Transfer Hydrogenative Couplings Hot Paper

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Iron-Catalyzed Regioselective Transfer Hydrogenative Couplings of Unactivated Aldehydes with Simple Alkenes

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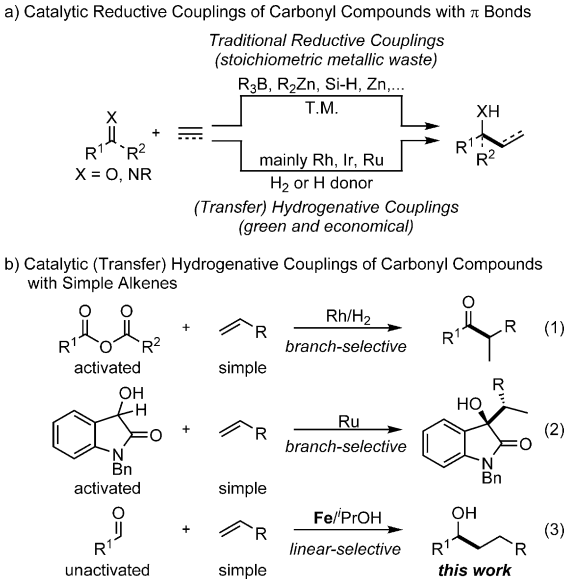
Abstract: *An $FeBr_3$-catalyzed reductive coupling of various aldehydes with alkenes that proceeds through a direct hydride transfer pathway has been developed. With ^{i}PrOH as the hydrogen donor under mild conditions, previously challenging coupling reactions of unactivated alkyl and aryl aldehydes with simple alkenes, such as styrene derivatives and α-olefins, proceeded smoothly to furnish a diverse range of functionalized alcohols with complete linear regioselectivity.*

The catalytic hydrogenative or transfer hydrogenative coupling of π-unsaturated reactants with carbonyl compounds has recently emerged as one of the most attractive C–C bond-forming methods.[1] Unlike traditional catalytic reductive C–C couplings that employ alkyl metal reagents,[2] metal hydrides,[3] or elemental metals[4] as the reducing agents (Scheme 1 a), (transfer) hydrogenative couplings using hydrogen gas or hydrogen donors as greener terminal reductants provide a much less expensive and more environmentally benign C–C bond-forming process without generating stoichiometric amounts of metallic wastes. Following an isolated report by Molander and Hoberg on the H_2-mediated reductive cyclization of 1,5- and 1,6-dienes,[5] Krische and co-workers pioneered the development of both hydrogenative and transfer hydrogenative couplings of carbonyl compounds with a variety of π-unsaturated compounds, including enones,[6a] alkynes,[6b] 1,3-dienes,[6c] enynes,[6d] allenes,[6e] and allyl compounds.[6f] However, readily available simple alkenes, such as styrenes and α-olefins, have always been challenging substrates for intermolecular couplings with carbonyl compounds owing to their low reactivity.[7] Although significant progress has already been made to address this challenge, for example, by introducing activated carbonyl compounds such as carboxylic anhydride [Scheme 1 b, Eq. (1)],[8] or by using hydroxyoxindole as the pyruvamide precursor[9] [Eq. (2)] to facilitate these couplings, a generally effective strategy to achieve regioselective (transfer) hydrogenative couplings of simple alkenes with abundant and accessible carbonyl compounds such as aryl and alkyl aldehydes remains elusive.



Scheme 1. Catalytic intermolecular reductive couplings of π-unsaturated reactants with carbonyl compounds.

On the other hand, catalysts based on noble metals such as Rh, Ir, or Ru dominate these (transfer) hydrogenative couplings of carbonyl compounds with various π-bonds.[1] The replacement of these noble metals with less toxic, inexpensive, and abundantly available metals is one of the most important challenges in this field. A major breakthrough was the nickel-catalyzed transfer hydrogenative coupling of 1,3-dienes with paraformaldehyde developed by Krische and co-workers.[10] Iron as the second most abundant and generally non-toxic metal on Earth has become an increasingly sought-after metal catalyst,[11] but iron-catalyzed (transfer) hydrogenative couplings have not been developed thus far. Herein, we report the first iron-catalyzed regioselective transfer hydrogenative coupling of unactivated aldehydes with simple alkenes, including styrene derivatives and α-olefins, which is mediated by ^{i}PrOH [Eq. (3)].

There are two most commonly proposed pathways for hydrogen transfer in metal-catalyzed (transfer) hydrogenations of carbonyl compounds. The first one involves the initial formation of a metal–hydride species and subsequent hydrogen transfer to the unsaturated bond.[12] The second one has been proposed for Meerwein–Ponndorf–Verley (MPV) reactions[13a] and alcohol dehydrogenase processes, which do not involve M–H species;[13b] direct hydride transfer from the H donor to the unsaturated bond catalyzed by various non-noble metal complexes is thus observed.[14] Currently, almost all (transfer) hydrogenative couplings of carbonyl compounds with π-unsaturated reactants have been developed on the

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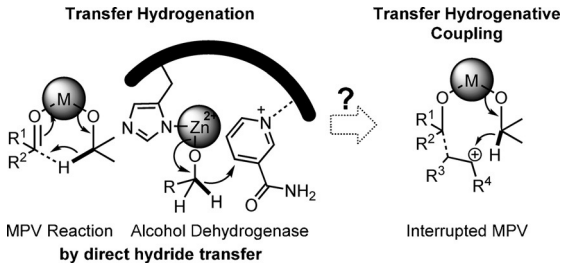
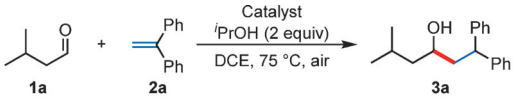
basis of the former mechanism and involve metal–hydride species,[1] whereas (transfer) hydrogenative couplings through the latter direct H transfer mechanism have not been reported to date. We envisaged that an alkene may be introduced in the MPV reaction to form a transient carbocation as the hydrogen trapping site instead of a carbonyl group. On this basis, we envisaged the development of an interrupted MPV-type transfer hydrogenative coupling of carbonyl compounds with alkenes in the presence of a non-noble-metal catalyst (Scheme 2).



Scheme 2. Proposed transfer hydrogenative coupling.

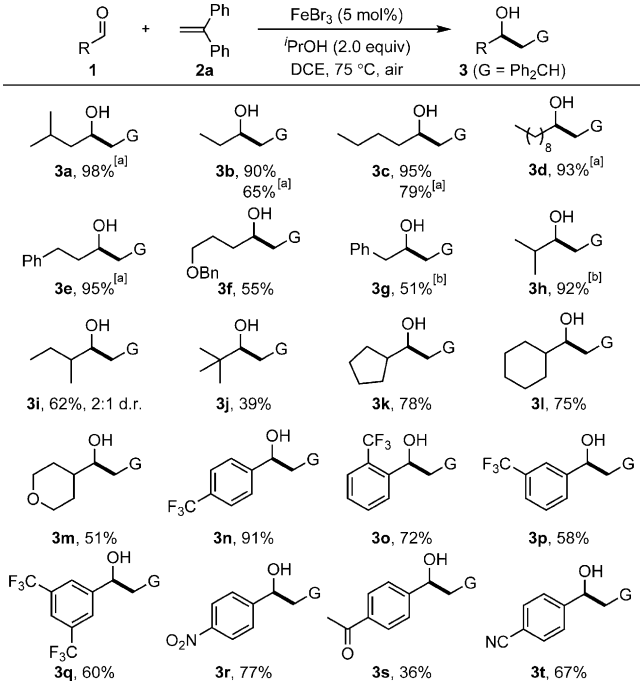
We commenced our studies by using isovaleraldehyde (**1a**) and 1,1-diphenylethylene (**2a**) as the model substrates. Using ^{i}PrOH as both the solvent and H donor, initial investigations of a wide range of metal catalysts at various temperatures failed to produce the expected product. Fortunately, lowering the loading of ^{i}PrOH to 10 equivalents in DCE in the presence of $Zn(OTf)_2$ as the catalyst led to a small amount of the expected reductive-coupling product with completely linear regiocontrol (Scheme 3, entry 1). Further reducing the ^{i}PrOH loading to 2 equivalents greatly improved the yield to 49% (entry 2). Many of the screened Lewis acids, including Cu, Ag, Sc, In, and Ga salts, successfully catalyzed this reaction with reasonable yields (entries 3–7). Notably, Brønsted acids could also catalyze this reaction, but were less efficient than Lewis acids (entry 8; see also the Supporting Information, Table S3). To our great delight, inexpensive and abundant Fe salts turned out to be an ideal choice for this reaction (entries 9–14). Among them, $FeBr_3$ proved to be the optimal catalyst and provided the desired compound in 98% yield (entry 14). Further reducing the catalyst loading resulted in a significant decrease in yields (entries 15 and 16).



Entry	Catalyst (mol%)	Yield[a] [%]	Entry	Catalyst (mol%)	Yield[a] [%]
1[b]	$Zn(OTf)_2$ (10)	5	9	$FeBr_2$ (1)	47
2	$Zn(OTf)_2$ (1)	49	10	$Fe(ClO_4)_2 \cdot xH_2O$ (1)	50
3	$Cu(OTf)_2$ (1)	11	11	$Fe(OTf)_3$ (1)	22
4	AgOTf (1)	12	12	$Fe(acac)_3$ (1)	0
5	$Sc(OTf)_3$ (1)	53	13	$FeCl_3$ (1)	96
6	$In(OTf)_3$ (1)	49	**14**	**$FeBr_3$ (1)**	**>99 (98)**
7	$Ga(OTf)_3$ (1)	38	15	$FeBr_3$ (0.5)	80
8	MsOH (1)	3	16	$FeBr_3$ (0.1)	14

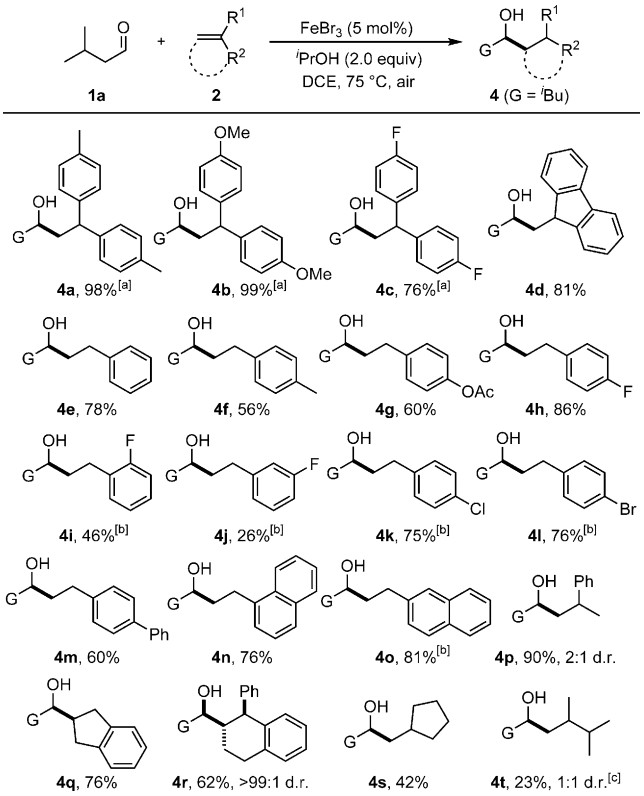
Scheme 3. Optimization of the reaction conditions. [a] Determined by ^{1}H NMR spectroscopy using CH_2Br_2 as the internal standard. Yields of isolated products given in parentheses. [b] ^{i}PrOH (2 mmol, 10 equiv). acac = acetylacetonate, DCE = 1,2-dichloroethane, Tf = trifluoromethanesulfonyl.

With optimized reaction conditions in hand, we first explored a series of alkyl and aryl aldehydes to explore the generality of the reaction (Scheme 4). Various alkyl aldehydes with linear alkyl chains were highly reactive under these conditions and afforded the corresponding products in good to excellent yields in the presence of 1 or 5 mol% of $FeBr_3$ (**3b**–**3d**). Alkyl aldehydes with phenyl (**3e** and **3g**) or benzyloxy (**3f**) moieties on the alkyl chain were also tolerated and gave the desired products in moderate to excellent yields. Impressively, various bulky alkyl aldehydes with large substituents in the α-position reacted well, providing compounds **3h**–**3m** in moderate to good yields. Notably, sterically very demanding pivaldehyde reacted smoothly to furnish the desired alcohol in 39% yield (**3j**). Aside from alkyl aldehydes, aryl aldehydes were also compatible with the reaction conditions. Various aryl aldehydes bearing electron-withdrawing groups, such as CF_3 (**3n**, **3o**, **3p**, and **3q**), NO_2 (**3r**), Ac (**3s**), and CN (**3t**), worked well and generated the corresponding products in 36 to 91% yield, whereas benzaldehyde and aryl aldehydes bearing electron-donating groups were found to be unsuitable for this reaction.



Scheme 4. Aldehyde scope. [a] $FeBr_3$ (1 mol%). [b] $FeBr_3$ (10 mol%).

Next, the compatibility of a variety of alkenes with this transfer hydrogenative coupling reaction was examined (Scheme 5). 1,1-Diaryl alkenes proved to be excellent coupling partners for this transformation and were converted into the corresponding products in high yields (**4a**–**4d**). Styrene (**4e**) and styrene derivatives with diverse substituents on the aryl group reacted efficiently in the presence of 5 or 10 mol% of $FeBr_3$ to afford the corresponding products in satisfactory

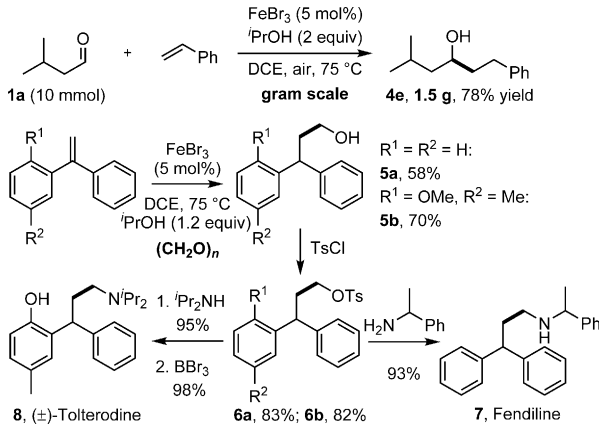


Scheme 5. Alkene scope. [a] $FeBr_3$ (1 mol%). [b] $FeBr_3$ (10 mol%). [c] 2,3-Dimethylbut-1-ene (0.6 mmol).

yields (**4f**–**4m**). Vinyl-substituted naphthalenes (**4n** and **4o**) were also suitable coupling partners (76–91%). More importantly, styrene derivatives bearing a 2-substituted alkyl group (**4p**, **4q**, and **4r**) reacted well in this coupling reaction, and the possible olefinated side product was not observed. Among them, a highly hindered trisubstituted alkene worked efficiently to provide the corresponding product with very high diastereoselectivity (**4r**; characterized by single crystal X-ray diffraction analysis, see the Supporting Information). Pleasingly, branched α-olefins (**4s** and **4t**) also reacted smoothly to deliver the expected products in reasonable yields.

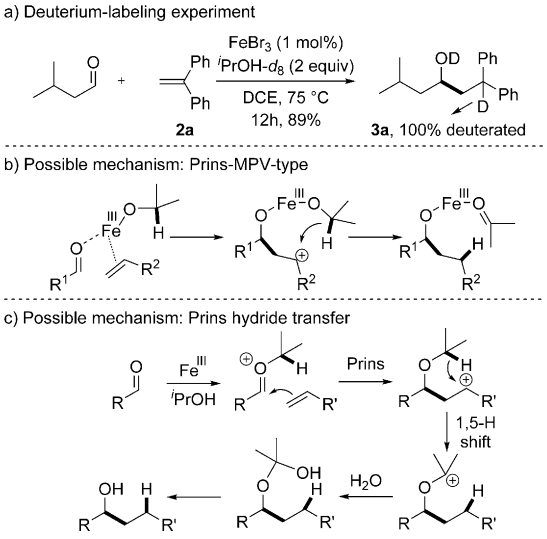
This transfer hydrogenative coupling of isovaleraldehyde **1a** with styrene could easily be scaled up to gram scale without an apparent decrease in yield (1.5 g of product **4e**; Scheme 6). To further study the synthetic utility of our method, two pharmaceutically active compounds were synthesized. Two 1,1-diaryl alkenes were coupled with paraformaldehyde under the optimized reaction conditions but with only 1.2 equiv of ^{i}PrOH to form the corresponding primary alcohols **5a** and **5b**, which were then transformed into tosylates **6a** and **6b**. Further amination of **6a** with 1-phenylethanamine afforded compound **7** (fendiline) in 93% yield, and amination of **6b** with diisopropylamine followed by demethylation furnished compound **8** (tolterodine). Compared with the industrial process, which requires six steps and air- and moisture-sensitive metallic hydrides for the synthesis of racemic tolterodine, our method could provide a promising alternative.[15]

To understand the mechanism of this hydrogenative coupling reaction, additional experiments were conducted.



Scheme 6. Gram-scale reaction and synthesis of two pharmaceutically active compounds.

First, no aldehyde or alkene hydrogenation was observed in the reactions of either the aldehyde or alkene itself under the optimized reaction conditions (see the Supporting Information). This result ruled out a possible iron-catalyzed alcohol–alkene direct coupling process.[16] Second, a deuterium-labeling experiment with isovaleraldehyde and 1,1-diphenylethylene (**2a**) in the presence of ^{i}PrOH-d_8 under our optimized conditions showed complete deuterium incorporation at the former alkene C2 position (Scheme 7a). Third, an obvious kinetic isotope effect ($k_H/k_D = 2.5$) was observed in a competition experiment with ^{i}PrOH and an equal amount of ^{i}PrOH-d_8, and a radical trapping experiment showed that neither 0.2 nor 0.5 equivalents of the radical scavenger BHT (butylated hydroxytoluene) have an apparent inhibiting effect on this coupling reaction (see the Supporting Information). These results suggest that a radical pathway can be ruled out. Finally, an intramolecular coupling reaction of olefinic aldehydes (see the Supporting Information) did not provide the reductive coupling product, which suggests that a cationic intermediate could be formed, but that the geometric constraints of the substrate prevent the hydride transfer. Based on these results, two possible pathways were proposed. The first one corre-



Scheme 7. Mechanistic studies.

sponds to an iron-catalyzed Prins–MPV-type reduction, in which both the C–C coupling and the hydride transfer are enabled by the iron catalyst (Scheme 7b). The second alternative is based on an iron-catalyzed Prins/hydride-transfer process, in which C–C coupling occurs via an oxocarbenium intermediate, followed by a hydride shift to furnish the reductive-coupling product (Scheme 7c). Although the results with the Brønsted acids suggest that the latter pathway involving a precedented 1,5-H shift could be preferred,[17] the former pathway cannot be excluded at this stage because of the superior reactivity of iron.

In summary, we have successfully developed an iron-catalyzed regioselective transfer hydrogenative coupling of aldehydes with alkenes using ^{i}PrOH as the hydrogen source under mild conditions. This new C–C bond-formation method enables the coupling of unactivated aldehydes, such as alkyl and aryl aldehydes, with simple alkenes, such styrene derivatives and branched α-olefins, for the first time and is based on the use of catalytic amounts of $FeBr_3$. Preliminary mechanistic studies suggest that the reaction could proceed through a Prins/hydride-transfer pathway. We are currently working towards obtaining further evidence for our proposed mechanism and towards expanding the applicability of our method to various transfer hydrogenative couplings.

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Keywords: aldehydes · alkenes · hydride transfer · iron · transfer hydrogenative couplings

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