ACS Catalysis

Subscriber access provided by Iowa State University | Library

Letter

Catalytic One-Pot Double Asymmetric Cascade Reaction: Synthesis of Chlorinated Oxindoles and geminal Diamines

Xiantao Fang, Zihang Deng, Wen-Hua Zheng, and Jon C Antilla

ACS Catal., **Just Accepted Manuscript** • Publication Date (Web): 29 Jan 2019

Downloaded from http://pubs.acs.org on January 29, 2019

Just Accepted

"Just Accepted" manuscripts have been peer-reviewed and accepted for publication. They are posted online prior to technical editing, formatting for publication and author proofing. The American Chemical Society provides "Just Accepted" as a service to the research community to expedite the dissemination of scientific material as soon as possible after acceptance. "Just Accepted" manuscripts appear in full in PDF format accompanied by an HTML abstract. "Just Accepted" manuscripts have been fully peer reviewed, but should not be considered the official version of record. They are citable by the Digital Object Identifier (DOI®). "Just Accepted" is an optional service offered to authors. Therefore, the "Just Accepted" Web site may not include all articles that will be published in the journal. After a manuscript is technically edited and formatted, it will be removed from the "Just Accepted" Web site and published as an ASAP article. Note that technical editing may introduce minor changes to the manuscript text and/or graphics which could affect content, and all legal disclaimers and ethical guidelines that apply to the journal pertain. ACS cannot be held responsible for errors or consequences arising from the use of information contained in these "Just Accepted" manuscripts.

ACS Publications

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Published by American Chemical Society. Copyright © American Chemical Society. However, no copyright claim is made to original U.S. Government works, or works produced by employees of any Commonwealth realm Crown government in the course of their duties.

Catalytic One-Pot Double Asymmetric Cascade Reaction: Synthesis of Chlorinated Oxindoles and *geminal* Diamines

Xiantao Fang,[†] Zihang Deng,[†] Wenhua Zheng,[‡] and Jon C. Antilla*[†]

[†]Institute for Molecular Design and Synthesis, School of Pharmaceutical Science and Technology, Health Science Platform, Tianjin University, Tianjin 300072, P. R. China

[‡]School of Chemistry and Chemical Engineering, Nanjing University, Jiangsu 210023, P. R. China

ABSTRACT: A multicomponent catalytic double asymmetric cascade reaction (DACR) for obtaining chlorinated oxindoles and C-N aminals simultaneously has been described. A calcium VAPOL phosphate complex was shown to catalyzed two enantiocontrolled multicomponent reactions utilizing 3-aryloxindoles, *N*-Boc imines and *N*-chlorophthalimide, which afforded two structurally complex and diverse chiral products with high levels of stereocontrol in one-pot. This transformation is facile and has a high degree of both step and atom economy.

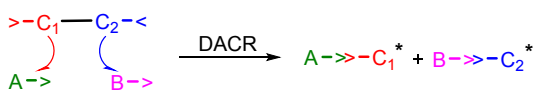
KEYWORDS: Multicomponent reactions; Phosphoric acid; Chiral metal phosphate; Enantioselective synthesis; Cascade reactions

It is widely known that substitution at the 3-position of oxindoles results in a stereogenic center that is found in a high number of pharmaceutically active compounds and natural products.[1] Additionally, chiral geminal diamines are also important structural motifs found in important biologically active compounds of interest.[2] We have achieved the preparation of both of these diverse chiral structures with high enantiocontrol using a new and unique process whereby one chiral catalyst achieves what we term as a *double asymmetric cascade reaction* (DACR).

In the past decades, multicomponent reactions (MCRs)[3] have been developed by a number of conceptually interesting and noteworthy approaches. Asymmetric multicomponent reactions (AMCRs), in particular the catalytic enantioselective MCRs, are a versatile and powerful strategy[4] for complex bond construction in organic and medicinal chemistry. These reactions often feature excellent step and atom economy, require simple operations, and are often employed in the enantioselective synthesis of natural products and potentially biologically active compounds.[5]

A double asymmetric cascade reaction or DACR will be defined herein as *the reaction of at least two or more reactants in a single reaction vessel where two different and distinct enantiocontrolled reactions are catalyzed by a single chiral catalyst*.

Scheme 1. General scheme for a double asymmetric cascade reaction with three reagents (DACR).



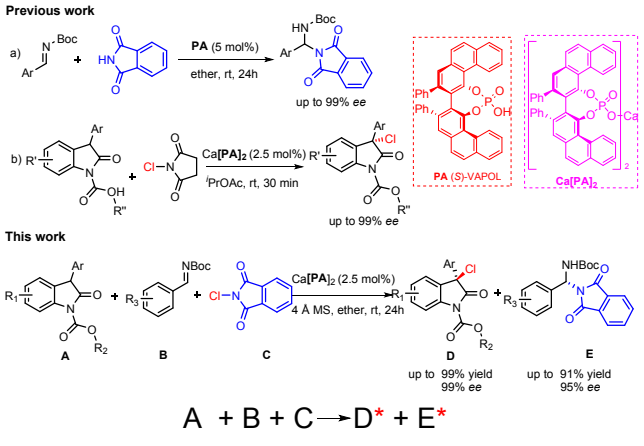
A DACR can conceivably produce at least two new chiral compounds utilizing all of the reactants. In one iteration of this reaction, one of the reactants is partitioned to react with each of the other two reactants (Scheme 1). However, one could envision other possible ways a DACR could occur.

Recently, the synergy of chiral phosphoric acids and efficient transition metal catalysts in enantiocontrolled reactions have allowed for more diverse synthetic tranformations to occur in a single reaction pot.[6-10] AMCRs have been used effectively in synthesis, due to their bond-forming efficiency, and excellent stereoselectivity, along with the potential to quickly assemble complex products.[10,11] Although there are many advantages for AMCRs, the controlled enantioselective cascade of two different reactions by only one catalyst in one pot is still one of the remaining unmet challenges. In addition to the catalyst, various other factors must be taken into consideration for asymmetric cascade reactions, such as solvent, substrates and intermediates.[12] Moreover, it is obviously much more difficult to control the enantioselectivity when the substrates combine in domino reactions because of the different catalytic mechanisms. Therefore, the development of a catalytic enantioselective MCR to access more than one optically pure chiral product from simple starting materials with a single catalyst is highly challenging and potentially desirable.

We envisioned that we could possible match two independent enantiocontrolled reactions first discovered in our laboratory with each other by utilizing the same chiral catalyst.[13] In the first reaction we knew our previously discovered chlorinations of 3-aryl oxindoles using NCS as the chlorine source was robust and highly selective using $Ca[PA]_2$ metal complexes.[13b] In the second reaction we thought the addition of imides to activated imines previously known to be catalyzed by chiral PA's could occur from the NCS byproduct (imide anion).[13a] In light of the fact that some reactions before Ishihara's 2010 discovery that metal-phosphates could be the true catalysts for early reactions assumed to be chiral PA's,[13c] we theorized that the imide additions could be occurring with

a chiral Ca-phosphate catalyst. Matching these two reactions with a single catalyst was the basis of our initial investigations (Scheme 2).

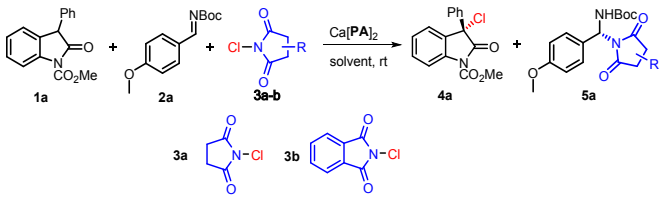
Scheme 2. The double asymmetric cascade reaction (DACR).



After some development we found that *N*-Moc-protected 3-phenyloxindole **1a**, *tert*-butyl (*E*)-(4-methoxybenzylidene) carbamate **2a**, and readily available *N*-chlorosuccinimide (NCS) **3a** were good substrates. By using catalytic amounts (2.5 mol %) of calcium VAPOL phosphate complex Ca[**PA**]$_2$ and *i*PrOH as the solvent (Table 1, entry 1), it was determined to that these were the best conditions for a DACR. The data obtained from these experiments are shown in Table 1. It was determined that by using NCS as the chlorine source in *i*PrOH, the proposed reaction allowed for asymmetric chlorination product formation but unfortunately did not produce the aminal product. DACR was also not possible when the reaction was run in ether (Table 1, entry 2). Then, *N*-chlorophthalimide was chosen as an alternate chlorinating agent. To our delight, it enabled the desired DACR to proceed. Ether was shown to provide conditions for a higher enantioselectivity (Table 1, entries 3-8). We also compared molecular sieves of different pore size and the *ee* was further improved to 96% and 91% with 4Å MS as an additive (Table 1, entry 10). The satisfactory yield and enantioselectivity for **4a** and **5a** were obtained in ether at room temperature.

We next intended to explore whether the catalyst loading could be reduced. It was found that lowering the catalyst amounts significantly gave poor results; when 2.0 mol % catalyst was used a longer reaction time and lower ee was obtained (Table 1, entry 13). Therefore, the subsequent reactions used 2.5 mol % catalyst. In order to better realize the green and step economy, we evaluated the optimal stoichiometry of the three starting materials. Interestingly, when the amounts of the three-substrate ratios were change to **1a**/**2a**/**3b** = 1:1:1 (Table 1, entry 14), the yield and enantioselective of **5a** were sharply lower. Therefore, two equivalents of *tert*-butyl imine were used to ensure an efficient and selective reaction.[14]

Table 1. Optimization of reaction conditions[a]



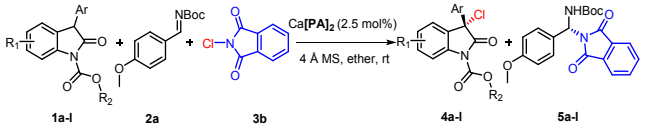
entry	Cl$^+$ source	Additive	Solvent	**4a** Yield (%)[b] /ee (%)[c]	**5a** Yield (%)[b] /ee (%)[c]
1	**3a**	-	*i*PrOH	99/90	-
2	**3a**	-	ether	99/86	-
3	**3b**	-	ether	99/88	88/87
4	**3b**	-	THF	99/85	72/80
5	**3b**	-	toluene	99/53	81/66
6	**3b**	-	DCM	99/44	79/64
7	**3b**	-	EtOAc	99/49	63/41
8	**3b**	-	CH_3CN	99/32	74/58
9	**3b**	4Å MS	*i*PrOH	99/93	85/79
10	**3b**	**4Å MS**	**ether**	**99/96**	**92/91**
11	**3b**	3Å MS	ether	99/92	86/88
12	**3b**	5Å MS	ether	99/91	90/87
13[d]	**3b**	4Å MS	ether	99/91	90/85
14[e]	**3b**	4Å MS	ether	95/94	78/82

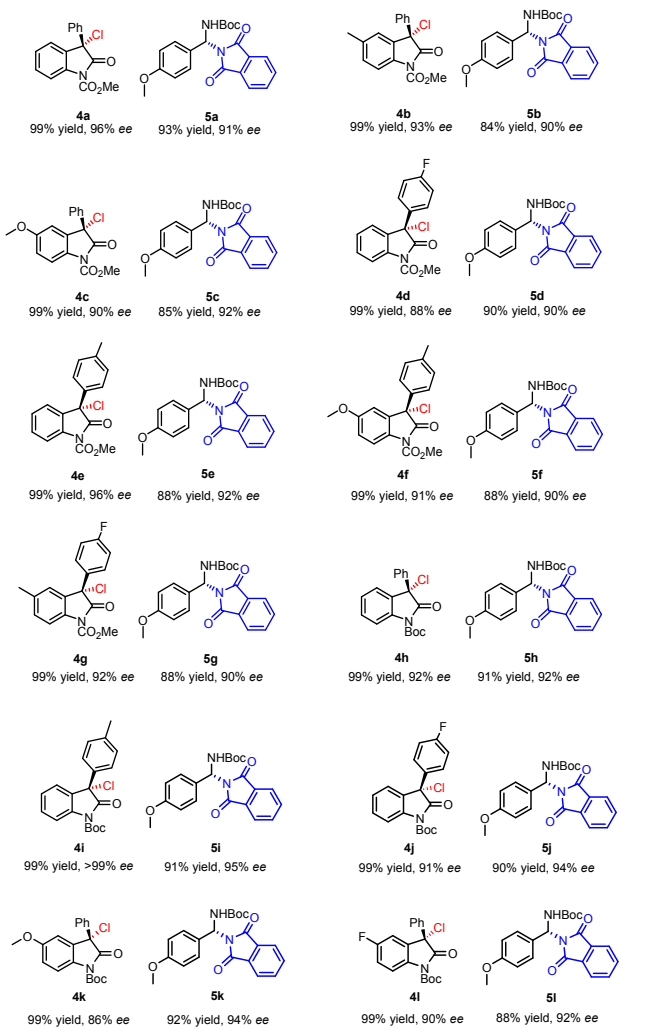
[a]Unless otherwise specified, all reactions were carried out with oxindole **1a** (0.05 mmol), *N*-Boc-imine **2a** (0.10 mmol), chlorine source **3** (0.055 mmol), 40 mg 4Å MS and the catalyst (2.5 mol %) in solvent (1.0 mL) at rt for 24h. [b]Isolated yield. [c]The *ee* values were determined by chiral HPLC analysis. [d]Catalyst loading (2.0 mol %). [e]Equivalent ratio of **1a**/**2a**/**3b** = 1:1:1.

Having found the optimal conditions the Ca[**PA**]$_2$-catalyzed DACR was evaluated with *N*-Moc/Boc-protected oxindoles **1**. The results are summarized in Scheme 3. Substrate generality for the oxindole core arene ring were first examined by the reaction with **2a** and **3b**. Complete conversion of chlorination products were observed in all cases, and the corresponding enantioenriched aminal products were all well tolerated. The electronic nature of the arene substituent on the C-3 and that of the oxindole core were evaluated. It was found that $\mathbf{R_1}$ group can be an electron-donating or -withdrawing group and still give the products in excellent yields (99%) and up to 86 - 93% *ee* values, respectively (Scheme 3, **4a**-**4c**, **4k**-**4l**). Substitutions at the C-3 arene can be both electron rich or poor for the reactions to be well tolerated, and the desired product **4d**, **4e**, **4i** and **4j** was formed in high yield (99%), and with high enantioselectivities of 88%, 96%, 99% and 91%, respectively. Notably, substrate **4i** allowed for a complete conversion and excellent enantioselectivity (99% yield, >99% *ee*) under the same reaction conditions, and when the electron-withdrawing substituents in 3-alkyloxindoles **2d** and **2j** were used, the corresponding chlorinated products **4d** and **4j** were found in high yields, but with lower ee's than the substrates with electron-donating groups **4e** and **4i** (Scheme 3, **4d**-**4e**, **4i**-**4j**). Substrates **2f** and **2g**, bearing the substituent groups at the oxindole core arene ring and at the C-3 arene simultaneously, also gave the corresponding products **4f** and **4g**, respectively, with good enantioselectivities. These seemed to have no obvious effect on the *ee* with only a slightly lower enantioselectivity (91% and 92%). The absolute configurations of compounds **4a** - **4r** were found to be "(***S***)"

by comparison of the observed optical rotation values and HPLC spectrum to the reported literature values.[13b, 15]

Scheme 3. Variation of N-Moc/Boc oxindole substrate for the Ca[PA]$_2$ catalyzed DACR[a]

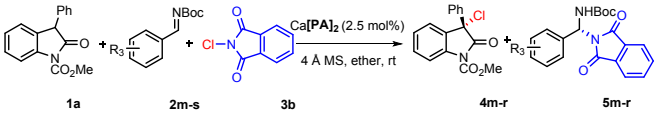


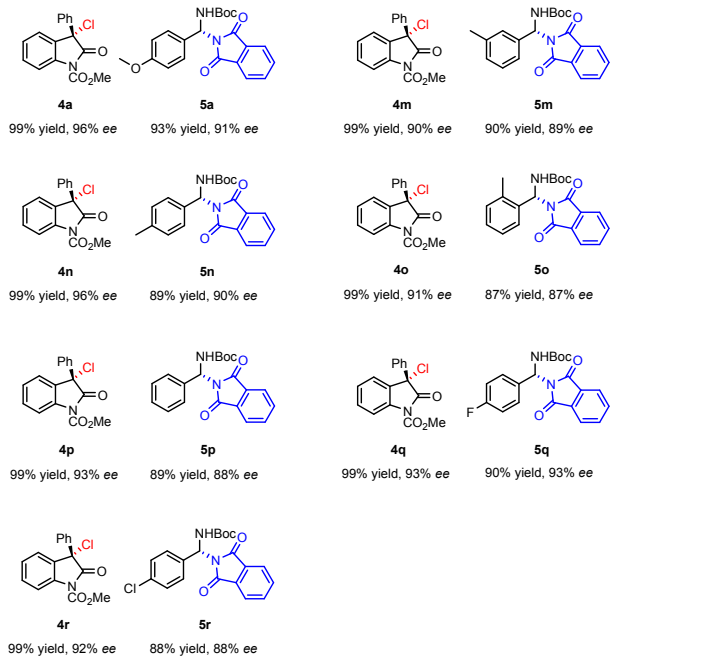


[a]Reaction condition: all reactions were carried out with oxindole **1a-h** (0.05 mmol), *N*-Boc imine **2a** (0.10 mmol), chlorine source **3b** (0.055 mmol), 40 mg 4Å MS and the catalyst (2.5 mol%) in ether (1.0 mL) at rt for 24h. [b]Isolated yield. [c]The *ee* values were determined by chiral HPLC analysis.

The reaction scope of imine substrates was next examined in Scheme 4. The reactions progressed well and gave products **4** and **5** in good yield and moderate to good *ee* using the general conditions already established. The chlorination products were available directly and in high yield along with excellent selectivity in all cases, and enantioenriched aminal products were all tolerated well. There appeared to be a good reaction scope with respect to aryl substituted imines for the DACR. A series of aryl-substituted imines were synthesized and performed for the double asymmetric cascade reaction, respectively. Both the electron-donating (**5m-5o**) and electron-withdrawing substituents (**5q-5r**) and no substituent (**5p**) on the arene ring were equally efficient using the reaction conditions. To our delight, Electron donating groups in the *ortho* (Scheme 4, **5o**), the *meta* (Scheme 4, **5m**), or the *para* (Scheme 4, **5n**) position were good substrates for the reaction, and the products were found in good yields (87%-90%) and *ee* values, 87% - 89% respectively (Scheme 4, **5m** - **5o**). In addition, electron-withdrawing groups (Scheme 4, **5q** - **5r**) in the *para*-position of the substrate gave excellent results. The absolute configurations of **5a-5r** were determined to be "(***R***)" by comparing the observed optical rotation values and HPLC spectrum to that reported in the literature.[13a, 2b]

Scheme 4. Variation of N-Boc imine substrate for the Ca[PA]$_2$ catalyzed DACR[a]





[a]Reaction condition: all reactions were carried out with oxindole **1a** (0.05 mmol), *N*-Boc imine **2m-r** (0.10 mmol), chlorine source **3b** (0.055 mmol), 40 mg 4Å MS and the catalyst (2.5 mol%) in ether (1.0 mL) at rt for 24h. [b]Isolated yield. [c]The *ee* values were determined by chiral HPLC analysis.

Due to insights in our previous studies with the individual reactions in this cascade, we believe the chiral chiral calcium phosphate complex binds to activate both the nucleophile and the electrophiles in each case, and the proposed reaction pathway and transition state is shown in Figure 1. Initially, the centralized chelation sphere of calcium and the carbonyl oxygen's of the Moc group (**1a**) and chlorine source (**3b**), increase the Brønsted basicity of the chiral phosphate and this allows for the oxindole tautomer to also be activated. These interactions together with the hydrogen-bonding interactions of the oxindole tautomer O-H group and the P=O group of the catalyst can give a rationale for the stereoselectivity of the

reaction. The imide anion from the chloride source provides for the subsequent asymmetric aminal formation again via the catalysis of Ca[**PA**]$_2$, to provide **5a**. The reaction progress was monitored by the removal of aliquots that were subsequently analysed by ^{1}H NMR. This analysis showed that the chlorination product was built-up significantly before the presumably slower N-H phthalimide addition to the imine was observed. In consideration of this transition state, the Lewis acidic Ca[**PA**]$_2$ could activate the imine via mono-activation (**TS II**). The chiral environment created by the Ca[**PA**]$_2$ backbone and the bulk of the ligand, thus providing the experimentally observed enantioenriched products (***S***)-**4a** and (***R***)-**5a**.

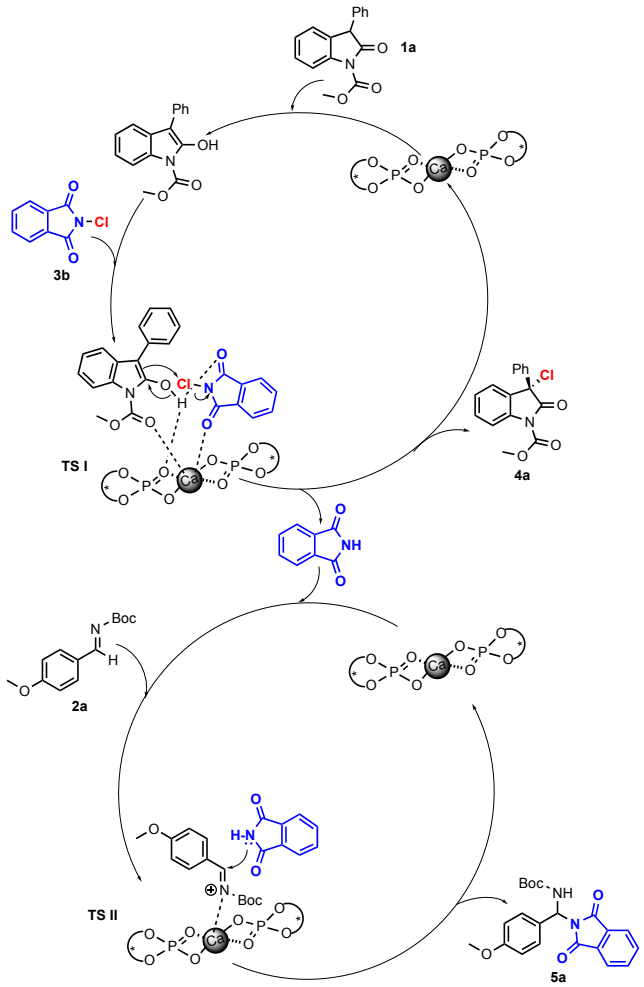


Figure 1. Possible mechanism for the DACR.

In conclusion, by using chiral calcium VAPOL phosphate catalyst, we establish what we believe is the first firm case for a DACR for the highly enantioselective preparation of both chlorinated 3-aryloxindoles *and* geminal diamines. This cascade reaction efficiency is conducted with mild conditions at room temperature, and with a relatively low catalyst loading (2.5 mol%). This DACR requires only readily available starting materials, has good functional group tolerance, and the atom-economy is excellent. In addition, our insight might allow for the future development of other asymmetric multicomponent/cascade type reactions. Further work into other possible cases where DACR can occur is currently underway.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
All detailed experimental procedures, characterizations, NMR and HPLC spectra are contained in the Supporting Information.

AUTHOR INFORMATION

Corresponding Author

*E-mail: jantilla@tju.edu.cn

ACKNOWLEDGMENT

We acknowledge National 1000 Talent Plan of China and Tianjin City for support, as well at Tianjin University for start-up funding.

REFERENCES

(1) a) Galliford, C. V.; Scheidt, K. A. Pyrrolidinyl-Spirooxindole Natural Products as Inspirations for the Development of Potential Therapeutic Agents. *Angew. Chem. Int. Ed.* **2007**, *46*, 8748-8758. b) Dounay, A. B.; Overman, L. E. The Asymmetric Intramolecular Heck Reaction in Natural Product Total Synthesis. *Chem. Rev.* **2003**, *103*, 2945-2963. c) Rahman, A. U.; Basha, A. *Indole Alkaloids*. Harwood Academic Publishers, Amsterdam **1998**. Vol. 2, 22-30. d) Marti, C.; Carreira, E. M. Construction of Spiro[pyrrolidine-3,3-oxindoles]-Recent Applications to the Synthesis of Oxindole Alkaloids. *Eur. J. Org. Chem*. **2003**, 2209-2219. e) Trost, B. M.; Brennan, M. K. Asymmetric Syntheses of Oxindole and Indole Spirocyclic Alkaloid Natural Products. *Synthesis* **2009**, 3003-3025. f) Burés, J.; Armstrong, A.; Blackmond, D. G. Curtin–Hammett Paradigm for Stereocontrol in Organocatalysis by Diarylprolinol Ether Catalysts. *J. Am. Chem. Soc.* **2012**, *134*, 6741–6750.

(2) a) Park, S. Y.; Liu, Y. D.; Oh, J. S.; Kweon, Y. K.; Jeong, Y. B.; Duan, M. Y.; Tan, Y.; Lee, Ji-Woong; Yan, H. L.; Song, C. E. Asymmetric Aminalization via Cation-Binding Catalysis. *Chem. Eur. J.* **2018**, *24*, 1020-1025. b) Hatano, M.; Ozaki, T.; Sugiura, Y.; Ishihara, K. Enantioselective Direct Aminalization with Primary Carboxamides Catalyzed by Chiral Ammonium 1,1′ -Binaphthyl-2,2′ -Disulfonates. *Chem. Commun*. **2012**, *48*, 4986-4989.

(3) a) Estvez, V.; Villacampa, M.; Menndez, J. C. Multicomponent Reactions for the Synthesis of Pyrroles. *Chem. Soc. Rev*. **2010**, *39*, 4402-4421. b) Tejedor, D.; Gonz, lez-Cruz D.; Santos-Exposito, A.; Marrero-Tellado, J. J.; Armas, P. F.; Garca-Tellado, F. Multicomponent Domino Processes Based on the Organocatalytic Generation of Conjugated Acetylides: Efficient Synthetic Manifolds for Diversity-Oriented Molecular Construction. *Chem. Eur. J*. **2005**, *11*, 3502-3510. c) Tour, B. B.; Hall, D. G. Natural Product Synthesis Using Multicomponent Reaction Strategies. *Chem. Rev.* **2009**, *109*, 4439-4486. d) Tietze, L. F.; Kinzel, T.; Brazel, C. C. The Domino Multicomponent Allylation Reaction for the Stereoselective Synthesis of Homoallylic Alcohols. *Acc. Chem. Res*. **2009**, *42*, 367-378. e) Dömling, A.; Wang, W.; Wang, K. Chemistry and Biology Of Multicomponent Reactions. *Chem. Rev.* **2012**, *112*, 3083-3135. f) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. Maximizing Synthetic Efficiency: Multi-Component Transformations Lead the Way. *Chem. Eur. J.* **2000**, *6*, 3321-3329. g) Weber, L. High-diversity Combinatorial Libraries. *Curr. Opin. Chem. Biol.* **2000**, *4*, 295-302. h) Weber, L. Multi-component Reactions and Evolutionary Chemistry. *Drug Discovery Today* **2002**, *7*, 143-147. i) Orru, R. V. A.; de Greef, M. Recent Advances in Solution-Phase Multicomponent Methodology for the Synthesis of Heterocyclic Compounds. *Synthesis* **2003**, 1471-1499.

(4) a) Wender, P. A.; Miller, B. L.; Organic. Synthesis: Theory and Applications. **1993**, Vol. 2, p 27. b) Pellissier, H. Stereocontrolled

Domino Reactions. *Chem. Rev.* **2013**, *113*, 442-524. c) van Berkel, S. S.; Bogels, B. G. M.; Wijdeven, M. A.; Westermann, B.; Rutjes, F. P. J. T. Recent Advances in Asymmetric Isocyanide-Based Multicomponent Reactions. *Eur. J. Org. Chem*. **2012**, 3543-3559. d) Marson, C. M. Multicomponent and Sequential Organocatalytic Reactions: Diversity with Atom-economy and Enantiocontrol. *Chem. Soc. Rev*. **2012**, *41*, 7712-7722. e) Ramón, D. J.; Yus, M. Asymmetric Multicomponent Reactions (AMCRs): The New Frontier. *Angew. Chem. Int. Ed.* **2005**, *44*, 1602-1634. f) Zhao, G. L.; Rios, R.; Vesely, J.; Eriksson L.; Córdova A. Organocatalytic Enantioselective Aminosulfenylation of α,β-Unsaturated Aldehydes. *Angew. Chem. Int. Ed.* **2008**, *47*, 8468-8472.

(5) a) Trost, B. M. The Atom Economy--A Search for Synthetic Efficiency. *Science* **1991**, *254*, 1471-1477. b) Trost, B. M. Atom Economy--A Challenge for Organic Synthesis: Homogeneous Catalysis Leads the Way. *Angew. Chem. Int. Ed.* **1995**, *34*, 259-281. c) Trost, B. M. On Inventing Reactions for Atom Economy. *Acc. Chem. Res*. **2002**, *35*, 695-705. d) Bienayme, H.; Hulme, C.; Oddon, G.; Schmitt, P. Maximizing Synthetic Efficiency: Multi-Component Transformations Lead the Way. *Chem. Eur. J*. **2000**, *6*, 3321-3329. e) Banfi, L.; Basso, A.; Moni, L. The Alternative Route to Enantiopure Multicomponent Reaction Products: Biocatalytic or Organocatalytic Enantioselective Production of Inputs for Multicomponent Reactions. *Eur. J. Org. Chem.* **2014**, 2005-2015.

(6) a) Zhou, J.; List, B. Organocatalytic Asymmetric Reaction Cascade to Substituted Cyclohexylamines. *J. Am. Chem. Soc.* **2007**, *129*, 7498-7499. b) Zhou, J.; List, B. Synthesis of trans-3-Substituted Cyclohexylamines via Brønsted Acid Catalyzed and Substrate-Mediated Triple Organocatalytic Cascade Reaction. *Synlett* **2007**, 2037-2040. c) Mukherjee, S.; List, B. Chiral Counteranions in Asymmetric Transition-Metal Catalysis: Highly Enantioselective Pd/Brønsted Acid-Catalyzed Direct α-Allylation of Aldehydes. *J. Am. Chem. Soc.* **2007**, *129*, 11336-11337. d) Xu, X.; Zhou, J.; Yang, L.; Hu, W. Selectivity Control in Enantioselective Four-component Reactions of Aryl Diazoacetates with Alcohols, Aldehydes and Amines: An Efficient Approach to Synthesizing Chiral β-amino- α-hydroxyesters. *Chem. Commun.* **2008**, 6564-6566. e) Hu, W.; Xu, X.; Zhou, J.; Liu, L. W. J.; Huang, H.; Hu, J.; Yang, L.; Gong, L. Z. Cooperative Catalysis with Chiral Brønsted Acid-$Rh_2(OAc)_4$: Highly Enantioselective Three-Component Reactions of Diazo Compounds with Alcohols and Imines. *J. Am. Chem. Soc.* **2008**, *130*, 7782-7783. f) Cai, Q.; Zhao, Z. A.; You, S. L. Asymmetric Construction of Polycyclic Indoles through Olefin CrossMetathesis/Intramolecular Friedel-Crafts Alkylation under Sequential Catalysis. *Angew. Chem. Int. Ed.* **2009**, *48*, 7428-7431. g) Han, Z. Y.; Xiao, H.; Chen, X. H.; Gong, L. Z. Consecutive Intramolecular Hydroamination/Asymmetric Transfer Hydrogenation under Relay Catalysis of an Achiral Gold Complex/Chiral Brønsted Acid Binary System. *J. Am. Chem. Soc.* **2009**, *131*, 9182-9183. h) Liu, X. Y.; Che, C. M. Highly Enantioselective Synthesis of Chiral Secondary Amines by Gold(I)/Chiral Brønsted Acid Catalyzed Tandem Intermolecular Hydroamination and Transfer Hydrogenation Reactions. *Org. Lett.* **2009**, *11*, 4204-4207.

(7) a) Pellissier, H. Recent Developments in Asymmetric Organocatalytic Domino Reactions. *Adv. Synth. Catal*. **2012**, *354*, 237-294. b) Hulme, C.; Gore, V. " Multi-component Reactions : Emerging Chemistry in Drug Discovery " 'From Xylocain to Crixivan'. *Curr. Med. Chem.* **2003**, *10*, 51-80.

(8) Shi, F.; Tan, W.; Zhu, R. Catalytic Asymmetric Five-Component Tandem Reaction: Diastereo- and Enantioselective Synthesis of Densely Functionalized Tetrahydropyridines with Biological Importance. *Adv. Synth. Catal.* **2013**, *355*, 1605-1622.

(9) Wang, Y.; Tu, M. S.; Shi, F.; Tu, S. J. Enantioselective Construction of the Biologically Significant Dibenzo[1,4]diazepine Scaffold via Organocatalytic Asymmetric Three-Component Reaction. *Adv. Synth. Catal*. **2014**, *356*, 2009-2019.

(10) Yu, J.; Shi, F.; Gong, L. Z. Brønsted-Acid-Catalyzed Asymmetric Multicomponent Reactions for the Facile Synthesis of Highly Enantioenriched Structurally Diverse Nitrogenous Heterocycles. *Acc. Chem. Res*. **2011**, *44*, 1156-1171.

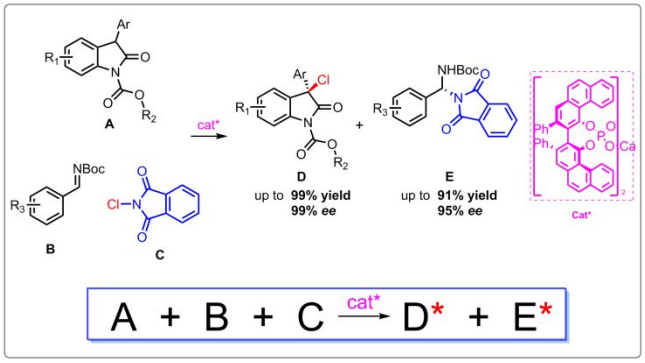
(11) a) de Graaff, C.; Ruijter, E.; Orru, R. V. A. Recent Developments in Asymmetric Multicomponent Reactions. *Chem. Soc. Rev*. **2012**, *41*, 3969-4009. b) Chen, Z; Wang, B; Wang, Z. Complex Bioactive Alkaloid-Type Polycycles through Efficient Catalytic Asymmetric Multicomponent Aza-Diels-Alder Reaction of Indoles with Oxetane as Directing Group. *Angew. Chem. Int. Ed.* **2013**, *52*, 2027-2031.

(12) For reviews, see: a) Zhou, J. Recent Advances in Multicatalyst Promoted Asymmetric Tandem Reactions. *Chem. Asian J*. **2010**, *5*, 422-434. b) Enders, D.; Grondal, C.; Huttl, M. R. M. Asymmetric Organocatalytic Domino Reactions. *Angew. Chem. Int. Ed.* **2007**, *46*, 1570-1581. c) Dondoni, A.; Massi, A. Asymmetric Organocatalysis: From Infancy to Adolescence. *Angew. Chem. Int. Ed.* **2008**, *47*, 4638-4660. d) Walji, A. M.; MacMillan, D. W. C. Strategies to Bypass the Taxol Problem. Enantioselective Cascade Catalysis, a New Approach for the Efficient Construction of Molecular Complexity. *Synlett* **2007**, 1477-1489.

(13) a) Liang, Y. X.; Rowland, E. B.; Rowland, G. B.; Perman, J. A.; Antilla, J. C. VAPOL Phosphoric Acid Catalysis: The Highly Enantioselective Addition of Imides to Imines. *Chem. Commun*. **2007**, 4477-4479. b) Zheng, W. H.; Zhang, Z. H; Kaplan, M. J.; Antilla, J. C. Chiral Calcium VAPOL Phosphate Mediated Asymmetric Chlorination and Michael Reactions of 3-Substituted Oxindoles. *J. Am. Chem. Soc*. **2011**, *133*, 3339-3341. c) Hatano, M.; Moriyama, K.; Maki, T.; Ishihara, K. Which Is the Actual Catalyst: Chiral Phosphoric Acid or Chiral Calcium Phosphate. *Angew. Chem. Int. Ed*. **2010**, *49*, 3823-3826. d) Gao, X.; Han, J. W.; Wang, L. M. Design of Highly Stable Iminophosphoranes as Recyclable Organocatalysts: Application to Asymmetric Chlorinations of Oxindoles. *Org. Lett*. **2015**, *17*, 4596-4599.

(14) Zheng, W. H.; Wojtas, L.; Antilla, J. C. Chiral Phosphoric Acid Catalyzed Peroxidation of Imines. *Angew. Chem. Int. Ed.* **2010**, *49*, 6589-6591.

(15) a) Wang, D.; Jiang, J. J.; Zhang, R.; Shi, M. Axially chiral BINIM and Ni(II)-catalyzed asymmetric chlorination of 3-substituted oxindoles. *Tetrahedron: Asymmetry* **2011**, *22,* 1133-1141. b) Zhao, M. X.; Zhang, Z. W.; Chen, M. X.; Tang, W. H.; Shi, M. Cinchona Alkaloid Catalyzed Enantioselective Chlorination of 3-Aryloxindoles. *Eur. J. Org. Chem.* **2011**, 3001-3008.


A
B
C
D
up to 99% yield
99% ee
E
up to 91% yield
95% ee
cat*
A + B + C cat* D* + E*