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Iron-catalyzed cross etherification of alcohols to form unsymmetrical benzyl ethers

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ABSTRACT

A Fe(II)-catalyzed direct synthesis of unsymmetrical benzyl ethers from two different alcohols has been developed. In the presence of a catalyst in situ generated by combining Fe(OTf)₂ (OTf = trifluoromethanesulfonate) with a pyridine bis-imidazoline ligand, benzyl alcohols underwent cross dehydrative etherification with a wide range of aliphatic alcohols in good to excellent yields under mild, operationally simple conditions with low catalyst loading. The catalyst tolerates a number of functional groups in both coupling partners, and is highly chemoselective, affording no symmetrical ether by-products. Ligand is shown to play a crucial role to the success of this dehydrative transformation, and preliminary mechanistic studies indicate that a benzylic cation is involved in the cross etherification.

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1. Introduction

The efficient construction of ethers has long been the subject of intense interest in the synthetic community, because these compounds are ubiquitous structural motifs in natural products and pharmaceuticals while serving as versatile synthetic intermediates and solvents in organic synthesis [1]. Over the past several decades, many reagents and conditions for etherification have been reported in the literature [1]. Nonetheless, the Williamson ether synthesis is still the most commonly employed method to prepare symmetrical and unsymmetrical ethers [2]. However, this method suffers from two major drawbacks, i.e. the necessity of preparation of organic halide precursors from alcohols, which is tedious and less environmentally friendly, and the strong reliance on basic conditions, which cause generation of copious quantities of inorganic salts, issues of undesired side reactions and limited substrate scope. Aiming to circumvent these shortcomings, chemists have opted to develop catalytic systems based on transition-metal complexes for preparation of ethers, and considerable advances have been achieved in Pd and Cu-catalyzed Ullmann-type C–O coupling reactions [3,4], transition metal-catalyzed hydroalkoxylation of alkenes [5] and direct alkoxylation of unactivated C–H bonds [6].

Dehydrative etherification of alcohols provides one of the most attractive methods for accessing ethers, given the ready availability of various alcohols and the generation of water as the only byproduct. Hence, extensive research has gone into this area in recent years, using various metal catalysts including precious metal complexes [7,8]. Examples of the dehydration of alcohols with more economic and less toxic iron catalysts are also known; however, the narrow substrate scope strictly limits their application in organic synthesis [9]. In view of the substantial economic and safety gains associated with the use of iron catalysts [10] and the importance of ethers [1], the development of more efficient and general iron catalytic systems to prepare ethers would be highly valuable.

We recently revealed that Fe(II)-pyridine bis-sulfonamide complexes catalyze efficient α -oxygenation of ethers at 1 bar O₂ with excellent chemoselectivity under mild conditions [11a], and the analogous Fe(III) catalyst consisting of Fe(OTf)₃ and a pyridine bis-imidazoline ligand works well for the selective aerobic oxidation of aromatic olefins to carbonyl compounds under similar conditions [11b]. It is notable that the tridentate N,N,N-ligand is essential for securing high catalytic activity and selectivity in these reactions. Encouraged by these results, we became interested in exploring the catalytic activity of iron complexes with tridentate N,N,N-ligands in other synthetically useful reactions. Herein we report that the combination of Fe(OTf)₂ with a pyridine bis-imidazoline ligand in 1,2-dichloroethane (DCE) leads to an efficient catalytic system that permits the highly selective preparation of unsymmetrical benzyl

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ethers from different alcohols. It is shown that the choice of ligand has a strong impact on the reaction efficiency. This new cross etherification protocol exhibits good tolerance to a number of functional groups, providing a new complementary route to unsymmetrical benzyl ethers.

2. Experimental section

2.1. General

Unless otherwise noted, all experiments were carried out in air, and all commercially available chemicals were used as received without further purification. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Model Advance DMX 400 Spectrometer (^1H 400 MHz and ^{13}C 100.6 MHz, respectively). Chemical shifts (δ) are given in ppm and are referenced to residual solvent peaks, and coupling constants (J) were reported in Hertz. The N-ligand **L1** [11a], **L2** [12a], **L3** [12b] and **L6** [12c] were prepared according to the previous reports. All the ligands and alcohols used in this work can be found in Fig. 1.

2.2. General procedure for cross etherification of alcohols

To an oven dried pressure tube were sequentially added $\text{Fe}(\text{OTf})_2$ (1.7 mg, 0.005 mmol), **L2** (2.6 mg, 0.005 mmol) and dry DCE (1.0 mL). The mixture was stirred for 30 min at room temperature. Then alcohol **1** (0.5 mmol) and alcohol **2** (0.5 mmol) were added to the mixture, and the tube was heated and stirred vigorously at 80 °C for 12 h. Then the tube was removed from the oil bath and cooled to room temperature. The solvent was removed by vacuum evaporation, and the residue was purified by column chromatography on silica gel using a mixture of ethyl acetate and hexane to give the pure product.

3. Results and discussion

We commenced our investigation by choosing the dehydrative reaction of (4-methoxyphenyl)methanol (**1a**) with benzyl alcohol (**2a**) as our model system (Table 1). With $\text{Fe}(\text{OTf})_2$ as the catalyst precursor and DCE as the solvent, we first examined the ligand effect. In the presence of ligand **L1**, which showed superior behavior in the previous ether oxygenation and olefin cleavage reactions [11], the etherification reaction gave a mixture of the target unsymmetrical ether, benzyl (*p*-methoxyphenyl)methyl ether (**3aa**) (32%), and the symmetrical ether, bis(*p*-methoxyphenyl)methyl ether (**4**) (16%), with, however, no dibenzyl ether being detected (Table 1, entry 1). Delightfully, switching to ligand **L2** led to the exclusive generation of the cross-etherification product **3aa** in 88% isolated yield without any detectable contamination of the homoeetherification by-product derived from **1a** or **2a** (Table 1, entry 2). The catalytic behavior of other tri- and bi-dentate nitrogen ligands was then investigated, but none of them performed better than **L2** in terms of reactivity and selectivity (Table 1, entries 3–10). Subsequent optimization showed that both the yield and selectivity of **3aa** were decreased when replacing $\text{Fe}(\text{OTf})_2$ with $\text{Fe}(\text{BF}_4)_2$ or $\text{Fe}(\text{OTf})_3$ (Table 1, entries 13 and 17), and no etherification was observed with other iron sources including FeCl_2 , FeBr_2 , $\text{Fe}(\text{OAc})_2$, FeCl_3 and $\text{Fe}(\text{acac})_3$ (Table 1, entries 11, 12, 14–16). Further studies revealed that DCE stood out as the optimal choice, as variation of the solvent gave no better results (Table 1, entries 18–26). Lowering the reaction temperature retarded the reaction, as the yield of **3aa** dropped to 38% at 50 °C (Table 1, entry 27). Likewise, when the catalyst loading was reduced, a diminished yield was obtained (Table 1, entry 28). Control experiments showed that no reaction took place in the absence of either $\text{Fe}(\text{OTf})_2$ or **L2** (Table 1, entries 29

Table 1
Optimization of reaction conditions for cross etherification.^a

Entry	[Fe]	Ligand	Solvent	3aa/4 ^b	Yield(%) ^c
1	$\text{Fe}(\text{OTf})_2$	L1	DCE	2/1	32
2	$\text{Fe}(\text{OTf})_2$	L2	DCE	>99/1	88
3	$\text{Fe}(\text{OTf})_2$	L3	DCE	6/1	49
4	$\text{Fe}(\text{OTf})_2$	L4	DCE	1/1	16
5	$\text{Fe}(\text{OTf})_2$	L5	DCE	1/6	5
6	$\text{Fe}(\text{OTf})_2$	L6	DCE	ND	NR
7	$\text{Fe}(\text{OTf})_2$	L7	DCE	1/1	33
8	$\text{Fe}(\text{OTf})_2$	L8	DCE	2.5/1	39
9	$\text{Fe}(\text{OTf})_2$	L9	DCE	38/1	53
10	$\text{Fe}(\text{OTf})_2$	L10	DCE	2/1	32
11	FeCl_2	L2	DCE	ND	NR
12	FeBr_2	L2	DCE	ND	NR
13	$\text{Fe}(\text{BF}_4)_2$	L2	DCE	1/1	24
14	$\text{Fe}(\text{OAc})_2$	L2	DCE	ND	NR
15	FeCl_3	L2	DCE	ND	NR
16	$\text{Fe}(\text{acac})_3$	L2	DCE	ND	NR
17	$\text{Fe}(\text{OTf})_3$	L2	DCE	3/1	51
18	$\text{Fe}(\text{OTf})_2$	L2	dioxane	9/1	7
19	$\text{Fe}(\text{OTf})_2$	L2	toluene	4/1	22
20	$\text{Fe}(\text{OTf})_2$	L2	xylene	2/1	52
21	$\text{Fe}(\text{OTf})_2$	L2	CH_3CN	1/1	16
22	$\text{Fe}(\text{OTf})_2$	L2	DMF	ND	NR
23	$\text{Fe}(\text{OTf})_2$	L2	THF	2.3/1	14
24	$\text{Fe}(\text{OTf})_2$	L2	CH_2Cl_2	2/1	23
25	$\text{Fe}(\text{OTf})_2$	L2	PhCl	4/1	49
26	$\text{Fe}(\text{OTf})_2$	L2	DMSO	ND	NR
27 ^d	$\text{Fe}(\text{OTf})_2$	L2	DCE	99/1	38
28 ^e	$\text{Fe}(\text{OTf})_2$	L2	DCE	99/1	33
29	$\text{Fe}(\text{OTf})_2$	none	DCE	ND	NR
30	none	L2	DCE	ND	NR

^a Reaction Conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), [Fe] (1.0 mol%), ligand (1.0 mol%), solvent (1.0 mL), 80 °C, 12 h; ND: not detected; NR: no reaction.

^b The ratio was determined by ^1H NMR.

^c Isolated yield of **3aa**.

^d Reaction temperature 50 °C.

^e $\text{Fe}(\text{OTf})_2$ (0.5 mol%) and **L2** (0.5 mol%) were used.

and 30). Thus the optimal reaction conditions were finally determined as following: $\text{Fe}(\text{OTf})_2$ (1.0 mol%), **L2** (1.0 mol%) in DCE at 80 °C for 12 h. It is worth noting that the reaction is operationally simple, requiring no inert atmosphere protection.

Under the optimized conditions, we explored the cross etherification of **1a** with a range of benzyl alcohols and alkyl alcohols. As shown in Scheme 1, benzyl alcohols **2b–2g** bearing different substituent groups on the phenyl ring were effectively converted to the expected cross ether products in good yields (**3ab–3ag**) regardless of their electronic properties. Notably, thiophen-2-yl methanol (**2h**) was reactive and did not poison the catalyst, furnishing the desired product **3ah** in 84% yield. The sterically more demanding 1-arylethanol (**2i–2l**) also reacted well with **1a**, giving the corresponding unsymmetrical ethers (**3ai–3al**) in good yields with no styrene byproducts being detected [13]. Similarly, the etherification of 1-phenylpropan-1-ol (**2m**) with **1a** afforded selectively the corresponding ether product **3am**.

The reaction is not limited to benzyl alcohols, and aliphatic alcohols also participated well. Thus, the aliphatic primary (**2n, 2q, 2s–2v**) and secondary (**2o, 2p, 2r**) alcohols all underwent smooth etherification with **1a**, affording the products (**3an–3av**) in good to excellent yields. Still interestingly, the present protocol is effective for the etherification of allylic alcohol (**2w**) and propargyl alcohol (**2x**), with the desired products (**3aw, 3ax**) obtained in good yields. It should be stressed that the unsymmetrical ethers were formed exclusively in all cases, with no symmetrical ether being detected. We also note that the yield of the ether products **3** does not vary considerably with the electronic or steric characteristics of **2**, e.g. **3ab–3ah** and **3ai–3al**. This appears to indicate that the turnover limiting step of the cross etherification does not involve **2** (vide infra).

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