Asymmetric Catalysis

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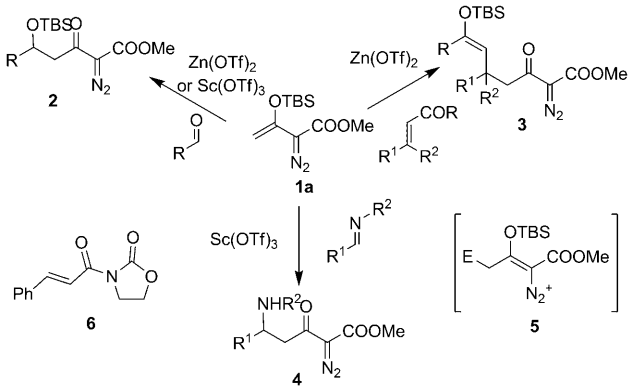
Highly Enantioselective Catalytic Synthesis of Functionalized Chiral Diazoacetoacetates**

*Xinfang Xu, Wen-Hao Hu, and Michael P. Doyle**

The Michael reaction is one of the most general and versatile methods for carbon–carbon bond formation,[1] and its Mukaiyama–Michael variant provides an efficient strategy for the addition of silyl enol ethers to α,β-unsaturated carbonyl compounds.[2] Catalytic asymmetric reactions with broad variations in the α,β-unsaturated carbonyl compounds and chiral catalysts (Lewis acid and Brønsted acid) are well documented,[3,4] and the enantioenriched 1,5-dicarbonyl compounds formed from these reactions have proven to be useful building blocks. However, there has been limited variation in the silyl enol ethers used in these reactions, and none of them have incorporated multiple functional groups.

We have recently reported condensation reactions of methyl 3-(trialkylsilanoxy)-2-diazo-3-butenoates (e.g. **1a**) in Mukaiyama–aldol,[5] Mukaiyama–Michael,[6] and Mannich[5] processes (Scheme 1) in our efforts to construct functionalized diazo compounds. These reactions are especially facile because of the stabilization afforded by the diazo functional group to the intermediate formed by electrophilic addition ($E^+ + \mathbf{1a} \rightarrow \mathbf{5}$). The resulting multifunctional diazoacetoacetates have proven to be valuable building blocks for the efficient synthesis of functionally complex organic compounds.[5,7] However, attempts to construct chiral multifunctional diazoacetoacetates have only been moderately successful, with the only example being the asymmetric catalytic Mukaiyama–aldol reactions of a limited array of aromatic aldehydes with **1a** in the presence of a AgF/(*R*)-binap (binap = 2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl) catalyst.[8] We now report the first examples of a broadly applicable, highly enantioselective synthesis of chiral γ-functionalized diazoacetoacetates by catalytic Mukaiyama–Michael addition reactions of 3-(*tert*-butyldimethylsilyloxy)-2-diazo-3-butenoate (**1**).



Scheme 1. Synthesis of diazoacetoacetates by condensation reactions of **1a**. TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl.

A survey of chiral Lewis acids for the direct Mukaiyama–aldol or Mukaiyama–Michael reactions of **1** with α,β-unsaturated carbonyl compounds showed limited reactivity and low enantioselectivity. The success of the *N*-oxazolidinone-derivatized α,β-unsaturated carbonyl compounds prepared by Evans and co-workers in chiral Lewis acid catalyzed asymmetric reactions[9] prompted us to use **6**, but no reaction with **1a** was observed, even using copper(II) triflate ligated with chiral bis(oxazoline) (box) or bis(oxazolinyl)pyridine (pybox). Since the oxazolidinone basicity of **6** was too strong to effect activation of the α,β-unsaturated carbonyl unit for electrophilic addition, we turned to the less basic α,β-unsaturated 2-acylimidazole **7a**.[10] In a reaction of **7a** with **1a** catalyzed by copper(II) triflate ligated with the (*S*,*S*)-*t*Bu-box **L1** (Table 1, entry 5), the Mukaiyama–Michael condensation product **8** was formed in 66% yield but with only 10% *ee*. In a screening of potential Lewis acids (Table 1), scandium(III) triflate, a preferred catalyst for Mukaiyama–aldol reactions,[2c,11] was ineffective for addition to **1a** (Table 1, entry 1). In contrast, the mild Lewis acids, $Ni(OTf)_2$, $Zn(OTf)_2$, and $Mg(OTf)_2$, combined with **L1**, offered moderate enantioselectivity with moderate to low product yields (Table 1, entries 2–4), but $Cu(SbF_6)_2$[12] proved to be the most active and effective, giving the desired product in 77% yield with 46% *ee* (Table 1, entry 7). The enantioselectvity was improved to 54% *ee* with this copper(II) catalyst by reducing the temperature to −78°C (Table 1, entry 8). Since $Cu(SbF_6)_2$ in combination with **L1** exhibited the highest reactivity in these reactions, this catalytic system was selected for further elaboration.

Optimization of this Mukaiyama–Michael transformation was effected on **7a** by initially changing the ester alkyl and silyl ether groups of **1** (**1a**–**1d**). Compared to the TBS group

[*] Dr. X. Xu, Prof. M. P. Doyle
Department of Chemistry and Biochemistry, University of Maryland
College Park, MD 20742 (USA)
Fax: (+11) 301-314-2779
E-mail: mdoyle3@umd.edu
Prof. W. Hu
Institute of Drug Discovery and Development
East China Normal University
3663 Zhongshan Bei Road, Shanghai 200062 (China)

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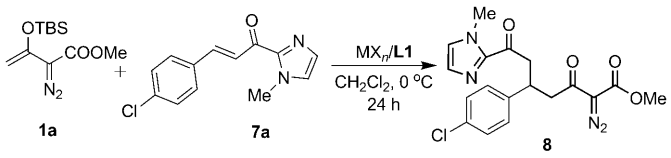
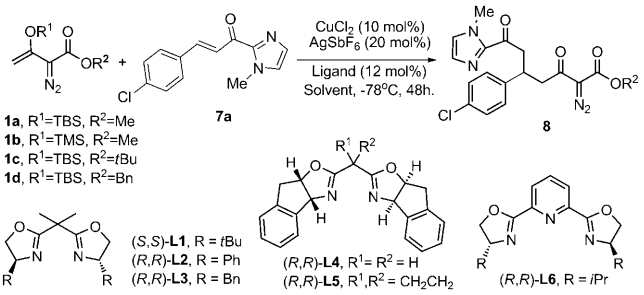
Table 1: Selection of Lewis acid for the enantioselective Mukaiyama–Michael addition.[a]



Entry	Lewis acid MX_n	Yield [%][b]	*ee* [%][c]
1	$Sc(OTf)_3$	< 5	0
2	$Ni(OTf)_2$	30	54
3	$Zn(OTf)_2$	42	39
4	$Mg(OTf)_2$	26	47
5	$Cu(OTf)_2$	66	10
6	CuOTf	31	26
7[d]	$Cu(SbF_6)_2$	77	46
8[d]	$Cu(SbF_6)_2$	43	54

[a] Reactions were performed with **7a** (0.25 mmol), Lewis acid (10 mol%), and **L1** (12 mol%) in CH_2Cl_2 (1.5 mL); **1a** (1.5 equiv) in CH_2Cl_2 (0.5 mL) was added over 30 min to the reaction mixture at 0°C (except entry 8, which was carried out at −78°C) under N_2. The reaction solution was stirred overnight at 0°C. [b] Yield of isolated **8** after chromatography. [c] Determined by HPLC on a chiral stationary phase (AD-H, hexanes/*i*PrOH = 50:50, flow rate 1.0 mL min^{-1}, 254 nm, t_{r1} = 9.0 min, t_{r2} = 11.1 min). [d] $Cu(SbF_6)_2$ was formed in situ from $CuCl_2$ and $AgSbF_6$ under N_2 (Ref. [12]).

Table 2: Optimization of the reactant, ligand, and reaction conditions for the enantioselective Mukaiyama–Michael addition.[a]



Entry	**1**	Ligand	Solvent	Additive	Yield [%][b]	*ee* [%][c]
1	**1a**	**L1**	CH_2Cl_2	–	43	54
2	**1b**	**L1**	CH_2Cl_2	–	64	12
3	**1c**	**L1**	CH_2Cl_2	–	33	50
4	**1d**	**L1**	CH_2Cl_2	–	42	93
5	**1d**	**L2**	CH_2Cl_2	–	30	65
6	**1d**	**L3**	CH_2Cl_2	–	33	76
7	**1d**	**L4**	CH_2Cl_2	–	40	87
8	**1d**	**L5**	CH_2Cl_2	–	34	88
9	**1d**	**L6**	CH_2Cl_2	–	< 5	ND
10	**1d**	**L1**	CH_2Cl_2	HFIP (1.0 equiv)	67	83
11	**1d**	**L1**	CH_2Cl_2	4 Å M.S. (0.1 g)	44	94
12	**1d**	**L1**	THF	4 Å M.S. (0.1 g)	< 5	ND
13	**1d**	**L1**	toluene	4 Å M.S. (0.1 g)	35	90
14[d]	**1d**	**L1**	CH_2Cl_2	HFIP (1.0 equiv)	78	93
15[e]	**1d**	**L1**	CH_2Cl_2	HFIP + 4 Å M.S.	81	94

[a] Reactions were performed as described in Table 1. The chiral catalyst was prepared according to Ref. [12]. [b] Yield of isolated **8** after chromatography. [c] Determined by HPLC on a chiral stationary phase (See the Supporting Information). [d] 30 mol% catalyst was used. [e] The catalyst was prepared in a glove box, and the reaction was run for three days. Bn = benzyl, M.S. = molecular sieves, TMS = trimethylsilyl.

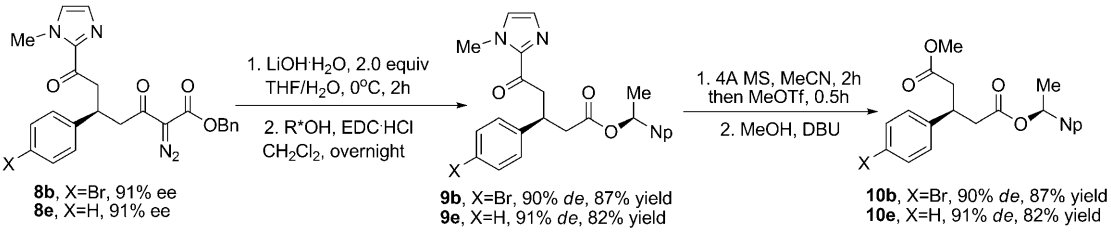
of **1a** (Table 2, entry 1), the TMS analogue **1b** exhibited higher reactivity but gave a much lower enantiomeric excess (Table 2, entry 2). However, although no significant change in the enantioselectivity was observed with the *tert*-butyl ester of **1c**, a dramatic improvement was achieved when the ester alkyl group was changed from methyl to benzyl (**1d**), with the enentioselectivity improving to 93% (Table 2, entry 4). This vinyl diazoester was used in further optimization studies.

A survey of chiral ligands showed the catalyst with the box ligands **L1**–**L5** had comparable reactivity (Table 2), but the enantioselectivity was considerably lower with **L2** and **L3**, compared with **L1**. Although **L4** and **L5** gave product yields and *ee* values that were comparable to those obtained with **L1**, there was no apparent advantage to their use. Pybox **L6** exhibited very low reactivity, and the enantioselectivity obtained with this ligand was not determined.

Changing the solvent from dichloromethane to THF completely shut down the reaction, but the reaction in toluene led to an *ee* value comparable to that in dichloromethane; however, the reaction rate was slower in toluene. A significantly improved yield of **8** was obtained (up to 78% yield with 83 and 93% *ee* in Table 2, entries 10 and 14) by using hexafluoroisopropyl alcohol (HFIP) as an additive[3b] or using 30 mol% of the catalyst instead of 10 mol%, and the same high enantioselectivity could be obtained by adding 4 Å molecular sieve (Table 2, entry 11).[13] Having established the optimum conditions with $[Cu^{II}\{(S,S)$-*t*Bu-box$\}](SbF_6)_2$, efforts were undertaken to reduce the amount of catalyst required to obtain high product yields: an 81% yield of **8** with 94% *ee* was obtained with 10 mol% catalyst, which was prepared in a glove box and allowed to undergo reaction over three days (Table 2, entry 15).

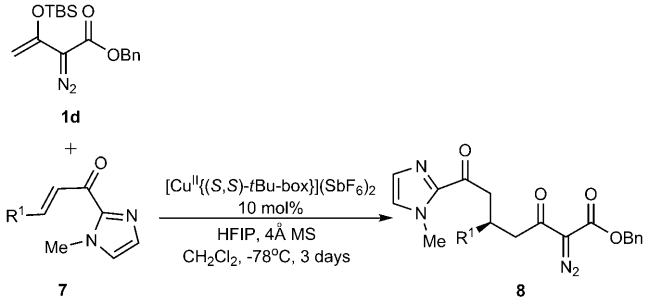
Reactions with a diverse set of α,β-unsaturated 2-acylimidazoles were examined with Michael donor **1d** under these optimized conditions (Table 3). Aryl and alkyl substitutions all gave high yields and high to excellent enantioselectivity. Those with electron-donating substituents showed higher reactivity and selectivity compared to those with electron-withdrawing substituents (Table 3, entries 1–6 versus 7). α,β-Unsaturated 2-acylimidazoles with aromatic heterocyclic and naphthyl substituents exhibited comparable reactivities and high *ee* values (Table 3, entries 11 and 12). As expected from the electronic effects of aryl substituents, higher enantioselectivity was achieved with the *meta*-nitro-substituted **7h** than with *para*-nitro-substituted **7g** (Table 3, entries 8 and 7, respectively). Surprisingly, the enantioselectivity of the reaction with **7m** (R = *t*Bu; Table 3, entry 13) was greater than that with **7n** (R = cyclohexyl; Table 3, entry 14).

The absolute configuration of the generated stereocenter in **8** was determined by converting the Michael addition product (Scheme 2) into a chiral diester with a known absolute configuration formed by desymmetrization of the substituted glutaric anhydride with chiral oxazolidinones.[14] Cleavage of the diazoacetoacetate to the diazoacetate and carboxylic acid, a well-known and widely used transformation,[15] followed by esterification of the resulting carboxylic acid with chiral (*S*)-1-(1-naphthyl)ethanol formed the β-



Scheme 2. Synthesis of chiral 3-substituted pentanedioic acid esters. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, EDC = *N*-(3-dimethylaminopropyl-*N*-ethylcarbodiimide, Np = 1-naphthyl.

Table 3: Catalytic enantioselective Mukaiyama–Michael addition of vinyl diazoacetate **1d** with representative Michael acceptors.[a]



Entry	R^1 (**7**)	Product **8**	Yield [%][b]	*ee* [%][c]
1	4-ClC_6H_4 (**7a**)	**8a**	81	94
2	4-BrC_6H_4 (**7b**)	**8b**	83	91
3	4-FC_6H_4 (**7c**)	**8c**	76	93
4	4-MeC_6H_4 (**7d**)	**8d**	77	91
5	C_6H_5 (**7e**)	**8e**	75	91
6	4-$MeOC_6H_4$ (**7f**)	**8f**	88	96
7	4-$NO_2C_6H_4$ (**7g**)	**8g**	62	86
8	3-$NO_2C_6H_4$ (**7h**)	**8h**	68	94
9	2-ClC_6H_4 (**7i**)	**8i**	75	95
10	2,6-$Cl_2C_6H_3$ (**7j**)	**8j**	65	91
11	2-furanyl (**7k**)	**8k**	80	80
12	2-naphthyl (**7l**)	**8l**	72	91
13	*t*Bu (**7m**)	**8m**	62	95
14	cyclohexyl (**7n**)	**8n**	79	81

[a] Reactions were carried out on a 0.25 mmol scale in CH_2Cl_2 with HFIP (1.0 equiv), 4 Å molecular sieves (0.1 g), and catalyst (10 mol%), which was prepared in situ according to Ref. [12]. **1d** (1.5 equiv) in CH_2Cl_2 (0.5 mL) was added over 30 min to the reaction mixture at −78 °C under N_2 in a dry ice/acetone bath. The reaction solution was stirred for three days at this temperature. [b] Yield of isolated **8** after chromatography. [c] Determined by HPLC on a chiral stationary phase (see the Supporting Information).

substituted esters **9** in high yield without loss of chirality. Methylation of the imidazole functional group according to the reported procedure[16] smoothly removed the imidazole and produced chiral diesters **10** in good yield. Comparison of the NMR data of compound **10e** with reported data for the known (1*S*,3*S*)-**10e** and (1*S*,3*R*)-**10e**[14a] confirmed that the product formed from the Mukaiyama–Michael reaction of **1d** with **7e** is indeed (5*S*)-**8e**.

In summary, we have developed a catalytic, highly enantioselective Mukaiyama–Michael addition of 3-(trialkylsilanoxy)-2-diazo-3-butenoate to α,β-unsaturated 2-acylimidazoles with a chiral copper(II) Lewis acid. This method offers access to a broad selection of highly functionalized chiral diazoacetoacetates that can be conveniently transformed into chiral diester compounds whose asymmetric center is chemically differentiated solely by different alkyl ester groups. The further utility of these Michael addition products is under investigation.

Experimental Section

The copper catalyst was prepared in a glove box according to the Evans procedure:[12] $CuCl_2$ (0.025 mmol), and chiral ligand (0.030 mmol) in CH_2Cl_2 (0.5 mL) were stirred for 2 h in an oven-dried flask, then $AgSbF_6$ (0.050 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise, and this solution was stirred for another 3 h in the absence of light. The resulting green catalyst suspension was filtered through cotton, and the solution was added to the oven-dried reaction flask, which contained 4 Å molecular sieves (100 mg) and the Michael acceptor (0.25 mmol). The reaction flask was then sealed with a rubber stopper before being removed from the glove box. The temperature of the reaction was lowered to −78 °C with a dry ice/acetone bath, and the additive (0.25 mmol) was then introduced followed by dropwise addition by syringe of the diazo compound (0.38 mmol) in CH_2Cl_2 (0.5 mL). The reaction mixture was maintained at this temperature for three days, then quenched with saturated NH_4Cl and purified by flash chromatography on silica gel (eluent: hexanes/EtOAc = 5:1 to 2:1) to give the pure products.

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