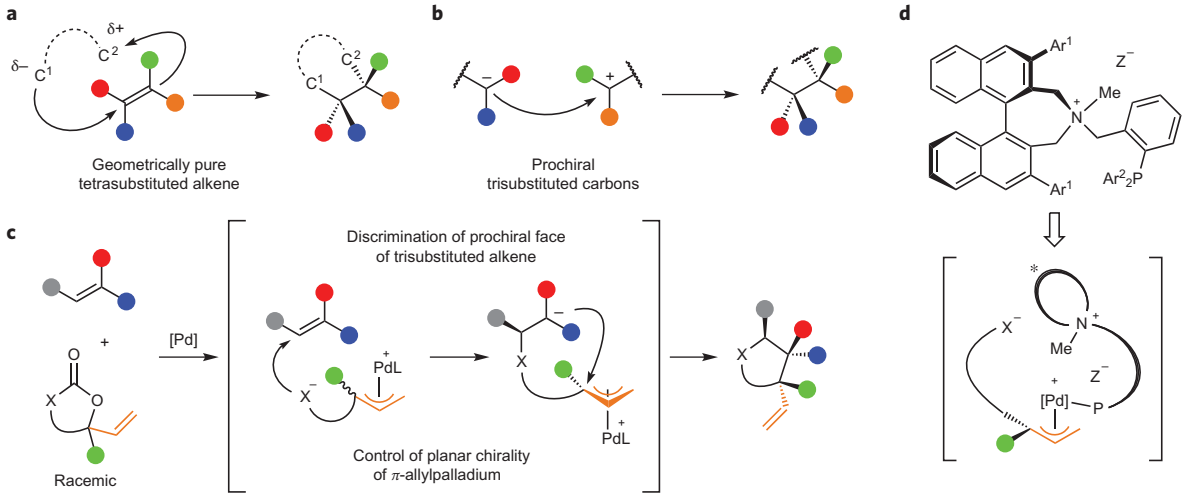


Figure 1 | Overview of stereoselective construction of contiguous all-carbon quaternary stereocentres. a, Reaction of tetrasubstituted alkenes. **b**, Reaction between prochiral trisubstituted carbon reagents. **c**, Concept of multiple absolute stereocontrol in palladium-catalysed cycloaddition for asymmetric construction of contiguous stereocentres. **d**, Structure of chiral onium–phosphine hybrid ligand and proposed doubly ion-pairing intermediate.

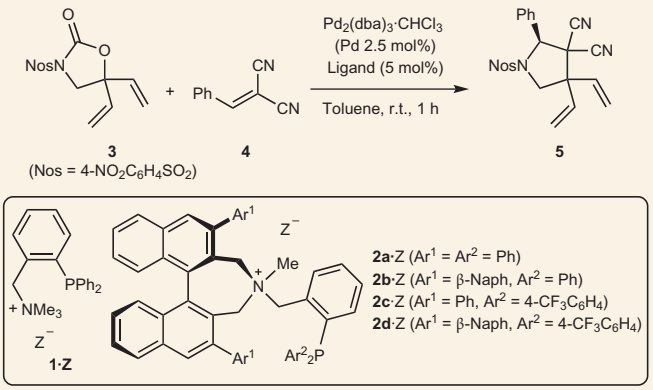
zwitterionic constituent could be recognized by the chiral ammonium ion moiety of the ligand coordinated to the cationic palladium centre. Here, we report the highly enantio- and diastereoselective construction of contiguous all-carbon quaternary stereocentres based on this strategy. Specifically, a palladium-catalysed asymmetric [3+2] annulation reaction of 5-vinyloxazolizinones and activated trisubstituted alkenes was developed, thereby offering a reliable catalytic process for the asymmetric synthesis of densely substituted pyrrolidines[34–36].

Results and discussion

The studies initially focused on the development of an effective ligand for promoting the palladium-catalysed asymmetric [3+2] cycloaddition. For this purpose, *N*-(4-nitrobenzenesulfonyl)-5,5-divinyloxazolidin-2-one (**3**) and 2-benzylidenemalononitrile (**4**) were selected as model substrates for the following reasons: (i) these compounds can be readily prepared from a commercially available glycine derivative and malononitrile, respectively; (ii) the enantioselectivity of the cycloadduct would be a suitable parameter for evaluating the ability of the chiral onium–phosphine hybrid ligand to discriminate prochiral **4** in the conjugate addition of the anionic site of the allylpalladium species generated from **3**; (iii) this transformation could provide straightforward access to optically active, highly functionalized chiral pyrrolidines, which are ubiquitous structural cores in biologically relevant natural products and pharmaceuticals[37–39].

The reaction of **3** with **4** was first attempted under the influence of the catalyst generated *in situ* from the tris(dibenzylideneacetone)-dipalladium–chloroform complex [$Pd_2(dba)_3$·$CHCl_3$] and triphenylphosphine (PPh_3) as a ligand in toluene at room temperature. After stirring for 1 h, the desired *N*-protected pyrrolidine **5** was obtained in moderate yield (Table 1, entry 1). This insufficient reactivity was ascribed to the reluctant addition of the sulfonamide ion moiety of the zwitterionic allylpalladium to **4**, probably due to the internal association of this weak nucleophile with the cationic palladium centre. This unproductive interaction could be suppressed by the addition of an external anion with strong coordinating affinity for palladium such as a halide ion[40], as previously observed by Knight and Aggarwal in related reaction systems[35,36]. Indeed, in the presence of a catalytic amount of tetrabutylammonium bromide, the cycloaddition proceeded much faster under otherwise identical conditions to give **5** in 79% yield (entry 2). This observation led us to envision further enhancement of the reactivity by the use of a phosphine ligand incorporating a quaternary ammonium halide component, not only to assist the preferable halide–palladium contact but also to recognize the anionic site via facile pairing with the ammonium ion. Accordingly, the reaction with *o*-diphenylphosphinobenzylammonium bromide **1·Br**, a ligand recently developed in our laboratory[32,33], was evaluated. As anticipated, bond formation reached completion within 1 h, affording **5** quantitatively (entry 3). Notably, replacement of the bromide ion of the ligand by the acetate ion resulted in a substantial decrease

Table 1 | Optimization of catalytic system for cycloaddition of 5-vinyloxazolidinone 3 with benzylidenemalononitrile 4.



Entry	Ligand	Yield (%)*	e.e. (%)†
1	PPh_3	43	-
2‡	PPh_3	79	-
3	**1·Br**	99	-
4	**1·OAc**	49	-
5	**2a·Br**	94	63
6	**2b·Br**	99	63
7	**2c·Br**	99	57
8	**2d·Br**	99	75
9	**2d·Cl**	99	72
10	**2d·I**	99	90
11§	**2d·I**	99	92

Unless otherwise noted, reactions were carried out with 0.10 mmol of **3** and 0.12 mmol of **4** in the presence of $Pd_2(dba)_3$·$CHCl_3$ (Pd, 2.5 mol%) and ligand (5 mol%) in 1.0 ml of toluene at room temperature for 1 h. *Isolated yield. †Determined by high-performance liquid chromatography (HPLC) analysis. ‡Performed with 5 mol% of tetrabutylammonium bromide (TBAB). §Carried out at 0 °C for 3 h.

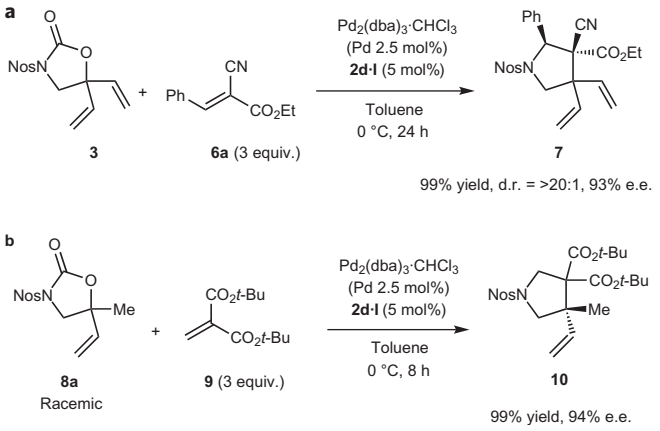


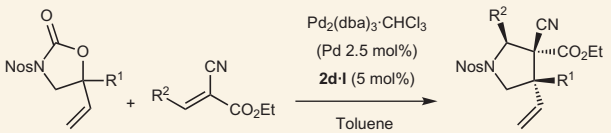
Figure 2 | Examinations of individual absolute stereocontrol. a, Reaction to generate an all-carbon quaternary stereocentre at the C3 position of pyrrolidine. **b**, Reaction to generate an all-carbon quaternary stereocentre at the C4 position of pyrrolidine.

in reactivity, giving credence to the postulate that the coordinating ability of the anion is crucial to the catalytic performance (entry 4). Based on the prime efficacy of **1·Br** as a ligand for promoting the zwitterionic allylpalladium-mediated cycloaddition, this ligand was evolved into chiral ammonium phosphines with the capacity for rigorous control of the absolute stereochemistry at the initial conjugate addition stage of the present system. This strategy involved the introduction of a chiral 1,1′-binaphthyl-derived azepinium skeleton[41] into the ammonium ion component; the effectiveness of **2a·Br**, having simple phenyl appendages at the 3,3′-positions of the binaphthyl unit (Ar^1) as well as the phosphorus centre (Ar^2), was immediately evident, thus inducing an appreciable level of enantiocontrol on **5** without detrimental impact on the reactivity profile (entries 5–8). The subsequent structural modifications of the aromatic substituents of **2·Br** (Ar^1 and Ar^2) revealed that **2d·Br** was a promising candidate for further optimization. Interestingly, the identity of the halide ion, a remaining structural parameter to be varied, appeared to have a profound effect on the stereo-directing ability of the ligand. The use of the chloride variant (**2d·Cl**) subtly affected the selectivity (entry 9), whereas a dramatic improvement in the enantioselectivity was achieved when the counterion was substituted with iodide (**2d·I**) (entry 10). This correlation supports the claim that the halide ion experiences intimate contact with positively charged palladium in the transition state, and has a critical effect on stereocontrol as well as the catalytic efficiency, in concert with the chiral ammonium ion component, which is a distinctive feature of this new chiral onium phosphine ligand. Finally, lowering the reaction temperature to 0 °C allowed the quantitative isolation of **5** with 92% e.e. (entry 11).

Having established the optimal ligand structure and reaction conditions for realizing precise discrimination of prochiral alkene **4** in the cycloaddition, this catalytic system was extended to the stereoselective construction of all-carbon quaternary stereocentres using a trisubstituted alkene with different geminal substituents as an electrophilic substrate. Thus, the reaction of oxazolidinone **3** with (*E*)-ethyl 2-cyano-3-phenylacrylate (**6a**) was conducted under optimized conditions to furnish diastereomerically pure pyrrolidine **7** in quantitative yield with excellent enantioselectivity (Fig. 2a). The potential ability of ligand **2d·I** to control the planar chirality of π-allylpalladium through the π–σ–π isomerization process was also evaluated by using racemic 5-methyl-5-vinyloxazolidinone **8a** in combination with 2-methylidenemalonate **9** for similar annulation. To our delight, this trial efficiently produced pyrrolidine **10** in a stereoconvergent manner with 94% e.e. (Fig. 2b). These data strongly suggest that chiral ammonium phosphine **2d·I** should pave the way to achieving individual yet simultaneous absolute stereocontrol during the plural bond-forming events involved in the palladium-catalysed asymmetric cycloaddition reaction.

On the basis of this prospect, the viability of the asymmetric construction of contiguous all-carbon quaternary stereocentres via the [3+2] annulations of racemic oxazolidinones **8** with trisubstituted alkenes **6** was assessed (Table 2). Subjection of oxazolidinone **8a** and 2-cyano-3-phenylacrylate **6a** to catalysis by $Pd_2(dba)_3$·$CHCl_3$ and **2d·I** in toluene at 0 °C gave rise to the desired densely substituted pyrrolidine **11a** in a stereochemically pure form (entry 1).

Table 2 | Asymmetric construction of contiguous all-carbon quaternary stereocentres through palladium-catalysed cycloaddition.



Entry	R^1	8	R^2	6	Temperature	11	Yield (%)*	d.r.†	e.e. (%)‡
1	Me	**8a**	Ph	**6a**	0 °C	**11a**	98	>20:1:<1:ND	98
2	Me	**8a**	4-Br-C_6H_4	**6b**	0 °C	**11b**	99	17:1:<1:ND	97
3	Me	**8a**	4-MeO-C_6H_4	**6c**	0 °C	**11c**	99	>20:1:<1:ND	99
4	Me	**8a**	2-naphthyl	**6d**	0 °C	**11d**	94	>20:1:<1:ND	99
5	Me	**8a**	2-furyl	**6e**	0 °C	**11e**	99	>20:1:<1:ND	97
6	Et	**8b**	Ph	**6a**	0 °C	**11f**	99	>20:1:<1:ND	98
7	*i*-Bu	**8c**	Ph	**6a**	0 °C	**11g**	99	>20:1:<1:ND	99
8	$PhCH_2$	**8d**	Ph	**6a**	0 °C	**11h**	99	>20:1:<1:ND	95
9§	*i*-Pr	**8e**	Ph	**6a**	r.t.	**11i**	70	>20:1:<1:ND	94
10	Ph	**8f**	Ph	**6a**	r.t.	**11j**	99	9.8:1:<1:ND	93
11	4-Cl-C_6H_4	**8g**	Ph	**6a**	r.t.	**11k**	94	8.6:1:<1:ND	94
12	4-MeO-C_6H_4	**8h**	Ph	**6a**	r.t.	**11l**	97	9.3:1:<1:ND	95

Unless otherwise noted, reactions were carried out with 0.10 mmol of **8** and 0.30 mmol of **6** in the presence of $Pd_2(dba)_3$·$CHCl_3$ (Pd, 2.5 mol%) and **2d·I** (5 mol%) in 1.0 ml of toluene. For reaction time, see Supplementary pages 11-14. *Isolated yield of the mixture of diastereomers. †Determined based on ^{1}H NMR analysis of crude reaction mixture. ND, not detected. ‡Enantiomeric excesses of the major diastereomer are indicated, which were analysed by chiral stationary-phase HPLC. Absolute configurations of **11a** and **11j** were confirmed by X-ray diffraction analysis, and the stereochemistries of other examples were assumed by analogy. §Reaction was performed with $Pd_2(dba)_3$·$CHCl_3$ (Pd, 5 mol%) and **2d·I** (10 mol%). r.t., room temperature.

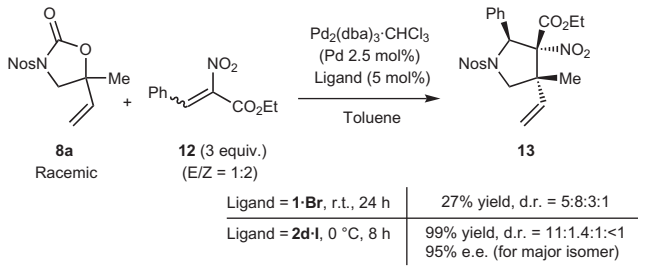


Figure 3 | [3+2] cycloaddition of oxazolidinone and nitroacrylate. Chiral ligand **2d·I** enabled multiple local stereocontrol in a [3+2] cycloaddition between oxazolidinone **8a** and a nitroacrylate **12** (which was used as a mixture of geometric isomers).

Parallel results were obtained with other 2-cyanoacrylates bearing different aromatic or heteroaromatic substituents at their 3-positions (entries 2–5). This virtually complete stereocontrol was also feasible in the cycloaddition between oxazolidinones **8** with various 5-alkyl substituents, including branched variations, and **6a** (entries 6–9). Notwithstanding the requirement for a higher reaction temperature, 5-aryl-substituted oxazolidinones were tolerated with preservation of high levels of diastereo- and enantiocontrol (entries 10–12).

The potential of the present strategy was further extended to achieve multiple absolute stereocontrol in the reaction of **8a** with ethyl 2-nitro-3-phenylacrylate (**12**; $E/Z = 1:2$) (Fig. 3). Exposure of these substrates to similar conditions resulted in smooth cycloaddition to furnish the corresponding adduct **13** quantitatively with high diastereoselectivity (11:1.4:1:<1) and excellent enantioselectivity (95% e.e.), despite the use of an isomeric mixture of **12**. The *E*/*Z* ratio of the remaining **12** was confirmed to be almost unchanged. It is of fundamental importance to note that **13** was obtained as a 5:8:3:1 mixture of the four diastereomers when the reaction was implemented using achiral ammonium phosphine **1·Br** as a ligand. These results clearly indicate that catalyst control overrides the geometrical nature of the trisubstituted alkene, and also demonstrate the inherent power of the chiral ammonium–phosphine hybrid ligand **2d·I** to enable efficient individual stereocontrol for the construction of the array of three contiguous chiral carbons in this single annulation process (Supplementary Figs 2 and 3).

The synthetic versatility of the present catalytic system was next demonstrated through a large-scale reaction and the product derivatizations (Fig. 4). The reaction of **8a** with **6a** on a 10 mmol scale was found to be completed in 48 h, even with a reduced amount of catalyst, yielding 4.7 g of cycloadduct **11a** without a notable decrease in stereoselectivity (Fig. 4a). Cycloadduct **11** can be readily transformed into *N*-unprotected pyrrolidines. For instance, the selective reduction of the ethyl ester moiety of **11a** by treatment with diisobutylaluminum hydride (DIBAL-H) and subsequent deprotection of the 4-nitrobenzenesulfonyl (Nos) group[42] under well-established conditions afforded the corresponding pyrrolidine **15** (Fig. 4b). In addition, **11a** was successfully converted into the densely substituted bicyclic lactam **19**, which is the core structure of the analogue of thrombin inhibitors[43–45]. Thrombin is a key serine protease in the blood coagulation cascade, and a series of lactams with a tricyclic core have been developed as non-peptidic, high-affinity inhibitors (Fig. 4c). The synthetic sequence from **11a** depicted in Fig. 4b could offer access to the previously elusive analogues bearing carbogenic substituents at the core. Thus, ozonolysis of the vinyl function in **11a** led to the corresponding aldehyde **16**. The formyl group of **16** could be selectively reduced to the primary alcohol by treating with DIBAL-H in tetrahydrofuran (THF), and subsequent exposure to TFA gave the bicyclic lactone **17**. Eventually, the transformation of lactone to lactam was executed by the transient opening of **17** with 4-methoxybenzylamine followed by the intramolecular Mitsunobu reaction, furnishing **19** as an essentially single stereoisomer.

In conclusion, a highly enantio- and diastereoselective [3+2] annulation reaction of 5-vinyloxazolidinones and activated trisubstituted alkenes catalysed by a palladium complex bearing a newly devised phosphine ligand with a chiral ammonium salt component was developed, which allows for the single-step construction of three contiguous stereocentres, including vicinal all-carbon quaternary stereocentres, on the pyrrolidine core. This system relies heavily on the remarkable ability of the chiral onium–phosphine hybrid ligand to facilitate the intermolecular cycloaddition with precise

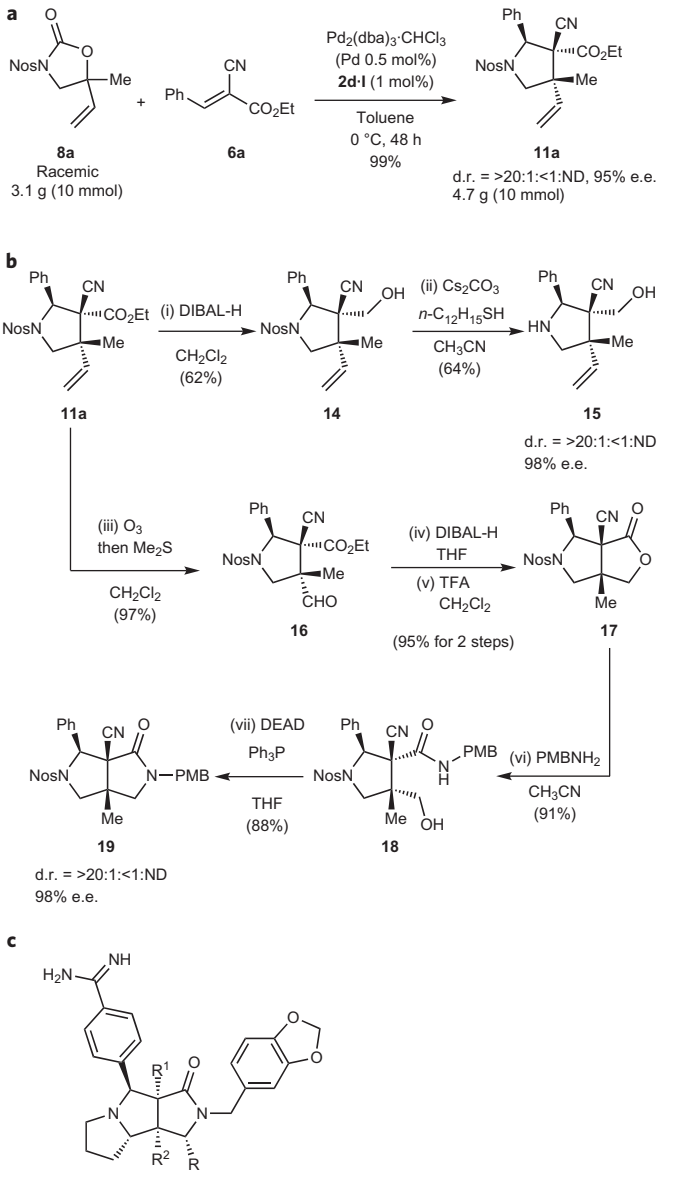


Figure 4 | Synthetic versatility of the present catalytic system. a, Scale-up of the cycloaddition process. **b**, Derivatization of cycloaddition product **11a** to unprotected pyrrolidine **15** and multi-substituted bicyclic lactam **19**. Reagents and conditions: (i) diisobutylaluminum hydride (DIBAL-H) (2 equiv.), CH_2Cl_2, −78 °C, 30 min then 0 °C, 1 h; (ii) Cs_2CO_3 (2 equiv.), *n*-$C_{12}H_{25}SH$ (2 equiv.), CH_3CN, r.t., 4 h; (iii) O_3, CH_2Cl_2, −78 °C, 10 min, then Me_2S (10 equiv.), −78 °C to r.t., 2 h; (iv) DIBAL-H (2 equiv.), THF, −78 °C, 2 h; (v) trifluoroacetic acid (TFA)/CH_2Cl_2 = 1:1, r.t., 7 h; (vi) 4-methoxybenzylamine ($PMBNH_2$) (2 equiv.), CH_3CN, reflux, 6 h; (vii) diethyl azodicarboxylate (DEAD) (1.1 equiv.), Ph_3P (1.1 equiv.), THF, r.t., 10 h. **c**, $R^1 = R^2 = H$; known thrombin inhibitor. R^1, R^2 = alkyl; previously elusive analogues.

control of the individual absolute stereochemistry across multiple bond formation, and represents a reliable catalytic process for the asymmetric synthesis of densely functionalized pyrrolidines and their derivatives.

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Author contributions

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

Additional information

Supplementary information and chemical compound information are available in the online version of the paper. Reprints and permissions information is available online at www.nature.com/reprints. Correspondence and requests for materials should be addressed to T.O.

Competing financial interests

The authors declare no competing financial interests.