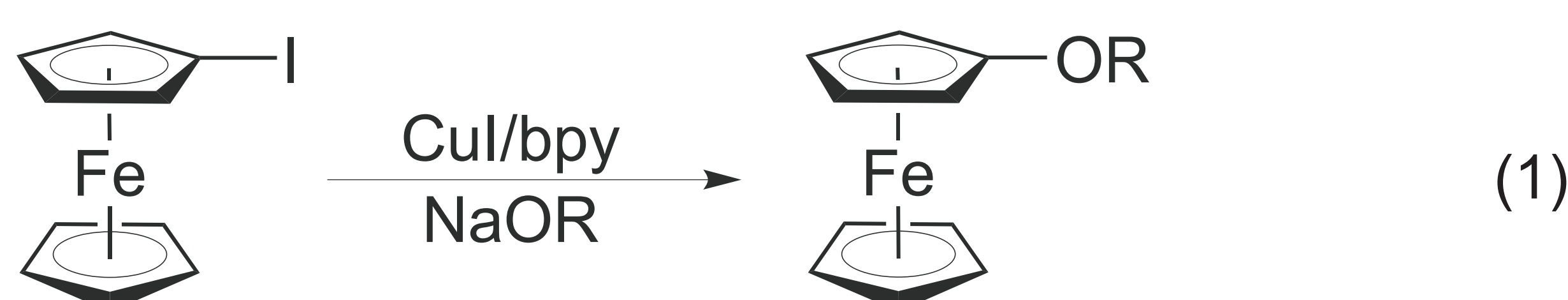


Introduction

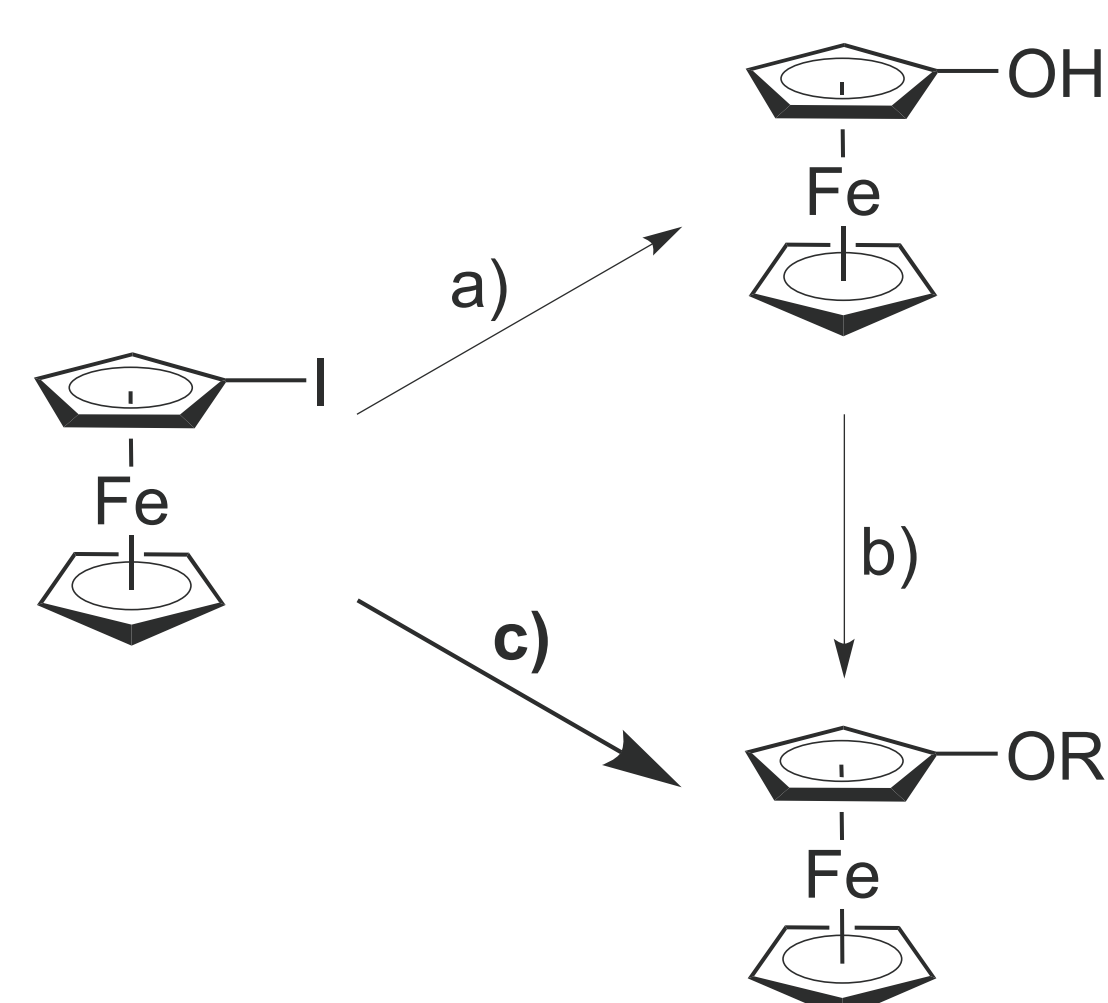
In the last decades ferrocene has emerged as an essential motif in organometallic chemistry. It has found numerous applications in academia and industry, the spectrum ranges from its use as highly selective and efficient ligand in asymmetric homogeneous catalysis to fuel additives for diesel engines.^[1] The field of oxygen-substituted ferrocenes is one aspect that is still not fully developed. This may be attributed to the sensitiveness of the phenol analogue hydroxyferrocene or the tendency of oxygen electrophiles, *e. g.* peroxides or peresters, to irreversibly oxidize the iron center. Since 1959, when Nesmeyanov and coworkers reported on the synthesis of some ferrocenyl alkyl ethers via etherification of hydroxyferrocene^[2], only a few new molecules have been prepared utilizing mostly primary alkyl halides or tosylates.^[3] To our knowledge the successful application of neither secondary nor tertiary alkyl derivatives has been reported so far. In contrast, ferrocenyl aryl ethers are easily accessible via copper(I) mediated coupling of iodoferrocene and various phenols as demonstrated by Plenio *et al.* recently.^[4] We report here on the copper(I)-mediated Ullman-type coupling of iodoferrocene with diverse alcoholates to give ferrocenyl alkyl ethers (Reaction 1).



Results and Discussion

The synthesis of ferrocenyl alkyl ethers via the established Williamson ether synthesis - starting from hydroxyferrocene - is limited to substrates that can successfully be attacked by the phenol analogue nucleophile (Scheme 1, path b). All our attempts to apply sterically demanding alkyl derivatives in this reaction failed. However, to still synthesize such ethers, we exerted a copper(I)-mediated Ullman-type coupling utilizing iodoferrocene and diverse alcoholates (Reaction 1; Scheme 1, path c).^[5] The coupling reaction proceeds efficient as besides the desired ferrocenyl ether only unreacted iodoferrocene and ferrocene could be identified.^[6]

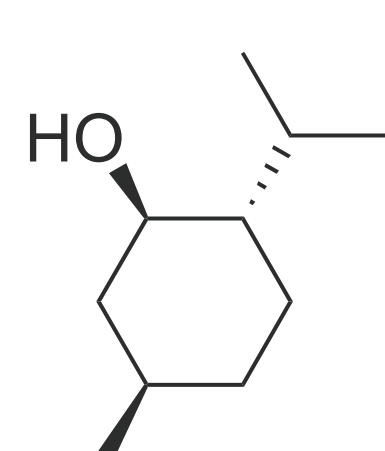
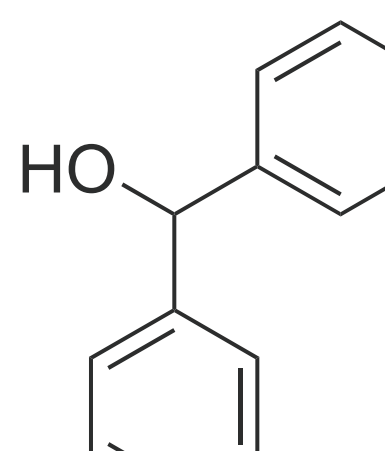
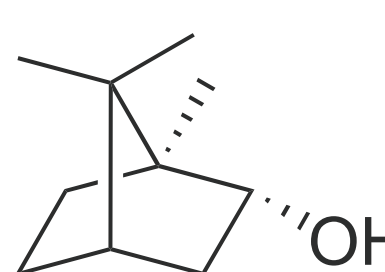
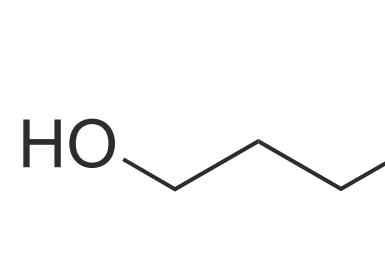

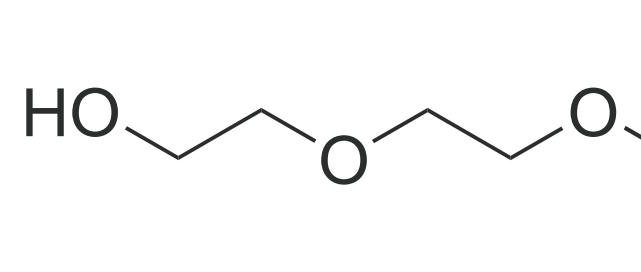
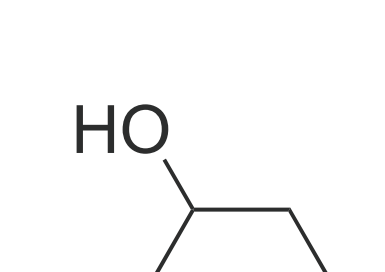
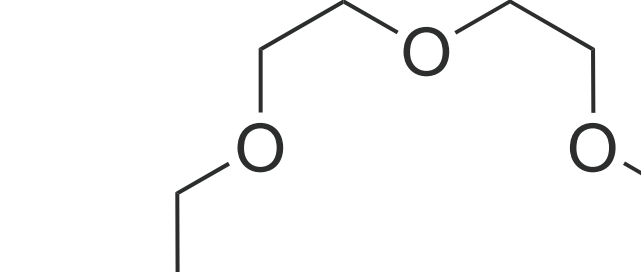
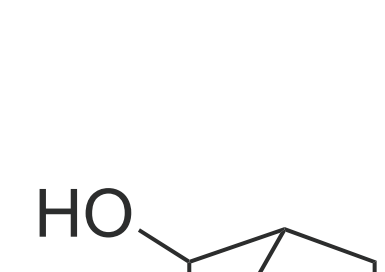
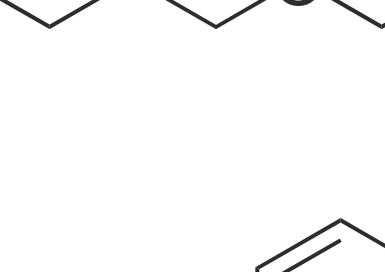
Table 1 exemplary shows a few alcohols that have been applied in this Ullman-type coupling reaction.



Scheme 1: Synthesis of ferrocenyl alkyl ethers starting from iodoferrocene.

a) 1. AcOH, Cu₂O, CH₃CN, reflux, 3 h (93 %); 2. KOH, H₂O, EtOH, reflux, 20 min; 3. HCl, H₂O, EtOH, ambient temperature, 10 min (95 %); b) base, menthylX (X = Cl, OS(O)₂CH₃, OS(O)₂-4-NO₂-C₆H₄), solvent, ambient temperature to 100 °C, 12-24 h; c) CuI, 2,2'-bipyridine, NaOR, NMP, 70 °C, 18 hours.

Table 1: Ullman-type coupling of iodoferrocene and various alcohols.^a

Entry	Alcohol	Yield / % ^b	Entry	Alcohol	Yield / % ^b
1		82, 19 ^c	6		76
2		57	7		24
3		38	8		22
4		45	9		18 ^d
5		74	10		13

^a Reaction conditions: 1.0 equiv. iodoferrocene, 3.0 equiv. NaOR, 1.0 equiv. CuI, 0.2 equiv. 2,2'-bipyridine, NMP (5 mL/mmol iodoferrocene), 70 °C, 18 hours.

^b Based on isolated material.

^c 0.1 equiv. CuI.

^d 2.0 equiv. NaOR.

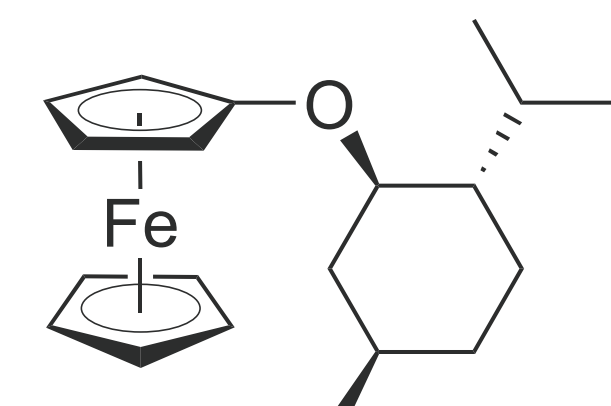
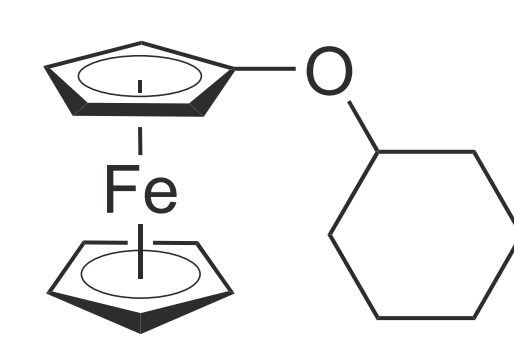
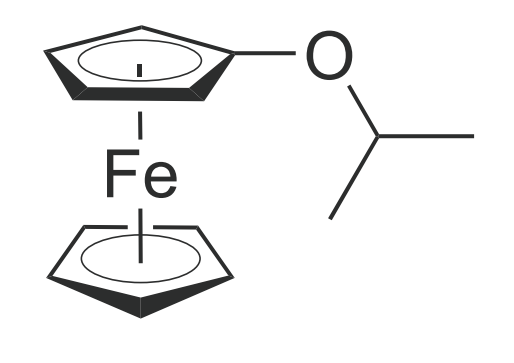
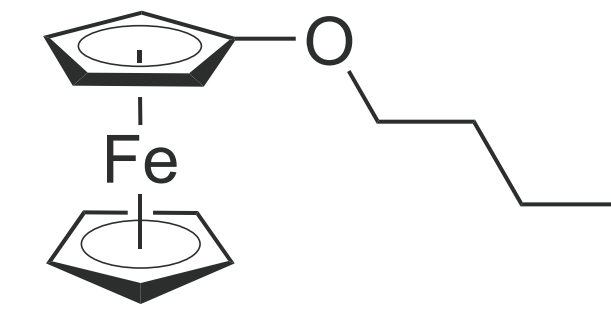
Secondary (Table 1, entries 1-6) and primary (entries 7-10) alcohols could successfully be applied in this coupling reaction, tertiary alcoholates NaOR are almost inactive (R = *t*-Bu, Ph₃C, 1-adamantyl, yields < 5 %).^[7] The following order of reactivity can be established:



Obviously secondary alcohols show better results in this Ullman-type coupling than primary ones. Considering the secondary alcohols it is obvious that steric hindrance at the β-carbons improves the yield of the reaction (entries 1, 2, 5 and 6 vs. 4) as long as the system is not overcrowded (entry 3). A beneficial property of this Ullman-type coupling is that chiral alcohols can be applied without any loss of stereoinformation. The reaction runs with full retention of configuration (entries 1-3). We also tried to perform this reaction catalytically based on copper(I) (entry 1, 0.1 equiv. CuI), which resulted in a dramatic loss of activity. Nevertheless, the yield of this experiment revealed that this coupling reaction is at least substoichiometric concerning copper(I).

Table 2 shows a comparison between the classical Williamson ether synthesis and the presented Ullman-type coupling. It comes clear that the coupling of iodoferrocene and an alcoholate is especially beneficial when sterically demanding alcohols are applied (Table 2, entries 1 and 2 vs. 3 and 4). Furthermore it is obvious that both synthesis methodologies are complementary.

Table 2: Comparison of Ullman-type coupling and Williamson ether synthesis.

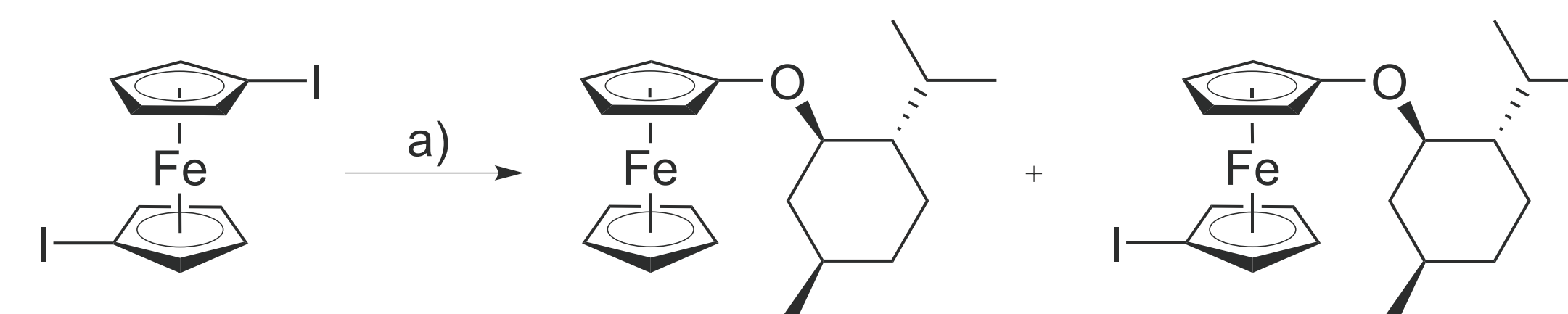
Entry	Product	Yield / % ^a	
		Ullman ^b	Williamson ^c
1		82	0
2		45	3
3		10	32
4		24	50

^a Based on isolated material.

^b Reaction conditions: 1.0 equiv. iodoferrocene, 3.0 equiv. NaOR, 1.0 equiv. CuI, 0.2 equiv. 2,2'-bipyridine, NMP (5 mL/mmol iodoferrocene), 70 °C, 18 hours.

^c Reaction conditions: 1.0 equiv. FcOAc, 2.0 equiv. KOH, 2.0 equiv. RX (X = Br, Cl, OS(O)₂CH₃, OS(O)₂-4-NO₂-C₆H₄), DMF (7 mL/mmol FcOAc), 100 °C, 18 hours.

We also applied 1,1'-diiodoferrocene in this coupling reaction. Using an excess of menthol we were able to isolate a disubstituted ferrocene besides menthoxyferrocene (Scheme 2, ratio 1 : 1) as the only products. A ferrocene proving a twofold reaction could not be identified. Unfortunately we were not able to separate the two ferrocenyl ethers by column chromatography. The formation of monosubstituted menthoxyferrocene can be explained by hydrodehalogenation (*vide supra*).^[6]



Scheme 2: Ullman-type coupling of 1,1'-diiodoferrocene and menthol.

a) 1.0 equiv. 1,1'-diiodoferrocene, 6.0 equiv. NaOmenthyl, 2.0 equiv. CuI, 0.4 equiv. 2,2'-bipyridine, 10 mL NMP, 70 °C, 18 hours.

Conclusion

Within this study the straightforward preparation of ferrocenyl alkyl ethers by an Ullman-type coupling of iodoferrocene and various alcohols has been developed, which is highly diastereoselective in case of chiral alcohols. Primary and secondary alcohols can successfully be applied in this reaction, tertiary alcohols are almost inactive. A comparison of the developed coupling reaction with the classical Williamson ether synthesis revealed that both methodologies are complementary. Especially when secondary alcohols are applied the respective ethers that are not accessible via etherification of ferrocenol can be isolated in good yields, which enriches this field of chemistry. Nevertheless there is still a need for a rational synthesis route which utilizes tertiary alkyl derivatives.

References and Acknowledgement

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- [4] M.R. an der Heiden, G.D. Frey, H. Plenio, *Organometallics* **2004**, 23, 3548.
- [5] The alcohols were deprotonated with sodium hydride prior to use. The direct use of an alcohol and a suitable base (*e. g.* KO₂Et) did result in significantly less yields (approx. 10 %).
- [6] Hydrodehalogenations are commonly observed in Ullman-type coupling reaction. See, for example: J.W. Tye, Z. Weng, R. Giri, J.F. Hartwig, *Angew. Chem.* **2010**, 122, 2231.
- [7] While the coupling of primary and secondary alcohols is well documented in literature, to the best of our knowledge the use of tertiary alcohols has not been reported so far.

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