# Regioselective ketone α-alkylation with simple olefins via dual activation

Fanyang Mo and Guangbin Dong

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## SUPPLEMENTARY MATERIALS

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C–H BOND ACTIVATION

# Regioselective ketone α-alkylation with simple olefins via dual activation

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**Alkylation of carbonyl compounds is a commonly used carbon-carbon bond–forming reaction. However, the conventional enolate alkylation approach remains problematic due to lack of regioselectivity, risk of overalkylation, and the need for strongly basic conditions and expensive alkyl halide reagents. Here, we describe development of a ketone-alkylation strategy using simple olefins as the alkylating agents. This strategy employs a bifunctional catalyst comprising a secondary amine and a low-valent rhodium complex capable of activating ketones and olefins simultaneously. Both cyclic and acyclic ketones can be mono-α-alkylated with simple terminal olefins, such as ethylene, propylene, 1-hexene, and styrene, selectively at the less hindered site; a large number of functional groups are tolerated. The pH/redox neutral and byproduct-free nature of this dual-activation approach shows promise for large-scale syntheses.**

The α-alkylation of carbonyl compounds, an old but fundamental organic transformation, is still widely used in complex molecule syntheses (*1*). Conventionally, carbonyl alkylation involves generation of metal enolates followed by addition of an alkylating agent, often alkyl halides (Fig. 1A). Although effective, as documented in almost all organic chemistry textbooks, this enolate alkylation approach suffers from many drawbacks (*1*), including (i) the need for stoichiometric strong metallic bases (e.g., lithium diisopropylamide) and cryogenic conditions (to avoid homolytic couplings); (ii) the challenge in controlling regioselectivity for unsymmetrical ketones and curtailing overalkylation to di- or trisubstituted products ; (iii) the expense of alkyl halide reagents (*2*–*4*); and (iv) the formation of stoichiometric metal halides and conjugate acids of the bases as byproducts. On the other hand, the Stork enamine reaction (*5*, *6*) (Fig. 1B) affords monoalkylation with high regioselectivity at the less hindered α carbons under less basic conditions; however, use of reactive alkylating agents (alkyl halides or Michael acceptors) is still required due to the reduced nucleophilicity of enamines versus metal enolates.

We foresaw substantial advantages in the prospective use of simple unactivated olefins as alkylating agents (Fig. 1C). Adding the ketone α-C–H bond across a C–C double bond under neutral conditions would furnish no byproducts and tolerate a broad range of functionality. This approach would also have economic advantages because olefins are much cheaper and more readily available feedstock than the corresponding alkyl halides (Fig. 1D); in fact, most terminal alkyl halides are ultimately prepared from olefins (*4*, *7*).

Although adding α-C–H bonds of activated methylene compounds across olefins and alkynes has been established (*8*–*11*), there are fewer examples of direct coupling of simple ketones and unactivated olefins. The intramolecular ketone-olefin coupling, known as the Conia-ene reaction (*12*), requires high temperature (>250°C), giving moderate yields with limited functional-group tolerance; the catalytic version was first reported by Widenhoefer (*13*) using palladium and recently by Che (*14*) using gold. In contrast, intermolecular ketone-olefin couplings are rare and mainly involve addition of stoichiometric metal enolates or enamides across olefins (*8*, *15*, *16*). To our knowledge, base-catalyzed additions of metal enolates to styrene derivatives (likely facilitated by formation of delocalized charges) (*17*, *18*) and a Mn/Co-initiated oxidative radical process for nonaromatic olefins (*19*) are the only approaches reported to date. Recently, enamine radical cation-mediated couplings with olefins emerged as an attractive catalytic strategy for α-functionalization of carbonyl compounds, albeit requiring oxidative conditions (*20*, *21*). Therefore, a general activation mode for coupling of simple ketones and unactivated olefins remains to be developed. Here, we describe our development of a catalytic dual-activation strategy for addition of normal ketone α-C–H bonds across unactivated olefins, which allows for direct ketone alkylation by simple olefins under both pH- and redox-neutral conditions.

We targeted a bifunctional catalyst capable of activating the ketone α-C–H bonds and the olefin simultaneously, which would incorporate a secondary amine and a low-valent transition metal complex. Seminal work by Jun and coworkers showed that metal-organic cooperative catalysis enables activation of aldehyde *ipso*-C–H bonds through imine formation with a bifunctional primary amine, i.e., 2-amino-3-picoline (*22*). We hypothesized that, by using a secondary amine, the ketone α-C–H bonds would instead be activated by enamine formation. As depicted in Fig. 2, first, the catalyst would bind the ketone substrate to form an enamine (step a), which would consequently convert the ketone α $sp^3$ C–H bond into a $sp^2$ C–H bond, thus enhancing the reactivity toward oxidative addition by a low-valent transition metal (*23*, *24*). Meanwhile, if a proper directing group (DG) were linked to the amine domain, the DG could facilitate insertion of a low-valent transition metal (e.g., $Rh^I$) into the resulting enamine C–H bonds, giving

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metal hydride species (M–H, step b). Upon olefin coordination to the metal, subsequent M–H migratory insertion (step c) and reductive elimination (step d) would provide an alkylated enamine, which upon hydrolysis would lead to α-alkylation and catalyst regeneration (step e).

In the Stork enamine reaction (*5*, *6*), enamine formation is regioselective for the less-hindered site of ketones; thus, this bifunctional catalyst would be expected to provide high regiocontrol for monoalkylation of unsymmetrical ketones. Moreover, as documented in enamine catalysis (*25*), enamine formation and hydrolysis can exist in equilibrium, but the less-hindered ketone (starting material) preferentially forms enamine over the more-hindered ketone (product), and thus product inhibition can be avoided. In addition, enamine formation/hydrolysis is known to be compatible with the $Rh^{I}$ to $Rh^{III}$ catalytic cycle (*26*). Therefore, both the amine and the metal components can be employed catalytically. [For our preliminary study of alkylation with 1,2-cyclic diketones using stoichiometric aminopyridine as the cofactor, see (*27*).]

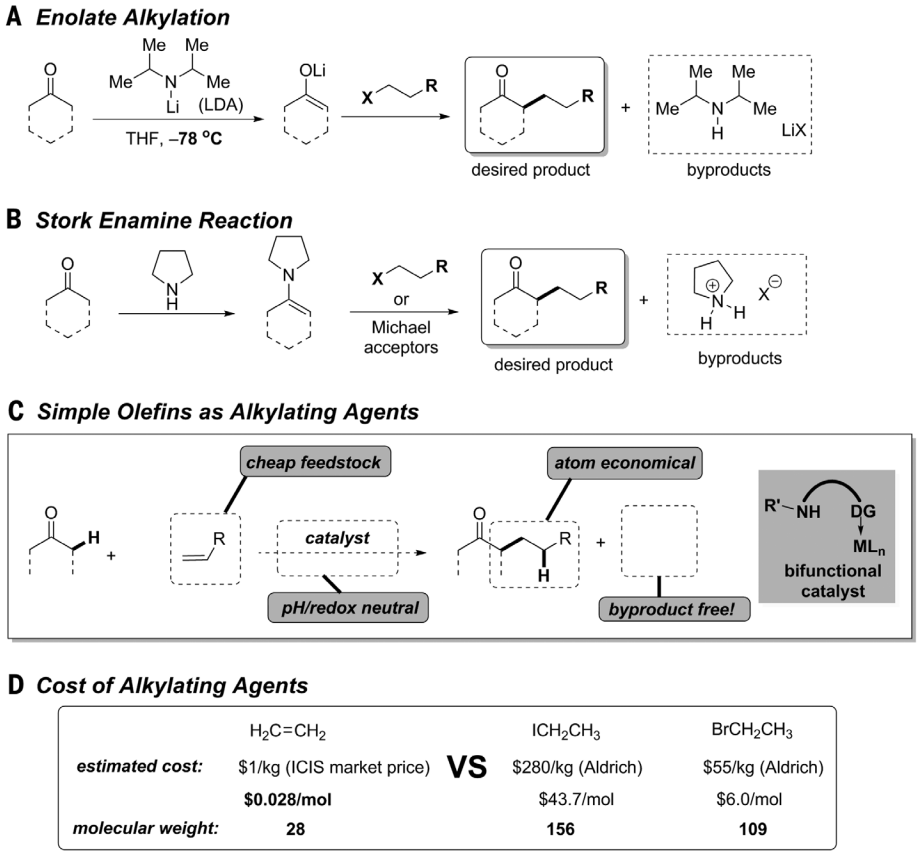


**Fig. 1. Different approaches to ketone alkylation.** (**A**) Enolate alkylation. (**B**) Stock enamine reaction. (**C**) Simple olefins as alkylating agents. (**D**) Cost of alkylating agents.

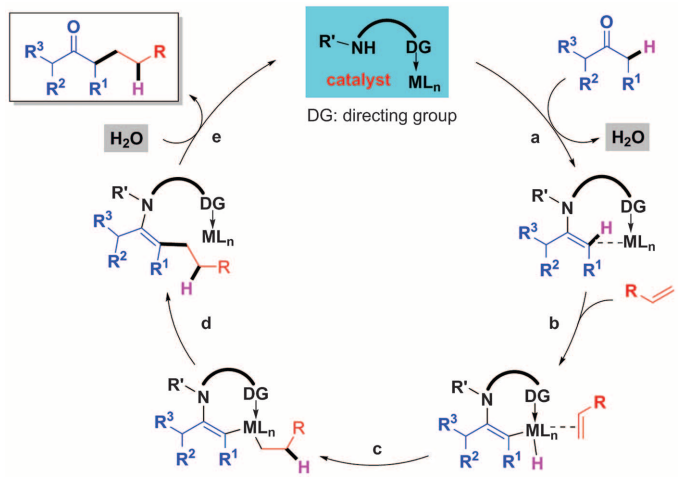


**Fig. 2. Design of a bifunctional catalyst and proposed catalytic cycle.** (a) Enamine formation; (b) Oxidative addition of enamine C–H bond; (c) Migratory insertion into olefins; (d) Reductive elimination to form C–C bond; (e) Enamine hydrolysis.

To examine the feasibility of the proposed strategy, we tested 3-phenylcyclopentanone (**1a**) and ethylene (**2a**) as model substrates. A variety of rhodium precatalysts/dative ligands, bifunctional ligands, solvents, additives, and pressure of ethylene were examined (see table S1). Given the crucial role of the bifunctional ligands in the proposed catalytic cycle, seven secondary amine compounds (**L1** to **L7** in table S1) containing an adjacent DG were designed and explored under the ethylation conditions. To our delight, 7-azaindoline (**L1**) exhibited unique and high catalytic activities, whereas others were inactive. In the presence of 2.5 mole percent (mol %) chlorobis(cyclooctene) rhodium(I) dimer {$[Rh(coe)_2Cl]_2$}, 5 mol % 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene (IMes) ligand, 10 mol % *p*-toluenesulfonic acid monohydrate ($TsOH{\cdot}H_2O$), and 25 mol % **L1** in toluene, the desired ethyl-substituted product **3a** was isolated in 82% yield using ethylene gas as the alkylating agent (table S1, entry 4). Subsequently, the role of each reactant was investigated through a series of control experiments. The absence of the $Rh^{I}$ complex or bifunctional ligand **L1** completely eliminates the reactivity (table S1, entries 5 and 6), supporting our hypothesis that enamine formation and low-valent metal are key for the C–H/olefin coupling reaction. To promote enamine formation, 10 mol % $TsOH{\cdot}H_2O$ was purposely employed as an acid catalyst; indeed, without this additive, no desired alkylation product was observed (table S1, entry 7). The bulky electron-rich N-heterocyclic carbene (NHC) ligand (IMes) was used to promote oxidative addition of enamine C–H bonds to Rh and subsequent olefin insertion (*28*). Considerably diminished yields were found in the absence of this ligand or using Wilkinson's catalyst instead (table S1, entries 8 and 20). The reaction exhibited complete regioselectivity for the less-hindered 5 position of cyclopentanone; neither alkylation at the 2 position nor multiple alkylations was observed for ketone **1a**. Moreover, while the reaction requires 2 days at toluene reflux temperature when 2.5 mol % $[Rh(coe)_2Cl]_2$, 5 mol % IMes, and 25 mol % **L1** were employed, increasing the catalyst loading can result in a full conversion within 12 to 24 hours (table S1, entries 1 and 2).

With the optimized conditions in hand, we examined the substrate scope. A wide range of different functional groups were tolerated under the alkylation conditions (Fig. 3A). Ethers, aryl bromides, carboxylic esters, methylenedioxys, nitriles, and thioethers proved compatible (**3b** to **3h**). Substrates containing competitive alkylation sites, such as secondary amides (**3i**), malonates (**3j**) and aliphatic esters (**3k** and **3t**), gave chemo- and regioselective ethylation exclusively at the ketone C5 position. Furthermore, reactive functional

groups, including free tertiary and primary alcohols (**3l** and **3m**), free phenols (**3n**), unprotected indoles (**3o**), and amines (**3p**), survived, giving moderate to high yields of ketone-alkylation products. Acid-sensitive substrates, such as those containing a *tert*-butyldimethyl silyl (TBS) ether (**3q**), a tertiary alcohol (**3l**), and a trimethylsilyl (TMS) group (**3ad** in Fig. 3C), were also suitable for this transformation. Furthermore, enolizable preexisting stereocenters were preserved during the reaction (**3t**) because no strong base was involved. Thus, this method provides complementary compatibility to the conventional enolate alkylation chemistry.

On a 2-mmol scale (2.0 M), the reaction of ketone **1a** provided full conversion and 96% isolated yield with a lower catalyst loading (versus the 0.2-mmol scale). In addition, using 10 mmol (0.98 g) 3-methylcyclopentanone as the starting material, we obtained the desired ethylation product (**3s**) in nearly quantitative yield [determined by $^1$H nuclear

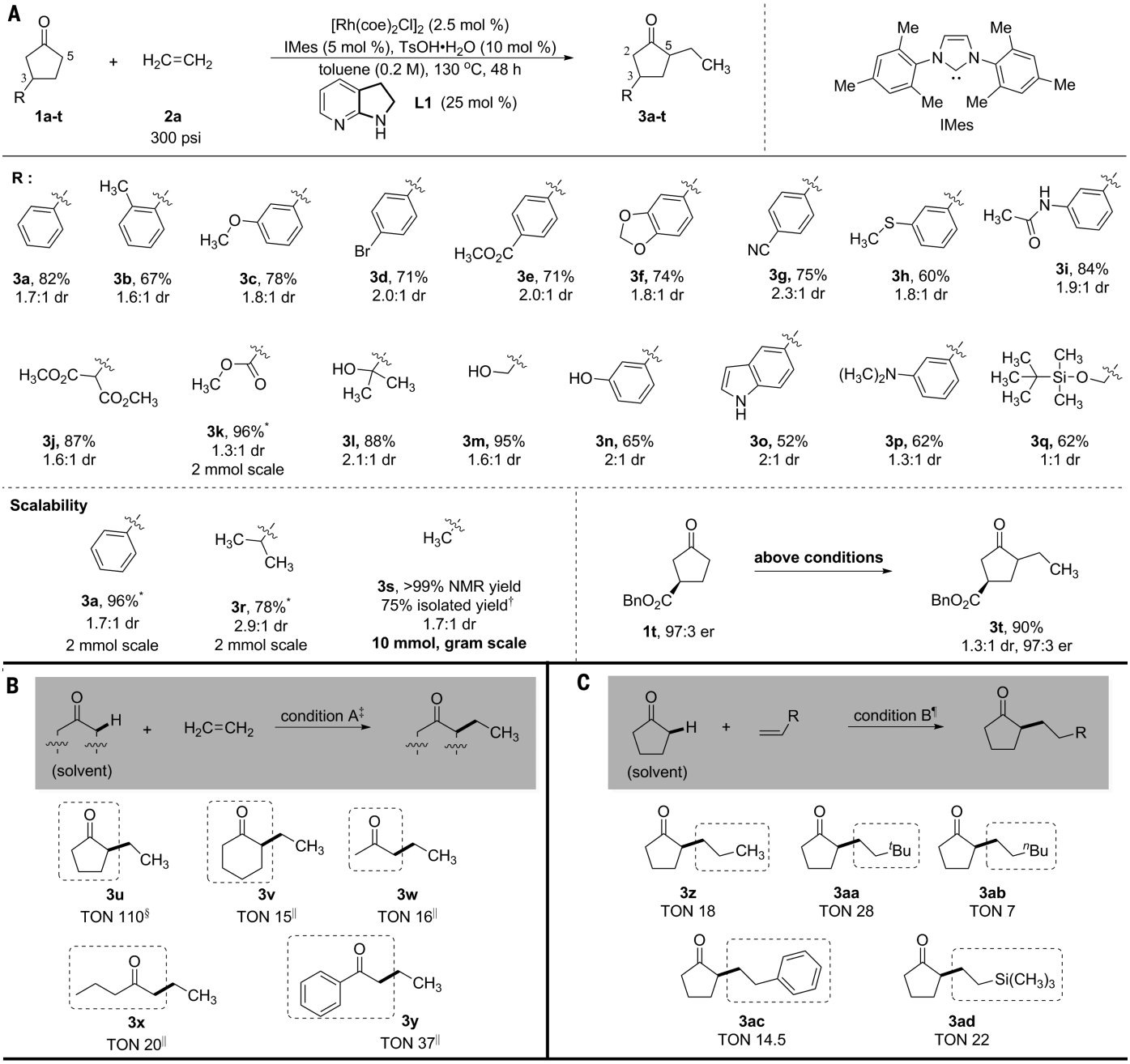


**Fig. 3. Regioselective ketone $\alpha$-alkylation with simple olefins.** (**A**) Ethylation of various cyclopentanones. Unless otherwise mentioned, the reactions were run on a 0.2-mmol scale; the data are reported as percent isolated yield. Diastereomeric ratio (dr) was determined by $^1$H NMR. *$[Rh(coe)_2Cl]_2$ (1 mol %), IMes (2 mol %), $TsOH{\cdot}H_2O$ (5 mol %), toluene 1 mL (2.0 M). †$[Rh(coe)_2Cl]_2$ (0.5 mol %), IMes (1 mol %), $TsOH{\cdot}H_2O$ (2 mol %), **L1** (15 mol %), toluene 3.0 mL (3.3 M). (**B**) Ethylation of various ketones. ‡Condition A: ketone 1 mL, ethylene 300 pounds per square inch, **L1** (0.2 mmol), $[Rh(coe)_2Cl]_2$ (0.005 mmol), IMes (0.01 mmol), $TsOH{\cdot}H_2O$ (0.02 mmol), 2,4,4-trimethylpentan-2-amine (0.1 mmol), neat, 130°C, 48 hours. The TON are based on [Rh] monomer, which are determined by GC with dodecane as an internal standard. §No 2,4,4-trimethylpentan-2-amine, but with $H_2O$ (10 μL); 2,5-diethyl-cyclopentanones were also obtained (TON 29). ||180°C. (**C**) Alkylation of cyclopentanone with various olefins. ¶Condition B: cyclopentanone (0.5 mL), olefin (0.5 mL, propene ~1 mL), **L1** (0.2 mmol), $[Rh(coe)_2Cl]_2$ (0.005 mmol), IMes (0.01 mmol), $TsOH{\cdot}H_2O$ (0.02 mmol), 2,4,4-trimethylpentan-2-amine (0.1 mmol), $H_2O$ (10 μL), neat, 130°C, 48 hours. The TON are based on [Rh] monomer, which are determined by GC with dodecane as an internal standard.

magnetic resonance (NMR)] with only 0.5 mol % of the Rh-dimer catalyst and 15 mol % of L1 (75% isolated yield due to the volatility of **3s**). This reaction can tolerate a range of concentrations (from 0.2 M to 3.3 M), which can be critical for large-scale applications. Structures of the products were unambiguously characterized by $^{1}H/^{13}C$ NMR, infrared (IR), and high-resolution mass spectrometry (HRMS); x-ray structures of several hydrazone derivatives were also obtained. For all substrates, the products were obtained as a pair of diastereoisomers with the cis-isomer predominating. It is likely that in the last step (enamine hydrolysis), the proton preferentially attacks the less-hindered face of the enamine, resulting in cis disposition of the two substituents. The diastereomeric ratio (dr) of the alkylation product can be enhanced by conversion to the corresponding silyl enol ether followed by treatment with a chiral Lewis acid (supplementary materials).

We next explored the scope of ketones and olefins for this transformation. Both cyclic and acyclic ketones could be directly coupled with ethylene gas to afford the ethyl-substituted ketones (Fig. 3B). In general, cyclopentanones were more reactive than cyclohexanones and acyclic ketones, consistent with the established tendencies toward enamine formation (*29*). By further investigating the reaction conditions, we discovered that a catalytic amount of an additional amine, such as triethylamine, 1,4-diazabicyclo[2.2.2]octane (DABCO), or 2,4,4-trimethylpentan-2-amine, could increase the efficiency of the ketone α-alkylation. Although the exact reason remains unclear, with the help of the amine additive, simple aliphatic ketones, such as acetone and 2-pentanone, coupled with ethylene to afford the desired monoalkylation products. It is well established that aromatic ketones, such as acetophenone, can undergo metal-catalyzed C–H/olefin couplings through activation of the *ortho* aromatic C–H bond, initially reported by Murai and co-workers (*30*). In contrast, our strategy completely switched the chemoselectivity from the normal aromatic C–H bond to the ketone α-C–H bond, providing homologated ketone **3y**.

Using cyclopentanone as the ketone substrate, different classes of terminal olefins were also explored. All these α-olefins provided the desired monoalkylation products with complete regioselectivity for the anti-Markovnikov addition products. Sterically hindered and less-hindered, isomerizable and non-isomerizable, aliphatic and aromatic olefins all reacted, suggesting a broad scope of this methodology. Through this investigation, dialkylation was only observed when coupling the unsubstituted cyclopentanone (**1u**) with ethylene (Fig. 3B); however, we discovered that simply adding water to the reaction enhanced the selectivity for monoalkylation (supplementary materials). For examples exhibited in Fig. 3, B and C, the ketones were employed as the solvents for optimal performance, and the turnover numbers (TON) based on the Rh monomer were used to measure the efficiency of these reactions. Given the volatility of these alkylation products, their accurate yields were determined by gas chromatography (GC) or $^{1}H$ NMR analysis; a portion of the pure products could be isolated via silica gel chromatography and fully characterized (supplementary materials), although compounds **3w** and **3x** were identified by comparison of their crude $^{1}H$ NMR, GC, and GC–mass spectrometry data with authentic samples.

To gain more mechanistic insight into this bifunctional catalyst-mediated ketone/olefin coupling, we conducted several additional experiments (Fig. 4). First, we isolated a key Rh-enamine complex (**4**) from enamine **5** and $[Rh(coe)_2Cl]_2$ (Fig. 4A). The x-ray structure of **4** shows that the azaindoline plane is twisted 62.5° (compared with the x-ray structure of free enamine **5**) to allow chelation of the metal with the pyridine and the olefin, suggesting a preactivated conformation for the subsequent C–H insertion (see step a in Fig. 2). Second, attempts to capture the metal-hydride intermediate incorporating an IMes ligand were unfruitful; however, we successfully isolated and obtained the x-ray structure of Rh–H complex **6** with $PMe_3$ as the dative ligand (Fig. 4B). Although complex **6** did not react with ethylene, it demonstrated the feasibility of insertion of a low-valent transition metal into enamine vinyl C–H bonds by oxidative addition (see step b in Fig. 2). Third, two deuterium-labeling experiments (Fig. 4C) were carried out to examine the proposed metal-hydride migratory insertion and reductive elimination steps (see steps c and d in Fig. 2). Following the proposed sequence, an α hydrogen of the ketone substrate should be transferred to the terminal position of the ethyl substituent of the alkylation product. Indeed, when the α and α′-deuterated (at the 93% D level) 3-methylcyclopentanone (**1s′**) was subjected to the standard reaction conditions, more than 82% deuterium incorporation was observed at the C2 position of the ethyl group. In addition, a stable conjugated enamine (**8**) could be isolated in good yield through coupling cyclopentanone (**1u′** α and α′-92% deuterated), amine **L1**, and diphenylacetylene. Similarly, significant deuterium incorporation (68%) was observed at the vinyl hydrogen of compound **8**. X-ray diffraction analysis confirmed the E olefin geometry, further supporting a syn-migratory insertion pathway (see step c in Fig. 2). The erosion in deuterium incorporation for both labeling experiments is likely caused by proton exchange with the NH hydrogen of **L1** and/or the protons of $TsOH{\cdot}H_2O$ (for more details, see the supplementary materials, section 3.6). Altogether, these results are consistent with our proposed mechanism in Fig. 2.

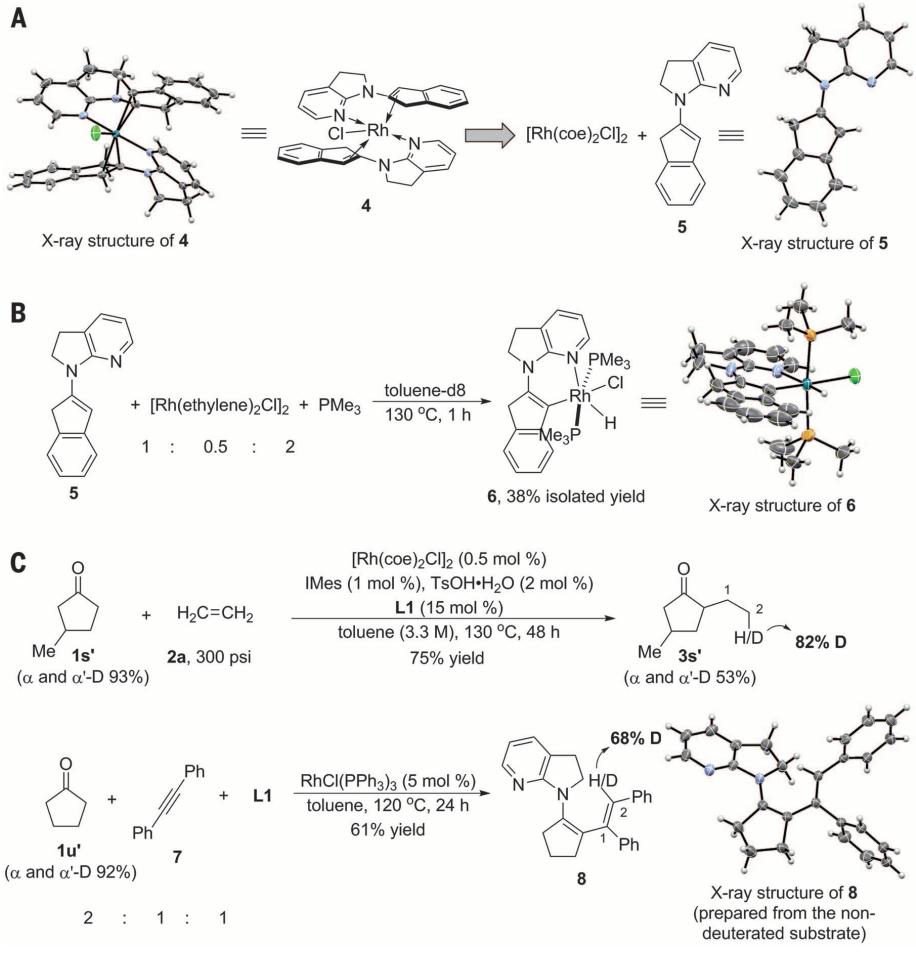


**Fig. 4. Preliminary mechanistic studies.** (**A**) Structure of the enamine-Rh complex. (**B**) Synthesis of a Rh–H complex. (**C**) Deuterium-labeling experiments.

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## SUPPLEMENTARY MATERIALS

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Materials and Methods
Supplementary Text
Table S1
References (*31*–*58*)

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SEPARATION MEMBRANES

# Interfacial microfluidic processing of metal-organic framework hollow fiber membranes

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**Molecular sieving metal-organic framework (MOF) membranes have great potential for energy-efficient chemical separations, but a major hurdle is the lack of a scalable and inexpensive membrane fabrication mechanism. We describe a route for processing MOF membranes in polymeric hollow fibers, combining a two-solvent interfacial approach for positional control over membrane formation (at inner and outer surfaces, or in the bulk, of the fibers), a microfluidic approach to replenishment or recycling of reactants, and an in situ module for membrane fabrication and permeation. We fabricated continuous molecular sieving ZIF-8 membranes in single and multiple poly(amide-imide) hollow fibers, with $H_2/C_3H_8$ and $C_3H_6/C_3H_8$ separation factors as high as 370 and 12, respectively. We also demonstrate positional control of the ZIF-8 films and characterize the contributions of membrane defects and lumen bypass.**

Molecular sieving membranes have created interest as high-performance separation systems for production of petro-based and renewable fuels and chemicals. Compared to thermodynamically driven separation methods such as distillation, membrane-based processes can substantially reduce the energy and capital costs of separating molecules on a large scale. Membranes composed of molecular sieving materials such as zeolites (*1*), layered zeolites (*2*), or metal-organic frameworks (MOFs) (*3*) have intrinsic advantages over polymeric membranes, such as a simultaneously high permeability and selectivity. Despite their performance limitations, polymeric membranes have continued to dominate industrial membrane separations owing to their relative ease of processing into morphologies such as hollow fibers (*4*). One challenge facing molecular sieving membranes is the lack of an easily scalable, reliable, and benign fabrication process (*5*–*7*). Zeolite membranes are further hampered by the need for hydrothermal synthesis on high-cost support materials. MOFs consist of metal centers connected by coordination bonds to organic linker molecules. They have been used to grow crystalline membranes on disk and tubular substrates through techniques similar to those developed for zeolitic membranes (*8*). The zeolitic imidazolite framework (ZIF) subclass of MOFs is of particular interest for membrane fabrication because of its tunable pore size and chemistry (*9*) and relatively good thermal and chemical stability (*10*, *11*). In an early demonstration of scalable ZIF membrane processing (*12*), we synthesized ZIF-90 membranes by seeded growth on the outer surfaces of porous polymeric poly(amide-imide) (Torlon) hollow fibers of ~250-μm outer diameter by immersion in a methanolic precursor solution at mild conditions (65°C). Free-standing MOF films can also be synthesized at the interfaces between two immiscible solvents (*13*). However, molecular sieving membranes on the inner surfaces of hollow fibers also have advantages for rapid, scalable fabrication due to the ability to be bundled in close proximity while avoiding membrane-membrane contact points and interfaces that lead to defects during synthesis. Synthesis of selective membranes in microscopic confined spaces faces a number of challenges: reactant availability and transport, positional control of the membrane, and scalability. As the bore size (and hence volume) is decreased to microscopic dimensions, film formation becomes limited by reactant availability and local inhomogeneities (*14*).

We report a methodology for fabricating molecular sieving MOF membranes (specifically, ZIF-8), which we refer to as interfacial microfluidic membrane processing (IMMP) (Fig. 1). IMMP thus combines three key concepts: (i) in situ ZIF-8 film synthesis in the membrane module (Fig. 1A); (ii) a two-solvent interfacial approach (Fig. 1, B and C) that can be tuned to achieve positional control over membrane formation (at inner and outer surfaces, as well as inside the bulk, of the porous fiber); and (iii) the controlled supply, replenishment, and recycling of reactants at microfluidic conditions in the hollow fiber bore. Our approach can be applied more generally to other MOF materials, but we demonstrate our key findings here with the example of ZIF-8, which has been identified as a promising candidate for important separations such as $H_2$ from hydrocarbons and propylene from propane (*3*, *15*). To study the IMMP concept, we designed and fabricated a reusable flow module that serves as

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