An enantioselective four-component reaction via assembling two reaction intermediates

Huang Qiu (qiuhuang@mail.sysu.edu.cn)  
Sun Yat-sen University  https://orcid.org/0000-0002-5439-2949

Sifan Yu  
Sun Yat-sen University

Wenju Chang  
Nanjing University  https://orcid.org/0000-0002-3403-0748

Ruyu Hua  
Sun Yat-sen University

Xiaoting Jie  
Sun Yat-sen University

Mengchu Zhang  
Sun Yat-sen University

Wenxuan Zhao  
Nanjing University  https://orcid.org/0000-0001-5535-252X

Jinzhou Chen  
Sun Yat-sen University

Dan Zhang  
Sun Yat-sen University

Yong Liang  
Nanjing University  https://orcid.org/0000-0001-5026-6710

Wenhao Hu  
Sun Yat-sen University

Article

Keywords:

Posted Date: July 25th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1763948/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
**Version of Record:** A version of this preprint was published at Nature Communications on November 18th, 2022. See the published version at [https://doi.org/10.1038/s41467-022-34913-2](https://doi.org/10.1038/s41467-022-34913-2).
Abstract

Reaction intermediate is a key molecular entity that has been used in explaining how the starting materials converts into the final products in the reaction, and it is always unstable, high-reactive, and short-lived. Extensive efforts have been devoted in identifying and characterizing such species via advanced physico-chemical analytical techniques. As an appealing alternative, trapping experiment with additional chemicals represents an efficient and powerful tool in this field. More importantly, this trapping strategy opens an opportunity to discovering new multicomponent reactions, and theoretically, novel multicomponent reactions with a 'higher order' variant could be developed via assembling two reaction intermediates. Herein, we report a highly diastereoselective and enantioselective four-component reactions (containing alcohols, diazoesters, enamines/indoles and aldehydes) that involve the coupling of in situ generated two intermediates (iminium and enol). These four-component reactions proceed under mild reaction conditions and show high functional group tolerance as well as broad substrate scope, affording the desired four-component coupling products (> 100 examples) with high efficiency. Notably, present four-component reaction is well compatible with a number of classic MCRs. A plausible mechanism with cross interception of the two active intermediates is also proposed based on a set of experimental and computational analyses. We hope that this strategy provides a new avenue for the development of novel higher-order MCRs in future research.

Full Text

Reaction intermediate is a molecular entity generated from starting materials that further converts into the final products, thus playing an important role in understanding the reaction mechanisms. However, one such class of substances is highly reactive and has a short lifetime, and its concentration in many reactions is always extremely low. Therefore, studies on this entity have remained a tremendous challenge in regard to its structure, reactivity, and synthetic applications. Over the years, remarkable progress has been achieved in identifying and characterizing the structure of these intermediate species via advanced physico-chemical analytical techniques (e.g. time-resolved spectroscopy, mass spectrometry). Recently, the interception of the reaction intermediate with bench-stable chemicals represents an appealing alternative, not only providing the evidence for the existence of specific intermediates, but also offering an efficient approach to observe its chemical reactivity. Additionally, this method opens an opportunity to discovering new chemical reactions, which could have a great impact on in pharmaceutical, material and fine chemical industry.

Multicomponent reactions (MCRs) that involve multiple starting materials simultaneously react to rapidly yield an immediately seen products in a greener and more economical manner, have been recognized as an “ideal” synthetic method for constructing complex molecules with high efficiency. Among these advances, since each component represents a variable dimension in generation of libraries of compounds, MCRs have much higher exploratory power with regard to chemical space compared with traditional reactions and, mathematically, the attainable chemical space could have an exponential
increase with the component number of chemical reactions.\textsuperscript{15,16} The discovery of novel MCRs, especially with a ‘higher order’ variant, are particularly challenging and have emerged as the frontiers in contemporary organic synthesis.\textsuperscript{17,18} Furthermore, the stereochemical issues could be extraordinary challenging while the formation of multiple chemical bonds simultaneously takes place and various types of highly reactive intermediates are rapidly produced in the process.\textsuperscript{12} For example, Ugi-4CR, the most well-known textbook reaction with four variants (an aldehyde, an amine, a carboxylic acid and an isocyanide), firstly reported by Ugi and coworkers in 1959,\textsuperscript{13} and stereochemical challenge has yet to be recently addressed until by Tan, Houk and coworkers in 2018,\textsuperscript{19} although its four-component product owns only one chiral center. In light of increasing demand for the development of highly attainable and selective MCRs, the robust and general strategy that can introduce new transformations with a ‘higher order’ variant is highly needed.\textsuperscript{17,18}

As shown in Fig.1a, previously developed three-component reactions involved using a bench-stable chemical to trap the reaction intermediate generated from traditional reactions.\textsuperscript{20} Through sequential assembly of reaction intermediates and trapping reagents, rare examples of MCRs with four variants (four-component reactions) are discovered in the history.\textsuperscript{19,21,22} Given that the transient reaction intermediate could be successfully trapped by various bench-stable components, we further questioned whether it would be possible to trap such intermediate with another intermediate generated by another independent process. The whole resultant process would be used for discovering novel MCRs with four variants if both reaction intermediates are generated by distinct substrates.\textsuperscript{17,23} However, this strategy suffered numerous challenges in a \textit{spatial-temporal} version, requiring each intermediate should be generated simultaneously in similar rates, the reaction of these two intermediates occurred in a highly efficient, specific and selective manner.\textsuperscript{3,10,24} Otherwise, incompatibility of various reactants, uncontrollable sequence of chemical bond formation, and irreversible side reactions would hamper the development of such type of transformations.\textsuperscript{25} Our previous findings suggested that the generation of reaction intermediates and their compatibility with trapping reagents are heavily influenced by the catalyst system.\textsuperscript{26} With an elegant choice of catalytic systems,\textsuperscript{27-34} simultaneous generation of two types of reaction intermediates with compatible chemical reactivity via distinct catalytic cycles could be possible,\textsuperscript{3,24} thus providing an opportunity to be of use-discovering unprecedented MCRs.

It has been extensively explored that diazoester could react with alcohol under catalysis of transition metal to afford oxonium ylide intermediate (or its enol form), a highly reactive nucleophilic species, which could be trapped by various electrophiles according to previous findings.\textsuperscript{20} In addition, generation of \(\alpha,\beta\)-unsaturated iminium intermediate using indole and aldehyde under the catalysis of Brønsted acid and amine via Knoevenagel-type reaction was well-documented.\textsuperscript{35} Coupling of the two aforementioned intermediates would finally deliver the desired novel 4CRs (Fig.1b), to our best knowledge, this intermediate cross interception has not been disclosed. Although this designed strategy was simple and straightforward, numerous potential side reactions would irreversibly consume newly generated reactive intermediates to produce an array of undesired side products.\textsuperscript{36-38} For example, the metal carbenoid
species has been reported to react with various reagents,\textsuperscript{39,40} including aldehydes, imines, indoles, and amines in current chemical system, generating those undesired ylides or zwitterionic intermediates.\textsuperscript{20} Other potential side reactions of oxonium ylide with aldehydes or imines are also possible in this design.\textsuperscript{7} Furthermore, the stereocontrol issue also remains a formidable challenge, especially involving two vicinal quaternary/tertiary stereocenters.\textsuperscript{41} To validate our conceptual hypothesis, we firstly explored the proposed four-component reaction with 4-bromobenzyl alcohol 1a, tert-butyl phenyldiazoesters 2a, 2-methylindole 3a, and 3-phenylpropiolaldehyde 4a as model substrates. Thorough optimizations involved the evaluation of reaction parameters and ultimately led to the following optimal reaction conditions: 5 mol\% Pd(CH\textsubscript{3}CN)\textsubscript{2}Cl\textsubscript{2}, 10 mol\% SPINOL-derived chiral phosphoric acid 6a, and 50 mol\% 2,5-bis(trifluoromethyl)aniline 5a at -20 °C in DCE (see Supplementary Table S1 and S2).

Under the optimized conditions, the substrate scope and limitation of this four-component reaction were then investigated (Fig.2). Initially, we examined the alcohols 1 and found that benzyl alcohols with diverse functional groups were proven to be suitable substrates (7–10). We were pleased to observe that heteroaromatic alcohols, such as those with furanyl and benzothienyl groups, could readily be employed with high efficiency (11–12). Moreover, cinnamyl alcohol, allyl alcohol and 3-phenyl-2-propyn-1-ol were highly applicable to the present reaction and gave desired products in synthetically useful yields without compromising the diastereo- and enantioselectivity (13–15). With respect to the α-diazoesters, a variety of ortho-, meta-, and para-substituted α-aryl-α-diazoesters with various functional groups underwent efficient and highly enantioselective four-component reactions (16–21), and the absolute configuration of 21 was confirmed by X-ray crystallographic analysis. 2-Ethyl indole also resulted in excellent ee (96%) of desired product. Notably, 2,5 or 2,6-disubstituted indoles containing bromo, alkyl, phenyl, Bpin, amino and sulfanyl groups were converted to their corresponding products in satisfied yields with good to excellent enantioselectivity (22–29). With respect to the aldehyde various substituted (hetero)aromatic ynals were well tolerated in our conditions, leading to corresponding products in good yield and diastereo- and enantioselectivity (30–37).

We next explored extension of present asymmetric four-component reactions to other compounds containing enamine motifs. 4-(1-Phenylvinyl)morpholine was identified as a proper substrate under condition B (see Supplementary Table S3 and S4). Fig.3 summarized the detailed results for the asymmetric four-component reaction. A broad spectrum of alcohols, α-diazoesters, enamines, and aldehydes was then investigated (38–86). Similar to the aforementioned four-component reaction, the alcohols and α-diazoesters with various functional groups and heterocycles were well-tolerated, delivering the corresponding four-component products with satisfied reactivity and selectivity (38–65). Of particularly noted, we were delighted to find that α-alkyl-α-diazoesters also readily participate in this reaction (66 & 67), demonstrating the diversity of substituents. Enamines with different substituents were also amenable to this protocol, affording the desired products (68–70) in good yields and with excellent diastereo- and enantioselectivities. We next evaluated the scope of aldehydes. Diverse propiolaldehydes showed excellent reactivity regardless of whether the substituents were electron-donating or electron-withdrawing groups (71–77). To further broaden the utility of this protocol, we further explored α,β-
unsaturated aldehydes. Interestingly, α,β-unsaturated aldehydes bearing ester and ketone groups were perfectly tolerated under condition B, furnishing the desired products (78–82) in good yields and with excellent diastereo- and enantioselectivities. Moreover, aromatic aldehydes could also function efficiently in this four-component coupling protocol. For example, para-nitro aldehyde and its 3-methyl analogue readily reacted with diverse alcohols in the current protocol (83–86) (more substrates see Supplementary Fig.S2).

The high functional group tolerance encouraged us to further investigate the practical utility of this protocol. Notably, this enantioselective 4CR is also compatible with several classic MCRs, including Passerini-3CR13, Petasis-3CR42, Hantzsch-4CR43, Catellani-4CR44, Ugi-Tetrazole-4CR16, and enantioselective Ugi-4CR13,19, affording the desired products (87–92) with 6 or 7 variants in satisfying yields and excellent enantioselectivities in two steps (Fig.4a, more detail also see Supplementary Fig.S3). We also performed several transformations of the obtained four-component products, which were shown in Fig.4b. For example, when 38 was reduced by H2 in the presence of Pd/C, the product 39 that contains three chiral carbon centres was obtained in satisfying yield with excellent diastereoselectivity. 42 could readily be converted into benzoxepine 94 in 72% yield via a palladium-mediated reductive Mizoroki–Heck cyclization, and we were delighted to observe the excellent diastereoselectivity and geometric selectivity (Z:E > 20:1) of the desired product. Notably, treatment of 83 with 20 mol% Yb(OTf)3 could effectively remove tert-butyl group to form the carboxylic acid 95 in 75% yield without losing the diastereo- and enantioselectivity. In addition, treatment of 47 with 1.0 equiv. trifluoroacetic acid (TFA) readily afforded the formal product of the four-component reaction with H2O (96) in 60% yield. When 20.0 equiv. TFA was used, we were able to obtain the α-hydroxyl acid 97 in 65% yield without losing the diastereo- and enantioselectivity (more synthetic applications see Supplementary Fig.S4).

DFT calculations were performed to explore the mechanism of this enantioselective four-component reaction and the origin of stereoselectivity (see Supplementary Fig.S5-S9). Combining with the aforementioned mechanistic studies, a catalytic cycle was proposed in Fig.5a. In the amine-CPA catalyzed cycle, intermediate INT-2 formed via a CPA catalyzed nucleophilic addition of aniline 5b on aldehyde 4a and elimination of a water molecule. Subsequently, INT-2 was attacked by enamine 3a, resulting in the formation of INT-4. After a subsequent CPA anion assisted proton transfer, INT-5 was generated, which delivered the key intermediate INT-6 and aniline 5b via transition state TS-5. Calculations showed that the overall energy barrier was 19.4 kcal/mol for the formation of intermediate INT-6. In the transition-metal-catalyzed cycle, the dissociation of palladium dimer precatalyst by imine gave INT-7, which took an exchange with diazoester 2a to give INT-8. Then palladium catalyzed decomposition of diazoester 2a led to carbene intermediate INT-9 and the nitrogen release. Oxonium ylide INT-10 was formed from carbene INT-9 by the attack of benzyl alcohol, and then transformed into a more stable Pd-associated enol INT-11 through a quick intramolecular [1,3]-proton shift. An exchange between INT-11 and imine gave free enol INT-12 and regenerated palladium catalyst in an exergonic process. For the formation of free enol INT-12, the overall barrier was 21.0 kcal/mol. Finally, cross interception of the two active intermediates, INT-6 and INT-12, took place in the chiral pocket of CPA 6b anion, providing the
four-component product with simultaneously regenerated CPA 6b. The main challenge of cross interception of the in situ formed two active intermediates is that they need a comparable formation rate to avoid consumption before cross interception occurs. DFT calculations demonstrated that the generation of the two active intermediates, INT-6 and free enol INT-12, had matched energy barriers (19.4 kcal/mol versus 21.0 kcal/mol) enabling the four-component reaction to proceed smoothly.

Asymmetric Michael addition afforded products with successive $\alpha,\beta$-stereocenters, and the stereoisomeric TSs are presented in Fig.5b. Among them, TS-SR had lower free energy than that of TS-RS and TS-SS by 2.4 and 3.8 kcal/mol, respectively. This is in accordance with the 92% ee and 94:6 dr obtained experimentally. In comparing TS-SR with the others (TS-RS, TS-RR and TS-SS), favorable C-H...π and C-H...O interactions between CPA and the large tert-butyl group in enol led to preference for formation of the predominant product. While less C-H...π interactions were present in the other transition states. This result indicated that non-covalent interaction plays a critical role in controlling stereoselectivity. Additional DFT calculations were conducted to further clarify the importance of nonbonding interactions between CPA and substrate (Fig.5b, bottom). Replacing tert-butyl group by a much smaller methyl group in enol, the C-H...π and C-H...O interactions disappeared in the asymmetric Michael addition transition states. As a result, the relative free Gibbs energy difference between TS-SR-Me and TS-RS-Me ($\Delta\Delta G^\ddagger = 0.4$ kcal/mol) became smaller than that between TS-SR and TS-RS ($\Delta\Delta G^\ddagger = 2.4$ kcal/mol), indicating a poor stereoselectivity without a tert-butyl group. Moreover, using 6c, a CPA with smaller chiral pocket, and diazoester 2a with large tert-butyl group, TS-SR-Ph and TS-RS-Ph became flexible where these non-covalent interactions were also not present. The significant decrease in relative free Gibbs energy ($\Delta\Delta G^\ddagger = 0.2$ kcal/mol) demonstrated that 9-anthryl group was essential in determining the stereoselectivity.

Control experiments were carried out and shown in Fig.5c, poor selectivity was obtained using either CPA 6b and diazoester 2b (21% ee, 83:17 dr) or CPA 6c and diazoester 2a (6% ee, 84:16 dr). It is clear that both tert-butyl group in diazoester (2a) and 9-anthryl group in CPA (6b) are critical to enable the asymmetric Michael addition with high selectivities through non-covalent interactions.

In conclusion, the first four-component reaction of alcohols, diazoesters, enamines/indoles and aldehydes are developed, affording the corresponding products in satisfying yields with good to excellent chemo-, diastereo- and enantioselectivity. These novel four-component reactions proceed under mild reaction conditions and shows high functional group tolerance. In addition, present four-component processes are well compatible with other classic MCRs, affording several unprecedented examples of higher-order MCRs. Mechanism studies demonstrated that the comparable energy barriers of iminium and enol intermediates formation through independent processes ensure the success of this enantioselective four-component reaction. Both CPA and diazoester are critical to our reaction and responsible for acquiring excellent stereoselectivity. Furthermore, these multicomponent methods open new opportunities for developing novel MCRs by assembling two reaction intermediates that are generated by independent catalytic processes.

Declarations
**Data availability**

CCDC contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Experimental procedures, characterization of all new compounds, Supplementary Tables and Supplementary Figures are available in the Supplementary Information. Further data that support the plots within this paper and other finding of this study are available from the corresponding author upon reasonable request.

**Acknowledgements**

We thank M. P. Doyle for comments and suggestions on the preparation of the manuscript. We thank B. Tan for generously providing chiral SPINOL phosphoric acid S61. W.H. and H.Q. acknowledge the financial support from Guangdong Innovative and Entrepreneurial Research Team Program (No. 2016ZT06Y337). H.Q. acknowledges support from NSFC grant 21801255. Y.L. acknowledges support from the Fundamental Research Funds for the Central Universities (020514380253), the Natural Science Foundation of Jiangsu Province (BK20211555), and the Jiangsu Innovation & Entrepreneurship Talents Plan. We thank the High Performance Computing Center (HPCC) of Nanjing University for doing the numerical calculations in this paper on its blade cluster system.

**Author contributions**

H.Q. and W.H. conceived and designed the project; S.Y. and R.H. developed the catalytic asymmetric four-component reactions, and conducted most of the experiments; Z.C., X.J., M.Z. performed parts of substrate scope experiments and synthetic applications; W.C. and W.Z. conducted the DFT calculations and provided mechanism analysis; Y.L. directed the DFT calculations and mechanism; D.Z. helped the direction of the project; S.Y., W.C., R.H., H.Q., Y.L., and W.H. prepared the manuscript.

**Competing interests**

The authors declare no competing interests.

**References**

1. Trost, B. M. & Tracy, J. S. Catalytically generated vanadium enolates formed via interruption of the Meyer-Schuster rearrangement as useful reactive intermediates. Acc. Chem. Res. 53, 1568–1579 (2020).

2. Seath, C. P., Trowbridge, A. D., Muir, T. W. & MacMillan, D. W. C. Reactive intermediates for interactome mapping. Chem. Soc. Rev. 50, 2911–2926 (2021).

3. Allen, A. E. M., D. W. Synergistic catalysis: a powerful synthetic strategy for new reaction development. Chem. Sci. 2012, 633–658 (2012).
4. Kalek, M. & Himo, F. Combining Meyer-Schuster rearrangement with aldol and Mannich reactions: theoretical study of the intermediate interception strategy. J. Am. Chem. Soc. **134**, 19159–19169 (2012).

5. Wendlandt, A. E., Vangal, P. & Jacobsen, E. N. Quaternary stereocentres via an enantioconvergent catalytic $\text{S}_\text{N}1$ reaction. Nature **556**, 447–451 (2018).

6. Nong, Z. S. et al. Palladium-catalysed branch- and enantioselective allylic C–H alkylation of $\alpha$-alkenes. Nat. Synth. **1**, 487–496 (2022).

7. Wang, Y. et al. Sml$_2$-mediated enantioselective reductive dearomatization of non-activated arenes. Nat. Synth. **1**, 401–406 (2022).

8. Roithova, J. Characterization of reaction intermediates by ion spectroscopy. Chem. Soc. Rev. **41**, 547–559 (2012).

9. Yamano, M. M. et al. Intercepting fleeting cyclic allenes with asymmetric nickel catalysis. Nature **586**, 242–247 (2020).

10. Trost, B. M., Luan, X. & Miller, Y. Contemporaneous dual catalysis: chemoselective cross-coupling of catalytic vanadium-allenoate and pi-allylpalladium intermediates. J. Am. Chem. Soc. **133**, 12824–12833 (2011).

11. Romiti, F. D. P., J. Paioti, P. H. S. Gonsales, S. A. Li, X. Hartrampf, F. W. W. & Hoveyda, A. H. Different strategies for designing dual-catalytic enantioselective processes: from fully cooperative to non-cooperative systems. J. Am. Chem. Soc. **141**, 17952–17961 (2019).

12. Ruijter, E., Scheffelaar, R. & Orru, R. V. Multicomponent reaction design in the quest for molecular complexity and diversity. Angew. Chem. Int. Ed. **50**, 6234–6246 (2011).

13. Wang, Q., Wang, D. X., Wang, M. X. & Zhu, J. Still unconquered: enantioselective Passerini and Ugi multicomponent reactions. Acc. Chem. Res. **51**, 1290–1300 (2018).

14. Trost, B. M. The atom economy-a search for synthetic efficiency. Science **254**, 1471–1477 (1991).

15. Domling, A., Wang, W. & Wang, K. Chemistry and biology of multicomponent reactions. Chem. Rev. **112**, 3083–3135 (2012).

16. Neochoritis, C. G., Zhao, T. & Domling, A. Tetrazoles via multicomponent reactions. Chem. Rev. **119**, 1970–2042 (2019).

17. Brauch, S., van Berkel, S. S. & Westermann, B. Higher-order multicomponent reactions: beyond four reactants. Chem. Soc. Rev. **42**, 4948–4962 (2013).

18. Zarganes-Tzitzikas, T., Chandgude, A. L. & Domling, A. Multicomponent reactions, union of MCRs and beyond. Chem. Rec. **15**, 981–996 (2015).

19. Zhang, J. et al. Asymmetric phosphoric acid-catalyzed four-component Ugi reaction. Science **361**, eaas8707 (2018).

20. Zhang, D. & Hu, W. Asymmetric multicomponent reactions based on trapping of active intermediates. Chem. Rec. **17**, 739–753 (2017).
21. Xiong, Q., Dong, S., Chen, Y., Liu, X. & Feng, X. Asymmetric synthesis of tetrazole and dihydroisoquinoline derivatives by isocyanide-based multicomponent reactions. Nat. Commun. 10, 2116 (2019).

22. Zhang, S., Del Pozo, J., Romiti, F., Mu, Y., Torker, S., & Hoveyda, A. H. Delayed catalyst function enables direct enantioselective conversion of nitriles to NH$_2$-amines. Science 364, 45–51 (2019).

23. Wender, P. A. et al. Structural complexity through multicomponent cycloaddition cascades enabled by dual-purpose, reactivity regenerating 1,2,3-triene equivalents. Nat. Chem. 6, 448–452 (2014).

24. Kim, B., Kim, Y. & Lee, S. Y. Stereodivergent carbon-carbon bond formation between iminium and enolate intermediates by synergistic organocatalysis. J. Am. Chem. Soc. 143, 73–79 (2021).

25. Xu, J. H., Zheng, S. C., Zhang, J. W., Liu, X. Y. & Tan, B. Construction of tropane derivatives by the organocatalytic asymmetric dearomatization of isoquinolines. Angew. Chem. Int. Ed. 55, 11834–11839 (2016).

26. Kang, Z. et al. Ternary catalysis enabled three-component asymmetric allylic alkylation as a concise track to chiral alpha,alpha-disubstituted ketones. J. Am. Chem. Soc. 143, 20818–20827 (2021).

27. Sancheti, S. P., Urvashi, Shah, M. P., & Patil, N. T. Ternary catalysis a stepping stone towards multicatalysis. ACS Catal. 10, 3462–3489 (2020).

28. Brak, K. & Jacobsen, E. N. Asymmetric ion-pairing catalysis. Angew. Chem. Int. Ed. 52, 534–561 (2013).

29. Milo, A., Neel, A. J., Toste, F. D., & Sigman, M. S. A data-intensive approach to mechanistic elucidation applied to chiral anion catalysis. Science 347, 737–743 (2015).

30. Mahlau, M. & List, B. Asymmetric counteranion-directed catalysis: concept, definition, and applications. Angew. Chem. Int. Ed. 52, 518–533 (2013).

31. Wang, P. S., Lin, H. C., Zhai, Y. J., Han, Z. Y. & Gong, L. Z. Chiral counteranion strategy for asymmetric oxidative C(sp$^3$)-H/C(sp$^3$)-H coupling: enantioselective alpha-allylation of aldehydes with terminal alkenes. Angew. Chem. Int. Ed. 53, 12218–12221 (2014).

32. Capacci, A. G., Malinowski, J. T., McAlpine, N. J., Kuhne, J. & MacMillan, D. W. C. Direct, enantioselective alpha-alkylation of aldehydes using simple olefins. Nat. Chem. 9, 1073–1077 (2017).

33. Phipps, R. J., Hamilton, G. L. & Toste, F. D. The progression of chiral anions from concepts to applications in asymmetric catalysis. Nat. Chem. 4, 603–614 (2012).

34. Li, M. L., Yu, J. H., Li, Y. H., Zhu, S. F., & Zhou, Q. L. Highly enantioselective carbene insertion into N–H bonds of aliphatic amines. Science 366, 990–994 (2019).

35. Lancianesi, S., Palmieri, A. & Petrini, M. Synthetic approaches to 3-(2-nitroalkyl) indoles and their use to access tryptamines and related bioactive compounds. Chem. Rev. 114, 7108–7149 (2014).

36. Padwa, A., Dean, D. C., Osterhout, M. H., Precedo, L., & Semones, M. A. Synthesis of functionalized azomethine ylides via the Rh (II)-catalyzed cyclization of alpha-diazo carbonyls onto imino pi-bonds. J. Org. Chem. 59, 5347–5357 (1994).
37. Terada, M. & Toda, Y. Relay catalysis using a rhodium complex/chiral Bronsted acid binary system: enantioselective reduction of a carbonyl ylide as the reactive intermediate. Angew. Chem. Int. Ed. 51, 2093–2097 (2012).
38. Yan, M., Zhao, W. J., Huang, D., & Ji, S. J. Unusual reaction of aryldiazoacetates with enamines: highly effective synthesis of γ-ketoesters. Tetrahedron Lett. 45, 6365–6367 (2004).
39. Doyle, M. P. Electrophilic metal carbenes as reaction intermediates in catalytic reactions. Acc. Chem. Res. 19, 348–356 (1986).
40. Davies, H. M. L. & Liao, K. Dirhodium tetracarboxylates as catalysts for selective intermolecular C-H functionalization. Nat. Rev. Chem. 3, 347–360 (2019).
41. Krautwald, S., Sarlah, D., Schafroth, M. A., Carreira, E. M. Enantio- and diastereodivergent dual catalysis: α-allylation of branched aldehydes. Science 340, 1065–1068 (2013).
42. Wu, P., Givskov, M. & Nielsen, T. E. Reactivity and synthetic applications of multicomponent Petasis reactions. Chem. Rev. 119, 11245–11290 (2019).
43. Evans, C. G., & Gestwicki, J. E. Enantioselective organocatalytic Hantzsch synthesis of polyhydroquinolines. Org. Lett. 11, 2957–2959 (2009).
44. Chen, S. et al. The discovery of a palladium(II)-initiated borono-Catellani reaction. Angew. Chem. Int. Ed. 57, 7161–7165 (2018).
45. Li, B., Xu, H., Dang, Y. & Houk, K. N. Dispersion and steric effects on enantio-/diastereoselectivities in synergistic dual transition-metal catalysis. J. Am. Chem. Soc. 144, 1971–1985 (2022).

Figures
Figure 1

Patterns of chemical reactions. a, Lego-like synergistic organic synthesis. b, This 4CR via intermediate cross interception.
Figure 2

Substrate scope of enantioselective four-component reactions of alcohol, diazoester, indole and aldehyde derivatives.
Figure 3

Substrate scope of enantioselective four-component reactions of alcohol, diazoester, enamine and aldehyde derivatives.
**Figure 4**

**Higher-order MCRs design and synthetic applications. a, Higher-order MCRs design. b, Synthetic applications.**
Figure 5

Mechanistic studies of enantioselective four-component reaction. a, Proposed catalytic cycle. b, Optimized transition state geometries of symmetric Michael addition and origin of stereoselectivity. c, Control experiments. In a and b, the Gibbs free energies were computed with CPCM(DCM)-M06-2X/6-311+G(d,p)[SDD for Pd]//CPCM(DCM)-B3LYP/6-31G(d)[LANL2DZ for Pd]. Most hydrogen atoms are omitted for clarity. All distances are in angstroms.
Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SI20220616.pdf