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Migrating Group Strategy for Remote Functionalization of Seven-Membered Rings

Wenlai Han,[‡] Taehwan Hwang,[‡] Christina Lian, Simon Kolb, Mina Yamane, Vignesh Palani, and Alison E. Wendlandt*

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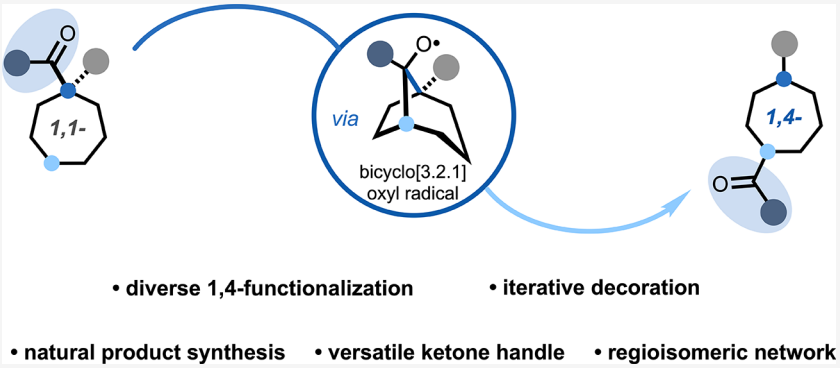

ABSTRACT: Seven-membered rings are essential structural components in bioactive compounds, yet their precise synthesis remains challenging compared to smaller ring systems. While traditional approaches rely on ring assembly strategies, direct functionalization of simpler cyclic precursors offers an attractive alternative to substituted building blocks. We report a photocatalytic transannular ketone migration strategy that converts 1,1-disubstituted acylcycloheptanes into 1,4-disubstituted products under mild conditions, promoted by sodium decatungstate and thiol cocatalysts under light-emitting diode (LED) irradiation. The process operates via reversible hydrogen atom abstraction and donation at multiple sites within the ring, followed by site-selective migration via radical addition and β-scission at the exocyclic carbonyl group. This dynamic kinetic approach to site-selective C−H functionalization provides regioselective access to densely substituted seven-membered rings, addressing a longstanding gap in synthetic methodology.

INTRODUCTION

Seven-membered rings are prevalent structural motifs in bioactive compounds and natural products (Figure 1A), yet the precise synthesis of even simple substituted seven-membered ring building blocks is challenging.[1−6] While robust ring assembly strategies (e.g., ring closing metathesis and pericyclic reactions) provide convergent access to small (3−4 membered) and normal-sized rings (5−6 membered), medium-sized rings (7−9 membered) face intrinsic enthalpic and entropic constraints that limit cyclization steps and/or necessitate elaborate precursor synthesis.[7−11] A complementary approach to ring assembly is through the precise installation of desired functionality onto simpler, progenitor rings. Peripheral functionalization reactions exhibit more nuanced reactivity differences across ring sizes, and in some cases even favor larger ring sizes possessing more relaxed conformational landscapes.[12,13] Nonetheless, current ring decoration approaches are similarly constrained by the limited availability of suitably prefunctionalized starting materials. The resulting disparity in synthetic accessibility across ring size is reflected in their relative abundance in commercial and proprietary compound libraries and in reaction methodology: compared with corresponding 6-membered rings, orders of magnitude fewer 7-membered rings have ever been synthesized (Figure 1A, right).

Direct C−H bond functionalization is a powerful strategy for increasing molecular complexity without the need for substrate preactivation (Figure 1B).[14,15] The ubiquitous presence and chemical similarity of C−H bonds in aliphatic frameworks presents significant site-selectivity challenges that have inspired innovative solutions, including state-of-the-art strategies leveraging intramolecular hydrogen atom transfer,[16,17] directing groups,[18] and transient auxiliaries,[19] as well as approaches

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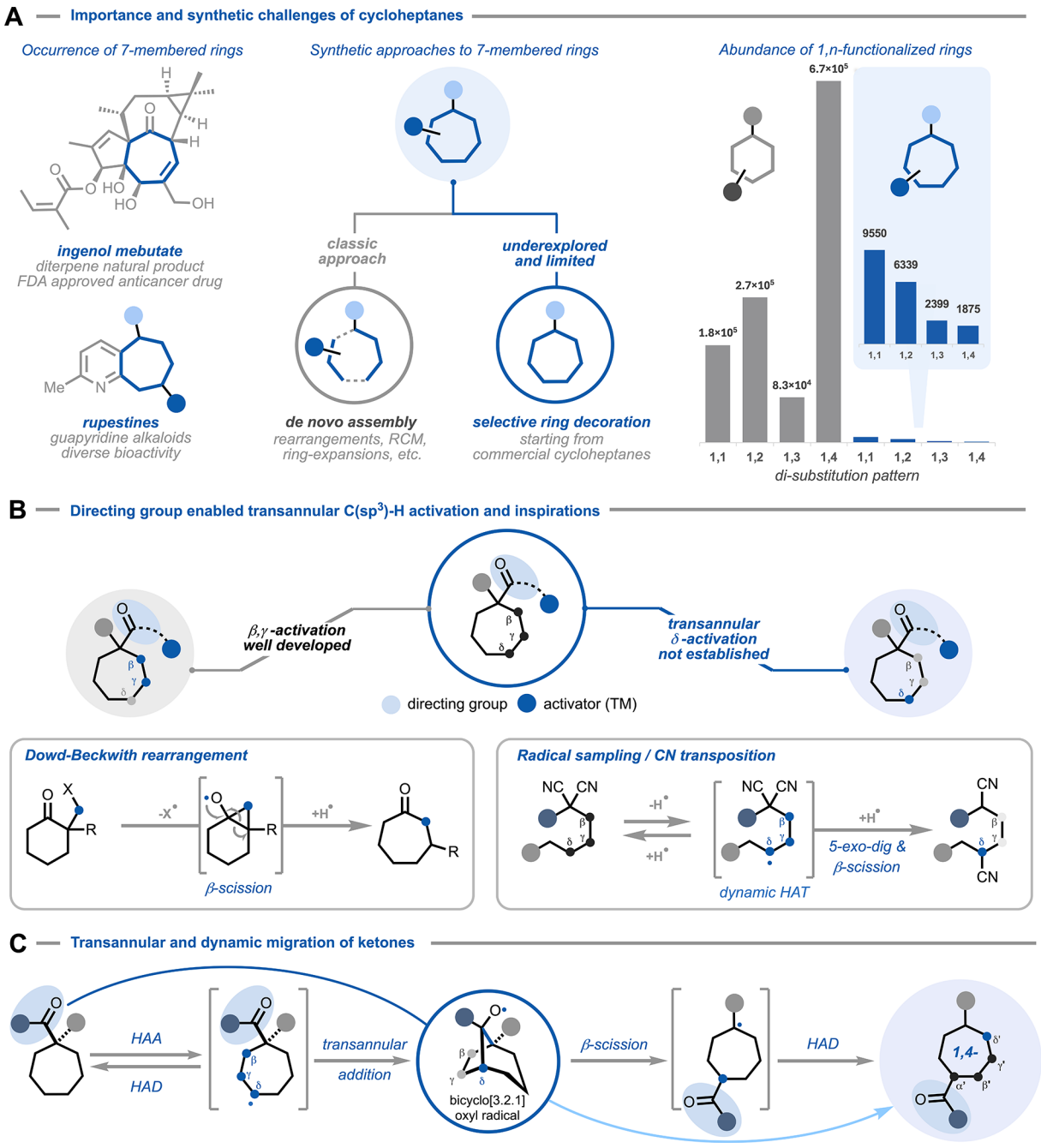

Figure 1. Synthesis of substituted cycloheptanes using a migrating group strategy. (A) Seven-membered rings are challenging to access due to limited methods for ring construction and peripheral modification. Relative abundance of known difunctionalized cyclohexanes and cycloheptanes shown as Reaxys search hits (see Supporting Information Section S1.4 for details); RCM, ring-closing metathesis. (B) State-of-the-art C−H activation methods enable efficient access to proximal sites, while remote positions remain largely inaccessible. Reaction design inspired by the Dowd-Beckwith rearrangement and radical sampling group migration methods; TM, transition metal; HAT, hydrogen atom transfer. (C) This work: a transannular ketone migration reaction to access substituted cycloheptanes; HAA, hydrogen atom abstraction; HAD, hydrogen atom donation.

that exploit inherent steric and electronic reactivity gradients within a substrate.[20,21] While current approaches enable access to positions proximal (α and β) to an existing directing group or recognition element in cyclic systems,[22] the selective transannular functionalization of remote (γ or δ) positions remains largely inaccessible.[23−25]

Here, we report a highly regioselective, remote C−H functionalization of 7-membered rings via transannular acyl group migration (Figure 1C). This "migrating group" strategy draws inspiration from the Dowd-Beckwith reaction,[26−29] wherein acyl group migration occurs under radical conditions via sequential 1,2-addition and β-scission steps,[30] as well as by recent work from Xu, who reported regioselective 1,4-migration of nitrile groups under radical sampling conditions.[31−33] While radical-mediated nitrile and (hetero)aryl migrations have been extensively explored,[34−39] the synthetic potential of ketone migration remains largely untapped, despite the unmatched versatility of the carbonyl functional group in

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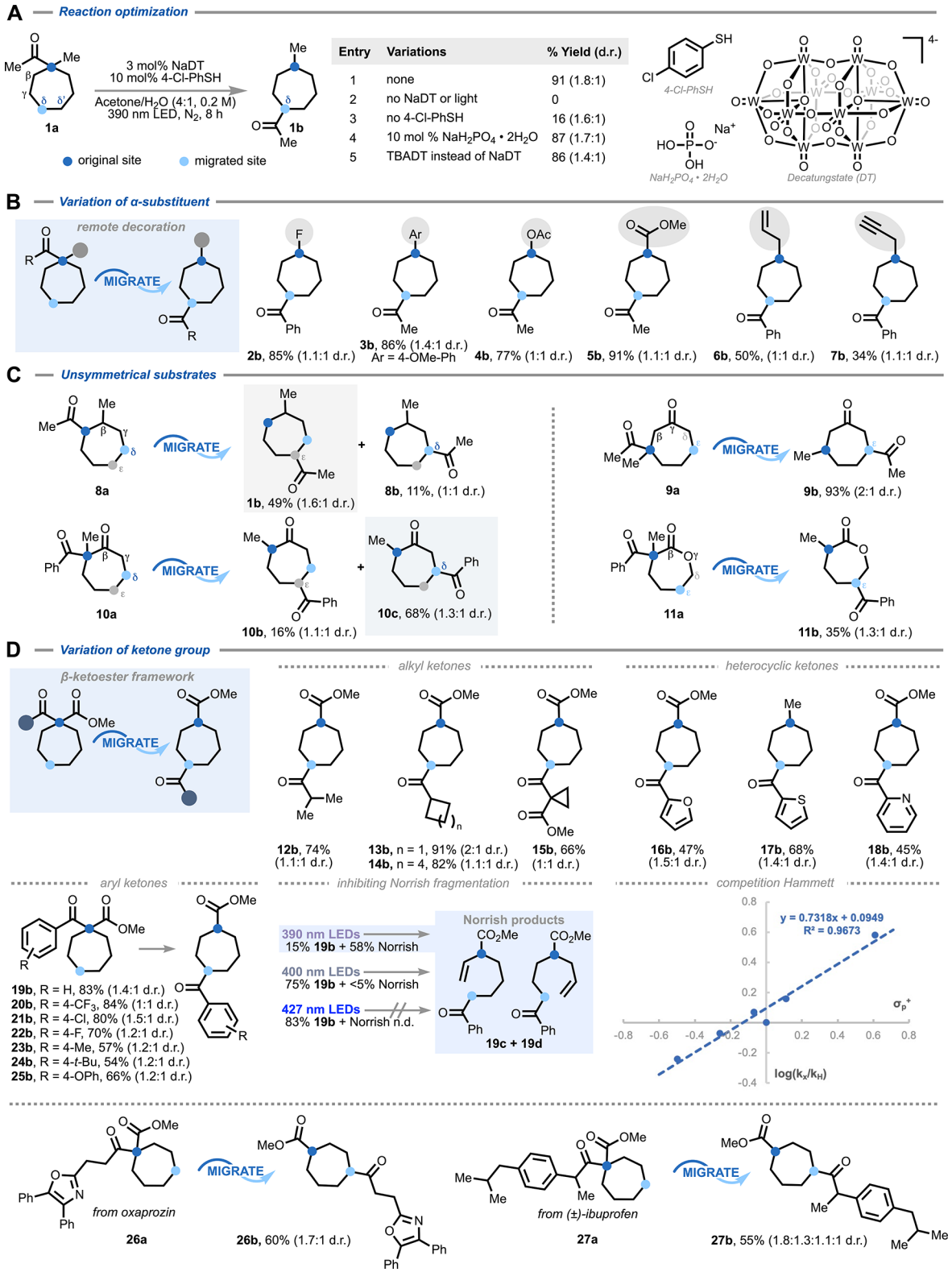

Figure 2. Reaction optimization and substrate scope. (A) Reaction optimization; d.r., diastereomeric ratio. (B) Formal δ-functionalization of cycloheptanes with diverse functional groups via ketone migration. Reactions were performed on 0.1−0.6 mmol scale with 3 mol % NaDT, 10 mol % 4-Cl-PhSH, and with or without 10 mol % $NaH_2PO_4 \bullet H_2O$ under 390 or 427 nm LED irradiation in acetone/H_2O (v/v 4:1, 0.2 M) or MeCN/H_2O (v/v 4:1, 0.2 M). Specific optimal reaction conditions vary across substrate: see Supporting Information Section S4 for details. Reported yields are quantitative proton nuclear magnetic resonance (^{1}H NMR) yields determined using nitrobenzene as an external standard. (C) Assessment of regioselectivity patterns using unsymmetrical substrates. (D) Scope of the migrating ketone group and mechanistic studies.

organic synthesis.[40−43] Building on these precedents, we envisioned that α-functionalization of an acyl-cycloheptane followed by transannular acyl group migration would provide efficient, selective access to 1,4-disubstituted rings, while

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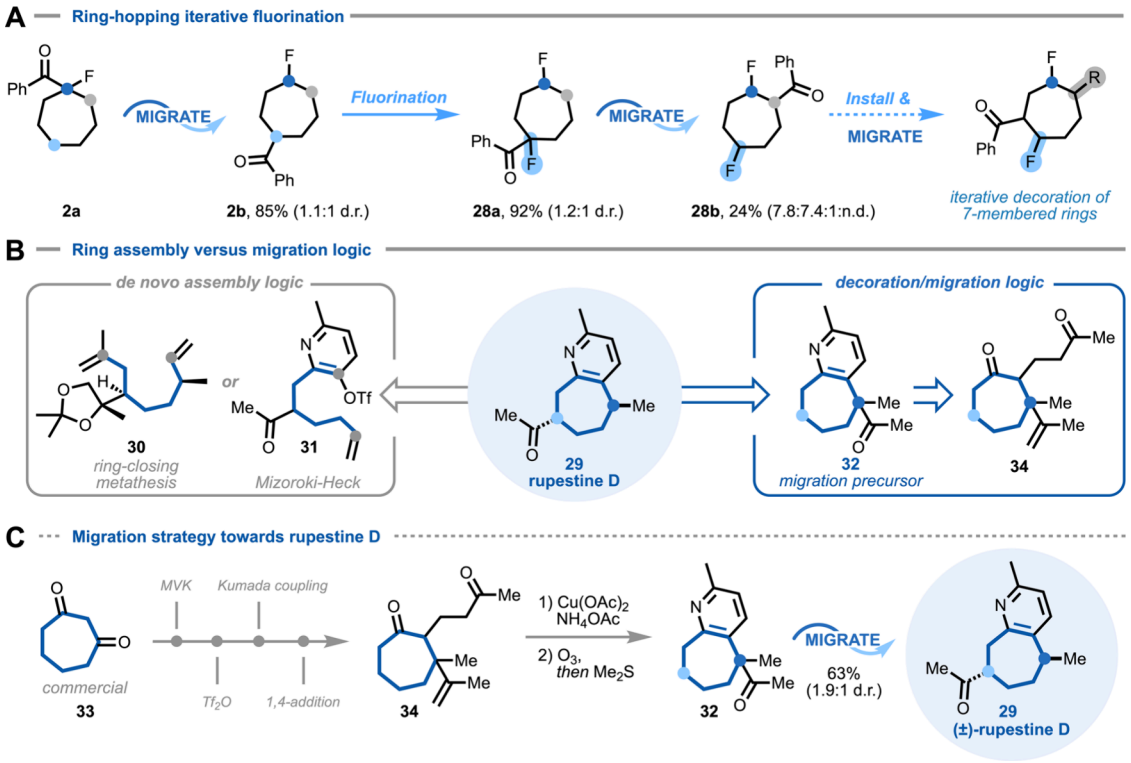

Figure 3. Application to iterative functionalization and complex multistep synthesis. (A) Iterative fluorination of a saturated cycloheptane scaffold by sequential α-functionalization and migration steps; *n.d.*, not detected. (B) Key intermediates enabling *de novo* assembly versus migration logic toward rupestine D. (C) Synthesis of rupestine D and 8-epi-rupestine D (1.9:1 d.r.); for an alternative route see Supporting Information Section S6.6. MVK, methyl vinyl ketone.

retaining the functional ketone handle for downstream manipulation.

RESULTS AND DISCUSSION

We selected 1-acyl-1-methylcycloheptane (**1a**) as a model substrate to assess the feasibility of transannular ketone migration. Under optimal reaction conditions employing 3 mol % sodium decatungstate (NaDT), and 10 mol % 4-chlorothiophenol, in acetone/H_2O under 390 nm LED irradiation, we observed the formation of 4-acetyl-1-methylcycloheptane (**1b**) in 91% yield (1.4:1 d.r.) (Figure 2A). While a range of thiol/disulfide additives proved to be effective, 4-chlorothiophenol (and 2,4,6-triisopropylbenzenethiol, TRIPSH) has consistently provided superior yields in DT-promoted radical sampling processes.[31−33] Minimal variation in diastereoselectivity was observed under any of the conditions tested, reflecting limited diastereofacial discrimination in the hydrogen atom donation (HAD) step (see Supporting Information, Section 3.4). In the absence of thiol, only modest product formation was observed; no reaction was observed in the absence of DT or light. While the addition of NaH_2PO_4•$2H_2O$ (10 mol %) did not influence the reaction of **1a** to **1b**, in some cases this additive was found to improve reaction yield and mass balance (see Supporting Information Section S3.6).

A range of acylcycloheptanes was evaluated as substrates for ketone group migration (Figure 2B). Starting from the corresponding 1,1-disubstituted isomers, acyl migration proceeded in the presence of diverse α-substitution to form 1,4-disubstituted isomers bearing fluoro (**2b**), aryl (**3b**), *O*-acetate (**4b**), methyl ester (**5b**), allyl (**6b**), and propargyl (**7b**) substituents with uniformly high (>15:1) regioselectivity. In the case of fluorinated cycloheptane **2b,** the *cis*- and *trans*-diastereomers could be readily separated by column chromatography, allowing for the unambiguous structural assignment of their hydrazone derivatives (**2e**$_{cis}$ and **2f**$_{trans}$) by X-ray crystallography (Figures S10 and S11).

Acyl migration is also feasible in the absence of α-substitution. For example, the reaction of 1-acyl-2-methylcycloheptane (**8a**) leads to a 4.5:1 mixture of regioisomers **1b** and **8b**, arising from migration to the desymmetrized ε and δ positions, respectively. That acyl migration arises from **8a** suggests that thermodynamic stabilization of the postmigration radical is not essential for acyl migration/β-scission to occur and implicates other factors as product-determining. To understand the basis for regioselectivity, we carried out a DFT analysis of the reaction trajectories leading to both δ and ε products. These studies reveal similar transition state energies leading to the formation of corresponding oxyl intermediates, but there is significant torsional strain in the β-scission transition structure leading to the formation of **8b** that is absent from that leading to **1b**. We hypothesized that the regioselectivity of migration might be improved by electronic deactivation of one of the two migration sites, and prepared substrate **9a** whose δ-methylene C−H bonds are polarity mismatched for efficient hydrogen atom abstraction (HAA) by DT.[44] Under standard reaction conditions, **9a** reacts to form **9b** as a single regioisomer (2:1 d.r.) in 93% yield. A mixture of regioisomers was also obtained using α,β-substituted substrate **10a**. However, in this case the δ-isomer **10c** is favored (4.2:1 r.r.) due to substantial strain-induced destabilization of the oxyl-formation step leading to minor isomer **10b** (see Supporting Information).[45,46] The corresponding lactone

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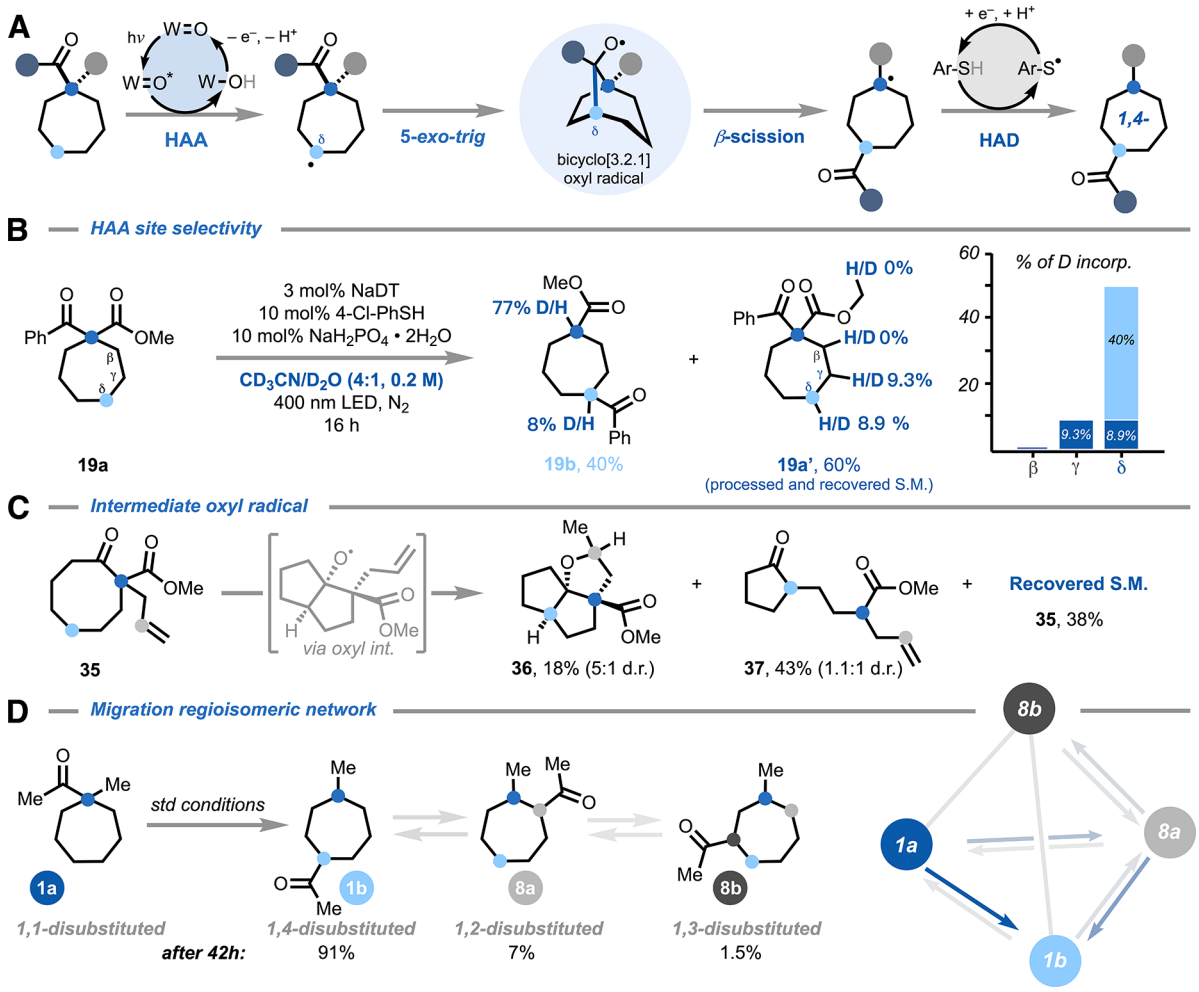

Figure 4. Mechanistic studies. (A) Proposed mechanism of transannular ketone migration. (B) H/D isotope exchange experiments designed to probe HAA site-selectivity; S.M., starting material. (C) Intramolecular substrate probe to intercept the proposed oxyl radical intermediate; int., intermediate. (D) Regioisomerization network under migration conditions; std, standard. See Supporting Information Section S7.5 for details of kinetic fitting.

substrate **11a** reacts selectively to form ε-isomer **11b**, albeit in modest yield.

To evaluate the scope of ketone migrating groups, we employed a β-ketoester scaffold enabling an install-and-migrate strategy (Figure 2D). This approach enables access to diverse 1,4-disubstituted products bearing aliphatic (**12b**–**15b**), heteroaromatic (**16b**–**18b**), and substituted aryl (**19b**–**25b**) ketones in synthetically useful yields. Electron-deficient aryl ketone substrates initially suffered diminished yields due to the competitive formation of ring fragmentation products (e.g., **19c** and **19d**) arising from Norrish fragmentation under 390 nm irradiation.[47,48] This pathway was significantly suppressed by employing longer-wavelength light sources (400 or 427 nm LEDs) or by using a long-pass filter to eliminate wavelengths below 400 nm during 390 nm LED irradiation. Efficient migration was observed across all aryl ketone substrates using 427 nm LED irradiation with no or minimal fragmentation observed.

Aryl ketone substrates (**19a**–**25a**) also provided an opportunity to interrogate the electronic sensitivity of the product-selective step. A linear correlation with a moderately positive slope (ρ = 0.7, R^2 = 0.95) was observed between σ^+ parameters and $\log(k_x/k_H)$ values in a competition Hammett experiment, where k_x/k_H was determined from conversion-corrected yield measurements.[49,50] This analysis implicates a product-selective radical addition step and is supported by natural bonding orbital (NBO) analysis of the unsubstituted phenylketone substrate **19a**: natural population analysis from the NBO studies reveal a systematic decrease in natural positive charge at the reactive carbonyl carbon atom during formation of the alkoxyl radical, and concomitant increase in positive charge through the β-scission step toward **19b** (Figure S42). The fractional ρ value compared to polar carbonyl addition reactions (e.g., $\rho > 3$) is consistent with a mechanism of radical addition that is formally neutral, but possesses partial polar character.[51]

Finally, we investigated more diverse migrating ketone groups, including those derived from pharmaceuticals oxaprozin **26a** and ibuprofen **27a**. In both cases, the corresponding migration products **26b** and **27b** were obtained in good yields and regioselectivities.

We next envisioned that an iterative functionalization and migration sequence could enable the construction of more densely functionalized 7-membered ring building blocks in a programmable way. To test this hypothesis, we selected 1-fluoro-1-acylcycloheptane (**2a**) which reacts to form 1-fluoro-4-acylcycloheptane (**2b**) in 85% yield (Figure 3A). We then carried out a selective α-fluorination of **2b** using *N*-

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fluorobenzenesulfonimide, to afford 1,1,4-trisubstituted cycloheptane **28a** in 92% yield. A second migration delivered the 1,2,5-substituted isomer **28b** in 24% yield.

We sought to explore the strategic implications of acyl migration in the context of multistep synthesis,[52] selecting rupestine D (**29**) as a potential target. This guaipyridine alkaloid natural product possesses a pyridine-fused 7-membered ring scaffold, and has previously been prepared via ring assembly strategies starting from linear precursors (Figure 3B, c.f. **30**, **31**).[53,54] We envisioned an alternative approach featuring late-stage acyl migration from a preassembled cycloheptane core (Figure 3B, right). Starting from commercial 1,3-cycloheptadione (**33**), intermediate **34** was obtained in four steps via α-alkylation, *O*-triflation, Kumada coupling, and 1,4-addition (see Supporting Information Section S6). Next, oxidative pyridine ring formation followed by ozonolysis afforded **32**, which reacted under migration conditions to deliver (±)-rupestine D (**29**) in 66% yield (1.9:1 d.r.), along with diastereomer (±)-8-epi-rupestine D (Figure 3C).

We next carried out a series of mechanistic experiments to gain insight into the underlying mechanism of acyl migration. A proposed pathway involving hydrogen atom abstraction, 5-*exo-trig* radical carbonyl addition to form an alkoxyl radical intermediate, followed by β-scission and H atom or proton/electron transfer is shown in Figure 4A. An H/D isotope exchange experiment was carried out using substrate **19a** under standard conditions in the presence of D_2O and sodium dihydrogen phosphate dihydrate. After 16 h, we analyzed the position and extent of deuterium incorporation at both the productive δ (8.9% per H/D + 40% migrated product) and nonproductive γ (9.3% per H/D) positions of both starting and product isomers (Figure 4B). Although these studies suggest that HAA site-selectivity favors the δ position (~5:1 δ/γ), the presence of deuterium in recovered starting material provides evidence for a recovery pathway for radical generation at nonproductive positions. Rapid and reversible HAA/HAD allows site-selectivity to arise under dynamic kinetic control and implicates a subsequent product-selective step (e.g., radical 1,2-addition) in governing site-selectivity.

Next, we sought to assess the feasibility of oxyl radical intermediate formation under the reaction conditions. DFT studies carried out using substrate **19a** predict low barrier radical addition and β-scission steps between nearly isoenergetic carbon and oxygen centered radical species (See Supporting Information, Figure S41). While efforts to intercept the relevant bridged oxyl were unsuccessful, a related substrate probe **35** was found to form ether product **36** in 18% yield, alongside cyclopentanone product **37** (43% yield) which arises from β-scission (Figure 4C). Though a nontrivial structural deviation from the target transformation, these findings implicate a discrete but short-lived oxyl radical intermediate, that undergoes β-scission at a rate competitive with 5-*exo-trig* cyclization (~10^8 s^{-1}).[55]

An earlier observation that migration can occur in the absence of an α-substituent (c.f. **8a**) led us to investigate whether iterative 1,4-migration to access 1,2- and 1,3-substituted products could occur at longer reaction times (Figure 4D). Careful analysis of a reaction of substrate **1a** after 42 h revealed the presence of 1,2-, 1,3- and 1,4-disubstituted regioisomers in 7.1%, 1.5% and 91% yields, respectively. We next carried out reaction timecourse studies starting from independently prepared **1a**, and its 1,2-, 1,3, and 1,4-disubstituted regioisomers, followed by whole reaction kinetic modeling to understand possible reaction pathways. Surprisingly, this data fit poorly to a strictly linear network topology involving sequential 1,4-migration events (Figure 4D, left). We thus evaluated other network topologies, derived from a fully connected tetrahedral network with each regioisomer occupying one vertex, where 1,2- and 1,3-regioisomers might also arise via direct migration through minor 3-*exo-trig* and 4-*exo-trig* pathways (see Supporting Information Section S7.5). The optimal regioisomerization network implicates direct 1,2-migration from **1a** to **8a**, in addition to sequential 1,4-migration proceeding through **1b** and **8a** (Figure 4D, right). DFT studies further support the feasibility of a *concerted* 1,2-migration step (see Supporting Information). Based on our prior studies on sugar cube diastereomeric networks, we postulate that targeted catalyst perturbation could selectively steer migration pathways in this system, to enable selective regioisomer synthesis through network control.[56]

CONCLUSIONS

We report a ketone group migration strategy that enables the remote C−H functionalization of 7-membered rings from readily accessed 1,1-disubstituted precursors. The method achieves site-selective C−H bond functionalization by coupling unselective, reversible radical generation with a product-selective 5-*exo-trig* radical carbonyl addition and β-scission steps. While dynamic kinetic resolution manifolds are common in stereoselective catalysis, this work is an uncommon application of this mechanistic manifold to achieve a site-selective process. This work adds another dimension to the emerging concept of network control in out-of-equilibrium steady state catalysis.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.5c10470.

Additional computed energies and coordinates (XLSX)

General methods, synthetic procedures, product isolation and characterization, computational details, and NMR spectra (PDF)

Accession Codes

Deposition Numbers 2446248−2446249 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge Crystallographic Data Centre (CCDC) and Fachinformationszentrum Karlsruhe Access Structures service.

AUTHOR INFORMATION

Corresponding Author

Alison E. Wendlandt − *Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States;* orcid.org/0000-0003-2970-9817; Email: awendlan@mit.edu

Authors

Wenlai Han − *Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States;* orcid.org/0000-0001-8648-2300

Taehwan Hwang − *Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States; Process Research and Development, Merck &*

Co., Inc., Rahway, New Jersey 07065, United States; orcid.org/0000-0002-8396-0255

Christina Lian − *Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States*

Simon Kolb − *Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States;* orcid.org/0000-0001-6352-4619

Mina Yamane − *Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States; Graduate School of Pharmaceutical Sciences, The University of Tokyo, Tokyo 113-0033, Japan;* orcid.org/0009-0005-8195-9946

Vignesh Palani − *Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States; Department of Organic Chemistry, Indian Institute of Science, Bangalore 560 012, India*

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.5c10470

Author Contributions

‡These authors contributed equally. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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