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Synthesis of α-Alkylated Ketones via Selective Epoxide Opening/Alkylation Reactions with Primary Alcohols

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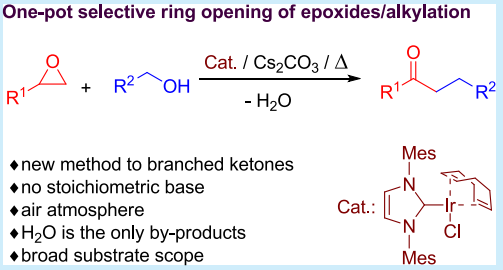
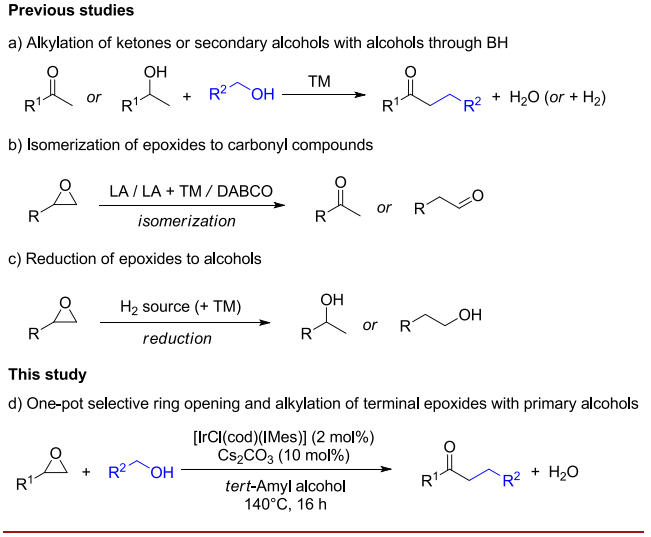
ABSTRACT: A new method for converting terminal epoxides and primary alcohols into α-alkylated ketones under borrowing hydrogen conditions is reported. The procedure involves a one-pot epoxide ring opening and alkylation via primary alcohols in the presence of an N-heterocyclic carbene iridium(I) catalyst, under aerobic conditions, with water as the side product.



Ketones are versatile key intermediates that are widely used in the organic synthesis of valuable pharmaceutical compounds, polymers, and natural products.[1] Of the numerous protocols for synthesizing α- or β-alkylated ketones, the transition-metal (TM)-catalyzed alkylation of ketones or secondary alcohols with alcohols through a borrowing hydrogen (BH) methodology has recently attracted a great deal of interest over conventional alkylation methods.[2] The use of readily available and inexpensive alcohols as both alkylating agents and hydrogen sources in the BH strategy offers a greener and more sustainable alternative to conventional alkylating methods, avoiding the use of mutagenic alkyl halides or excessive amounts of a strong base.[2] In this context, alkylation of ketones or secondary alcohols with alcohols for the synthesis of α- or β-alkylated ketones using various precious (Ru, Rh, Pd, and Ir)[3−6] and nonprecious (Ti, Mn, Fe, Co, Ni, and Cu)[7−12] TM catalysts has been reported (Scheme 1a).

Epoxides are useful intermediates that can be transformed into various valuable organic molecules through ring opening reactions.[13] One of the well-known epoxide ring opening reactions is their acid-catalyzed isomerization into aldehydes and/or ketones, usually termed the Meinwald rearrangement (Scheme 1b).[14] In the case of terminal epoxides, corresponding aldehydes are formed as the major product.[13e,14b,15] Inverse selectivity from the nucleophilic ring opening of terminal epoxides into the corresponding methyl ketones has also been reported in the presence of TM catalysts, Lewis acidic (LA) metal catalysts, or the nucleophilic organic base DABCO.[16] Another important approach to the transformation of epoxides is reductive ring opening reactions to produce industrially valuable primary and/or secondary alcohols (Scheme 1c).[13a−d] The major challenge in this transformation is the control of regioselectivity into anti-Markovnikov selective primary alcohols or Markovnikov selective secondary alcohols. Traditional methods for reductive ring opening of epoxides in the presence of either a stoichiometric amount or an excess of strong reducing reagents (MBH_4, where M = Li, Na, or K) result in the selective formation of secondary alcohols.[17] Heterogeneous Pd[18] and Pt[19] catalysts were also studied for hydrogenation or transfer hydrogenation of epoxides, where

Scheme 1. Catalytic Methods for the Synthesis of α-Alkylated Ketones and Selective Ring Opening of Epoxides



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primary alcohols are the major product from aryl epoxides and secondary alcohols are the major product from alkyl epoxides. Recently, homogeneous catalysis-enabled hydrogenation,[20] hydrosilylation,[21] and hydroborylation[22] of epoxides have been reported for the selective formation of primary alcohols. In contrast, Markovnikov selective secondary alcohols were obtained by Ru-catalyzed hydrogenation[23] and Mg-catalyzed hydroboration[24] of terminal epoxides.

Recently, the superior catalytic activities of [IrCl(cod)-(NHC)] (cod = 1,5-cyclooctadiene) complexes for the selective α-alkylation of ketones,[6d] secondary alcohols,[6d,e] nitriles,[25b] and β-alkylation of secondary alcohols[25a] by primary alcohols have been reported by our group. With this in mind, we decided to explore whether these NHC−Ir catalysts would enable the one-pot selective ring opening of terminal epoxides, leading to either ketones or secondary alcohols, and alkylation by primary alcohols for the synthesis of α-alkylated ketones through a BH methodology. We report an efficient NHC−Ir-based catalytic system that enables selective ring opening and alkylation of terminal epoxides with primary alcohols to the corresponding ketones (Scheme 1d). This catalytic system uses primary alcohols as both the hydrogen source and the alkylating agent and liberates water as the only byproduct under aerobic conditions.

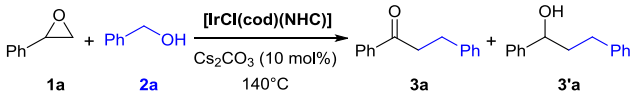
Initially, the reaction of styrene oxide (1 mmol) with benzyl alcohol (0.5 mmol) was selected as the benchmark experiment to probe the potential of the previously prepared **Ir-1** complex as the catalyst, which is one of the most active NHC-based catalysts for the transfer hydrogenation of carbonyl compounds.[26] The progress of the reaction was monitored by ^{1}H NMR spectroscopy, and the yields are based on 1,3,5-trimethoxybenzene as an internal standard (Table 1). The reaction was performed in the presence of the **Ir-1** catalyst (1 mol %) and Cs_2CO_3 (10 mol %) in different solvents (1 mL) at 140 °C (maintained by an oil bath) for 20 h while open to air (Table 1, entries 1−3). Using *tert*-amyl alcohol as the solvent gave a better yield and exclusively resulted in ketone product **3a** in 57% NMR yield (entry 3). Increasing the catalyst loading to 2 mol % (entry 4) resulted in a higher yield of **3a** (88%) along with a smaller amount of over-reduced alcohol **3′a** (5%). Replacing Cs_2CO_3 with KOH, NaOH, or KO^{t}Bu (entries 5−7) did not improve the activity. Furthermore, decreasing the amount of styrene oxide (**1a**) to either 0.75 or 0.6 mmol resulted in slightly lower yields (entry 8 or 9, respectively). Upon replacement of the NHC ligand in the [IrCl(cod)(NHC)] complex with IMes (**Ir-2**) or IPr (**Ir-3**) (entry 10 or 11, respectively), better outcomes were achieved, with a 98% NMR yield (92% isolated yield) of product **3a** obtained with [IrCl(cod)(IMes)] (**Ir-2**) as the catalyst. Additionally, when the reaction time was decreased to 16 h (entry 12), the activity was maintained. Control experiments (entries 13 and 14) demonstrated that both the catalyst and the base are essential to the reaction. Finally, using inert conditions did not improve the yield of the reaction (entry 15).

We next examined the scope of the reaction (Scheme 2). First, styrene oxide (**1a**) was reacted with various primary alcohols (**2**) under the optimized reaction conditions (Table 1, entry 12). The reaction of **1a** with a variety of electron-donating and electron-withdrawing *para*- or *ortho*-substituted benzyl alcohols having -Me, -OMe, -^{i}Pr, -Cl, -Br, -CF_3, or -NMe_2 groups, 2-naphthalene methanol, and ferrocene methanol afforded a range of ketone products (**3b−m**) with good to excellent isolated yields (52−96%). The corresponding ketones (**3n−q**) were isolated in moderate yields (38−51%) when heteroaromatic or aliphatic primary alcohols were tested. The reaction of 2.4 equiv of styrene oxide with 1,4-phenylene dimethanol in the presence of 4 mol % catalyst and 20 mol % Cs_2CO_3 gave corresponding diketone product **3r** in a 60% yield. Finally, the reaction of styrene oxide with 2-aminobenzyl alcohol provided 2-phenylquinoline (**3s**) in 27% isolated yield.

The reactions of benzyl alcohol with -Me-, -OMe-, -Cl-, -Br-, or -CF_3-substituted styrene oxides and 2-(naphthalen-2-yl)oxirane were robust, and the corresponding ketones **3t−y** were isolated with moderate to good yields (30−88%). However, under similar conditions, when aliphatic 1,2-epoxydodecane was reacted with benzyl alcohol, the formation of a corresponding product **3z** was detected in the reaction mixture with a 32% yield determined by ^{1}H NMR analysis together with a number of other undesired side products. This was probably due to more than one reactive α-carbon existing in the molecule. Unfortunately, we failed to isolate **3z** from the complex reaction mixture.

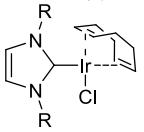
The one-pot sequential epoxide opening/alkylation reaction for the selective synthesis of β-alkylated alcohol product **3′a** upon addition of 2-propanol as an external hydrogen source at a specified point during the reaction (Scheme 3) resulted in a 94% yield of the desired product. Similarly, dialkylated ketone product **4a** was also obtained in 48% yield upon addition of 1

Table 1. Optimization of the Reaction Conditions[a]



1a **2a** **3a** **3'a**

entry	catalyst (mol %)	solvent	1a:2a (mmol)	time (h)	yield[b] (%) 3a	3′a
1	**Ir-1** (1)	PhMe	1:0.5	20	29	–
2	**Ir-1** (1)	dioxane	1:0.5	20	49	4
3	**Ir-1** (1)	*t*-AmOH	1:0.5	20	57	–
4	**Ir-1** (2)	*t*-AmOH	1:0.5	20	88	5
5[c]	**Ir-1** (2)	*t*-AmOH	1:0.5	20	18	–
6[d]	**Ir-1** (2)	*t*-AmOH	1:0.5	20	17	–
7[e]	**Ir-1** (2)	*t*-AmOH	1:0.5	20	60	–
8	**Ir-1** (2)	*t*-AmOH	0.75:0.5	20	72	–
9	**Ir-1** (2)	*t*-AmOH	0.6:0.5	20	71	–
10	**Ir-2** (2)	*t*-AmOH	0.6:0.5	20	98	–
11	**Ir-3** (2)	*t*-AmOH	0.6:0.5	20	86	–
12	**Ir-2** (2)	*t*-AmOH	0.6:0.5	16	97	–
13	–	*t*-AmOH	0.6:0.5	16	–	–
14[f]	**Ir-2** (2)	*t*-AmOH	0.6:0.5	16	–	–
15[g]	**Ir-2** (2)	*t*-AmOH	0.6:0.5	16	98	–



Ir-1: R = TIPB (2,4,6-triisopropylbenzyl)
Ir-2: R = Mes (2,4,6-trimethylphenyl)
Ir-3: R = DIPP (2,6-diisopropylphenyl)

[a]Reaction conditions: **1a** (0.6−1 mmol), **2a** (0.5 mmol), catalyst (1−2 mol %), Cs_2CO_3 (10 mol %), solvent (1 mL), 140 °C (oil bath temperature), open to air. [b]NMR yields were determined from ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as the internal standard. [c]KOH (10 mol %) used as the base. [d]NaOH (10 mol %) used as the base. [e]KO^{t}Bu (10 mol %) used as the base. [f]Without a base. [g]The reaction was performed under an argon atmosphere.

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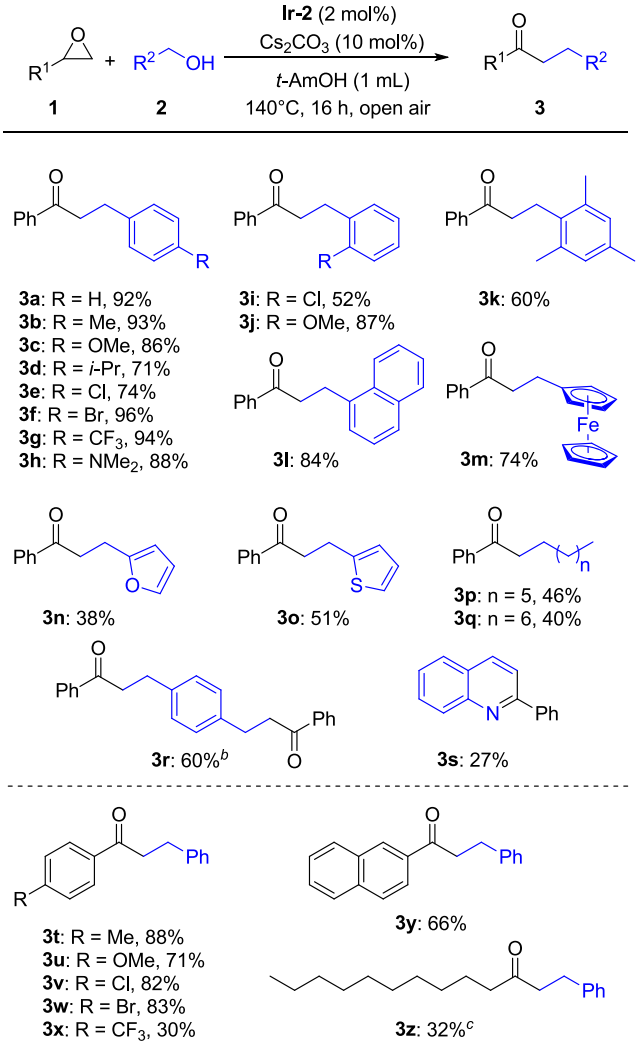
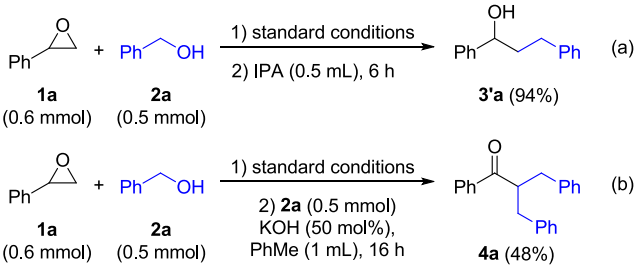
Scheme 2. Scope of the NHC−Ir-Catalyzed Regioselective Ring Opening and Alkylation of Terminal Epoxides[a]



[a]Reaction conditions: **1** (0.6 mmol), **2** (0.5 mmol), **Ir-2** (2 mol %), Cs_2CO_3 (0.05 mmol, 10 mol %), *t*-AmOH (1 mL), 140 °C (oil bath temperature), 16 h, open to air. Isolated yields. [b]**1** (1.2 mmol), **Ir-2** (4 mol %), and Cs_2CO_3 (0.1 mmol, 20 mol %) were used. [c]The yield was determined from ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as the internal standard.

Scheme 3. Synthesis of *β*-Alkylated Alcohols and *α,α*-Dialkylated Ketones[a]



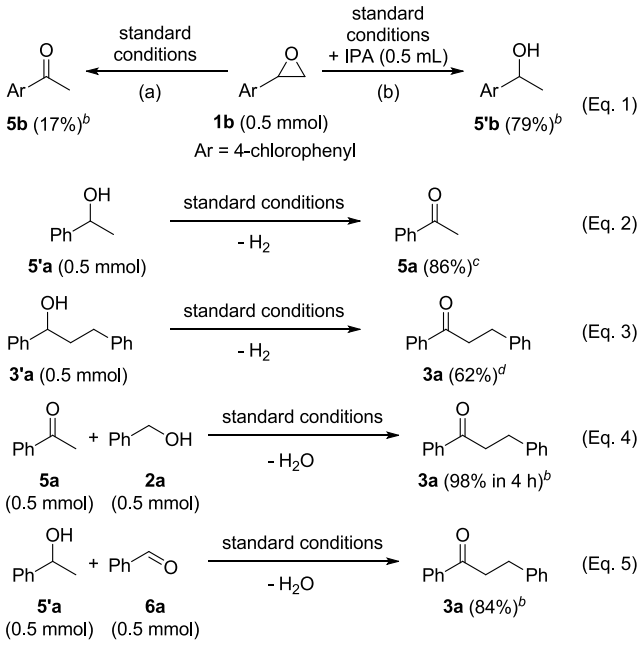
[a]Reaction conditions: (a) (1) standard conditions (Table 1, entry 12) and then (2) IPA (0.5 mL), 6 h (isolated yield); (b) (1) standard conditions (Table 1, entry 12) and then (2) **2a** (0.5 mmol), KOH (0.25 mmol), PhMe (1 mL), 16 h (isolated yield).

equiv of benzyl alcohol and 0.5 equiv of KOH, together with 1 mL of toluene, to the reaction mixture under the standard conditions.

We investigated the time profile of the reaction between styrene oxide and 4-methoxybenzyl alcohol (**2c**) under the optimized conditions by performing individual experiments over different reaction times to understand the mechanism of the reaction (Figure S1). The results showed that an induction period is required in the early stages of the reaction (4% conversion to **3c** after 1 h) most probably due to decoordination of Cl from [IrCl(cod)(IMes)] in the presence of the base to generate the transient [Ir(cod)(IMes)]$^+$ intermediate and formation of iridium alkoxo species with **2c**.[27] Subsequently, the complete conversion of the starting materials to **3c** (89% yield) and over-reduced alcohol **3′c** (4% yield) was observed over a period of 16 h in total. No accumulation of the intermediate chalcone was observed during the course of the reaction, suggesting the rapid hydrogenation of chalcone. In addition, acetophenone, 1-phenylethanol, and 4-methoxybenzaldehyde were detected during the reaction; however, their individual abundances never exceeded 5%.

Several control experiments were performed to gain insight into the mechanism (Scheme 4). As noted previously, the

Scheme 4. Control Experiments[a]



[a]Standard conditions: **Ir-2** (2 mol %), Cs_2CO_3 (0.05 mmol, 10 mol %), *t*-AmOH (1 mL), 140 °C (oil bath temperature), 16 h, open to air. [b]^{1}H NMR yields based on 1,3,5-trimethoxybenzene as the internal standard. [c]GC conversion. [d]NMR conversion.

selective ring opening of epoxides can result in the formation of either ketones (**5**) or secondary alcohols (**5′**) (Scheme 1b,c) and NHC−Ir-catalyzed alkylation of these species[6d] with primary alcohols will allow the synthesis of *α*-alkylated ketones (Scheme 1a). To prove that **5** and **5′** are indeed the reaction intermediates, control experiments were conducted using **1b** as the starting material under standard conditions (eq 1a) and in the presence of an additional hydrogen source (0.5 mL of 2-propanol, eq 1b). In the absence of a hydrogen source,

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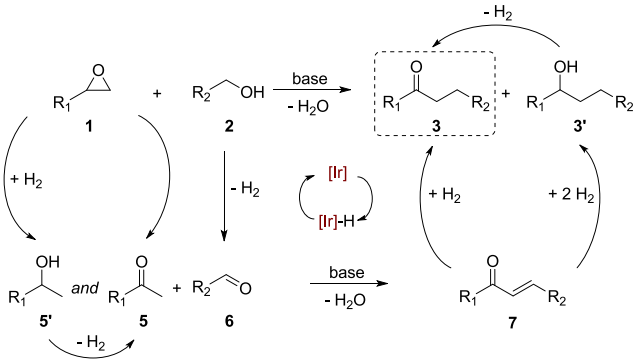
isomerization product **5b** was obtained in only 17% (eq 1a), while under transfer hydrogenation conditions, the corresponding hydrogenation product **5′b** was obtained in 79% yield (eq 1b). This result demonstrates the importance of the hydrogen source (primary alcohol in the case of the current protocol) in the selective epoxide ring opening step. Dehydrogenation of possible intermediates **5′a** and **3′a** was also confirmed by independent control experiments under the standard conditions, wherein these secondary alcohols were dehydrogenated to their corresponding ketones, **5a** (86%) and **3a** (62%), respectively (eqs 2 and 3). In addition, the reaction of acetophenone with benzyl alcohol gave the desired product **3a** in 98% yield after just 4 h (eq 5). Similarly, the reaction of 1-phenylethanol with benzaldehyde under optimized conditions provided alkylated product **3a** in 84% yield (eq 6).

On the basis of the experimental evidence presented herein, and our previous report,[6d] a catalytic cycle for the reaction is proposed in Scheme 5. The mechanism involves the Ir-

Scheme 5. Proposed Mechanism



catalyzed dehydrogenation of a primary alcohol (**2**) to an aldehyde (**6**) and isomerization/transfer hydrogenation of a terminal epoxide to a ketone (**5**) or secondary alcohol (**5′**) [which can also undergo dehydrogenation to form the ketone (**5**)]. The low conversion of the epoxide to the isomerization product (Scheme 4, eq 1a) indicates that this step of the reaction mainly proceeds via a metal-catalyzed reduction/oxidation pathway instead of Meinwald rearrangement. A base-mediated cross-aldol condensation reaction between **5** and **6** can produce **7**.[6d] A rapid hydrogenation of **7** to **3** and **3′** (and dehydrogenation of over-reduced byproduct **3′**) gives the desired ketone **3**.

In summary, we have developed an efficient catalytic method for converting terminal epoxides and primary alcohols into α-alkylated ketones via a BH methodology. Mechanistic studies revealed that the readily available [IrCl(cod)(IMes)] catalyst enables the one-pot selective ring opening of terminal epoxides into both ketones and secondary alcohol and the further alkylation of these species with primary alcohols to yield α-alkylated ketones under aerobic conditions. Remarkably, water is the only byproduct. This study is the first example of a tandem epoxide ring opening/alkylation reaction and provides an alternative approach to the synthesis of α-alkylated ketones.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01765.

Experimental details and traces of ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Otera, J., Ed. *Modern Carbonyl Chemistry*; Wiley-VCH: Weinheim, Germany, 2000.

(2) (a) Hamid, S. A. M. H.; Slatford, P. A.; Williams, J. M. J. Borrowing Hydrogen in the Activation of Alcohols. *Adv. Synth. Catal.* **2007**, *349*, 1555−1575. (b) Gunanathan, C.; Milstein, D. Applications of Acceptorless Dehydrogenation and Related Transformations in Chemical Synthesis. *Science* **2013**, *341*, 1229712. (c) Obora, Y. Recent Advances in α-Alkylation Reactions using Alcohols with Hydrogen Borrowing Methodologies. *ACS Catal.* **2014**, *4*, 3972−3981. (d) Huang, F.; Liu, Z. Q.; Yu, Z. K. C-Alkylation of Ketones and Related Compounds by Alcohols: Transition-Metal-Catalyzed Dehydrogenation. *Angew. Chem., Int. Ed.* **2016**, *55*, 862−875. (e) Corma, A.; Navas, J.; Sabater, M. J. Advances in One-Pot Synthesis Through Borrowing Hydrogen Catalysis. *Chem. Rev.* **2018**, *118*, 1410−1459. (f) Reed-Berendt, B. G.; Polidano, K.; Morrill, L. C. Recent Advances in Homogeneous Borrowing Hydrogen Catalysis Using Earth-Abundant First Row Transition Metals. *Org. Biomol. Chem.* **2019**, *17*, 1595−1607. (g) Kwok, T.; Hoff, O.; Armstrong, R. J.; Donohoe, T. J. Control of Absolute Stereochemistry in Transition-Metal-Catalysed Hydrogen-Borrowing Reactions. *Chem. - Eur. J.* **2020**, *26*, 12912−12926. (h) Reed-Berendt, B. G.; Latham, D. E.; Dambatta, M. B.; Morrill, L. C. Borrowing Hydrogen for Organic Synthesis. *ACS Cent. Sci.* **2021**, *7*, 570−585.

(3) (a) Martínez, R.; Brand, G. J.; Ramon, D. J.; Yus, M. $[Ru(DMSO)_4]Cl_2$ catalyzes the α-alkylation of ketones by alcohols. *Tetrahedron Lett.* **2005**, *46*, 3683−3686. (b) Kuwahara, T.; Fukuyama,

T.; Ryu, I. RuHCl(CO)(PPh_3)$_3$-Catalyzed α-Alkylation of Ketones with Primary Alcohols. *Org. Lett.* **2012**, *14*, 4703−4705. (c) Schlepphorst, C.; Maji, B.; Glorius, F. Ruthenium-NHC Catalyzed α-Alkylation of Methylene Ketones Provides Branched Products through Borrowing Hydrogen Strategy. *ACS Catal.* **2016**, *6*, 4184−4188. (d) Chakrabarti, K.; Maji, M.; Panja, D.; Paul, B.; Shee, S.; Das, G. K.; Kundu, S. Utilization of MeOH as a C1 Building Block in Tandem Three-Component Coupling Reaction. *Org. Lett.* **2017**, *19*, 4750−4753. (e) Thiyagarajan, S.; Gunanathan, C. Catalytic Cross-Coupling of Secondary Alcohols. *J. Am. Chem. Soc.* **2019**, *141*, 3822−3827. (f) Bhattacharyya, D.; Sarmah, B. K.; Nandi, S.; Srivastava, H. K.; Das, A. Selective Catalytic Synthesis of αAlkylated Ketones and βDisubstituted Ketones via Acceptorless Dehydrogenative Cross-Coupling of Alcohols. *Org. Lett.* **2021**, *23*, 869−875.

(4) Chan, L. K. M.; Poole, D. L.; Shen, D.; Healy, M. P.; Donohoe, T. J. Rhodium-Catalyzed Ketone Methylation Using Methanol Under Mild Conditions: Formation of α-Branched Products. *Angew. Chem., Int. Ed.* **2014**, *53*, 761−765.

(5) (a) Kwon, M. S.; Kim, N.; Seo, S. H.; Park, I. S.; Cheedrala, R. K.; Park, J. Recyclable Palladium Catalyst for Highly Selective a Alkylation of Ketones with Alcohols. *Angew. Chem., Int. Ed.* **2005**, *44*, 6913−6915. (b) Cho, C. S. Palladium-Catalyzed Route for α-Alkylation of Ketones by Primary Alcohols. *J. Mol. Catal. A: Chem.* **2005**, *240*, 55−60. (c) Yamada, Y. M. A.; Uozumi, Y. A Solid-Phase Self-Organized Catalyst of Nanopalladium with Main-Chain Viologen Polymers: α-Alkylation of Ketones with Primary Alcohols. *Org. Lett.* **2006**, *8*, 1375−1378. (d) Mamidala, R.; Biswal, P.; Subramani, M. S.; Samser, S.; Venkatasubbaiah, K. Palladacycle-Phosphine Catalyzed Methylation of Amines and Ketones Using Methanol. *J. Org. Chem.* **2019**, *84*, 10472−10480.

(6) (a) Ogawa, S.; Obora, Y. Iridium-Catalyzed Selective α-Methylation of Ketones with Methanol. *Chem. Commun.* **2014**, *50*, 2491−2493. (b) Wang, D.; Zhao, K.; Xu, C.; Miao, H.; Ding, Y. Synthesis, Structures of Benzoxazolyl Iridium(III) Complexes, and Applications on C−C and C−N Bond Formation Reactions under Solvent-Free Conditions: Catalytic Activity Enhanced by Non-coordinating Anion without Silver Effect. *ACS Catal.* **2014**, *4*, 3910−3918. (c) Shen, D.; Poole, D. L.; Shotton, C. C.; Kornahrens, A. F.; Healy, M. P.; Donohoe, T. J. Hydrogen Borrowing and Interrupted Hydrogen Borrowing Reactions of Ketones and Methanol Catalyzed by Iridium. *Angew. Chem., Int. Ed.* **2015**, *54*, 1642−1645. (d) Genç, S.; Günnaz, S.; Çetinkaya, B.; Gülcemal, S.; Gülcemal, D. Iridium(I)-Catalyzed Alkylation Reactions to Form α-Alkylated Ketones. *J. Org. Chem.* **2018**, *83*, 2875−2881. (e) Genç, S.; Gülcemal, S.; Günnaz, S.; Çetinkaya, B.; Gülcemal, D. Iridium-Catalyzed Alkylation of Secondary Alcohols with Primary Alcohols: A Route to Access Branched Ketones and Alcohols. *J. Org. Chem.* **2020**, *85*, 9139−9152.

(7) Li, P.; Xiao, G.; Zhao, Y.; Su, H. Tuning the Product Selectivity of the α-Alkylation of Ketones with Primary Alcohols using Oxidized Titanium Nitride Photocatalysts and Visible Light. *ACS Catal.* **2020**, *10*, 3640−3649.

(8) (a) Peña-López, M.; Piehl, P.; Elangovan, S.; Neumann, H.; Beller, M. Manganese-Catalyzed Hydrogen-Autotransfer C−C Bond Formation: α-Alkylation of Ketones with Primary Alcohols. *Angew. Chem., Int. Ed.* **2016**, *55*, 14967−14971. (b) Kabadwal, L. M.; Das, J.; Banerjee, D. Mn(II)-Catalysed Alkylation of Methylene Ketones with Alcohols: Direct Access to Functionalised Branched Products. *Chem. Commun.* **2018**, *54*, 14069−14072. (c) Lan, X.-B.; Ye, Z.; Huang, M.; Liu, J.; Liu, Y.; Ke, Z. Nonbifunctional Outer-Sphere Strategy Achieved Highly Active α-Alkylation of Ketones with Alcohols by N-Heterocyclic Carbene Manganese (NHC-Mn). *Org. Lett.* **2019**, *21*, 8065−8070. (d) Lan, X.-B.; Ye, Z.; Liu, J.; Huang, M.; Shao, Y.; Cai, X.; Liu, Y.; Ke, Z. Sustainable and Selective Alkylation of Deactivated Secondary Alcohols to Ketones by Nonbifunctional Pincer N-heterocyclic Carbene Manganese. *ChemSusChem* **2020**, *13*, 2557−2563.

(9) (a) Polidano, K.; Allen, B. D. W.; Williams, J. M. J.; Morrill, L. C. Iron-Catalyzed Methylation Using the Borrowing Hydrogen Approach. *ACS Catal.* **2018**, *8*, 6440−6445. (b) Alanthadka, A.; Bera, S.; Banerjee, D. Iron-Catalyzed Ligand Free α-Alkylation of Methylene Ketones and β-Alkylation of Secondary Alcohols Using Primary Alcohols. *J. Org. Chem.* **2019**, *84*, 11676−11686. (c) Bettoni, L.; Seck, C.; Mbaye, M. D.; Gaillard, S.; Renaud, J. L. Iron-Catalyzed Tandem Three-Component Alkylation: Access to αMethylated Substituted Ketones. *Org. Lett.* **2019**, *21*, 3057−3061. (d) Bettoni, L.; Gaillard, S.; Renaud, J. L. Iron-Catalyzed α-Alkylation of Ketones with Secondary Alcohols: Access to β-Disubstituted Carbonyl Compounds. *Org. Lett.* **2020**, *22*, 2064−2069.

(10) (a) Zhang, G.; Wu, J.; Zeng, H.; Zhang, S.; Yin, Z.; Zheng, S. Cobalt-Catalyzed α-Alkylation of Ketones with Primary Alcohols. *Org. Lett.* **2017**, *19*, 1080−1083. (b) Chakraborty, P.; Gangwar, M. K.; Emayavaramban, B.; Manoury, E.; Poli, R.; Sundararaju, B. α-Alkylation of Ketones with Secondary Alcohols Catalyzed by Well-Defined Cp*Co^{III}-Complexes. *ChemSusChem* **2019**, *12*, 3463−3467. (c) Pandey, B.; Xu, S.; Ding, K. Selective Ketone Formations via Cobalt-Catalyzed β-Alkylation of Secondary Alcohols with Primary Alcohols. *Org. Lett.* **2019**, *21*, 7420−7423.

(11) (a) Das, J.; Singh, K.; Vellakkaran, M.; Banerjee, D. Nickel-Catalyzed Hydrogen-Borrowing Strategy for α-Alkylation of Ketones with Alcohols: A New Route to Branched gem-Bis(alkyl) Ketones. *Org. Lett.* **2018**, *20*, 5587−5591. (b) Das, J.; Vellakkaran, M.; Banerjee, D. Nickel-Catalyzed Alkylation of Ketone Enolates: Synthesis of Monoselective Linear Ketones. *J. Org. Chem.* **2019**, *84*, 769−779.

(12) Tan, D.-W.; Li, H.-X.; Zhu, D.-L.; Li, H.-Y.; Young, D. J.; Yao, J.-L.; Lang, J.-P. Ligand-Controlled Copper(I)- Catalyzed Cross-Coupling of Secondary and Primary Alcohols to α-Alkylated Ketones, Pyridines, and Quinolines. *Org. Lett.* **2018**, *20*, 608−611.

(13) (a) Gorzynski Smith, J. Synthetically Useful Reactions of Epoxides. *Synthesis* **1984**, *1984*, 629−656. (b) Thiery, E.; Le Bras, J.; Muzart, J. Reactivity versus Stability of Oxiranes under Palladium-Catalyzed Reductive Conditions. *Eur. J. Org. Chem.* **2009**, *2009*, 961−985. (c) Huang, C.-Y.; Doyle, A. G. The Chemistry of Transition Metals with Three-Membered Ring Heterocycles. *Chem. Rev.* **2014**, *114*, 8153−8198. (d) Park, S. Catalytic Reduction of Cyclic Ethers with Hydrosilanes. *Chem. - Asian J.* **2019**, *14*, 2048−2066. (e) Hubbell, A. K.; Coates, G. W. Nucleophilic Transformations of Lewis Acid-Activated Disubstituted Epoxides with Catalyst-Controlled Regioselectivity. *J. Org. Chem.* **2020**, *85*, 13391−13414.

(14) (a) Meinwald, J.; Labana, S. S.; Chadha, M. S. Peracid Reactions. III. The Oxidation of Bicyclo[2.2.1]heptadiene. *J. Am. Chem. Soc.* **1963**, *85*, 582−585. (b) Jat, J. L.; Kumar, G. Isomerization of Epoxides. *Adv. Synth. Catal.* **2019**, *361*, 4426−4441.

(15) (a) Suda, K.; Baba, K.; Nakajima, S.; Takanami, T. Metalloporphyrin-Catalyzed Regioselective Rearrangement of Monoalkyl-Substituted Epoxides into Aldehydes. *Tetrahedron Lett.* **1999**, *40*, 7243−7246. (b) Ertürk, E.; Göllü, M.; Demir, A. S. Efficient Rearrangement of Epoxides Catalyzed by a Mixed-Valent Iron Trifluoroacetate [$Fe_3O(O_2CCF_3)_6(H_2O)_3$]. *Tetrahedron* **2010**, *66*, 2373−2377. (c) Vyas, D. J.; Larionov, E.; Besnard, C.; Guénée, L.; Mazet, C. Isomerization of Terminal Epoxides by a [Pd−H] Catalyst: A Combined Experimental and Theoretical Mechanistic Study. *J. Am. Chem. Soc.* **2013**, *135*, 6177−6183.

(16) (a) Milstein, D. The First Isolated, Stable cis-Hydridoalkylrhodium Complexes and Their Reductive Elimination Reaction. *J. Am. Chem. Soc.* **1982**, *104*, 5227−5228. (b) Prandi, J.; Namy, J. L.; Menoret, G.; Kagan, H. B. Selective Catalyzed-Rearrangement of Terminal Epoxides to Methyl Ketones. *J. Organomet. Chem.* **1985**, *285*, 449−460. (c) Kulasegaram, S.; Kulawiec, R. J. Chemo- and Regioselective Isomerization of Epoxides to Carbonyl Compounds via Palladium Catalysis. *J. Org. Chem.* **1994**, *59*, 7195−7196. (d) Jürgens, E.; Wucher, B.; Rominger, F.; Törnroos, K. W.; Kunz, D. Selective Rearrangement of Terminal Epoxides into Methylketones Catalysed by a Nucleophilic Rhodium-NHC-Pincer Complex. *Chem. Commun.* **2015**, *51*, 1897−1900. (e) Tian, Y.; Jürgens, E.; Kunz, D. Regio- and Chemoselective Rearrangement of Terminal Epoxides into Methyl Alkyl and Aryl Ketones. *Chem. Commun.* **2018**, *54*, 11340−11343.

https://doi.org/10.1021/acs.orglett.1c01765
Org. Lett. 2021, 23, 5229−5234

(f) Li, S.; Shi, Y.; Li, P.; Xu, J. Nucleophilic Organic Base DABCO-Mediated Chemospecific Meinwald Rearrangement of Terminal Epoxides into Methyl Ketones. *J. Org. Chem.* **2019**, *84*, 4443−4450.
(17) (a) Ookawa, A.; Hiratsuka, H.; Soai, K. Chemo- and Regioselective Reduction of Epoxides with Sodium Borohydride in Mixed Solvent Containing Methanol. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1813−1817. (b) Azizi, N.; Batebi, E.; Bagherpour, S.; Ghafuri, H. Natural Deep Eutectic Salt Prompted Regioselective Reduction of Epoxides and Carbonyl Compounds. *RSC Adv.* **2012**, *2*, 2289−2293.
(18) (a) Sajiki, H.; Hattori, K.; Hirota, K. Pd/C(en)-Catalyzed Regioselective Hydrogenolysis of Terminal Epoxides to Secondary Alcohols. *Chem. Commun.* **1999**, 1041−1042. (b) Ley, S. V.; Mitchell, C.; Pears, D.; Ramarao, C.; Yu, J.-Q.; Zhou, W. Recyclable Polyurea-Microencapsulated Pd(0) Nanoparticles: An Efficient Catalyst for Hydrogenolysis of Epoxides. *Org. Lett.* **2003**, *5*, 4665−4668. (c) Kwon, M. S.; Park, I. S.; Jang, J. S.; Lee, J. S.; Park, J. Magnetically Separable Pd Catalyst for Highly Selective Epoxide Hydrogenolysis under Mild Conditions. *Org. Lett.* **2007**, *9*, 3417−3419.
(19) Hirakawa, H.; Shiraishi, Y.; Sakamoto, H.; Ichikawa, S.; Tanaka, S.; Hirai, T. Photocatalytic Hydrogenolysis of Epoxides Using Alcohols as Reducing Agents on TiO_2 Loaded with Pt Nanoparticles. *Chem. Commun.* **2015**, *51*, 2294−2297.
(20) (a) Yao, C.; Dahmen, T.; Gansäuer, A.; Norton, J. Anti-Markovnikov Alcohols via Epoxide Hydrogenation Through Cooperative Catalysis. *Science* **2019**, *364*, 764−767. (b) Liu, W.; Li, W.; Spannenberg, A.; Junge, K.; Beller, M. Iron-Catalysed Regioselective Hydrogenation of Terminal Epoxides to Alcohols Under Mild Conditions. *Nat. Catal.* **2019**, *2*, 523−528. (c) Rainsberry, A. N.; Sage, J. G.; Scheuermann, M. L. Iridium-Promoted Conversion of Terminal Epoxides to Primary Alcohols under Acidic Conditions Using Hydrogen. *Catal. Sci. Technol.* **2019**, *9*, 3020−3022. (d) Liu, W.; Leischner, T.; Li, W.; Junge, K.; Beller, M. A General Regioselective Synthesis of Alcohols by Cobalt-Catalyzed Hydrogenation of Epoxides. *Angew. Chem., Int. Ed.* **2020**, *59*, 11321−11324.
(21) (a) Wenz, J.; Wadepohl, H.; Gade, L. H. Regioselective Hydrosilylation of Epoxides Catalysed by Nickel(II) Hydrido Complexes. *Chem. Commun.* **2017**, *53*, 4308−4311. (b) Henriques, D. S. G.; Zimmer, K.; Klare, S.; Meyer, A.; Rojo-Wiechel, E.; Bauer, M.; Sure, R.; Grimme, S.; Schiemann, O.; Flowers, R. A., II; Gansäuer, A. Highly Active Titanocene Catalysts for Epoxide Hydrosilylation: Synthesis, Theory, Kinetics, EPR Spectroscopy. *Angew. Chem., Int. Ed.* **2016**, *55*, 7671−7675.
(22) Liu, X.; Longwitz, L.; Spiegelberg, B.; Tönjes, J.; Beweries, T.; Werner, T. Erbium-Catalyzed Regioselective Isomerization-Cobalt-Catalyzed Transfer Hydrogenation Sequence for the Synthesis of Anti- Markovnikov Alcohols from Epoxides under Mild Conditions. *ACS Catal.* **2020**, *10*, 13659−13667.
(23) (a) Ito, M.; Hirakawa, M.; Osaku, A.; Ikariya, T. Highly Efficient Chemoselective Hydrogenolysis of Epoxides Catalyzed by a $(\eta^5\text{-}C_5(CH_3)_5)$Ru Complex Bearing a 2-(Diphenylphosphino)-ethylamine Ligand. *Organometallics* **2003**, *22*, 4190−4192. (b) Thiyagarajan, S.; Gunanathan, C. Ruthenium-Catalyzed Selective Hydrogenation of Epoxides to Secondary Alcohols. *Org. Lett.* **2019**, *21*, 9774−9778.
(24) Magre, M.; Paffenholz, E.; Maity, B.; Cavallo, L.; Rueping, M. Regiodivergent Hydroborative Ring Opening of Epoxides via Selective C-O Bond Activation. *J. Am. Chem. Soc.* **2020**, *142*, 14286−14294.
(25) (a) Genç, S.; Arslan, B.; Gülcemal, S.; Günnaz, S.; Çetinkaya, B.; Gülcemal, D. Iridium(I)-Catalyzed C-C and C-N Bond Formation Reactions via the Borrowing Hydrogen Strategy. *J. Org. Chem.* **2019**, *84*, 6286−6297. (b) Arslan, B.; Gülcemal, S. α-Alkylation of Arylacetonitriles with Primary Alcohols Catalyzed by Backbone Modified N-Heterocyclic Carbene Iridium(I) Complexes. *Dalton Trans.* **2021**, *50*, 1788−1796.
(26) Gülcemal, S.; Gökçe, A. G.; Çetinkaya, B. N-Benzyl Substituted N-Heterocyclic Carbene Complexes of Iridium(I): Assessment in Transfer Hydrogenation Catalyst. *Inorg. Chem.* **2013**, *52*, 10601−10609.
(27) Jiménez, M. V.; Fernández-Tornos, J.; Modrego, F. J.; Pérez-Torrente, J. J.; Oro, L. A. Oxidationand β-Alkylation of Alcohols Catalysed by Iridium(I) Complexes with Functionalised N-Heterocyclic Carbene Ligands. *Chem. - Eur. J.* **2015**, *21*, 17877−17889.

https://doi.org/10.1021/acs.orglett.1c01765
Org. Lett. 2021, 23, 5229−5234