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NHC–Cu(I) catalysed asymmetric conjugate silyl transfer to unsaturated lactones: application in kinetic resolution†

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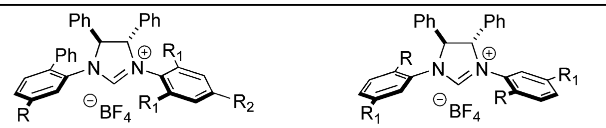
The scope of the asymmetric silyl transfer to unsaturated lactones utilising a C_2-symmetric NHC–Cu(I) catalyst has been established and kinetic resolutions mediated by silyl transfer have been used to prepare enantiomerically enriched *anti*-4,5-disubstituted 5-membered lactones. The method has been exploited in an expedient synthesis of (+)-blastmycinone.

The asymmetric conjugate addition of a silicon nucleophile to α,β-unsaturated carbonyl compounds is a valuable transformation in organic synthesis[1] as the resulting β-silyl carbonyl compounds are robust synthetic equivalents of β-hydroxy carbonyl compounds courtesy of the stereospecific Fleming–Tamao oxidation.[2] The β-hydroxy carbonyl moiety is synonymous with the aldol reaction and is a well-known motif: the ability to efficiently generate this valuable motif in stereoselective fashion remains an important goal in modern synthetic chemistry. Fleming's conjugate addition of silyl cuprates to electron-deficient alkenes remained for a long time the method of choice for establishing the β-silyl carbonyl motif.[2e,3] In the 1980s Hayashi and Ito pioneered the development of asymmetric silylation using palladium catalysis, however narrow substrate scope has limited adoption of the method.[4] In 2006, Oestreich disclosed an asymmetric conjugate silylation protocol using a Si–B reagent ($PhMe_2SiBpin$)[1a,5] in the presence of an enantiomerically pure rhodium catalyst.[6] In 2010, a complementary protocol from Hoveyda employed *N*-heterocyclic carbene (NHC) ligands[7] in Cu(I)-catalysed asymmetric addition of $PhMe_2SiBpin$ to α,β-unsaturated carbonyl systems.[8] Hoveyda's strategy exploits the use of readily accessible pre-catalysts with inexpensive Cu(I) salts and thus represents a highly attractive method for asymmetric conjugate silylation.[9]

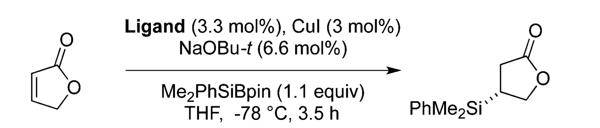
Although the Oestreich and Hoveyda protocols allow the asymmetric silylation of a wide range of cyclic and acyclic substrates (*e.g.* esters, ketones, nitriles), limited studies on silyl transfer to heterocyclic systems, and in particular α,β-unsaturated lactone substrates, have been described.[6,8] Furthermore, in general, asymmetric conjugate additions to 5-membered substrates are known to be challenging.[10] In this Communication we describe our studies to optimise and establish the scope of the Cu-catalysed asymmetric silyl transfer to unsaturated lactones. We also report the kinetic resolution of 5-substituted butenolides[11] mediated by the silyl transfer.

Building on Oestreich's studies involving furanone **1**,[6a,c] we began our investigation by studying silyl transfer to **1** using Hoveyda's protocol.[12] Employing **L1**, a ligand that has previously been used in conjugate silyl transfer to carbocyclic systems (Table 1),[8a] poor enantiocontrol was observed in the silylation of **1** (entry 1). Subtle modifications of the C_1-symmetric imidazolinium salt core did little to improve the outcome (entries 2–5). For furanone **1**, enantioselectivities were improved by a switch to C_2-symmetric ligands (entries 6–10). In particular, the best results were obtained using C_2-symmetric ligands

Table 1 Screen of NHC–Cu(I) complexes



C_1-symmetric imidazolinium salts **L1-L5** | C_2-symmetric imidazolinium salts **L6-L10**



1 → **2**

Entry	Ligand	Type	R	R_1	R_2	er
1	**L1**	C_1	Me	Et	H	62 : 38
2	**L2**	C_1	H	Et	H	56 : 44
3	**L3**	C_1	i-Pr	Et	H	60 : 40
4	**L4**	C_1	H	Me	Me	75 : 25
5	**L5**	C_1	Me	Me	Me	66.5 : 33.5
6	**L6**	C_2	H	Ph	—	80.5 : 19.5
7	**L7**	C_2	Me	Ph	—	72 : 28
8	**L8**	C_2	2-Naphthyl	H	—	93 : 7
9	**L9**	C_2	2-Naphthyl	i-Pr	—	54 : 46
10	**L10**	C_2	2-Anthryl	H	—	92 : 8

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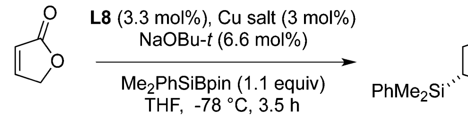
Table 2 Optimisation of the Cu(I) source



1 **2**

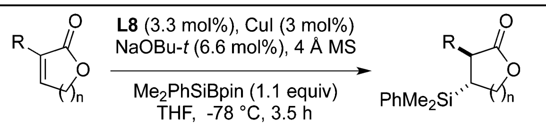
Entry	Cu salt	Additive	Conv. (%)	er
1	CuCl	—	71	93 : 7
2	CuBr	—	80	90.5 : 9.5
3	CuBr·SMe_2	—	68	89.5 : 10.5
4	CuOTf	—	91	89.5 : 10.5
5	CuI	—	>98	93 : 7
6	CuI	4 Å MS	>98	93 : 7

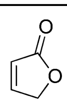
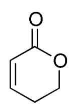
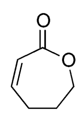
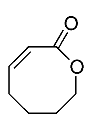
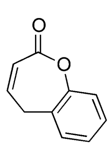
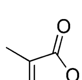
bearing extended aromatic systems (naphthyl and anthryl, entries 8 and 10) on the *N*-phenyl substituent. However, the presence of additional steric bulk had a detrimental effect on enantioinduction (entry 9). Thus, the use of a C_2-symmetric ligand **L8** gave the best results in silyl transfer to **1**.

With ligand choice completed, we turned our attention to further optimising the reaction conditions (Table 2). Although different Cu(I) sources[13] did not have a significant effect on enantioinduction, copper salt selection was important in maximizing conversions due to their moisture sensitivity.

In this sense, the use of CuI gave the best results (entry 5) and the addition of molecular sieves improved reproducibility. Importantly, we found that 'glove-box free' conditions could be used thus greatly simplifying operational procedures. With optimised conditions in hand, we applied the protocol to the asymmetric conjugate silylation of 5, 6 and 7-membered α,β-unsaturated lactones (Table 3). The desired β-silyl adducts were obtained in up to 96.5 : 3.5 er in good yield (entries 1–3). Interestingly, the 8-membered lactone did not react, presumably due to conformational effects (entry 4). When a 7-membered lactone was fused with an aromatic ring, there was a deleterious effect upon enantiocontrol although the yield remained high (entry 5). Moderate selectivity was also observed in the silylation of a 2-substituted lactone (entry 6).

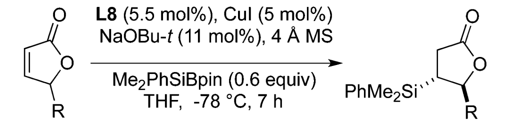
Table 3 Cu(I)–NHC catalysed asymmetric silyl transfer to unsaturated lactones

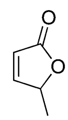
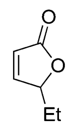
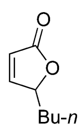
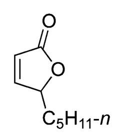
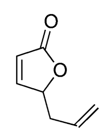
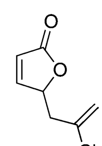
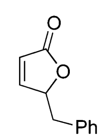
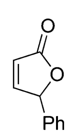


Entry	Lactone	Yield[a] (%)	er
1		79	93 : 7
2[b]		82	84 : 16
3		86	96.5 : 3.5
4		nr	—
5		84	82 : 18
6		65	77 : 23 (2 : 1 dr, *anti*)

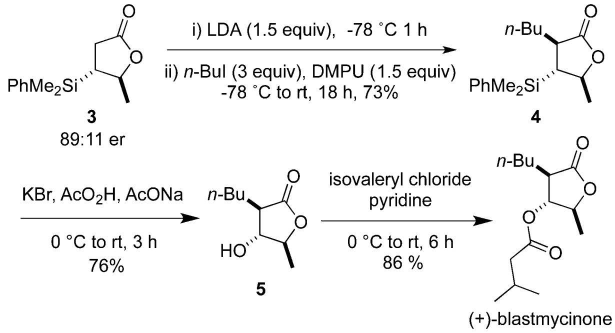
[a] Yield of isolated product. [b] **L3** gives a 92 : 8 er, see ref. 8*a*.

Table 4 Kinetic resolutions mediated by Cu(I)–NHC catalysed asymmetric silyl transfer to 5-substituted butenolides



Entry	Substrate	Conversion[a] (%)	Yield[b] (%)	er	s[c]
1		50	46	86 : 14	13
2		52	50	90 : 10	25
3[d]		43	43	91 : 9	19
4[d]		48	43	86 : 14	12
5		47	46	84 : 16	10
6[d]		49	48	89 : 11	18
7[d]		43	42	86 : 14	11
8		45	41	88.5 : 11.5	15

[a] Determined by ^{1}H NMR. [b] Yield of isolated product. [c] Selectivity factor determined according to ref. 16. [d] 10 mol% catalyst loading, 0.7 equiv. ($PhMe_2SiBpin$).



Scheme 1 Catalytic asymmetric approach to (+)-blastmycinone.

To further explore the scope of the protocol, the kinetic resolution of a series of 5-substituted butenolides was carried out using Cu(I)–NHC catalysed asymmetric silyl transfer.[14] Pleasingly, treatment of 5-substituted butenolides with 60–70 mol% of $PhMe_2SiBpin$ and the C_2-symmetric catalyst derived from **L8** and CuI afforded silylated products after kinetic resolution in good yields (up to a maximum of 50%), good enantiomeric ratios and as single *anti*-diastereoisomers (Table 4).[15]

The rate of addition to 5-substituted butenolides was slower than silyl transfer to unsubstituted lactones, presumably due to increased steric hindrance, therefore higher catalyst and silylborane loading was required.[17] Primary alkyl, allyl, benzyl and phenyl substituents at the 5-position of butenolides were found to be compatible with the process. To our knowledge, these examples represent the first kinetic resolutions achieved by Cu-catalysed silyl transfer from a Si–B reagent.

To demonstrate the value of Cu(I)–NHC catalysed asymmetric silyl transfer to unsaturated lactones, we report a concise approach to (+)-blastmycinone, a natural product arising from the hydrolysis of the antibiotic (+)-antimycin A_3 (Scheme 1).[18] Alkylation of silylated lactone **3** (see entry 1, Table 4) provided **4** with three contiguous stereocenters as a single diastereoisomer. Fleming–Tamao oxidation[2] then gave lactone **5**, which after esterification afforded (+)-blastmycinone.[19]

In summary, we have explored the scope of a convenient procedure for asymmetric silyl transfer to unsaturated lactones. The Cu(I)–NHC catalysed process delivers β-silylated lactones in good yields and enantioselectivities. In contrast to observations with other substrate classes, the use of C_2-symmetric imidazolinium salts as NHC precursors was crucial for efficient asymmetric silyl transfer to unsaturated 5-membered lactones. Kinetic resolution using Cu-catalysed silyl transfer from a Si–B reagent has been applied to racemic 5-butenolides and affords products with good enantiocontrol and excellent diastereocontrol. The method has been used in an expedient asymmetric synthesis of (+)-blastmycinone.

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