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Chiral lithiothiophenes as non-transferable ligands in organocuprate conjugate addition reactions

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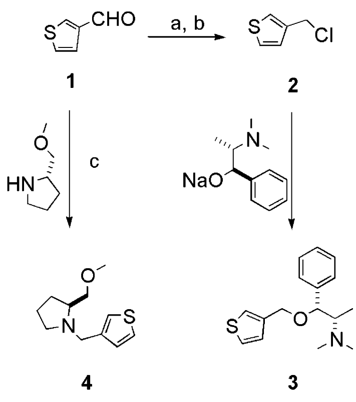
Abstract—Non-transferable carbon bound homochiral ligands have been developed for the asymmetric transfer of an alkyl or an aryl group to a prochiral α,β-unsaturated enone with copper reagents. These ligands are based on thiophene and chiral amino alcohols derived from L-proline and ephedrine.

1. Introduction

Organocuprates are some of the most important reagents for C–C bond-forming reactions available to synthetic chemists. Alkyl and aryl groups have been transferred enantioselectively to prochiral α,β-unsaturated enones using heterocuprates of the empirical formulas RCu(OR)Li[1–5] and RCu(NR*R′)Li[6–9] where the R* is a homochiral fragment. Several of these have been reported to give excellent enantioselectivities. These reagents are based upon earlier work using heterocuprates formed from alkyl and aryl lithium reagents and lithium alkoxides[10] and amides,[11,12] developed to transfer selectively the alkyl and aryl groups to enones as a way of conserving valuable carbanionic moieties. This methodology has also been used with non-transferable carbon-bound ligands.[13–16] One of the most effective of these carbon-bound mixed cuprates is the thienyl cuprate moiety, having both good reactivity[17] and stability.[15] The classic thiophene ligand developed by Nilsson has had perhaps the widest usage because of these advantages coupled with the low cost and ease of preparation. With this in mind, we have begun to develop chiral ligands based upon thiophene for enantioselective additions to enones.

2. Results and discussion

A recent description of a large scale preparation 3-thiophene carboxaldehyde, **1**, from cheap and readily available starting materials made this an attractive starting material for 3-substituted thiophene ligands.[18] A non-transferable ligand based upon ephedrine and thiophene was prepared from reduction of **1** to the alcohol and subsequent treatment with thionyl chloride to yield the benzylic chloride, **2**. The chloride was displaced using the sodium alkoxide of (−)-*N*-methylephedrine[19] to give **3**.[20] Similarly, the sodium alkoxide of (+)-*N*-methylpseudoephedrine derivative was used in the place of (−)-*N*-methylephedrine to give, the diastereomeric **5**. A second type of thiophene-based ligand was prepared directly from the carboxaldehyde by reductive amination with 2-methoxymethylpyrrolidine, derived from L-proline,[21] to give **4** (Scheme 1).



Scheme 1. *Reagents*: (a) $LiAlH_4$; (b) $SOCl_2$; (c) $Ti(O\text{-}i\text{-}pr)_4$/$NaCHBH_3$.

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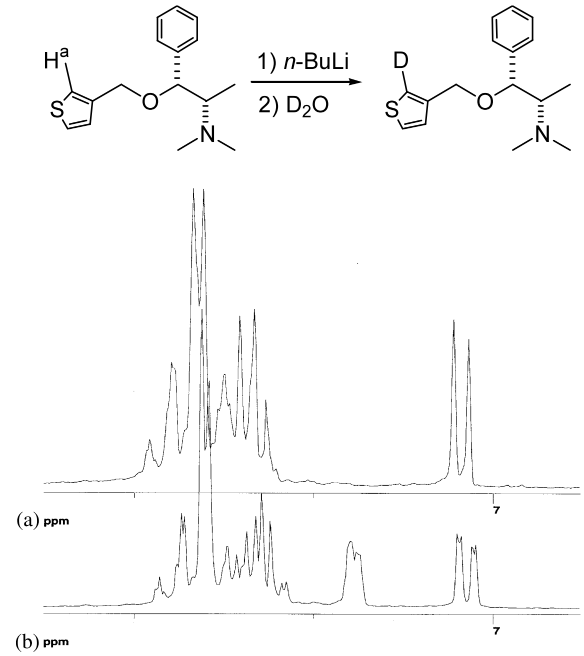
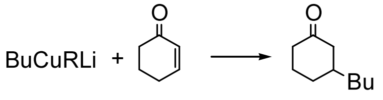


Figure 1. The ^1H NMR spectra of the aromatic region of **3**. (a) Starting material. (b) After the lithiation-deuteration sequence. Note that the resonance at 7.16 ppm corresponding to hydrogen H_a, has disappeared.

These ligands were regioselectively lithiated at the 2-position in THF or diethyl ether with *n*-BuLi at −20°C in 1 h.[22] The regioselectivity of the lithiation was determined by quenching the lithiated products with D_2O and comparing the ^1H NMR spectra to those of the original ligands. Using compound **3** as the example, the ^1H NMR spectra for this reaction sequence are shown in Figure 1. The hydrogen at 2-position of the thiophene ring (H_a) is assigned to the resonance at 7.16 ppm. The spectra of the lithiation and deuterium oxide quench product shows the clean replacement of H_a with a deuterium. Similar results were found with **4** and **5**. Because the coordination of the lithium by multi-dentate ligands can greatly retard the reactivity of organocuprate reactions,[23,24] we were interested in the relative reactivity of these new mixed cuprates. As shown in Table 1, logarithmic reactivity profiles were used to gauge the reactivities of these new heterocuprates (entries 5 and 6) against those of the di-*n*-butyl homocuprate (entries 1 and 2) and the *n*-butyl(thienyl) mixed cuprate (entries 3 and 4), using cyclohexenone as the substrate at −78°C.[17,25] The data in the table makes it evident that the homocuprate in diethyl ether is the most reactive combination. The new mixed cuprates in THF were comparable in reactivity to the homocuprate in THF and have nearly identical reactivity as Nilsson's unadulterated thienyl mixed cuprate in both THF and diethyl ether. The observed yields for entry 6 suggests that little if any of the thiophene ligand is being transferred.

Table 1. Yield of **6** at various times



6

Entry	R	Solvent	Yields (%) at time (s)			
			4	36	360	3600
1	*n*-Bu	THF	10	24	68	86
2	*n*-Bu	Et_2O	99	99	99	99
3	2-Thienyl	THF	9	32	57	75
4	2-Thienyl	Et_2O	82	84	89	92
5	Ar[a]	THF	8	22	59	87
6	Ar[a]	Et_2O	33	81	95	97

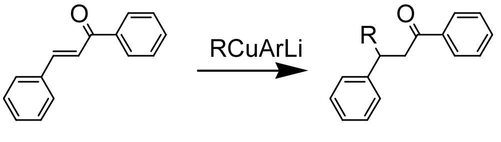
[a] Ar is derived from lithiated **3**. All reactions are carried out at −78°C. Data for entries 1–4 were taken from Ref. 17.

To test the enantioselectivity of the transfer, methyl and *n*-butyl were chosen as the transferable groups and chalcone was selected as the α-enone. The mixed cuprates of **3**, **4** and **5** were prepared by lithiating the corresponding thiophene derivative in the desired solvent. The freshly prepared the lithiothiophene was treated with $CuI·PBu_3$ at −78°C, annealed at 0°C, treated with the alkyllithium at −78°C and finally annealed again at 0°C. A solution of chalcone was slowly introduced into the stirred reaction mixture at −78°C and allowed to react overnight at that temperature. The reaction mixtures were quenched cold with saturated aqueous ammonium chloride. Chemical yields were determined by gas chromatography, using the internal standard method. Enantiomeric excesses were determined by chiral HPLC.[26,27] These results are shown in Table 2. Both the yields and selectivity were found to be better in diethyl ether than THF.[28]

3. Conclusions

Thiophenes substituted with chiral β-amino ethers in the 3-position are smoothly lithiated in the 2-position with *n*-butyllithium in ether solvents. These ligands

Table 2. Yields and selectivities with chalcone



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Entry	Ar	R	Solvent	**7** (%)	*Ee* (%)
1	3	Bu	THF	16	30 (*R*)
2	3	Bu	Et_2O	96	78 (*S*)
3	3	Me	Et_2O	89	60 (*S*)
4	4	Me	Et_2O	78	79 (*R*)
5	4	Bu	Et_2O	59	75 (*S*)
6	5	Me	Et_2O	62	40 (*R*)
7	5	Bu	Et_2O	76	46 (*R*)

All reactions were run at −78°C for 24 h.

were non-transferable and gave good to excellent chemical yields of the conjugate addition product with chalcone in diethyl ether. The enantiomeric excesses in ether were promising, giving moderate to good enantioselectivities. Further studies are underway with different substrates and reaction conditions to determine the generality of thiophene-based non-transferable chiral ligands. Multi-nuclear NMR studies to characterize the new mixed cuprates and their intermediate π-complexes are also ongoing.[29]

Acknowledgements

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