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Short Communication

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Direct construction of d_3-methylated all-carbon quaternary stereocenters through carbene-catalyzed desymmetrization

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Abstract

The construction of d_3-methylated all-carbon quaternary stereocenters has been successfully developed via carbene-catalyzed desymmetrization of prochiral d_3-methylated oxindolyl 1,3-diketones. Three new stereogenic centers were efficiently constructed with satisfactory outcomes. Diverse spiro-polycyclic molecules with a d_3-methylated all-carbon quaternary stereocenter were generated in good to excellent yields with good to excellent diastereoselectivities and excellent enantioselectivities. This reaction features a broad substrate scope, good functional-group tolerance, and easy scale-up.

Keywords: d_3-Methylated, all-carbon quaternary stereocenters, *N*-Heterocyclic carbene, organocatalysis, desymmetrization

As a result of the unique nature of deuterium, deuterium-labeled organic compounds have been widely used in organic chemistry[1,2], pharmaceuticals[3-5], and materials[6-10]. In the field of medicinal chemistry, replacing a hydrogen atom of a bioactive molecule with a deuterium atom can significantly improve the

pharmacokinetics, biological activities, and stability of chemically unstable stereoisomers while also reducing toxicities[11-14]. Furthermore, due to the well-known "magic methyl effect"[15-18], the synthesis and application of d_3-methylated organic molecules have received continuous interest. And several d_3-methylated organic molecules have become marketed drugs or are currently undergoing clinical trials [Figure 1]. For example, Austedo, with two CD_3 groups, as the first deuterated drug, is applied in the treatment of symptoms of Huntington's disease[19,20]. Donafenib, as an orally available multikinase inhibitor, was approved by the NMPA in 2021 for treating liver cancer[21]. CTP-518 (d_{15}-Atazanavir) displays an average 52% increase in half-life compared to atazanavir[22]. CTP-499 (d_5-Pentoxifylline) exhibits antifibrogenic, antioxidative, and anti-inflammatory activities, with higher plasma concentrations and related major metabolites compared to regular Pentoxifylline[23,24]. Despite these advancements, the asymmetric construction of chiral organic molecules with d_3-methylated all-carbon quaternary stereocenters remains underdeveloped. However, methylated all-carbon quaternary stereocenters have been widespread in natural products and biological molecules, offering a diverse set of promising biological activities[25].

N-heterocyclic carbene (NHC) catalysis, as one of the most efficient methods of asymmetric catalysis, has been widely used in the construction of diverse chiral molecules[26-39]. Among them, carbene-catalyzed desymmetrization of 1,3-diketones has been recognized as one of the most powerful strategies for the construction of chiral centers, especially chiral all-carbon quaternary centers[40-47]. Although NHC catalysis has shown potential applications in the construction of deuterated organic molecules[48-51], the application of NHC catalysis to construct chiral deuterated organic molecules remains underdeveloped. As part of our ongoing interest in organocatalysis[51-56], we designed novel prochiral d_3-methylated oxindolyl 1,3-diketones for the asymmetric construction of d_3-methylated all-carbon quaternary stereocenters based on NHC-catalyzed asymmetric desymmetrization. These readily available prochiral d_3-methylated oxindolyl 1,3-diketones could react with unsaturated acyl triazolium intermediates[57] obtained from bromoenals with NHC to construct spiro-polycyclic molecules with a d_3-methylated all-carbon quaternary stereocenter with excellent outcomes. Notably, spirocyclic and oxindole moieties of the products are proven among the most important scaffolds in natural products and bioactive molecules[58-61].

The reaction of (*Z*)-2-bromo-3-phenylacrylaldehyde **2a** and prochiral 2-(methyl-d_3)-2-[(1-methyl-2-oxoindolin-3-yl)methyl]-1*H*-indene-1,3(2*H*)-dione **1a** was initially selected to optimize reaction conditions. The key results are summarized in Figure 2. As expected, the desired chiral d_3-methylated product **3a'** could be found when aminoindanol-derived triazolium precatalyst NHC **A** was used in the presence of K_2CO_3 in toluene at room temperature. Notably, due to unavoidable release of CO_2 for product **3a'** during the reaction process and in the following purification step, one more decarbonation operation, adding SiO_2 to the reaction system under 70 °C for 10 h, was further performed. Accordingly, the asymmetrical d_3-methylated product **3a** was generated smoothly in 70% yield with 3:1 dr and 80% ee (Entry 1) [Figure 2]. Subsequently, base screening showed that sodium acetate was the best base, leading to the formation of the product **3a** in excellent yield (90%) with good diastereoselectivity (13:1 dr) and excellent enantioselectivity (95% ee) (Entries 2-4). Next, several NHC catalysts were examined (Entries 5-8). All selected NHC catalysts could promote reaction smoothly, with NHC precatalyst **C** bearing a NO_2 substituent on the indane moiety proving to be the better choice to deliver the product **3a** in both excellent yield (90%) with enantioselectivity (> 99% ee) and good diastereoselectivity (13:1 dr). Several solvents were then investigated to further improve the diastereoselectivity (Entries 9-14). The excellent diastereoselectivity (> 20:1) was realized with both excellent yield (95%) and enantioselectivity (> 99) by using mesitylene as the solvent (Entry 14). In the absence of the catalyst, no reaction occurred (Entry 15). The absolute configuration of products **3** was determined via X-ray structural analysis of **3 h**.

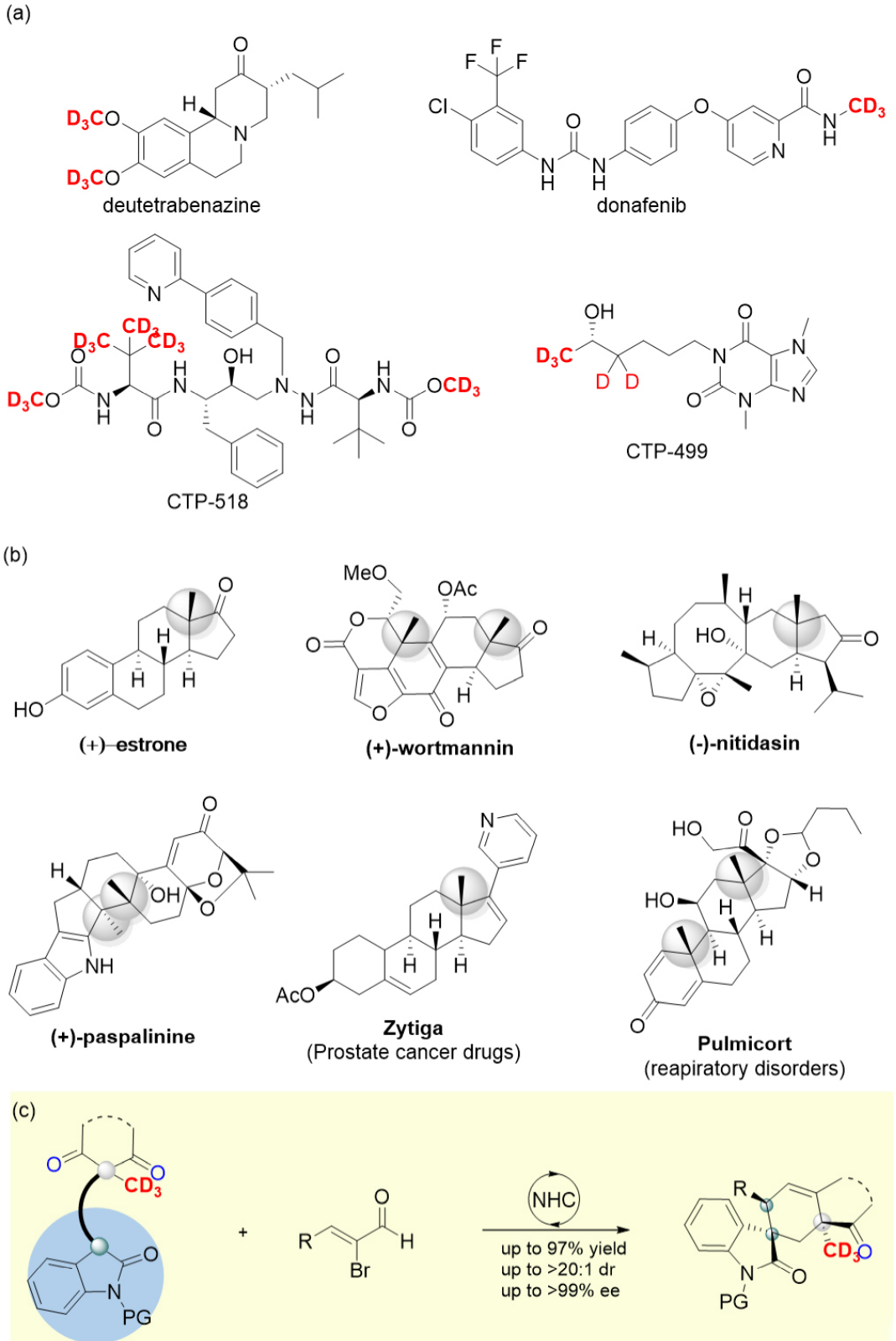
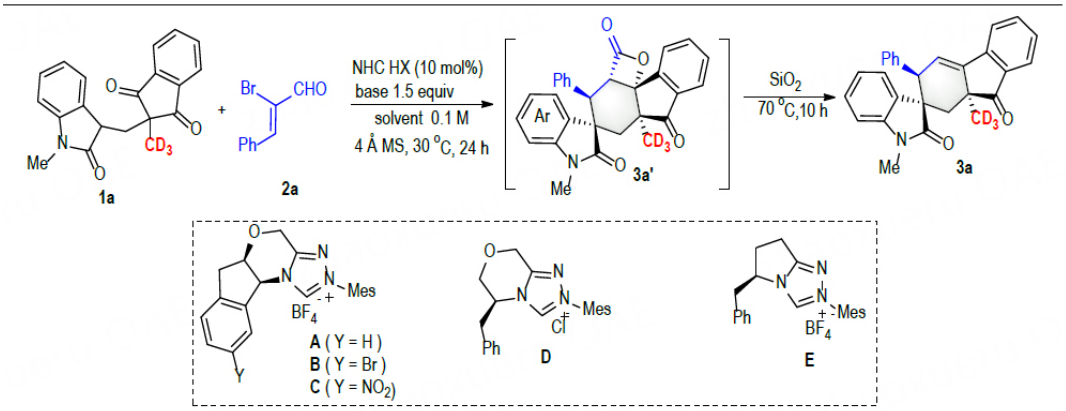


Figure 1. Asymmetric desymmetrization of d_3-methylated cyclic 1,3-diketones; (a) Representative examples containing CD_3; (b)

Naturally occurring and biologically active molecules with methylated all-carbon quaternary stereocenters; (c) This work: NHC-catalyzed asymmetric desymmetrization of d_3-methylated 1,3-diketones.



Entry[a]	NHC.HX	base	solvent	yield (%)[b]	dr[c]	ee[d]
1	**A**	K_2CO_3	Toluene	70	3:1	80
2	**A**	Cs_2CO_3	Toluene	80	5:1	87
3	**A**	NaOAc	Toluene	90	13:1	95
4	**A**	Et_3N	Toluene	81	10:1	91
5	**B**	NaOAc	Toluene	81	13:1	> 99
6	**C**	NaOAc	Toluene	90	11:1	> 99
7	**D**	NaOAc	Toluene	89	10:1	> 99
8	**E**	NaOAc	Toluene	92	11:1	80
9	**C**	NaOAc	DCM	87	12:1	90
10	**C**	NaOAc	THF	89	15:1	> 99
11	**C**	NaOAc	*m*-Xylene	85	13:1	> 99
12	**C**	NaOAc	$PhCF_3$	88	12:1	> 99
13	**C**	NaOAc	*o*-Xylene	91	10:1	> 99
14	**C**	NaOAc	Mesitylene	95	> 20:1	> 99
15	-	NaOAc	Mesitylene	n.d.	-	-

Figure 2. Optimized conditions[a]. [a] Standard condition: **1a** (0.1 mmol), **2a** (1.2 equiv), NHC.HX (10 mol%), solvent (0.1 M), 30 °C, and 24 h, then SiO_2, 70 °C, and 10 h; [b] Yield of the product **3a** after column chromatography; [c] Determined via ^{1}H NMR spectroscopy; [d] Determined by chiral HPLC, % ee = (R-S) / (R + S) * 100.

After successfully establishing the optimal conditions, the substrate scope of this desymmetrization strategy for enals was then evaluated by using **1a** as a model substrate [Figure 3]. For bromoenals with aromatic rings bearing electron-donating groups (such as Me, MeO) or electron-withdrawing groups (such as F, Cl, Br, and NO_2), all the reactions proceeded smoothly to form the d_3-methylated products **3b-i** in excellent yields (90%-94%) with good to excellent diastereoselectivities (16:1 dr-> 20:1 dr values) and excellent enantioselectivities (> 99% ee values for all the cases).

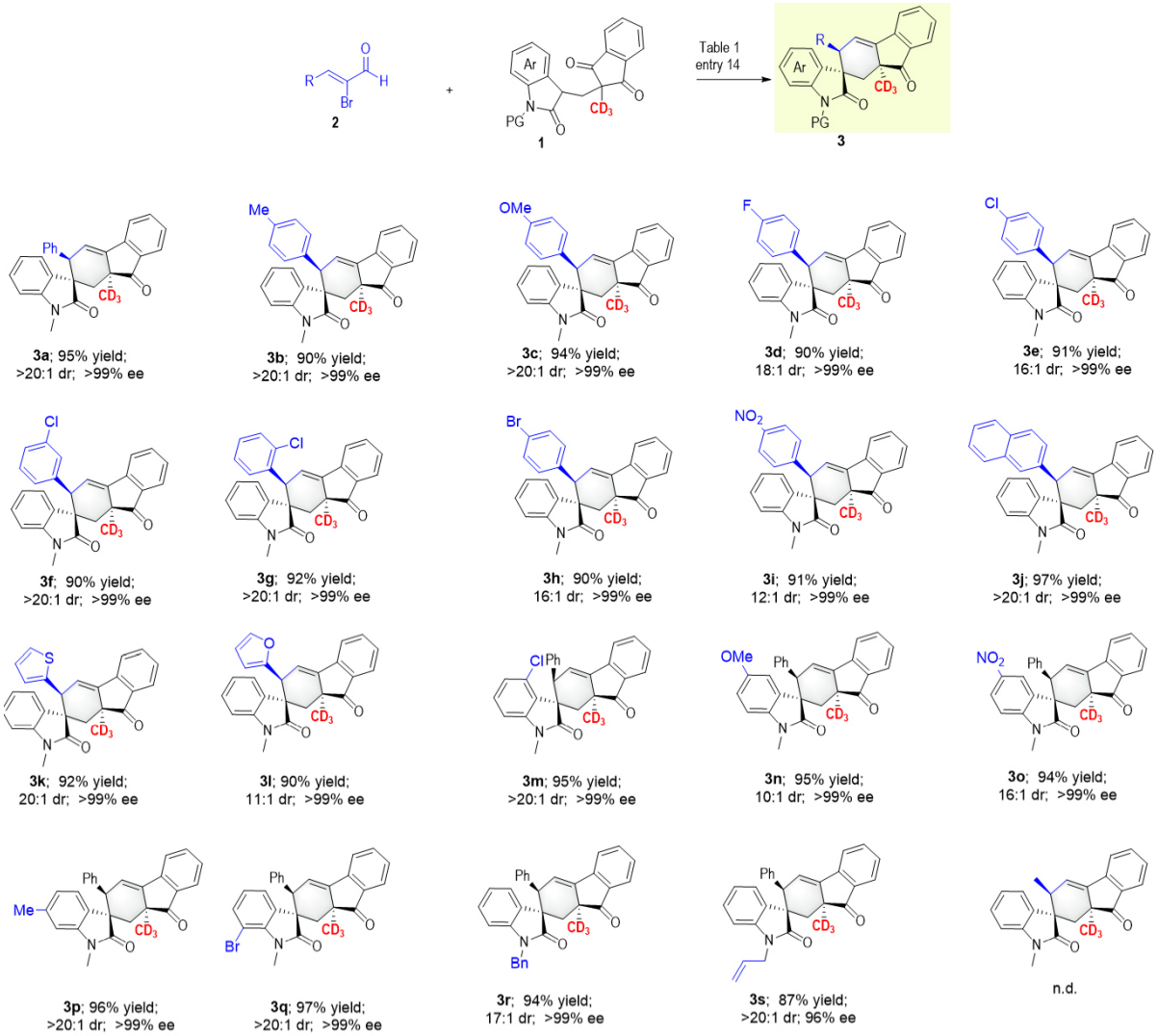


Figure 3. Scope of Reactions.

Bromoenals bearing naphthalene or heteroaromatic rings (2-furyl and 2-thienyl) did not influence the efficiency, affording the corresponding d_3-methylated products **3j-l** with good to excellent outcomes (90%-97% yields, 11:1-> 20:1 dr values and > 99% values for all the cases). Subsequently, the generation of trideuteromethyl oxindolyl 1,3-diketones **2** was evaluated. For trideuteromethyl oxindolyl 1,3-diketones, several substituents at the 4-, 5-, 6-, and 7-positons on the oxindole ring were also compatible with the reaction to generate the d_3-methylated products **3m-3q** in excellent yields (94%-97%) with good to excellent diastereoselectivities (10:1-> 20:1 dr values) and excellent enantioselectivities (> 99% ee values). Substrates with *N*-benzyl and *N*-allyl groups reacted efficiently to form d_3-methylated products **3r** and **3s** in 94% and 87% yields with 17:1 dr, > 20:1 dr values and > 99%, 96% ee values, respectively. Unfortunately, β-alkyl-substituted enals failed to deliver the product in our reaction.

After successfully documenting the synthesis of trideuteromethyl molecules with three stereogenic centers under NHC organocatalysis, to further evaluate the scope and limitations of this strategy, other alkyl groups were introduced into the prochiral substrates [Figure 4]. The CD_3 group can be replaced with a methyl group, with the corresponding product **4a** formed in 96% yield with 13:1 dr and > 99% ee. Compound **1**

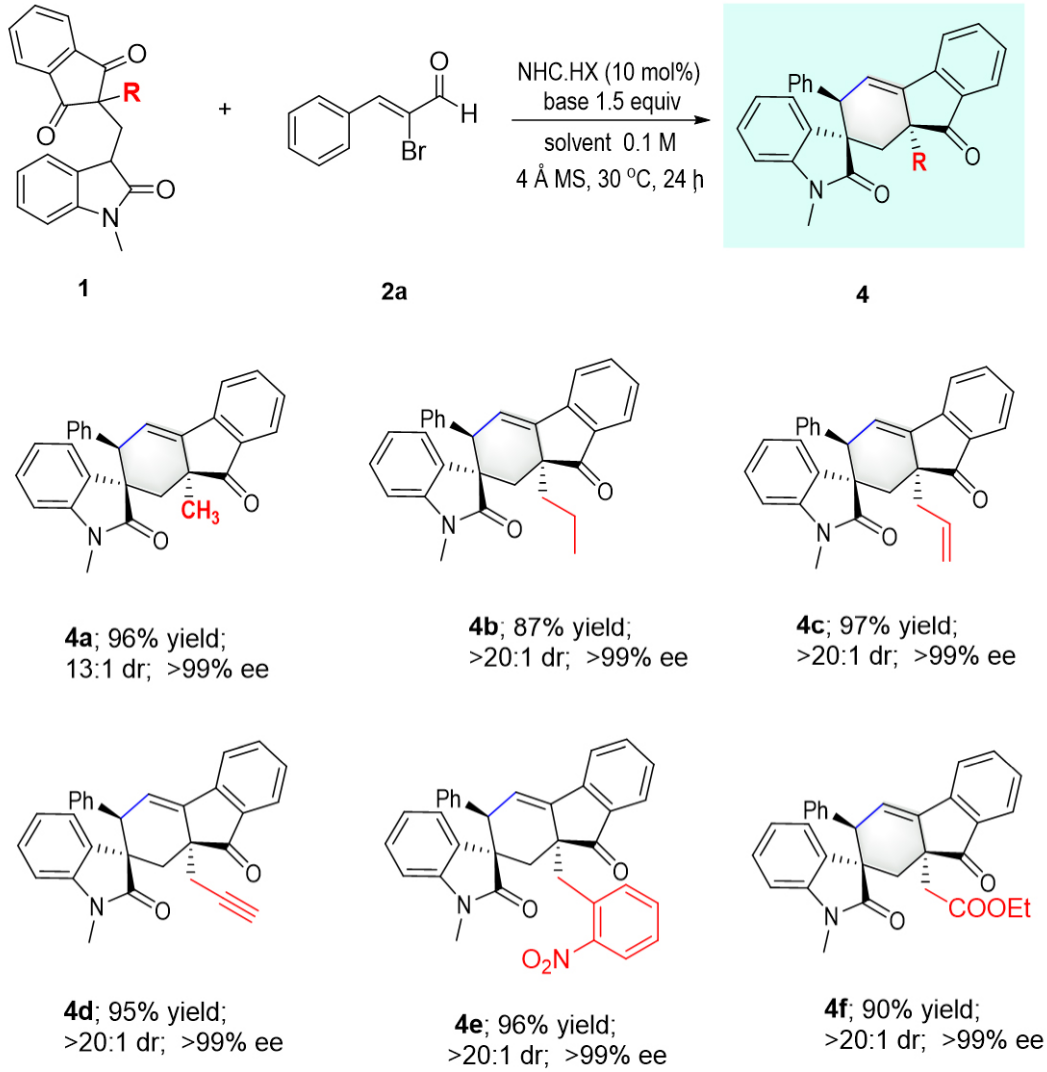


Figure 4. Scope of reactions. The reaction conditions are the same in Figure 2, Entry 14.

with a propyl group also works efficiently to result in the product **4b** in 87% yields with > 20:1 dr and > 99% ee. Notably, the substrates with functional groups, such as allyl, propargyl, and NO_2 substituted benzyl and acetylethoxy groups, were also compatible with this transformation, resulting in the formation of products **4c-f** in excellent yields (90%-97%) with excellent diastereoselectivities (> 20:1 dr values) and enantioselectivities (> 99% ee values).

To show the practicality of our method, a gram-scale reaction was carried out [Figure 5]. Pleasingly, with the use of 1.0 gram of prochiral substrate **2a** under the standard conditions, the reaction worked efficiently to afford 1.23 grams of the product **3a** (97% yield) without any erosion of dr value and ee value.

To show further potential applications of this method, the synthetic transformation was performed, as shown in Figure 6. One-pot ring-opening of intermediate **3a'** could give the molecules five stereogenic centers. Treatment of intermediate **3a'** with nucleophiles such as methanol, benzyl mercaptan, and benzylamine at room temperature led to the formation of ring-opening products **5-7** in good yields and

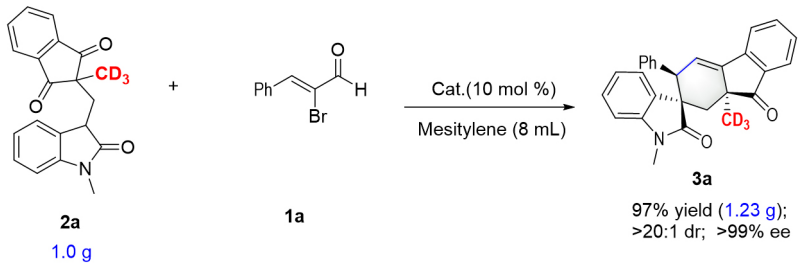


Figure 5. Gram-scale synthesis.

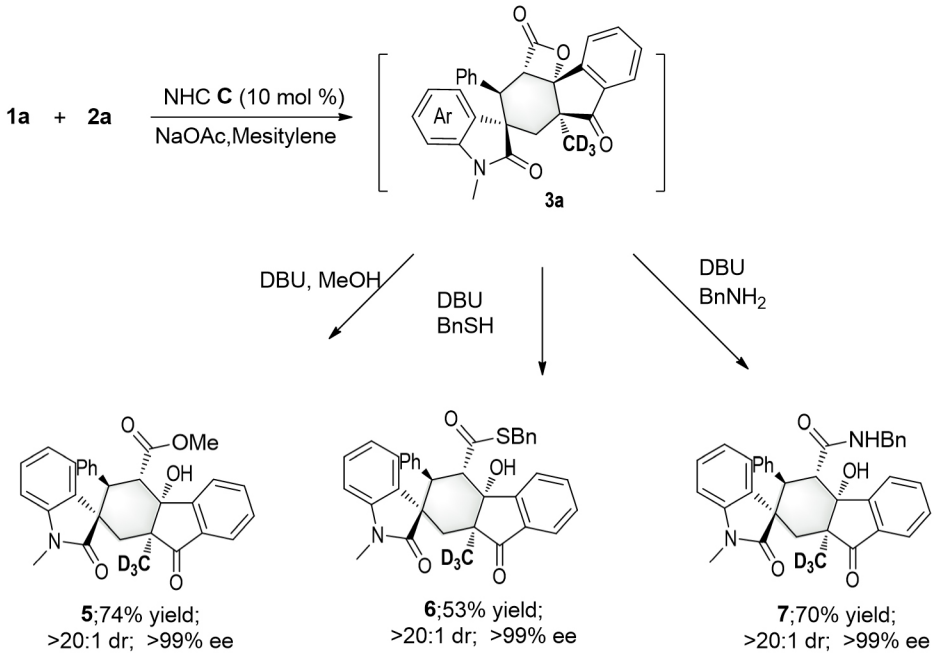


Figure 6. One pot process to ring-opening products.

without any erosion of dr values and ee values.

On the basis of previous reports and current results[46], a plausible mechanism is depicted in Figure 7. The process begins with the addition of carbene to bromoenal **1a**, followed by debromination to give α, β-unsaturated acyl azolium **I**. Deprotonation of trideuteromethyl oxindolyl 1,3-diketones **2a** results in the formation of intermediate **II**, which undergoes Michael addition to intermediate **I** to form intermediate **III**. Then, intramolecular cyclization of intermediate **III** could generate intermediate **IV**, which undergoes intramolecular lactonization to give **3a'** and regenerate free carbene. Subsequently, treatment of **3a'** with acidic SiO_2 affords the final product **3a** via a decarbonation process.

In summary, we have successfully established an efficient strategy for the asymmetric construction of spiro-polycyclic molecules with a d_3-methylated all-carbon quaternary stereocenter under carbene organocatalysis. This versatile and practical asymmetric desymmetrization features a broad substrate scope, good functional-group tolerance, and can be easily scaled-up. Notably, this strategy enables the efficient construction of three stereogenic centers, including two quaternary centers. Further investigations and explorations of this catalytic process and the resulting enantioenriched d_3-methylated molecules are currently underway in our laboratory.

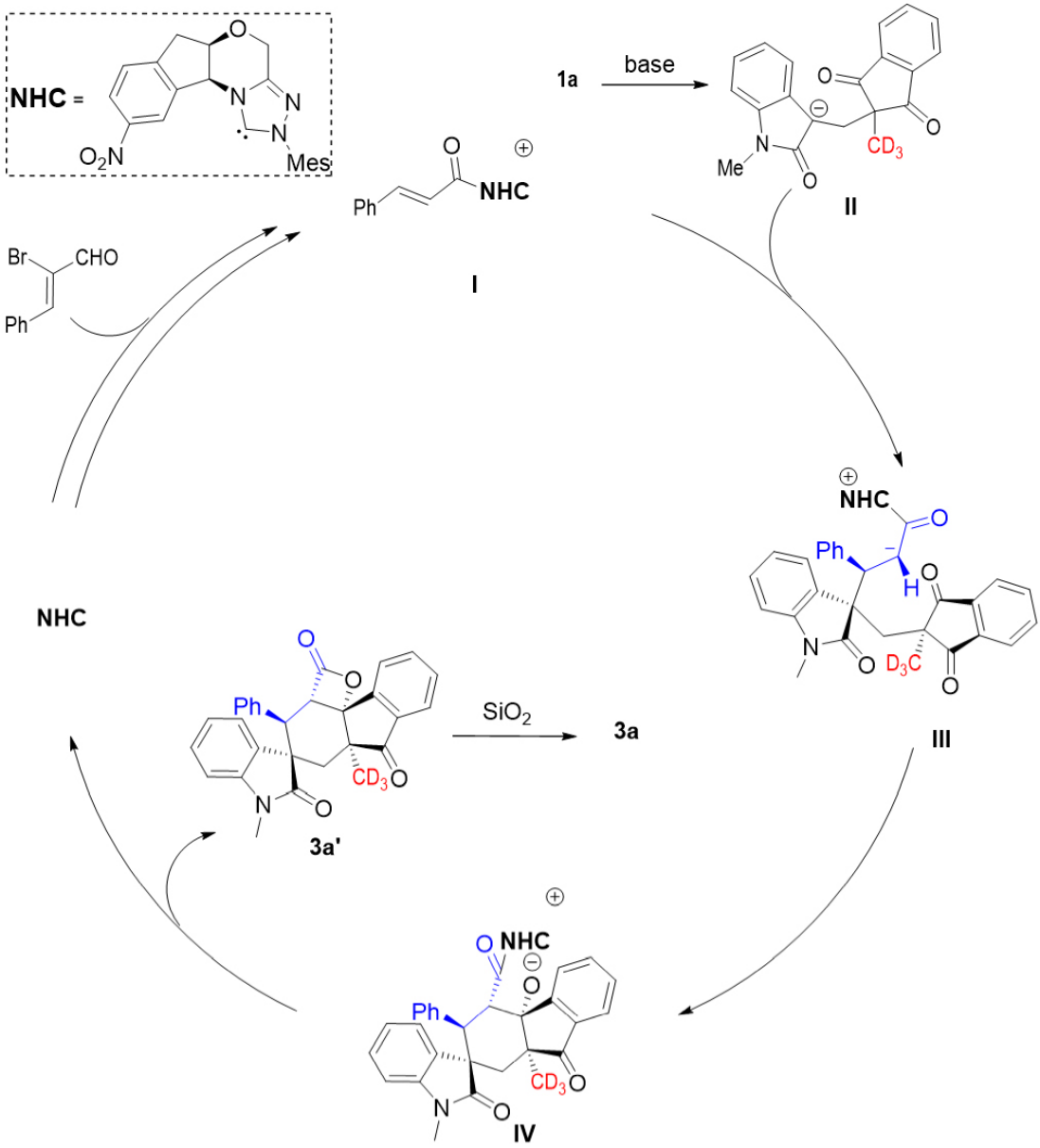


Figure 7. Proposed mechanism.

DECLARATIONS

Authors' contributions

Designing the experiments, writing the manuscript, and being responsible for the whole work: Fu Z, Zhang X

Performing the experiments: Guo J, Zhang Y

Synthesizing the substrates: Guo J, Zhang Y

Availability of data and materials

Detailed experimental procedures and spectroscopic data were published as Supplementary Materials in the journal.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

REFERENCES

1. Sun Q, Soulé JF. Broadening of horizons in the synthesis of CD_3-labeled molecules. *Chem Soc Rev* 2021;50:10806-35. DOI PubMed
2. Kopf S, Bourriquen F, Li W, Neumann H, Junge K, Beller M. Recent developments for the deuterium and tritium labeling of organic molecules. *Chem Rev* 2022;122:6634-718. DOI PubMed
3. Atzrodt J, Derdau V, Kerr WJ, Reid M. Deuterium- and tritium-labelled compounds: applications in the life sciences. *Angew Chem Int Ed Engl* 2018;57:1758-84. DOI PubMed
4. Pirali T, Serafini M, Cargnin S, Genazzani AA. Applications of deuterium in medicinal chemistry. *J Med Chem* 2019;62:5276-97. DOI PubMed
5. Prakash G, Paul N, Oliver GA, Werz DB, Maiti D. C-H deuteration of organic compounds and potential drug candidates. *Chem Soc Rev* 2022;51:3123-63. DOI
6. Wang P, Wang F, Chen Y, et al. Synthesis of all-deuterated tris(2-phenylpyridine) iridium for highly stable electrophosphorescence: the "deuterium effect". *J Mater Chem C* 2013;1:4821. DOI
7. Abe T, Miyazawa A, Konno H, Kawanishi Y. Deuteration isotope effect on nonradiative transition of fac-tris (2-phenylpyridinato) iridium (III) complexes. *Chem Phys Lett* 2010;491:199-202. DOI
8. Box CL, Zhang Y, Yin R, Jiang B, Maurer RJ. Determining the effect of hot electron dissipation on molecular scattering experiments at metal surfaces. *JACS Au* 2021;1:164-73. DOI PubMed PMC
9. Bae HJ, Kim JS, Yakubovich A, et al. Protecting benzylic C-H bonds by deuteration doubles the operational lifetime of deep-blue Ir-Phenylimidazole dopants in phosphorescent oleds. *Adv Opt Mater* 2021;9:2100630. DOI
10. Liu X, Chan C, Mathevet F, et al. Isotope effect of host material on device stability of thermally activated delayed fluorescence organic light-emitting diodes. *Small Science* 2021;1:2000057. DOI
11. Cleland WW. The use of isotope effects to determine enzyme mechanisms. *Arch Biochem Biophys* 2005;433:2-12. DOI PubMed
12. Shao L, Hewitt MC. The kinetic isotope effect in the search for deuterated drugs. *Drug News Perspect* 2010;23:398-404. DOI PubMed
13. Gómez-Gallego M, Sierra MA. Kinetic isotope effects in the study of organometallic reaction mechanisms. *Chem Rev* 2011;111:4857-963. DOI
14. Katsnelson A. Heavy drugs draw heavy interest from pharma backers. *Nat Med* 2013;19:656. DOI PubMed
15. Jones PA, Takai D. The role of DNA methylation in mammalian epigenetics. *Science* 2001;293:1068-70. DOI PubMed
16. Barreiro EJ, Kümmerle AE, Fraga CA. The methylation effect in medicinal chemistry. *Chem Rev* 2011;111:5215-46. DOI PubMed
17. Leung CS, Leung SS, Tirado-Rives J, Jorgensen WL. Methyl effects on protein-ligand binding. *J Med Chem* 2012;55:4489-500. DOI PubMed PMC
18. Zhang L, Ding X, Cui J, et al. Cysteine methylation disrupts ubiquitin-chain sensing in NF-κB activation. *Nature* 2011;481:204-8. DOI
19. Schmidt C. First deuterated drug approved. *Nat Biotechnol* 2017;35:493-4. DOI PubMed
20. Mullard A. FDA approves dupilumab for severe eczema. *Nat Rev Drug Discov* 2017;16:305. DOI PubMed
21. Zhong L, Hou C, Zhang L, Zhao J, Li F, Li W. Synthesis of deuterium-enriched sorafenib derivatives and evaluation of their biological activities. *Mol Divers* 2019;23:341-50. DOI
22. Barratt M J, Frail D E. Drug repositioning: bringing new life to shelved assets and existing drugs. Hoboken: John Wiley & Sons; 2012. DOI
23. Braman V, Graham P, Cheng C, et al. A randomized phase I evaluation of CTP-499, a novel deuterium-containing drug candidate for

diabetic nephropathy. *Clin Pharmacol Drug Dev* 2013;2:53-66. DOI

24. Sabounjian L, Graham P, Wu L, et al. A first-in-patient, multicenter, double-blind, 2-arm, placebo-controlled, randomized safety and tolerability study of a novel oral drug candidate, CTP-499, in chronic kidney disease. *Clin Pharmacol Drug Dev* 2016;5:314-25. DOI
25. Zeng XP, Cao ZY, Wang YH, Zhou F, Zhou J. Catalytic enantioselective desymmetrization reactions to all-carbon quaternary stereocenters. *Chem Rev* 2016;116:7330-96. DOI PubMed
26. Enders D, Niemeier O, Henseler A. Organocatalysis by *N*-heterocyclic carbenes. *Chem Rev* 2007;107:5606-55. DOI PubMed
27. Bugaut X, Glorius F. Organocatalytic umpolung: *N*-heterocyclic carbenes and beyond. *Chem Soc Rev* 2012;41:3511-22. DOI PubMed
28. Cohen DT, Scheidt KA. Cooperative lewis acid/*N*-heterocyclic carbene catalysis. *Chem Sci* 2012;3:53-7. DOI PubMed PMC
29. Sarkar S, Biswas A, Samanta RC, Studer A. Catalysis with *N*-heterocyclic carbenes under oxidative conditions. *Chemistry* 2013;19:4664-78. DOI PubMed
30. Ryan SJ, Candish L, Lupton DW. Acyl anion free *N*-heterocyclic carbene organocatalysis. *Chem Soc Rev* 2013;42:4906-17. DOI PubMed
31. Hopkinson MN, Richter C, Schedler M, Glorius F. An overview of *N*-heterocyclic carbenes. *Nature* 2014;510:485-96. DOI PubMed
32. Flanigan DM, Romanov-Michailidis F, White NA, Rovis T. Organocatalytic reactions enabled by *N*-heterocyclic carbenes. *Chem Rev* 2015;115:9307-87. DOI PubMed PMC
33. Chen XY, Gao ZH, Ye S. Bifunctional *N*-Heterocyclic carbenes derived from l-pyroglutamic acid and their applications in enantioselective organocatalysis. *Acc Chem Res* 2020;53:690-702. DOI PubMed
34. Ohmiya H. *N*-Heterocyclic carbene-based catalysis enabling cross-coupling reactions. *ACS Catal* 2020;10:6862-9. DOI
35. Chen X, Wang H, Jin Z, Chi YR. *N*-Heterocyclic carbene organocatalysis: activation modes and typical reactive intermediates. *Chin J Chem* 2020;38:1167-202. DOI
36. Zhang B, Yang G, Guo D, Wang J. Recent developments on NHC-driven dual catalytic approaches. *Org Chem Front* 2022;9:5016-40. DOI
37. Zhang B, Wang J. Assembly of versatile fluorine-containing structures via *N*-heterocyclic carbene organocatalysis. *Sci China Chem* 2022;65:1691-703. DOI
38. Gao J, Feng J, Du D. Generation of azolium dienolates as versatile nucleophilic synthons *via N* -heterocyclic carbene catalysis. *Org Chem Front* 2021;8:6138-66. DOI
39. Bellotti P, Koy M, Hopkinson MN, Glorius F. Recent advances in the chemistry and applications of *N*-heterocyclic carbenes. *Nat Rev Chem* 2021;5:711-25. DOI
40. Wadamoto M, Phillips EM, Reynolds TE, Scheidt KA. Enantioselective synthesis of alpha,alpha-disubstituted cyclopentenes by an *N*-heterocyclic carbene-catalyzed desymmetrization of 1,3-diketones. *J Am Chem Soc* 2007;129:10098-9. DOI PubMed PMC
41. Ema T, Akihara K, Obayashi R, Sakai T. Construction of contiguous tetrasubstituted carbon stereocenters by intramolecular crossed benzoin reactions catalyzed by *N*-Heterocyclic Carbene (NHC) organocatalyst. *Adv Synth Catal* 2012;354:3283-90. DOI
42. Zhuo S, Zhu T, Zhou L, et al. Access to all-carbon spirocycles through a carbene and thiourea cocatalytic desymmetrization cascade reaction. *Angew Chem Int Ed Engl* 2019;58:1784-8. DOI
43. Zhu T, Liu Y, Smetankova M, et al. Carbene-catalyzed desymmetrization and direct construction of arenes with all-carbon quaternary chiral center. *Angew Chem* 2019;131:15925-9. DOI
44. Hu JM, Zhang JQ, Sun BB, et al. Chiral *N*-Heterocyclic-Carbene-Catalyzed cascade asymmetric desymmetrization of cyclopentenediones with enals: access to optically active 1,3-indandione derivatives. *Org Lett* 2019;21:8582-6. DOI
45. Shee S, Mukherjee S, Gonnade RG, Biju AT. Enantioselective synthesis of tricyclic β-Lactones by NHC-Catalyzed desymmetrization of cyclic 1,3-Diketones. *Org Lett* 2020;22:5407-11. DOI PubMed
46. Wang G, Zhang M, Guan Y, et al. Desymmetrization of cyclic 1,3-Diketones under *N*-Heterocyclic carbene organocatalysis: access to organofluorines with multiple stereogenic centers. *Research* 2021;2021:9867915. DOI PubMed PMC
47. Geng H, Chen X, Gui J, et al. Practical synthesis of C-1 deuterated aldehydes enabled by NHC catalysis. *Nat Catal* 2019;2:1071-7. DOI PubMed PMC
48. Zhang X, Chen Q, Song R, et al. Carbene-Catalyzed α,γ-Deuteration of enals under oxidative conditions. *ACS Catal* 2020;10:5475-82. DOI
49. Sawama Y, Miki Y, Sajiki H. *N*-Heterocyclic carbene catalyzed deuteration of aldehydes in D_2O. *Synlett* 2020;31:699-702. DOI
50. Suresh P, Thamotharan S, Selva Ganesan S. NHC Organocatalysis in D_2O for the highly diastereoselective synthesis of deuterated spiropyran analogues. *ChemistrySelect* 2021;6:2036-40. DOI
51. Wang G, Fu Z, Huang W. Access to amide from aldimine via aerobic oxidative carbene catalysis and LiCl as cooperative lewis acid. *Org Lett* 2017;19:3362-5. DOI
52. Zhang Y, Huang J, Guo Y, Li L, Fu Z, Huang W. Access to enantioenriched organosilanes from enals and β□silyl enones: carbene organocatalysis. *Angew Chem* 2018;130:4684-8. DOI
53. Wang G, Shi Q, Hu W, et al. Organocatalytic asymmetric N-sulfonyl amide C-N bond activation to access axially chiral biaryl amino acids. *Nat Commun* 2020;11:946. DOI PubMed PMC
54. Hu Z, Wei C, Shi Q, et al. Desymmetrization of N-Cbz glutarimides through *N*-heterocyclic carbene organocatalysis. *Nat Commun* 2022;13:4042. DOI PubMed PMC
55. Wang G, Zhang QC, Wei C, et al. Asymmetric Carbene-Catalyzed Oxidation of Functionalized Aldimines as 1,4-Dipoles. *Angew*

Chem Int Ed Engl 2021;60:7913-9. DOI

56. Wang G, Huang J, Zhang L, et al. *N*-heterocyclic carbene-catalyzed atroposelective synthesis of axially chiral 5-aryl 2-pyrones from enals. *Sci China Chem* 2022;65:1953-61. DOI
57. Zhang C, Hooper JF, Lupton DW. *N* -Heterocyclic Carbene Catalysis via the α,β-Unsaturated Acyl Azolium. *ACS Catal* 2017;7:2583-96. DOI
58. Ding A, Meazza M, Guo H, Yang JW, Rios R. New development in the enantioselective synthesis of spiro compounds. *Chem Soc Rev* 2018;47:5946-96. DOI
59. Xu P, Yu J, Chen C, Cao Z, Zhou F, Zhou J. Catalytic enantioselective construction of spiro quaternary carbon stereocenters. *ACS Catal* 2019;9:1820-82. DOI
60. Hong L, Wang R. Recent advances in asymmetric organocatalytic construction of 3,3′-spirocyclic oxindoles. *Adv Synth Catal* 2013;355:1023-52. DOI
61. Cheng D, Ishihara Y, Tan B, Barbas CF. Organocatalytic asymmetric assembly reactions: synthesis of spirooxindoles via organocascade strategies. *ACS Catal* 2014;4:743-62. DOI