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Photocatalytic Stereoselective Editing of Alkynes to 3D Molecules via Hydrogen Atom Transfer-Mediated Dynamic Epimerization

Zhenyu Gu,[1] Tianqin Zeng,[1] Zheliang Yuan,[1] Hanliang Zheng,[1*] and Gangguo Zhu[1,2*]

[1]*Key Laboratory of the Ministry of Education for Advanced Catalysis Materials, College of Chemistry and Materials Science, Zhejiang Normal University, 688 Yingbin Road, Jinhua 321004, China.*

[2]*College of Pharmacy, Jinhua University of Vocational Technology, 888 Haitang West Road, Jinhua,321017, China.*

*Emails: hanliang@zjnu.edu.cn; gangguo@zjnu.cn

Abstract: Three-dimensional molecules have drawn tremendous attention due to their pivotal roles in drug discovery as saturated bioisosteres of benzenoids. The direct construction of these scaffolds from simple and readily available one-dimensional building blocks is highly attractive but challenging. This study presents a concise synthesis of bicyclo[2.2.1]heptanones and bicyclo[3.2.1]octanones via a photoinduced decatungstate-catalyzed bicyclization of internal alkynes with aldehydes. The reaction enables simultaneous formation of four chemical bonds and two carbocycles, demonstrating excellent site-, regio-, and diastereoselectivity. Experimental and theoretical investigations suggest that the initial cyclization produces a cyclopentanone intermediate with poor diastereoselectivity, and an uncommon dynamic kinetic resolution enabled by hydrogen atom transfer-mediated C-H epimerization yields bicyclic products with excellent diastereoselectivity. This method represents an in situ concurrent editing of skeleton and stereochemistry, which exhibits great potentials for increasing molecular diversity and complexity and changing the way to assemble biologically important compounds.

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Introduction

Aroused by the "escape from flatland" concept, all-carbon three-dimensional (3D) frameworks have garnered increasing attention from the pharmaceutical industry. These structures, characterized by a high proportion of sp^3 carbon atoms, offer the potential to explore a broader chemical space, which is beneficial for improving pharmacokinetic and physicochemical properties of biologically active compounds.[1-5] Traditionally, the construction of bridged scaffolds relies on a two-step process, comprising the preformation of two-dimensional (2D) molecules, usually cyclic dienes, and a subsequent cycloaddition (Fig. 1a).[6-9] The direct assembly of 3D frameworks from one-dimensional (1D) precursors is a more convenient and efficient approach. However, such 1D-to-3D protocols are tremendous challenging due to the entropic penalty and complexity of controlling various selectivities, including chemo-, regio-, and diastereoselectivity. To address the challenges, intramolecular bicyclizations have been developed, such as the crossed [2+2] cycloaddition,[10-14] type 2 Diels-Alder reaction,[15-17] and transition metal-catalyzed cyclization,[18,19] which can directly transform dienes, trienes, enynes, or diynes into bridged scaffolds. The development of intermolecular 1D-to-3D processes, particularly using simple and

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readily available starting materials like alkynes, is more demanding but also more practical, and still remains a pressing need.

Hydrogen atom transfer (HAT) has become a prominent tool for late-stage modifications of the stereochemistry of organic molecules, especially of unactivated tertiary stereocenters[20-41] that are challenging for the traditional base-mediated epimerization (Fig. 1b). Controllable editing of many C(sp^3)-H bonds has been successfully achieved, including those in cyclic alkanes,[20-23] cyclic ureas,[24] sugars,[25-27] aimines,[28-31] lactams,[32-35] and cyclic diols.[36-38] Despite these significant advancements, the preformation of cyclized precursors is required, thus representing a limitation of this methodology. The concurrent editing of molecular skeleton and stereochemistry has not been achieved yet. Given the reversibility of HAT-mediated C-H epimerization, it is likely that incorporation of a stereochemical resolution could transform the initially unselective reaction into a stereoselective one, thereby enabling a precise control over multiple stereocenters. Building upon this insight, we designed a strategy that couples an annulation process with *in situ* stereochemical editing for the controllable assembly of complex bridged structures from simple 1D molecules. Specifically, our design leverages HAT-mediated epimerization to interconvert diastereomeric cyclopentanones bearing the dynamically reactive β-carbonyl C(sp^3)-H generated *in situ* by a radical-mediated [3+2] cycloaddition protocol (Fig. 1c).[42,43] This sophisticated interplay establishes an uncommon dynamic kinetic resolution (DKR) with the incorporation of subsequent S_N2 cyclization from the less hindered side, offering a promising protocol for the high-yield and diastereoselective de novo synthesis of valuable bicyclo[2.2.1]heptanones, an important class of building blocks[44-48] widely utilized in natural product synthesis, pharmaceutical chemistry, and asymmetric catalysis. Herein, we report a photoinduced tetra-n-butylammonium decatungstate (TBADT)[49,50] catalyzed bicyclization of readily accessible internal alkynes with aldehydes. Structurally diverse bicyclic rings, such as bicyclo[2.2.1]heptanones and bicyclo[3.2.1]octanones, can be efficiently assembled under mild conditions with exceptional site-, chemo-, regio-, and diastereoselectivity. In contrast to the traditional intramolecular 1D-to-3D protocols, this work represents an intermolecular 1D-to-3D assembly, allowing for expeditious build-up of skeletal and stereochemical complexity from simpler and more common starting materials. Our method demonstrates that the low diastereoselectivity of an initial cyclization and inapplicability of stereochemical editing for acyclic precursors can be well resolved by merging these two processes, namely the in-situ concurrent editing of skeleton and stereochemistry, which will be valuable for designing and developing novel controlled bicyclization and polycyclization reactions.

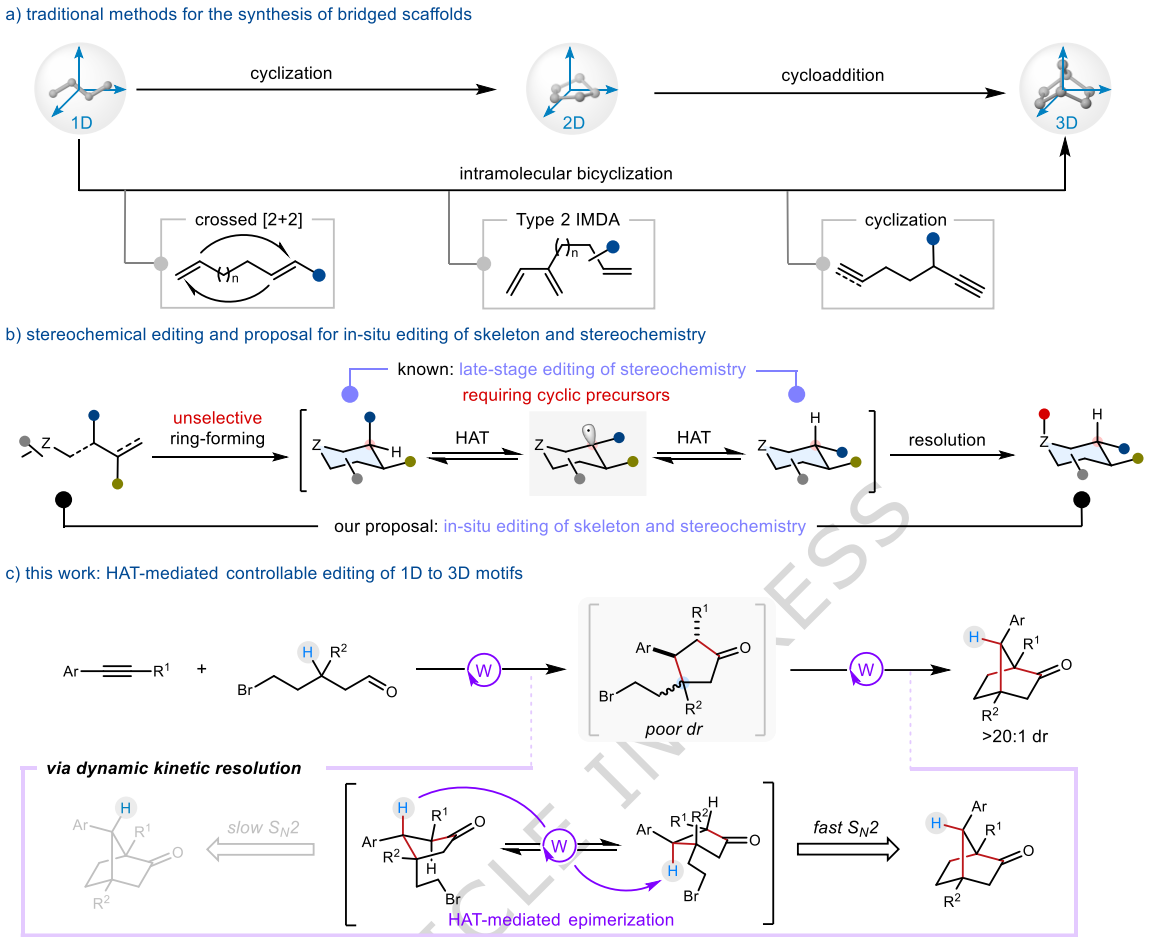

Fig. 1

Results

Reaction development

Initially, alkyne **1a** and 5-bromopentanal **2a** were selected as model substrates for screening reaction conditions. After some trials, we found that treatment with 2.0 equiv of K_2CO_3 and 2 mol % of TBADT in MeCN under irradiation of 40 W 390 nm purple LEDs at 50 °C for 10 h furnished bicyclo[2.2.1]heptanone **3** as a single diastereoisomer in 78% yield (Table 1, entry 1). A comparable yield (72%) was obtained when the reaction was scaled up to 2.0 mmol. Running the reaction in alternative solvents, such as MeCN/H_2O, acetone, and DMSO, resulted in reduced efficiencies (entries 2-4). Other bases, including Cs_2CO_3 and K_3PO_4, proved less effective (entries 5 and 6). Employing sodium decatungstate (NaDT) as an alternative photocatalyst gave a reduced yield of 66% (entry 7). Elevating the reaction temperature to 70 °C did not improve the yield but resulted in a reduced dr of 3:1 (entry 8). K_2CO_3 was found to be advantageous for this bicyclization, and a reduced yield (51%) was obtained without its addition, accompanied by forming *syn*-**4** (>20:1 dr) in 38% yield (see mechanistic investigation *vide infra*), which could not be fully consumed even by extending the reaction time to 60 h (entry

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9). As demonstrated by the control experiments, both TBADT and light irradiation are essential for this reaction (entries 10 and 11).

Please insert Table 1 here!

Examination of substrate scope

With the optimized reaction conditions in hands, the scope of this 1D-to-3D process was investigated with **2a** as the coupling partner (Fig. 2). A diverse array of arylpropiolate esters, bearing F (**5**), Br (**6**), Cl (**7** and **17**), I (**16** and **20**), CN (**8**), CF_3 (**9**), OMe (**10** and **20**), SMe (**11**), *t*-Bu (**12**), and Me (**13**-**15**) were well tolerated, forming anticipated bicyclo[2.2.1]heptanones in 68-80% yields with outstanding regio- and diastereoselectivity. The electronic effect and steric hindrance of aryl rings were evaluated, which demonstrated minimal impact on the reaction efficiency (**8** and **9** vs. **10**, **13** vs. **15**). Substitution of the aromatic ring with a terminal C-C triple bond was viable, as evidenced by the efficient production of **18**. Other (hetero)arenes, such as naphthalene (**21**), furan (**22**), thiophene (**23**), pyridines (**24** and **25**), and pyrazine (**26**), were well compatible and afforded desired products in good to high yields. Alkyl propiolate ester served as an ineffective substrate (**27**), probably due to the absence of spin delocalization to the adjacent aryl group.[51] Alkynes activated by common electron-withdrawing groups such as Ac (**28**), CN (**29**), $CONMe_2$ (**30**), Cl (**31**), $P(O)(OEt)_2$ (**33**), CF_3 (**34**), CF_2H (**35**), and SCF_3 (**36**), which are appealing for further derivatizations, all worked well for this reaction to form diversely functionalized bicyclo[2.2.1]heptanones in 65-84% yields. Nevertheless, the reaction of phenylethynyl bromide failed to provide the desired product **32** due to the interference of an acyl radical addition/β-bromo elimination sequence that furnished ynone.[42] The bicyclization of 1-phenyl-1-propyne, an unactivated alkyne, took place efficiently, producing **37**-**39** in good yields with excellent regio- and diastereoselectivity. In contrast, only a kinetic resolution was observed for the reaction of 1,3-diphenylpropyne, which afforded **40** in 40% yield with >20:1 dr (see page S26 in Supplementary Information for details). The competitive HAT between photocatalyst and the secondary benzylic C-H bond of *syn*-**41** may preclude the desired epimerization at the bulkier tertiary benzylic position.

Variation of the aldehyde component **2** was then conducted. Substitution of the R^3 group with *n*-Bu and *i*-Bu generated bicyclo[2.2.1]heptanones **42** and **43** in 74% and 70% yield, respectively. Introduction of OTBS, a sterically demanding substituent, was successful for the generation of **45**. The attempted coupling of **1a** with 5-bromo-3-phenylpentanal proved unfruitful (**46**), which may be attributed to the decreased nucleophilicity of benzyl radicals as compared to alkyl radicals. Replacing the methyl group of **1a** with a hydrogen atom failed as well (**47**), presumably due to lack of the Thorpe-Ingold effect for the initial cyclopentanone construction via 5-*endo*-trig radical cyclization. The structure and stereochemistry of bicyclo[2.2.1]heptanones were confirmed by the single crystal X-ray diffraction analysis of **31**.[52]

Having established a direct and controllable editing of alkynes to bicyclo[2.2.1]heptanones, we then examined the feasibility of assembling other bicyclic frameworks via this method. Pleasingly, the regio- and diastereoselective assembly of bicyclo[3.2.1]octanones was accomplished with 6-bromo-3-methylhexanal as a coupling partner, as exemplified by the effective production of **48**-**53**. However, the preparation of bicyclo[4.2.1]nonan-7-ones and bicyclo[2.1.1]hexan-2-ones was unsuccessful (**54** and **55**), reflecting the preferential formation of 5- and 6-membered rings over 7- and 4-membered counterparts.

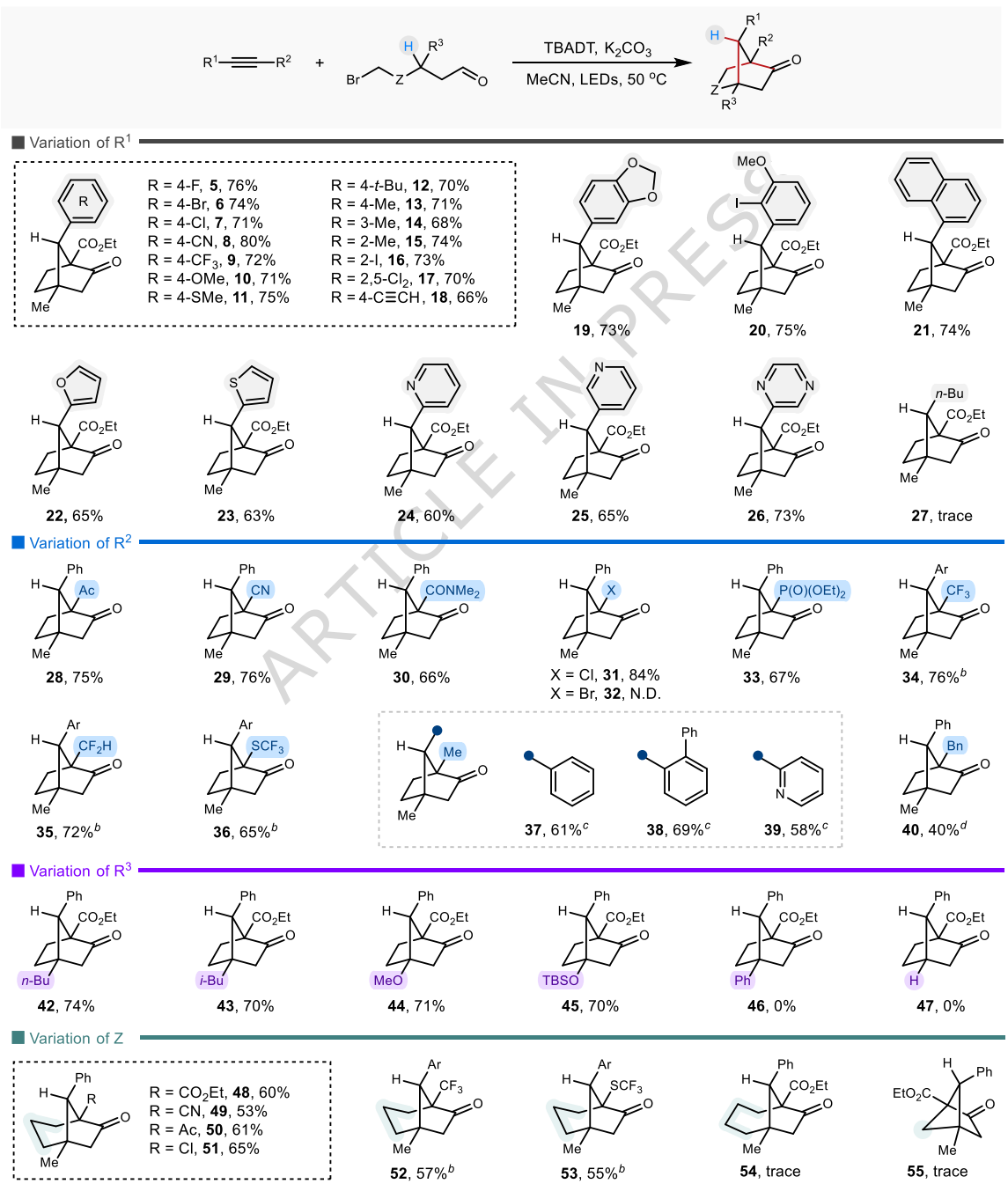

Fig. 2

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Synthetic applications

We then explored the application of this 1D-to-3D assembly protocol (Fig. 3). Treatment of **3** with $BnNHNH_2$ followed by reduction with $NaCNBH_3$ produced **57**, an analogue of the hydrazide organocatalyst **56**[53] for Diels–Alder reactions, in 58% yield. Condensation of **39** with $TsNHNH_2$ and a subsequent denitrogenation with MeLi afforded norbornene derivative **57** in 61% yield over 2 steps. The installation of a C7-handle offered promising potential for the more nuanced control over reactivity and selectivity, which may provide a broader chemical landscape for norbornene-catalyzed or -mediated transformations. The usefulness of this method was highlighted by the concise synthesis of fluorene **60**,[54] which was previously synthesized from **59** over 11 synthetic steps. In contrast, a three-step procedure, involving the Wolff-Kishner reduction of **38**, bromination, and intramolecular Friedel-Crafts reaction, was developed to deliver **60** in 57% overall yield. This success showcased the potential of our method for changing the retrosynthetic analysis and strategy for the synthesis of complex molecules. Furthermore, our investigations revealed that the dimensional expansion of bioactive molecules could enhance their pharmacological activity. An example was observed in the structural modification of WAY-100635, a potent 5-hydroxytryptamine ($5\text{-}HT_{1A}$) antagonist.[55] Replacement of the cyclohexane moiety with a bicyclo[2.2.1]heptanone unit resulted in an increase in bioactivity from 37.0 nM to 27.5 nM (**62**). In contrast, a significant decline in bioactivity (479.3 nM) was observed for **63** bearing a bicyclo[2.2.1]heptane motif, which highlighted the importance of bicyclo[2.2.1]heptanones constructed by this method.

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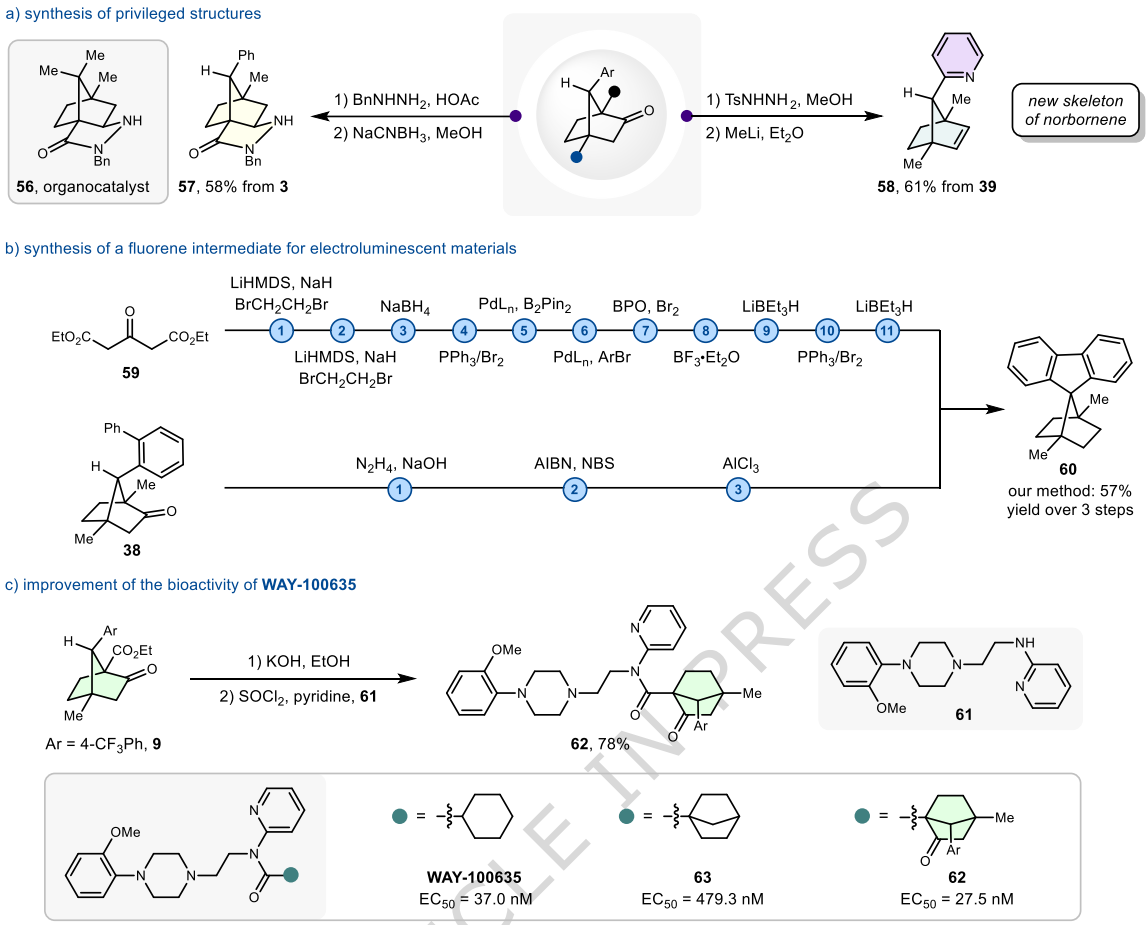

Fig. 3

Mechanistic investigations

To obtain an understanding of the mechanism of this protocol, some control experiments were conducted (Fig. 4). The reaction run at 0 °C without addition of K_2CO_3 furnished **4** in 80% yield as a mixture of two diastereomers (*anti*/*syn* = 1.8:1, Fig. 4a), which implied the intermediacy of cyclopentanones and a poor diastereoselectivity prior to the S_N2 cyclization. Upon treating *anti*-**4** or *syn*-**4** alone under the photocatalyzed conditions at 0 °C, the epimerization occurred smoothly, reaching an equilibrium with an *anti*/*syn* ratio of 1.8:1 after 24 h from both directions (Fig. 4b). These results suggested that the interconversion of *anti*-**4** and *syn*-**4** was kinetically viable, with the ratio determined by their thermodynamic stability. K_2CO_3-promoted S_N2 cyclization of **4** (*anti*/*syn* = 1.8:1) at 50 °C afforded **3** exclusively (>20:1 dr) in 58% yield, along with recovery of *syn*-**4** in 33% yield with >20:1 dr (Fig. 4c). Treatment of the isolated *anti*-**4** (>20:1 dr) with K_2CO_3 at 50 °C delivered **3** in 94% yield with >20:1 dr, whereas an elevated temperature of 100 °C was required for the cyclization of *syn*-**4** (>20:1 dr) to produce 91% yield of **3'** (>20:1 dr), a diastereoisomer of **3**. Consequently, only a kinetic resolution took place in the absence of DT and light irradiation. Treating either **3** or **3'** under standard conditions did not result in their

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interconversion, which implied that the observed diastereoselectivity is not a consequence of product epimerization. These control experiments indicated that only *anti*-**4** is capable of undergoing the S_N2 cyclization at 50 °C, and the epimerization of *syn*-**4** to *anti*-**4** followed by a rapid S_N2 cyclization likely accounts for the diastereoselective formation of **3**. Collectively, a tandem [3+2] cycloaddition and HAT-mediated DKR is proposed for this diastereoselective bicyclization (Fig. 4d). The excited decatungstate (DT*) undergoes a HAT with the aldehydic C-H bond of **2a** to furnish acyl radical **I** with concurrent formation of protonated/reduced decatungstate (DTH). A cascade process, consisting of radical addition of **I** to **1a**, 1,5-HAT, and 5-*endo*-trig cyclization,[56-58] then occurs to produce cyclopentanone radical **IV**, which undergoes back hydrogen abstraction (HA) with DTH to give a mixture of *anti*-**4** and *syn*-**4**. Due to the kinetically unfavorable S_N2 cyclization, *syn*-**4** is converted to *anti*-**4** via a tandem hydrogen atom abstraction/donation process. Finally, K_2CO_3-promoted S_N2 substitution leads to the exclusive production of **3**.

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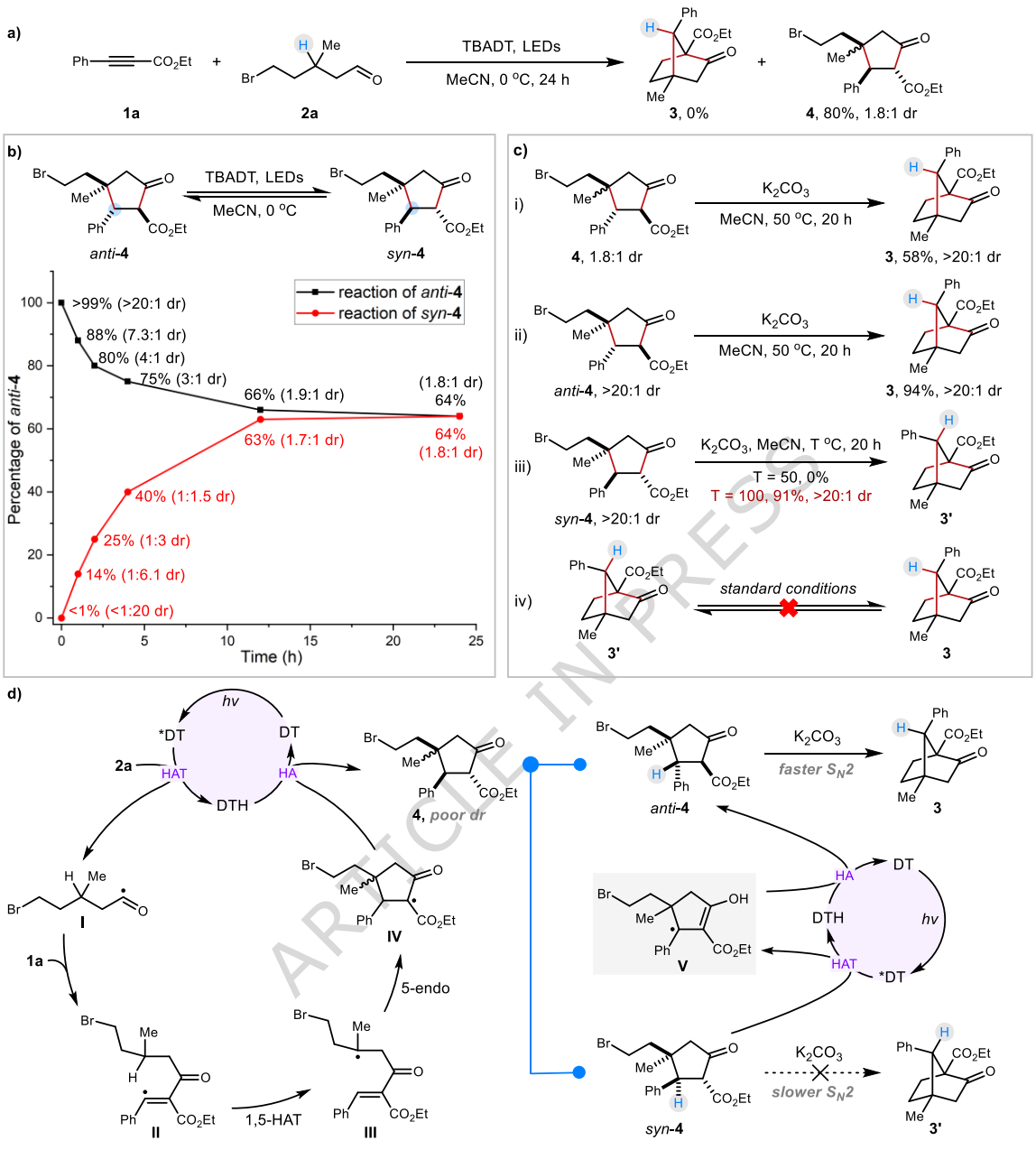

Fig. 4

To further probe the mechanistic details, DFT calculations were performed to provide a detailed energy diagram and insights into the C-H epimerization and DKR process (Fig. 5). Deprotonation at the most acidic position in both *anti*-**4** and *syn*-**4** is very fast with barriers less than 3.0 kcal mol^{-1} (via **TS1**$_a$ and **TS1**$_s$, respectively), leading to the formation of enolate intermediates **Int1**$_a$ and **Int1**$_s$. The S_N2 reaction of **Int1**$_a$ proceeds faster than that of **Int1**$_s$ (**TS3**$_a$ vs. **TS3**$_s$: 20.4 vs. 22.4 kcal mol^{-1}), aligning with the experimental results shown in Fig. 4c. The steric interaction between the Ph and CH_2CH_2Br groups in **TS3**$_s$ may be responsible for

the increased energy barrier for the S_N2 cyclization of **Int1$_s$**. With this kinetic preference elucidated, the pathway for the interconversion of enolate **Int1$_s$** and **Int1$_a$** was examined. Our calculations revealed that the combination of **Int1$_s$** and *DT is exergonic by 39.8 kcal mol^{-1}. As a potent hydrogen abstractor, *DT directly abstracts a hydrogen atom from the benzylic C-H bond of enolate **Int2$_s$** via **TS2** with a low barrier of 8.3 kcal mol^{-1} to deliver benzyl radical **Int3** and protonated/reduced decatungstate DTH. Severing as a strong reductant, DTH subsequently triggers a formal back hydrogen abstraction from the other side of **Int3** to afford the benzylic epimer **Int1$_a$**, thereby accomplishing the epimerization. Although the epimerization from **Int1$_s$** to **Int1$_a$** is thermodynamically unfavored (ΔG = 0.7 kcal mol^{-1}), the incorporation of DKR offers a good means for controlling the direction of C-H epimerization.

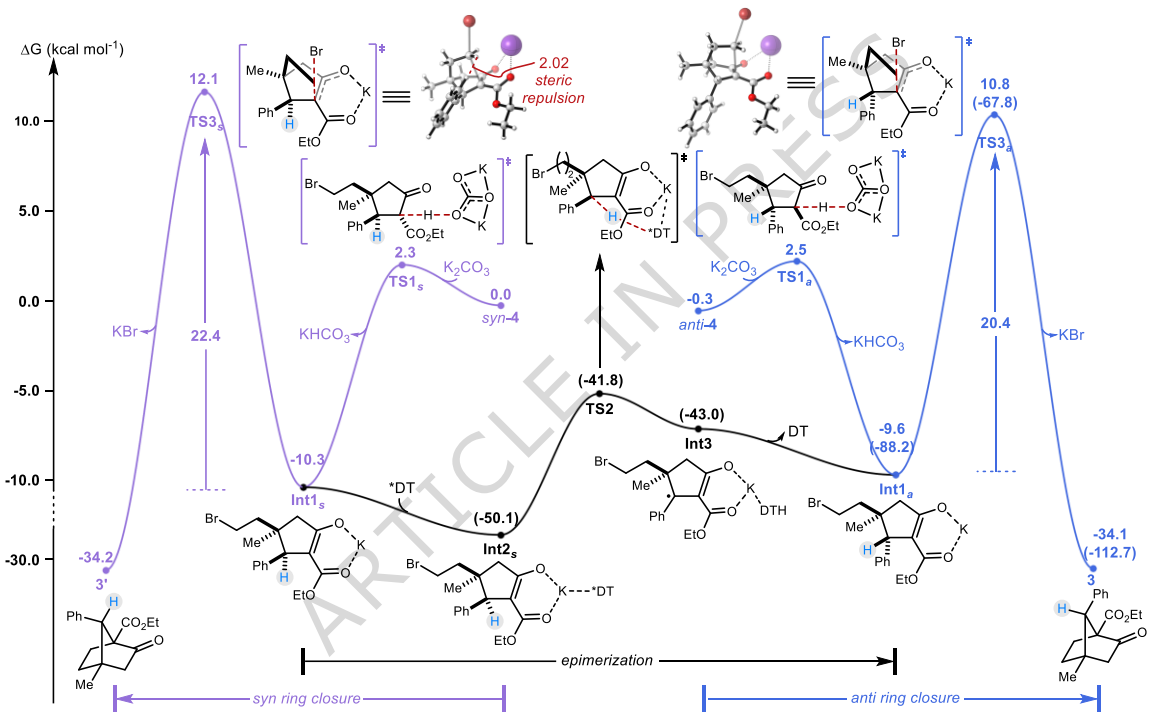

Fig. 5

Of note, the photocatalytic stereoselective bicyclization of ynones is operative (Fig. 6). Under the identical reaction conditions, ynones coupled smoothly with aryl or alkyl aldehydes to furnish a set of decorated bicyclo[2.2.1]heptanones **64**, **65**, **67-72** in promising yields with perfect control of diastereoselectivity (>20:1 dr). This extension clearly demonstrates the good applicability and robustness of this stereoselective 1D-to-3D protocol. Phenylacetaldehyde served as an ineffective substrate (**66**), due to the facile decomposition of benzoyl radical to a more stable but less reactive benzyl radical, which could be confirmed by the observation of its homo-coupling product, 1,2-diphenylethane (see page S36 in Supplementary Information).

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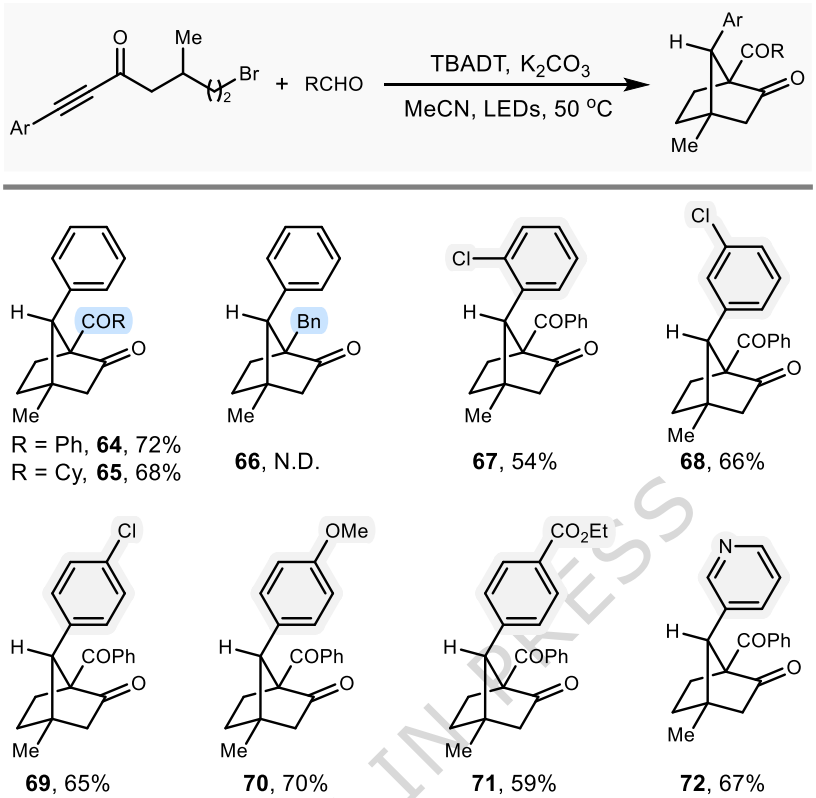

Fig. 6

Discussion

A photoinduced decatungstate-catalyzed controllable bicyclization of internal alkynes with aldehydes is developed. The reaction proceeds under mild conditions to produce a variety of polysubstituted bicyclo[2.2.1]heptanones and bicyclo[3.2.1]octanones in promising yields with excellent site-, regio-, and diastereoselectivity. Experimental and DFT studies reveal that the stereoselective bicyclization lies in an uncommon dynamic kinetic resolution enabled by HAT-mediated C-H epimerization. The versatility and robustness of this method in organic synthesis, pharmaceutical chemistry, and functional materials are well demonstrated by the concise syntheses of a hydrazide organocatalyst **57**, a C7-functionalized norbornene **58**, a fluorene **60**, and a more potent 5-HT_{1A} antagonist **62**. This stereoselective 1D-to-3D editing protocol exhibits remarkable potential for the dimensional expansion of ubiquitous alkynes, which holds significant promise for efficient utilization of bulk chemicals and can offer an unconventional disconnection strategy for assembling complex 3D molecules.

Methods

General procedure for the photocatalytic controllable bicyclization of internal alkynes with aldehydes

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To a mixture of aldehydes (0.4 mmol), TBADT (13 mg, 0.004 mmol) and K_2CO_3 (55 mg, 0.4 mmol) in 2 mL of MeCN was added internal alkynes (0.2 mmol) under a nitrogen atmosphere. After 20 h of irradiation with purple LEDs (100% intensity, Kessil PR160, 40 W, 390 nm, light irradiance at a distance of 3 cm: 76.41 mW cm^{-2}, and the light irradiance at the reaction site: 4.62 mW cm^{-2}) at 50 °C, the reaction mixture was quenched with water, extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The resulting residue was purified via column chromatography on silica gel to afford the desired product.

General procedure for the stereoselective bicyclization of ynones

To a mixture of ynone (0.2 mmol), TBADT (13 mg, 0.004 mmol), and K_2CO_3 (55 mg, 0.4 mmol) in 2 mL of MeCN was added aldehyde (0.4 mmol) under a nitrogen atmosphere. After 20 h of irradiation with purple LEDs (100% intensity, Kessil PR160, 40 W, 390 nm, light irradiance at a distance of 3 cm: 76.41 mW cm^{-2}, and the light irradiance at the reaction site: 4.62 mW cm^{-2}) at 50 °C, the reaction mixture was quenched with water, extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The resulting residue was purified via column chromatography on silica gel to afford the desired product.

General procedure for NanoBiT-based G-protein recruitment assay for 5-HT receptors

G-protein recruitment was analyzed using the NanoBiT system (Promega). HEK293T cells were transfected with plasmids encoding LgBiT-Gα ($G\alpha_i$ for 5-HT1AR or $G\alpha_q$ for 5-HT2AR), $G\beta_1$, SmBiT-$G\gamma_2$, and FLAG-tagged receptor constructs using polyethylenimine. After 24 h, cells were harvested, resuspended in assay buffer (HBSS containing 0.01% BSA and 5 mM HEPES, pH 7.4), and dispensed into 96-well plates. Following coelenterazine loading (10 μM final concentration) and 1 h incubation, baseline luminescence was measured. For antagonist assays, cells were pretreated with test compounds for 5 min before stimulation with 1 μM serotonin. For agonist assays, test compounds were added directly. Luminescence was recorded kinetically, and signals from 20-30 min were averaged, normalized to baseline and vehicle controls, and plotted as concentration-response curves. EC_{50} and span ("Top"–"Bottom") values were determined by four-parameter nonlinear regression using Prism 9 software (GraphPad Prism).

Data availability

Detailed experimental procedures and characterization of new compounds can be found in the Supplementary Information. Source data of cartesian coordinates of computed structures are provided with this paper. Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre as CCDC 2355780 (**31**). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Crystal data are also provided in Supplementary Information. Further relevant data are available from the authors upon request.

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Author contributions

G.Z. conceived the idea. Z.G. and T.Z. conducted the experiments. H.Z. performed the density functional computations. Z.Y., H.Z and G.Z. co-wrote the paper. All the authors discussed the results and commented on the manuscript.

Competing interests

The authors declare no competing interests.

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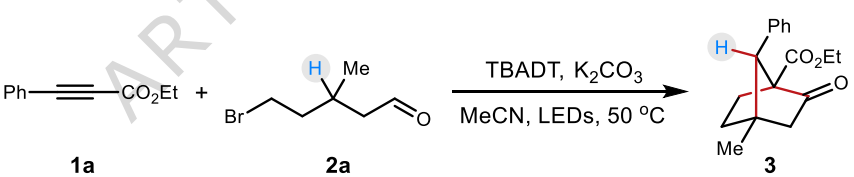
Table 1. Optimization of reaction conditions[a]



1a 2a 3

Entry	Deviations from standard conditions[a]	Yield (%)[b]
1	none	78 (72)[c]
2	MeCN/H_2O (10:1 v/v) instead of MeCN	70
3	acetone instead of MeCN	51
4	DMSO instead of MeCN	13
5	Cs_2CO_3 instead of K_2CO_3	66
6	K_3PO_4 instead of K_2CO_3	53
7	NaDT instead of TBADT	66
8	at 70 °C	78 (3:1 dr)
9	without K_2CO_3	51[d] (68)[e]
10	without TBADT	0

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11	without irradiation	0

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), K_2CO_3 (0.4 mmol), TBADT (2 mol %), MeCN, 50 °C, 40 W purple LEDs, 390 nm, 20 h. Unless otherwise noted, **3** was obtained with >20:1 dr. [b]Isolated yield. [c]Yield of 2.0 mmol scale. [d]Accompanied by forming *syn*-**4** in 38% yield with >20:1 dr. [e]Run for 60 h, coupled with forming *syn*-**4** in 18% yield with >20:1 dr. TBADT: tetra-*n*-butylammonium decatungstate; NaDT: sodium decatungstate; MeCN: acetonitrile; LEDs: light emitting diodes; DMSO: dimethyl sulfoxide. dr: diastereomeric ratio.

Fig. 1 Background and reaction design. a Traditional methods for the synthesis of bridged scaffolds. **b** Traditional stereochemical editing and our proposal for in-situ editing of skeleton and stereochemistry. **c** HAT-mediated controllable editing of 1D to 3D motifs. 1D: one-dimensional; 2D: two-dimensional; 3D: three-dimensional; IMDA: intermolecular Diels-Alder reaction; HAT: hydrogen atom transfer.

Fig. 2 Substrate Scope. Reaction conditions: internal alkyne (0.2 mmol), aldehyde (0.4 mmol), K_2CO_3 (0.4 mmol), TBADT (2 mol %), MeCN, 50 °C, 40 W purple LEDs, 390 nm, 20 h. [b]Ar = 4-*t*-BuC_6H_4. [c]36 h was used. [d]Accompanied by forming *syn*-**41** in 30% yield with >20:1 dr. Unless otherwise noted, bicyclo[2.2.1]heptanones or bicyclo[3.2.1]octanones were obtained with >20:1 dr, and no cyclopentanone by-products were isolated. All reported yields are isolated yields. TBS: *tert*-butyldimethylsilyl.

Fig. 3 Synthetic applications. a The synthesis of privileged structures from products obtained by this method. **b** The synthesis of a fluorene intermediate for electroluminescent materials. **c** Our attempts on improving the bioactivity of **WAY-100635**. All reported yields are isolated yields. LiHMDS: lithium hexamethyldisilazide; BPO: benzoyl peroxide.

Fig. 4 Mechanistic studies. a Attempt on synthesizing the cyclopentanone intermediates under standard conditions with the temperature reduced to 0 °C. **b** Dynamic interconversion of cyclopentanone *anti*-**4** and *syn*-**4**. The black and red lines depict the reaction profile of *anti*-**4** and *syn*-**4** under the given reaction conditions, respectively. ^{1}H NMR yields are given. **c** Investigations on the S_N2 cyclization of *anti*-**4** and *syn*-**4** (i-iii), and the inaccessible interconversion of **3** and **3'** (iv). **d** Proposed mechanism. Unless otherwise noted, all reported yields are isolated yields. DT: decatungstate; DT*: excited decatungstate; DTH: protonated/reduced decatungstate.

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Fig. 5 Computational studies. Calculated Gibbs free energy profile for the DKR resolution of **4** at the ωB97M-V/Def2-TZVP-SMD(MeCN)//PBEh-3c level of theory. Values in the parentheses refer to the Gibbs free energy with respect to *syn*-**4** and *DT.

Fig. 6 Substrate Scope for the Stereoselective Bicyclization of Ynones. Reaction conditions: ynones (0.2 mmol), aldehydes (0.4 mmol), K_2CO_3 (0.4 mmol), TBADT (2 mol %), MeCN, 50 ^oC, 40 W purple LEDs, 390 nm, 20 h. Unless otherwise noted, bicyclo[2.2.1]heptanones were obtained with >20:1 dr. All reported yields are isolated yields. N.D.: not detected.

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Three-dimensional molecules have drawn tremendous attention due to their pivotal roles in drug discovery as saturated bioisosteres of benzenoids. Here, the authors present a concise synthesis of bicyclo[2.2.1]heptanones and bicyclo[3.2.1]octanones via a photoinduced decatungstate-catalyzed bicyclization of internal alkynes with aldehydes.

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