Asymmetric Synthesis

Enantioselective Preparation of β,β-Disubstituted α-Methylenepropionates by MAO Promotion of the Zinc Schlenk Equilibrium**

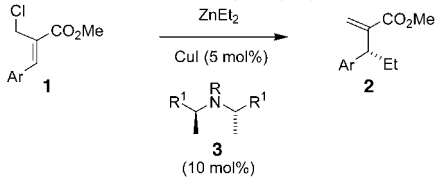
*Paul J. Goldsmith, Simon J. Teat, and Simon Woodward**

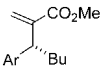
Dedicated to Dr. John M. Brown, FRS on the occasion of his 65th birthday

In the copper-catalyzed reactions of organometallic nucleophiles (RM) with allylic halides $R^1CH{=}CR^2CH_2X$, two reaction pathways are possible: either direct S_N2 displacement at the α carbon or S_N2' displacement γ to the leaving group. Recently, considerable progress has been made towards the development of asymmetric processes that result from copper-catalyzed S_N2' addition of organozinc or Grignard reagents.[1] These studies have generally used allylic halides that lack functional groups and have focused largely on (*E*)-cinnamyl halides or equivalent phosphate esters ($R^1 = Ph$, $R^2 = H$). Reactions with ester-functionalized electron-deficient allylic halides ($R^2 = CO_2R$, $R^1 =$ various, **1**) would offer rapid access to highly useful chiral β,β-disubstituted α-methylenepropionates **2** (see Table 1). Highly selective additions of ZnR_2 to the regioisomers of **1** have been demonstrated,[2] but the former substrates themselves have proved highly resistant to effective asymmetric catalysis.[3]

Stoichiometric groundwork by Xu and Kündig showed the viability of addition of organozinc reagents to halides of type **1**.[4] Using Baylis–Hillman chemistry (to obtain suitable allylic halides **1**), we developed a first-generation catalytic system for the addition of ZnR_2 to allylic chloride **1a** by employing a chiral thioether ligand.[5] However, only low levels of enantioselectivity were observed, and the system was resistant to further optimization. With high-throughput screening, the chiral secondary amines **3** were identified as alternative ligands for the transformation of **1a** to **2a** in the presence of $Cu^{I}I$ (Table 2). A number of the other 80 species tried produced significant ligand-accelerated catalysis (LAC)[6]

Table 1: Synthesis of chiral β,β-disubstituted α-methylenepropionates **2**.



1	Ar	3	R^1	R	2	Ar
a	Ph	**a**	Ph	H	**a**	Ph
b	4-(MeO)C_6H_4	**b**	Ph	Me	**b**	4-(MeO)C_6H_4
c	4-MeC_6H_4	**c**	Ph	CHO	**c**	4-MeC_6H_4
d	1-Naphthyl	**d**	*c*-C_6H_{11}	H	**d**	1-Naphthyl
e	2-BrC_6H_4	**e**	1-Naphthyl	H	**e**	2-BrC_6H_4
f	4-FC_6H_4	**f**	4-FC_6H_4	H	**f**	4-FC_6H_4
g	4-(CF_3)C_6H_4	**g**	4-MeC_6H_4	H	**g**	4-(CF_3)C_6H_4
h	4-(NO_2)C_6H_4	**h**	4-(MeO)C_6H_4	H	**h**	4-(NO_2)C_6H_4
		i	3-(MeO)C_6H_4	H		
		j	2-(MeO)C_6H_4	H		

2aa

Table 2: Addition of $ZnEt_2$ to allylic chloride **1a** using CuI and (*S*,*S*)-**3**.[a]

Entry	Ligand	R^1	R	Yield **2a** [%]	*ee* **2a** [%]
1	**3a**	Ph	H	50	65
2	**3a**·HCl	Ph	H	50	51
3	**3b**·HCl	Ph	Me	10	<5
4	**3c**·HCl	Ph	CHO	18	<5
5	**3d**·HCl	*c*-C_6H_{11}	H	41	<5
6	**3e**·HCl	1-Naphthyl	H	18	15
7	**3f**·HCl	4-FC_6H_4	H	28	47
8	**3g**·HCl	4-MeC_6H_4	H	60	72
9	**3h**	4-(MeO)C_6H_4	H	70	78
10	**3h**·HCl	4-(MeO)C_6H_4	H	69	74
11	**3i**·HCl	3-(MeO)C_6H_4	H	56	53
12	**3j**	2-(MeO)C_6H_4	H	53	6

[a] Addition of $ZnEt_2$ (0.7 mL of a solution in toluene (1.1 M), 0.77 mmol) to **1a** (0.5 mmol) in THF (1 mL) at −20 °C in the presence of (*S*,*S*)-**3** (10 mol%) and CuI (5 mol%). Yield and *ee* values determined after 1 h by chiral-GC analysis (see Supporting Information).

effects (see Supporting Information), but only compound **3** gave *ee* values over 35%. Subsequent investigation revealed that the presence of C_2 symmetry is vital for efficient stereoselection; for example, use of (*S*)-PhCH(Me)NHBn gave **2a** in high yield, but with less than 20% *ee*. The presence of the secondary amino group is also crucial as either its alkylation or formylation (Table 2, entries 3 and 4, respectively) dramatically reduced the activity and selectivity of the catalyst. Finally, it was noted that the presence of an aryl function in the ligand **3** was also vital as **3d**·HCl showed no enantioselectivity and poor conversion of **1a** (entry 5). The

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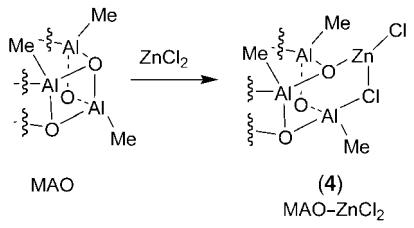
role of the ligand aryl group was further investigated by increasing the range of substituents in **3** (Table 2). These were mostly screened as their HCl salts as these are more convenient to handle than the free amines. A strong detrimental steric effect was noted for ligands with a 2-substituent (entries 6 and 12), but a favorable electronic effect (either +I or +M) existed at the 4-position (entries 8–10). Through these studies the 4-methoxy ligand **3h** was determined to be optimal (Table 2, entry 9).

These studies also highlighted that the free amines **3** outperformed their corresponding salts **3**·HCl in terms of product stereoselectivity (compare entries 1 and 9 versus 2 and 10, respectively; Table 2). Alongside this, kinetic studies had shown that the enantioselectivity of the reaction in THF was time-dependent: When substrate **1a** was treated with $ZnEt_2$ using ligand **3h**·HCl, the *ee* value fell from 80% at the onset of the reaction to 74% after one hour (69% yield, the mass balance being **1a**). Coupled together these facts indicated that EtZnCl, whose concentration increases as the reaction evolves, impairs the selective transition state. This could be confirmed by deliberate addition of EtZnCl (prepared from a 1:1 mixture of $ZnEt_2$ and $ZnCl_2$) [7] which led to an immediate and catastrophic collapse in the catalyst selectivity (30% *ee*, 12% yield at 1 h,). We therefore reasoned that if we could promote the forward reaction (k_1) of the zinc Schlenk equilibrium [Eq. (1)], the enantioselectivity of the reaction should improve with the lower concentration of EtZnCl. Conditions under which $ZnCl_2$ is scavenged from the reaction mixture should fulfil this requirement. After screening several additives, including crown ethers, we found that the addition of methylaluminoxane (MAO; [-Al(Me)O-]$_n$) which is known to strongly scavenge halides[8] led to the desired effect (83% *ee*, 48% yield of **2a** at 1 h, −20 °C). It has been speculated that MAO can act as a "latent Lewis acid" and sequester chlorides as shown in structure **4**. $ZnMe_2$



showed similar benefit, presumably through formation of unreactive MeZnCl, though catalyst turnover was reduced (84% *ee*, 35% yield of **2a** at 1 h, −20 °C).[9]

$$2\,EtZnCl \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ZnEt_2 + ZnCl_2 \qquad (1)$$

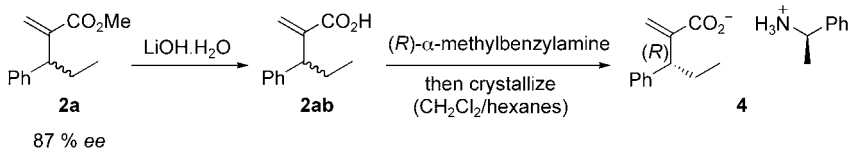
To the best of our knowledge, attempted manipulation of the zinc Schlenk equilibrium as a synthetic route to alkyl ZnR_2 species has not been reported before.[10] Alongside these additive trials, stronger coordinating solvents were screened, and we found that DME (1,2-dimethoxyethane) as solvent (with no additive) leads to a significant increase in enantioselectivity (88% *ee*, 47% yield of **2a** at 1 h, −20 °C). A combination of the use of MAO and DME and lowering the temperature led to the attainment of synthetically useful levels of enantioselectivity in the preparation of **2a**. Use of excess MAO led to *ee* values greater than 95%, but with low yields of **2a**. These results could be generalized across the range of substrates **1** (Table 3), with optimal results attained when CuTC (copper(I) thiophene-2-carboxylate)[11] was used as the source of copper(I). The origin of the enantioselectivity attained in this reaction unusually depends critically on electronic effects. Electron-rich substrates give products with higher enantioselectivities than electron-poor substrates (compare entry 3 versus 9, Table 3), which implicates a π-stacking interaction in the transition state.

Table 3: CuTC/(*S*,*S*)-**3h**-catalyzed addition of ZnR_2 (R = Et, Bu) to allylic chlorides **1** under conditions that promote Schlenk equilibration.[a]

Entry	Product	Ar	Yield [%]	$[\alpha]_D^{23}$[b]	*ee* [%] (stereoisomer)[b]
1	**2a**	Ph	92	−92.8	87 (*R*)
2	**2aa**	Ph	81	−76.2	78 (*R*)[c]
3	**2b**	4-(MeO)C_6H_4	80	−96.4	90 (*R*)
4	**2c**	4-MeC_6H_4	95	−94.4	89 (*R*)
5	**2d**	1-Naphthyl	53	−63.3	86 (*R*)
6	**2e**	2-BrC_6H_4	95	−82.7	80 (*S*)[d]
7	**2f**	4-FC_6H_4	95	−90.0	87 (*R*)
8	**2g**	4-(CF_3)C_6H_4	93	−80.3	83 (*R*)
9	**2h**	4-(NO_2)C_6H_4	95	−97.0	76 (*R*)

[a] Addition of $ZnEt_2$ (1.0 mL of a solution in toluene (1.1 M), 1.1 mmol) to **1** (0.5 mmol) in DME (1 mL) at −40 °C in the presence of (*S*,*S*)-**3h** (10 mol%), CuTC (5 mol%), and MAO (0.5 mL, 15 wt% solution in toluene). Yields of isolated products quoted. [b] (*c* 1.0, $CHCl_3$) for $[\alpha]_D^{23}$ in all cases. The absolute configuration of (−)-**2a** was confirmed crystallographically as *R*, and the products **2aa–h** were assumed to show the same sense of stereoinduction. [c] The reaction was performed using Zn(*n*Bu)$_2$ (1.0 mL of a solution in heptane (1 M), 1.0 mmol). [d] Yield from NMR spectroscopic studies based on isolation of a mixture of **1e** and **2e**. The absolute configuration has changed owing to a change in assignment priority of the aryl substituent.

The sense of the enantioselectivity in the addition of $ZnEt_2$ to the halide **1a** could be determined by X-ray crystallographic analysis of the carboxylic acid **2ab**, which resulted from the hydrolysis of **2a**, when crystallized as its (*R*)-α-methylbenzylamine salt (Scheme 1). Single recrystallizations of the acids derived from **2** and further derivatization with α-methylbenzylamine improved the enantioselectivity to >99% *ee* for the catalytic addition. This enrichment was considerably easier and more efficient than direct resolution of racemic **2ab**. The product **2ab** of the S_N2' reaction is of



Scheme 1.

direct use in the preparation of combined ACE–NEP (angiotensin-converting enzyme and neutral endopeptidase) inhibitors.[12]

In conclusion, we have described the first method for the copper-catalyzed enantioselective alkylation of Baylis–Hillman-derived electron-deficient allylic chlorides with organozinc reagents thorough the use of a simple chiral secondary amine and promotion by MAO of the zinc Schlenk equilibrium. Further intensive studies are underway to identify the nature of the π-stacking interactions responsible for the ordered transition state.

Experimental Section

General procedure for the CuTC-catalyzed alkylation of allylic chlorides **1**: A dried Schlenk tube was charged with chloride **1** (0.50 mmol), CuTC (4.8 mg, 0.025 mmol), and (*S*,*S*)-**3h** (14.3 mg, 0.05 mmol). Dry DME (1 mL) was introduced, the stirred mixture was cooled to −40 °C, and MAO (0.5 mL of a 15 wt % solution in toluene; Aldrich) was added. The yellow reaction mixture was stirred for 5 min at −40 °C, and then ZnR_2 (for R = Et: 1 mL of a 1.1 M solution in toluene, 1.1 mmol; for R = *n*Bu: 1 mL of a 1 M solution in heptane, 1.0 mmol) was added. Stirring was continued for 45 h at −40 °C, then the reaction was quenched by cautious addition of 2 M HCl (2 mL). The aqueous layer was extracted with Et_2O (2 × 5 mL), then the organic extracts were dried ($MgSO_4$), and the solvent was evaporated. The products were isolated by flash chromatography using mixtures of Et_2O/hexanes as eluent.

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