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Base-Mediated Meerwein–Ponndorf–Verley Reduction of Aromatic and Heterocyclic Ketones

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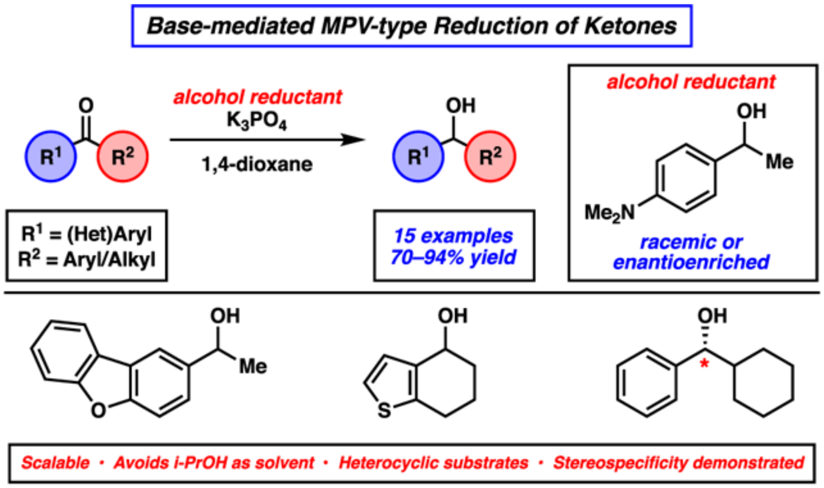
Abstract

An experimental protocol to achieve the Meerwein–Ponndorf–Verley (MPV) reduction of ketones under mildly basic conditions is reported. The transformation is tolerant of a range of ketone substrates, including *O*- and *S*-containing heterocycles, is scalable, and shows potential to be used as a platform to access enantioenriched products. These studies provide a general method for achieving the reduction of ketones under mildly basic conditions and offer an alternative protocol to more well-known Al-based MPV reduction conditions.

Graphical abstract



The Meerwein–Ponndorf–Verley (MPV) reaction is an important and powerful tool for the reduction of ketones and aldehydes because of its chemoselectivity, mild reaction conditions, scalability, and low operational cost.[1] Discovered nearly a century ago,[2] the traditional MPV reduction employs an aluminum alkoxide catalyst generated from a secondary alcohol (most commonly isopropanol) to achieve the reversible transfer hydrogenation of carbonyl

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Supporting Information
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Experimental details and compound characterization data (PDF)

The authors declare no competing financial interest.

substrates (Figure 1).[3] This venerable reaction has been featured in the syntheses of several natural products[4] and spurred numerous experimental[5] and computational studies.[6] Despite the synthetic utility of the traditional MPV reduction, several drawbacks exist. These include long reaction times, the need for a large excess of reducing agent, competing side reactions such as aldol condensation and the Tishchenko reduction of aldehydes, and low enantioselectivities in the case of intermolecular asymmetric variants.[1,3] Methodological advances to address these limitations include the use of additives,[7] microwave irradiation,[8] and the development of novel aluminum,[9] organoboron,[10] and metal alkoxide catalysts (i.e., transition[11] and lanthanide[12]). A particularly efficient aluminum siloxide catalyst has been reported by the Krempner group.[9c]

A largely unexplored approach to the MPV-type reduction of carbonyls uses simple alkali metal alkoxides (Figure 1).[13,14] This variant of the MPV reaction has several benefits including its avoidance of transition and main group metal catalysts, operational simplicity, and compatibility with heteroatoms known to inhibit metal catalysis.[3,13] Specifically, isopropoxide catalysts generated from strong alkali bases, such as NaOH[13a] and KOH[13b] and milder bases such as K_3PO_4,[13c] have been employed in the reduction of aldehydes and ketones. Nevertheless, a number of limitations of the base-mediated MPV reduction remain unaddressed including a limited scope and the reliance on *i*-PrOH as the solvent and hydride source.[15] Additionally, no examples of stereoselective base-mediated MPV reactions exist. We report the use of a simple potassium alkoxide reductant, generated in situ from the corresponding alcohol and K_3PO_4, for the reduction of a wide range of aromatic ketones. This methodology is tolerant of heterocycles, is scalable, and shows potential for the asymmetric reduction of alkyl–aryl ketones.

To initiate our studies, we examined the reduction of dihydrochalcone (**1**) using alkyl–alkyl secondary alcohols and K_3PO_4, a readily available and mild base (Table 1).[16] Subjecting **1** to catalytic K_3PO_4 using isopropanol or 3-pentanol (**3**, 2.5 equiv) in 1,4-dioxane at 80 °C provided none of the desired alcohol product **2** (entries 1 and 2).[16–18] Owing to the potential reversibility of the reaction,[1a–c,16] we turned to the use of aryl–alkyl reductants to bias the reaction equilibrium. Importantly, this class of alcohols enabled greater control of the redox properties of the reductant. We evaluated alcohol **4** and the more electron-rich derivative **5** as reductants,[19] anticipating that the stability of the respective aryl ketone and doubly vinylogous amide byproducts would drive the forward reaction to yield **2**. Gratifyingly, the use of 2.5 equiv of **4** or **5** provided **2** in 40% and 61% yield, respectively (entries 3 and 4). Employing reductant **5** at 120 °C furnished desired product **2** in 92% yield (entry 5). Finally, alcohol **2** was obtained in near-quantitative yield by utilizing excess base (entry 6).

With optimized conditions in hand, we examined a range of aryl ketone substrates in the reduction (Figure 2). Linear and α-branched substrates smoothly underwent reduction, giving rise to alcohols **2** and **6**–**8** in good yields. Of note, steric bulk on the alkyl substituent of the ketone was tolerated, as shown by the successful reduction of *tert*-butyl phenyl ketone to furnish alcohol **8** in 83% yield. The reduction of α-tetralone to give α-tetralol (**9**) in 86% yield demonstrates competence of a cyclic ketone substrate in this transformation. Notably, we found that electron-rich aromatic ketones and those highly decorated with heteroatom substituents underwent facile reduction, as demonstrated by the formation of alcohols **10** and

11 in 81% and 87% yield, respectively. Finally, both electron-rich and electron-deficient benzophenone derivatives were suitable substrates, as shown by the production of alcohol products **12** and **13** in good yields.

We next set out to evaluate the reactivity of a number of heterocyclic ketone substrates, as only a few examples of base-mediated MPV reductions of heterocyclic ketones have been previously reported (Figure 3).[20] Benzofuran- and dibenzofuran-containing ketones underwent reduction to provide alcohols **14** and **15** in 73% and 76% yield, respectively. Benzodioxole and benzodioxane moieties were also well tolerated, as seen by the formation of alcohols **16** and **17** in good yields. Lastly, ketones bearing thiophenes were successfully employed, as judged by the formation of benzothiophene **18** and tetrahydrobenzothiophene **19** in 70% and 73% yield, respectively.[21]

As a demonstration of the utility of the base-mediated MPV reduction of ketones, we performed the additional studies shown in Figure 4. In the first, we performed a gram-scale reduction of acetyldibenzofuran **20**.[22] Carrying out the reaction at 130 °C for 24 h delivered alcohol **15** in 66% yield, thus demonstrating the scalability of this methodology. Next, we questioned whether this reaction could be used for the synthesis of enantioenriched alcohols. Toward this end, we performed the reduction of phenylcyclohexyl ketone **21** using enantioenriched (*R*)-**5**. This proceeded to give alcohol (*S*)-**6** with 50% stereochemical transfer (96% *ee* of (*R*)-**5** → 48% *ee* (*S*)-**6**). This result underscores the potential of the base-mediated MPV reduction to generate enantioenriched products.[1e,12d,23]

In summary, we have developed the base-mediated MPV reduction of aromatic and heteroaromatic ketones.[24] This methodology employs the simple combination of K_3PO_4 as a mild base and secondary alcohol **5** as the reductant. The transformation is tolerant of a range of ketone substrates, including *O*- and *S*-containing heterocycles, and avoids the hydride source being used as the solvent. The reduction has been demonstrated on gram scale and shows potential to be used as a platform to provide enantioenriched products. These studies provide a general platform for achieving the reduction of ketones under mildly basic MPV conditions and offer an alternative protocol to the more classic Al-based MPV reduction. We hope this study will enable the greater utilization of the uncommon base-mediated variant of the MPV reduction in chemical synthesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

■ ACKNOWLEDGMENTS

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(15). Under the conditions reported by Chuah and co-workers (ref 12c), only cyclohexanone, 4-tert-butyl cyclohexanone, and acetophe-none were evaluated for reactivity using K3PO4/i-PrOH affording the respective alcohol products in 55%, 30%, and 38% yield.

(16). Subjecting dihydrochalcone (1) to previously reported conditions for the reduction of ketones using catalytic K3PO4 using i-PrOH as a solvent gave the desired product 2 in only 47% yield.

(17). Although 1,4-dioxane was chosen for these studies, we found other solvents could be employed (see SI for details).

(18). K3PO4 is roughly 103 less basic than NaOH and KOH: for the pKa of KH2PO4 and H2O, respectively, see:Bruice PY Organic Chemistry, 6th ed; Prentice Hall: Boston, 2011.Bordwell FG Equilibrium acidities in dimethylsulfoxide solution. Acc. Chem. Res 1988, 21, 456–463.

(19). Using DFT calculations (M06–2X/6–31G(d)), we estimate that the conversion of 1 and 5 to 2 and reduced 5 is thermodynamically favorable by ~2 kcal/mol.

(20). Previous reports on the base-mediated MPV reductions of ketones using NaOH and KOH have shown only a handful of heterocyclic substrates undergoing reduction (see refs 12a, b). The base-mediated MPV reduction of heterocyclic ketones using K3PO4 has not been previously reported.

(21). Subjecting N-containing heterocyclic ketones such as N-MOM 4-acetyl indole and 4-acetyl pyridine to base-mediated MPV reduction conditions led to lower yields of the products (20% and 11% yield, respectively).

(22). Dibenzofurans have found application in OLEDs, bioactive molecules, and chemical probes:Kim S-Y; Hwang S-H; Kim Y-K; Jung H-J; Lim J-O; Han S-H; Jeong E-J; Park J-H; Lee E-Y; Lee B-R; Lee J-H Condensed-cyclic compound and organic light-emitting device. U.S. Patent 20180248127, Jul. 25, 2012.Patpi SR; Pulipati L; Yogeeswari P; Sriram D; Jain N; Sridhar B; Murthy R; Devi TA; Kalivendi SV; Kantevari S Design, synthesis, and structure–activity correlations of novel dibenzo-[b,d]furan, dibenzo[b,d]thiophene, and *N*-methylcarbazole clubbed 1,2,3-triazoles as potent inhibitors of *Mycobacterium tuberculosis*. J. Med. Chem 2012, 55, 3911–3922. [PubMed: 22449006] Liu L-X; Wang X-Q; Yan J-M; Li Y; Sun C-J; Chen W; Zhou H-B; Yang X-D Synthesis and antitumor activities of novel dibenzo[b,d]furan–imidazole hybrid compounds. Eur. J. Med. Chem 2013, 66, 423–437. [PubMed: 23831807] Lusic H; Uprety R; Deiters A Improved synthesis of the two-photon caging group 3-nitro-2-ethyldibenzofuran and its application to a caged thymidine phosphoramidite. Org. Lett 2010, 12, 916–919. [PubMed: 20112966]

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(24). Based on a prior mechanistic proposal by Chuah and coworkers (ref 13c) and our observation that the reaction does not proceed in the presence of non-basic potassium salts, the term “base-mediated” was deemed an appropriate descriptor for this methodology. However, proposing a well-supported mechanism for this transformation would be premature.

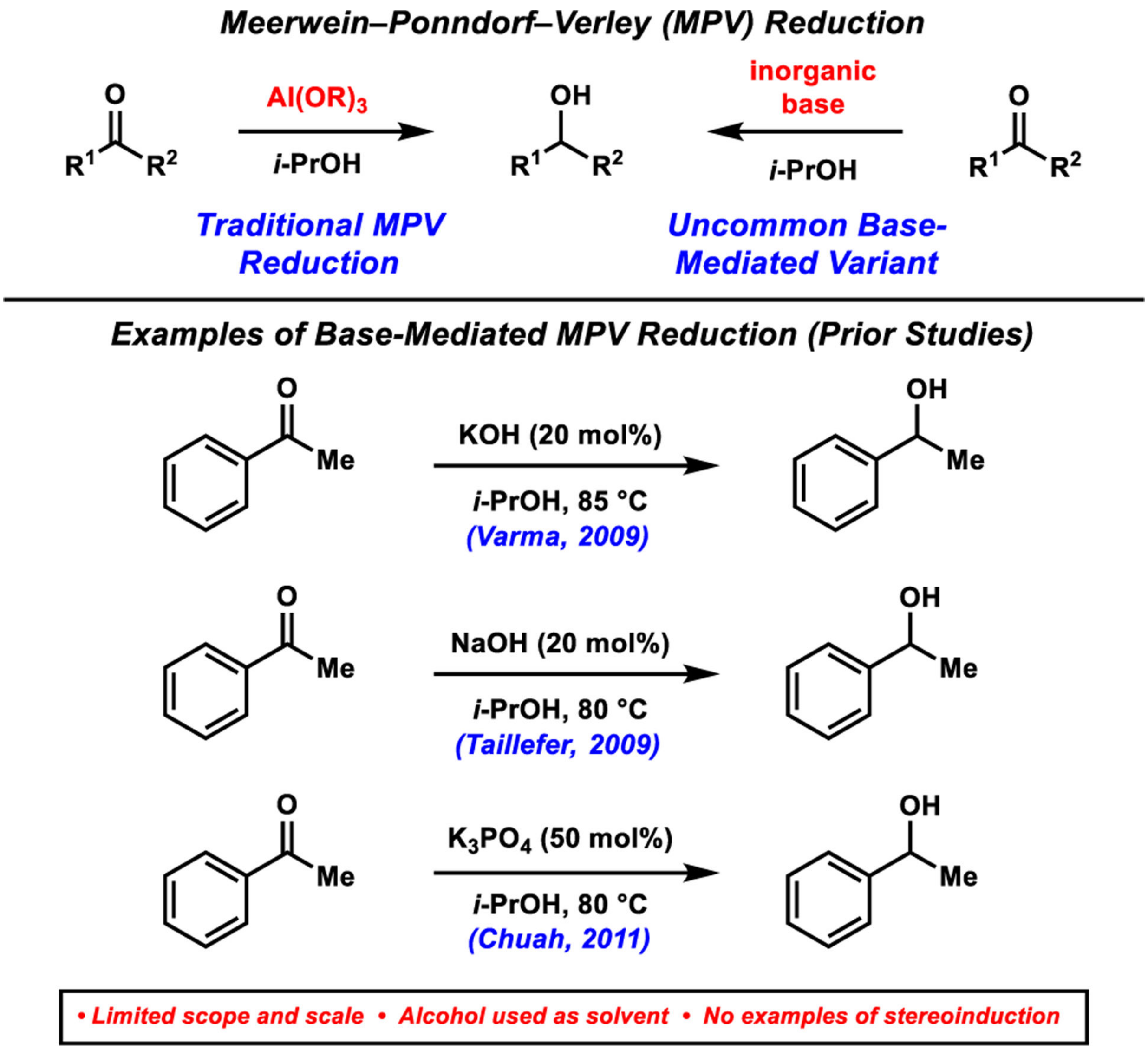


Figure 1.

Traditional MPV reduction of ketones and base-mediated variant (prior studies).

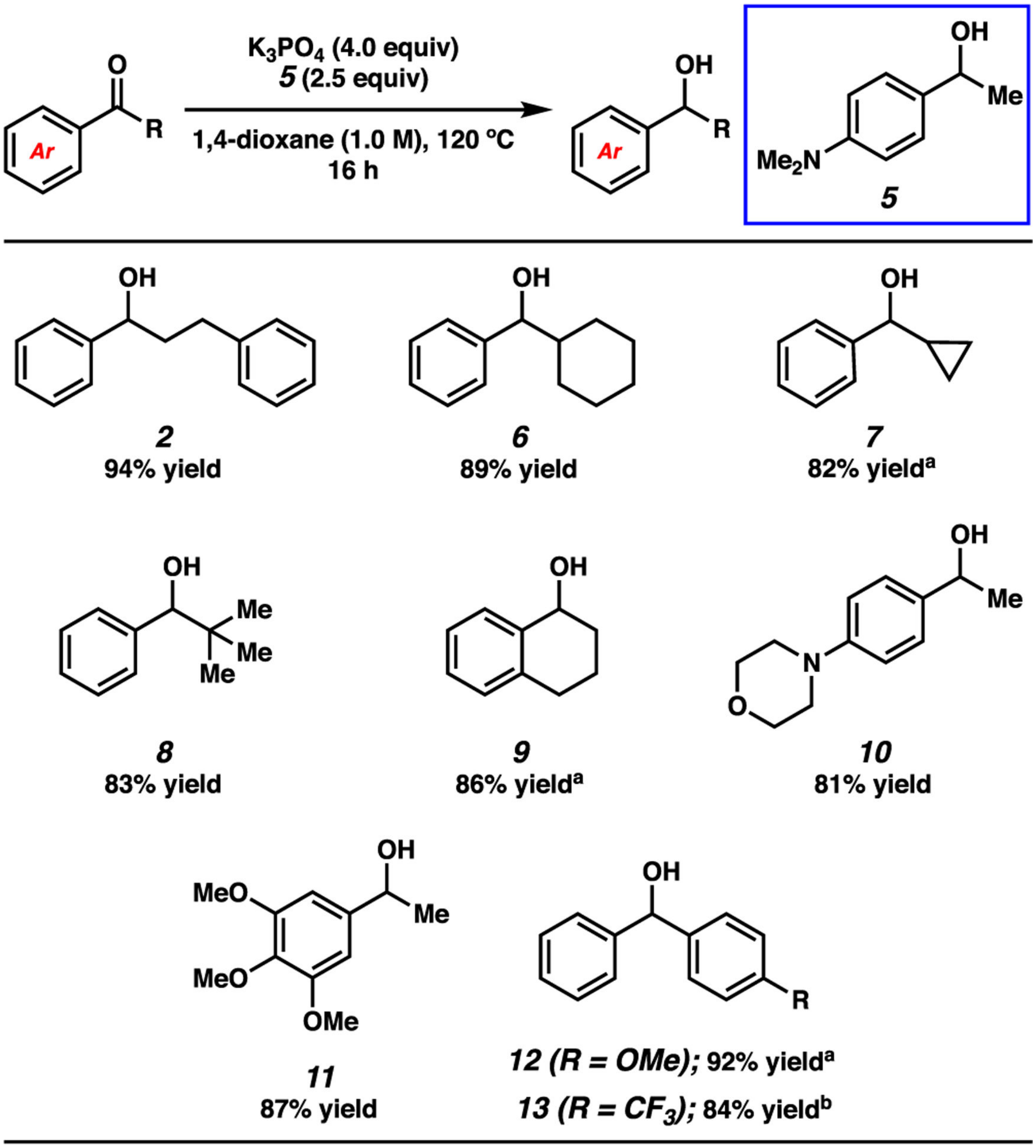


Figure 2.

Scope of the base-mediated MPV reduction of aromatic ketones. Conditions: substrate (1.0 equiv, 0.10 mmol), K_3PO_4 (4.0 equiv), reductant (2.5 equiv), and 1,4-dioxane (1.0 M) heated at 120 °C for 16 h in a sealed vial under an atmosphere of N_2. Unless otherwise noted, yields reflect the average of two isolation experiments. [a] Yield determined by ^{1}H NMR analysis using hexamethylbenzene as an external standard. [b] Reaction heated at 80 °C for 16 h.

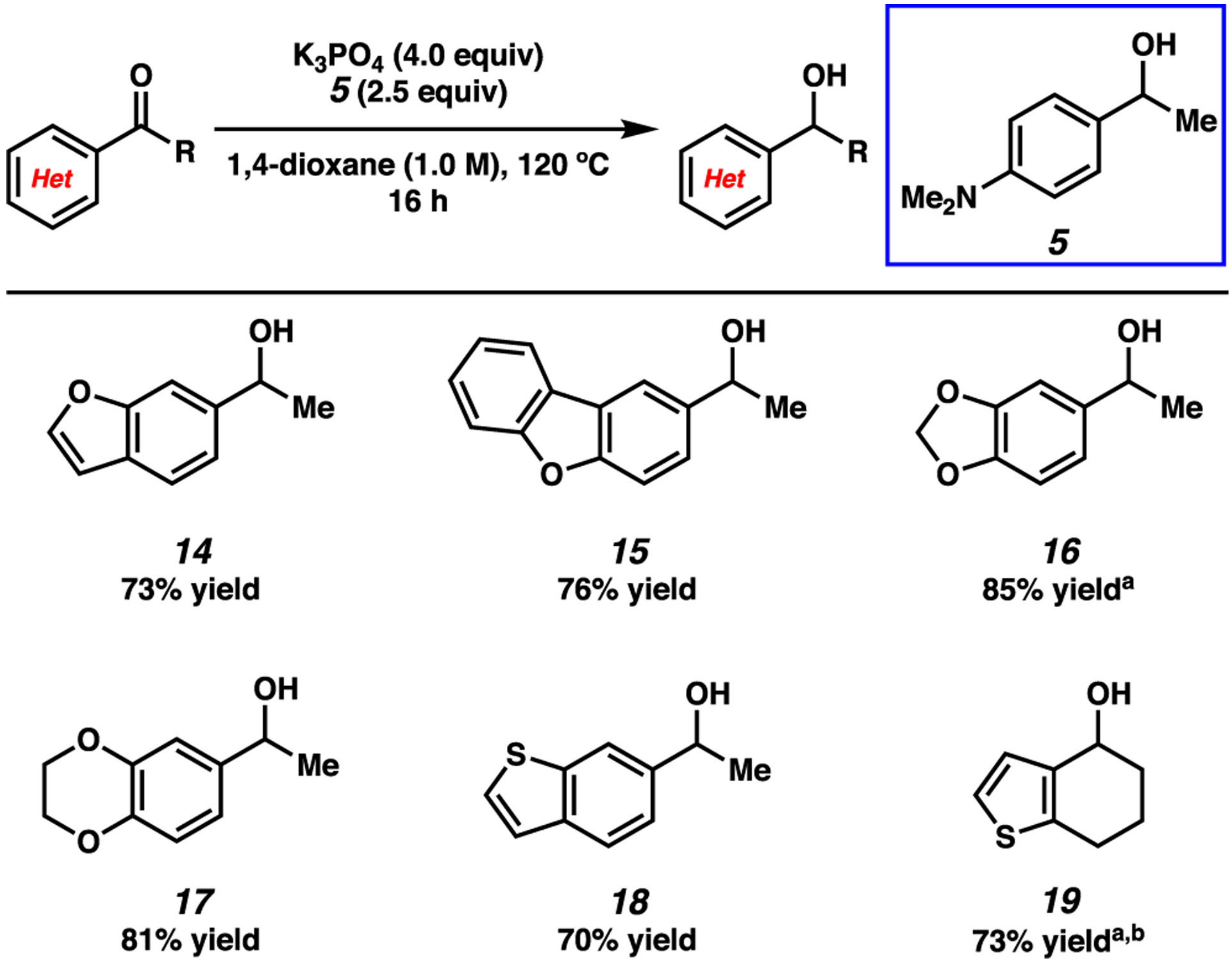


Figure 3.

Scope of the base-mediated MPV reduction of heteroaromatic ketones. Conditions: substrate (1.0 equiv, 0.10 mmol), K_3PO_4 (4.0 equiv), reductant (2.5 equiv), and 1,4-dioxane (1.0 M) heated at 120 °C for 16 h in a sealed vial under an atmosphere of N_2. Unless otherwise noted, yields reflect the average of two isolation experiments. [a] Yield determined by ^{1}H NMR analysis using hexamethylbenzene as an external standard. [b] Reaction heated at 130 °C for 16 h.

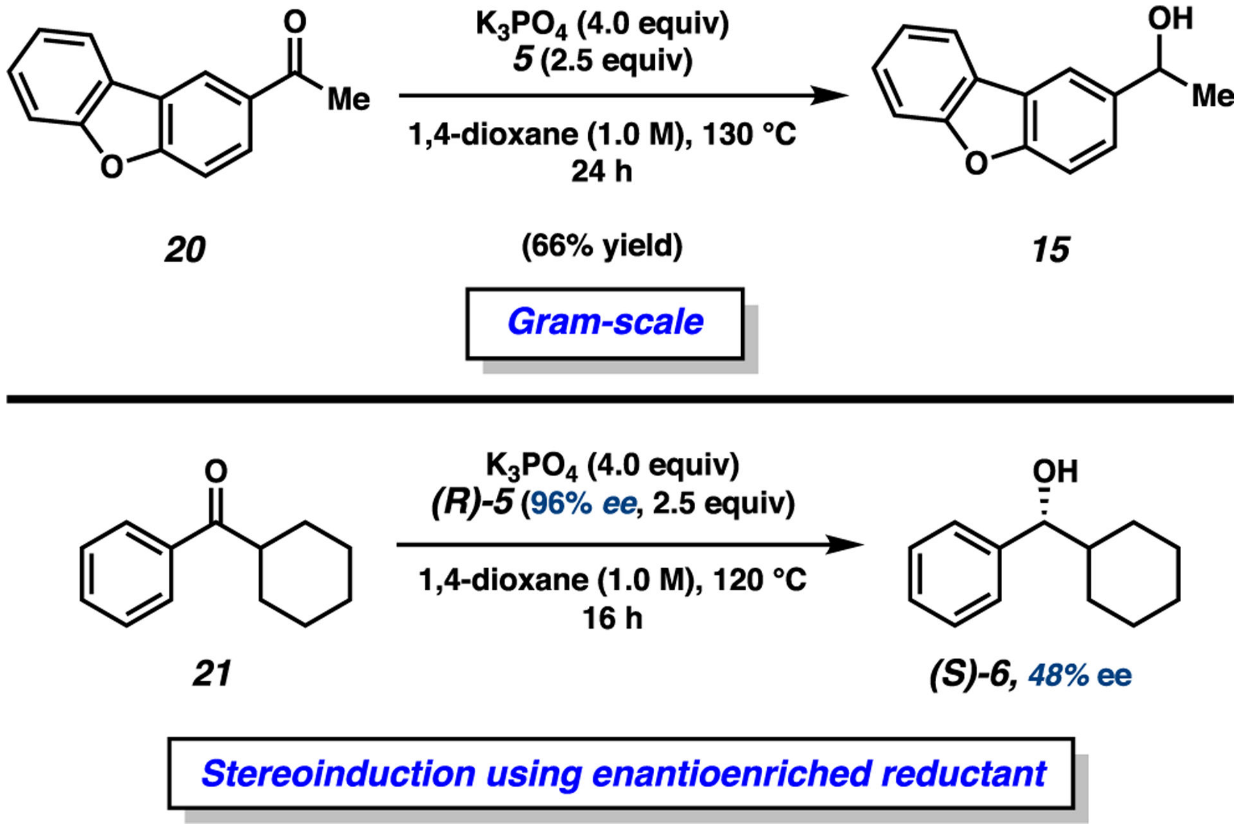
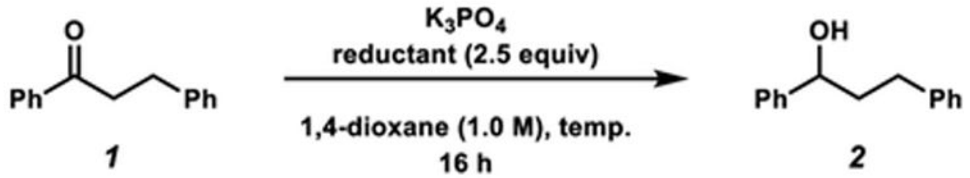


Figure 4.

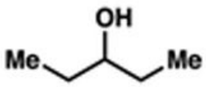
Gram-scale reduction and stereochemical transfer studies demonstrating the synthetic utility of the base-mediated MPV reduction. Conditions: substrate (1.0 equiv), K_3PO_4 (4.0 equiv), reductant (2.5 equiv), and 1,4-dioxane (1.0 M) heated at the indicated temperature and time in a sealed vial under an atmosphere of N_2.

Table 1.

Optimization of Reaction Conditions



entry	reductant	equiv K3PO4	temp (°C)	yield
1	i-PrOH	0.50	80	0%
2	3	0.50	80	0%
3	4	0.50	80	40%
4	5	0.50	80	61%
5	5	0.50	120	92%
6	5	4.0	120	99%



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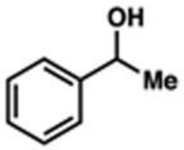

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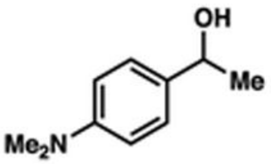

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[a] General conditions unless otherwise stated: substrate **1** (1.0 equiv, 0.10 mmol), K$_3$PO$_4$ (0.50–4.0 equiv), reductant (2.5 equiv), and 1,4-dioxane (1.0 M) heated at 80–120 °C for 16 h in a sealed vial under an atmosphere of N$_2$. Yields determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an external standard.