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Constructing chiral diazoacetoacetates by enantioselective catalytic Mukaiyama aldol reactions

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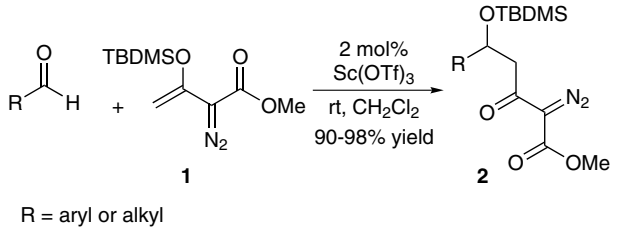
This article is dedicated to Professor Jack Halpern on the occasion of his 80th birthday

Abstract—Asymmetric catalysis of Mukaiyama aldol addition reactions of methyl 3-TMSO-2-diazo-3-butenoate **4** with aromatic aldehydes using AgF/(*R*)-BINAP at −20 °C produces chiral diazoacetoacetates in high chemical yields and with high enantiocontrol.

1. Introduction

Diazoacetoacetates are widely used reactants for metal carbene transformations in the syntheses of natural products and compounds of pharmaceutical interest.[1,2] Efficient and highly selective syntheses of carbocycles and hetereocycles via addition, insertion and association (ylide-derived processes) from diazoacetoacetates using dirhodium and copper catalysts have been developed.[1,3] However, although remarkable diastereoselection has been documented, enantiocontrol with achiral diazoacetoacetates in catalytic asymmetric metal carbene transformations has been disappointing.[5] With few exceptions,[4] neither chiral copper nor chiral dirhodium catalysts have provided enantioselectivities beyond 50% ee in reactions with either diazoacetoacetates or diazomalonates,[5] and these exceptions are only found in constrained systems. An alternative to this synthetic approach is the synthesis of enantiomerically enriched diazoacetoacetates that are amenable to subsequent catalytic reactions, but this synthetic strategy has generally relied on the use of reactants from the chiral pool.[2]

Asymmetric catalytic construction of chiral diazoacetates from a readily available reactant diazocarbonyl compound using a chiral promoter can be a practical solution to this problem. We recently reported[6] a highly efficient methodology for the synthesis of functionalized diazoacetoacetates via a scandium(III) triflate catalyzed Mukaiyama aldol addition[7] of TBDMSO-substituted vinyl diazoacetate **1** with aliphatic and aromatic aldehydes (Eq. 1). Addition occurs with transfer of the TBDMS group from the reactant vinyl ether oxygen to the product's ether oxygen **2**. Asymmetric induction using a chiral catalyst in this addition reaction can be expected to produce chiral diazoacetoacetates. An analogous undertaking using ethyl diazoacetate and a selection of aldehydes has recently been reported by Wang using a (*S*)-BINOL/Zr(O-^{t}Bu)$_4$ catalyst (Eq. 2). In this process, addition occurs so that, formally, the hydrogen on the diazo carbon becomes the alcohol hydrogen of the product **3**, and enantiomeric excesses ranging from 53% to 87% were achieved.



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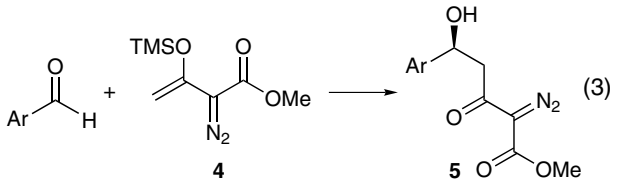
Among the challenges to catalytic asymmetric synthesis of chiral diazoacetoacetates are the presence of multiple functional groups in the diazo compound and the stereochemical control that is required for the overall process. Herein, we report our initial efforts to achieve highly efficient Lewis acid catalyzed asymmetric Mukaiyama aldol addition of aldehydes with vinyldiazoacetate **4** resulting in the synthesis of highly enantioenriched diazoacetoacetates.

2. Results and discussion

Catalytic enantioselective Mukaiyama aldol addition reactions of aldehydes with silyl enol ethers have been achieved using a broad selection of catalysts; generally with high enantiocontrol.[9–16] Several of the catalysts formed the basis of our early screening of Lewis acids. We first used catalysts and conditions reported by Carriera,[10a] Keck,[13a] and Yamamoto[14d] for Mukiyama aldol reactions between aldehydes and silyl vinyl ethers. However, the TBDMS protected vinyldiazoacetate **1** was found to be unreactive with these catalysts both at −78 and −20 °C. Switching to the TMS-protected **4** was rewarding, as it offered moderate enantiocontrol (66% ee) with 2 mol % CuF_2/(*R*)-tol-BINAP(**6**) (Table 1, entry 1) when the reaction was carried out at −78 °C. The lower yield in this Cu(II) catalyzed addition is due, we believe, to slow decomposition of the diazo moiety of **4** and/or **5**. Changing catalyst loading to 1 mol % or 4 mol % did not improve enantiomeric excess or chemical yield. With Ti(O*i*Pr)$_4$/(*S*)-BINOL(**7**) at −20 °C, both the yield (15%) and enantioselectivity (40% ee) were poor (Table 1, entry 2).

Table 1. Asymmetric Mukaiyama aldol reaction of diazo silyl enol ether **4**



4 **5**

Ar	Lewis acid + ligand	Yield of **5** (%)[a]	ee (%)[b]
Ph	CuF_2 + **6**[c]	53	66
Ph	Ti(O^{i}Pr)$_4$ + **7**[d]	15	40
Ph	AgF + **8**[e]	80	91
4-MeOC$_6$H$_4$	AgF + **8**[e]	82	87
4-MeC$_6$H$_4$	AgF + **8**[e]	80	88
4-ClC$_6$H$_4$	AgF + **8**[e]	78	92
β-styryl	AgF + **8**[e]	74	88

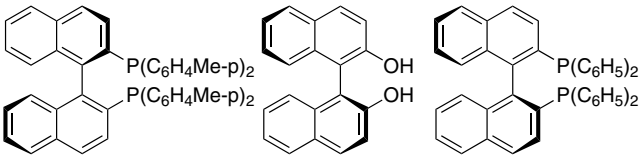
[a] Yield of isolated **5** following column chromatography (see experimental section for details).

[b] Determined by HPLC on chiral Chirapack-AD column (see experimental section for details). Racemic material was used as the standard to certify enantiomeric excess.

[c] Used the same experimental procedure as that reported by Carreira: 2 mol % (*R*)-Tol-BINAP/CuF_2, THF, −78 °C, mildly acidic work-up (see Ref. 10).

[d] Used the same procedure as that reported by Keck (see Ref. 13).

[e] See experimental section for details. Absolute stereochemistry of the products was not determined. The major isomers formed from Cu(II)/(*R*)-tol-BINAP, Ti(IV)/(*S*)-BINOL, and Ag(I)/(*S*)-BINAP catalysts are the same.



6 **7** **8**

The AgF/(*S*)-BINAP **8** catalyst was first reported by Yamamoto[14] and was successfully utilized for asymmetric Mukaiyama aldol addition and allylation reactions with high product conversion and enantiocontrol.[14d] Recently, AgF/(*R*)-tol-BINAP catalyst was being utilized in the highly enantioselective α-protonation of ketones.[15] Using AgOTf (10 mol %), KF (10 mol %), 18-Crown-6 (10 mol %) and (*S*)-BINAP (6 mol %) as catalyst at −20 °C vinyldiazoacetate **4** reacted with benzaldehyde in 6 h to give the Mukaiyama aldol adduct in 80% isolated yield and 91% enantiomeric excess (Table 1). These reaction conditions were found to be general for aromatic aldehydes. Those with electron donating groups, *p*-anisaldehyde and *p*-tolualdehyde, produced the Mukaiyama aldol adducts in good yields (>80%) and good enantiomeric excess (>85%). Good chemical yield and good stereocontrol were also obtained with the aromatic aldehyde, *p*-chlorobenzaldehyde, having a weakly electron withdrawing chlorine substituent.

Tentative assignment of the absolute configuration of **5** as *S* comes from comparison of the sign of rotation of **5** (Ar = 4-ClC$_6$H$_4$) with the product of Mukaiyama aldol addition of benzaldehyde to isopropenyloxytributylstannane catalyzed by AgOTf/(*R*)-BINAP (leading to *R* adduct)[14c] and this assignment is consistent with similar results reported by Carrierra with Ti(IV)/(*R*)-tridentate ligand[13c] and Kobayashi with Zr(IV)/(*R*)-BINOL.[15]

The α,β-unsaturated aldehyde cinnamaldehyde (**1e** in Table 1) also produced the aldol adduct in 74% yield and 88% ee. The aliphatic aldehyde octanal was found to be the only exception. Under the same condition, octanal reacted with vinyldiazoacetate **2b** giving only 20% conversion and 11% enantiomeric excess. Low reactivity of aliphatic aldehydes was also observed by Yamomoto[14] and by Wang in reactions with ethyl diazoacetate.[8]

3. Conclusion

In summary, we have developed an efficient enantioselective synthesis of chiral diazoacetoacetates via catalytic Mukaiyama aldol addition of 3-trimethylsilyloxy-vinyldiazoacetate **4** without simultaneously decomposing the acid-sensitive diazo moiety. This method presents a straightforward approach for accessing chiral diazoacetoacetates from a readily accessible diazo compound using commercially available ligand and silver(I) triflate.

4. Experimental

4.1. General information

Reactions were performed in oven-dried (140 °C) or flame-dried glassware under an atmosphere of dry N_2. Dichloromethane was passed through a solvent column prior to use and was not distilled. Tetrahydrofuran and diethyl ether were distilled over sodium/benzophenone ketyl. Thin layer chromatography (TLC) was carried out using EM Science silica gel 60 F_{254} plates. The developed chromatogram was analyzed by UV lamp (254 nm), ethanolate phosphomolybdic acid, potassium permanganate ($KMnO_4$), or cerium ammonium molybdate (CAM). Liquid chromatography was performed by flash chromatography on silica gel (230–400 mesh). Silver(I) triflate was purchased from Aldrich and used as received. (*S*)-BINOL, (*S*)-BINAP, and (*R*)-tol-BINAP were purchased from Strem.

4.2. Synthesis of methyl 3-trimethylsilanyloxy 2-diazobut-3-enoate 2b[17]

To an oven-dried 250 mL round-bottomed flask were added 3.90 g (27.4 mmol) of methyl diazoacetoacetate and 3.84 mL (27.4 mmol) of triethylamine sequentially, followed by 100 mL anhydrous dichloromethane and the resultant solution was stirred at rt for 30 min. The reaction mixture was then cooled to 0 °C and 6.09 g (27.4 mmol) of trimethysilyl trifluoromethanesulfonate (TMS-OTf) was added dropwise via a 10-mL syringe over 10 min. The resultant orange solution was stirred at 0 °C for an additional 30 min. The reaction mixture was concentrated to ~5 mL, and then anhydrous hexane (50 mL) was added. The mixture was stirred for 20 min at ambient temperature and was then kept undisturbed for 10 min. Two immiscible liquid layers appeared over that time. The top orange hexane layer was decanted and passed through a funnel fitted with a cotton plug. The solvent was removed under reduced pressure to give methyl 3-trimethylsilanyloxy-2-diazobut-3-enoate as bright orange liquid (9.8 g, 92%).

4.3. General procedure for asymmetric Mukaiyama aldol addition

To an oven-dried 5-mL round-bottomed flask containing a stir bar and fitted with a septum, were added (*S*)-BINAP (21 mg, 0.033 mmol), KF (3.2 mg, 0.055 mmol), 18-crown-6 (14 mg, 0.055 mmol), and anhydrous AgOTf (14 mg, 0.055 mmol) followed by 1 mL dry THF via syringe. The reaction mixture was stirred for 10 min at rt before cooling to −20 °C. Methyl 3-trimethylsilanyloxy-2-diazobut-3-enoate (120 mg, 0.550 mmol) was then added dropwise using a 1-mL syringe, followed by benzaldehyde (58 mg, 0.55 mmol). The flask was kept at −20 °C for 6 h under nitrogen with stirring. After which the reaction mixture was treated with brine (5 mL) and solid KF (ca. 1 g) at ambient temperature for 30 min. The resulting solution was then extracted with CH_2Cl_2 (3 × 1 mL), dried over anhydrous Na_2SO_4. The product was isolated by flash chromatography on silica gel, eluting with 4:1 hexane/ethyl acetate. Compounds **5b**[18a] and **5e**[18b] have been prepared previously and their full spectroscopic data were reported. Enantiomeric excesses of the products from the asymmetric Mukaiyama aldol addition were determined by chiral stationary phase HPLC analysis using a Daicel Chirapack AD-H chiral column (0.5 cm × 25 cm).

4.3.1. Methyl 2-diazo-5-hydroxy-5-(*p*-methoxyphenyl)-3-oxopentanoate 5b. IR (neat): 3509, 2912, 2138, 1720, 1641, 1508; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (d, $J = 8.8$ Hz, 2H), 6.82 (d, $J = 8.8$ Hz, 2H), 5.10 (dd, $J = 7.8$, 4.2 Hz 1H), 3.81 (s, 3H), 3.78 (s, 3H), 3.24–3.23 (comp, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 192.2, 161.5, 159.1, 135.0, 127.0, 114.3, 69.8, 55.2, 52.3, 48.5; HRMS (FAB) for $C_{13}H_{14}N_2O_5$ $[M+H]^+$ calcd: 303.0940; found 303.0946; HPLC (Chirapack-AD): hexanes: *i*PrOH 85:15, 1.5 mL/min; minor 15.2 min, major 17.8 min ($R_f = 0.37$ in 4:1 hexane and ethyl acetate).

4.3.2. Methyl 2-diazo-5-hydroxy-5-(*p*-tolyl)-3-oxopentanoate 5c. IR (neat): 3507, 2908, 2135, 1727, 1651, 1441; ^{1}H NMR (400 MHz, $CDCl_3$):δ 7.26 (d, $J = 8.0$ Hz, 2H), 7.13 (d, $J = 8.0$ Hz, 2H), 5.15 (dd, $J = 8.4$, 3.6 Hz, 1H), 3.80 (s, 3 H), 3.31–3.20 (comp, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 192.1, 161.6, 139.8, 137.3, 129.1, 125.7, 70.1, 52.3, 48.6, 21.1; HRMS (ESI) for $C_{13}H_{14}O_4N_2$ $[M+H]^+$ calcd: 263.1928; found 263.1932. HPLC (Chirapack-AD): hexanes: *i*PrOH 85:15, 1.0 mL/min; major 15.1 min, minor 16.8 min ($R_f = 0.37$ in 4:1 hexane and ethyl acetate).

4.3.3. Methyl 5-(*p*-chlorophenyl)-2-diazo-5-hydroxy-3-oxopentanoate 5d. IR (neat): 3503, 2956, 2141, 1719, 1653, 1437, 1313; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28–7.31 (comp, 4H), 5.16 (m, 1H), 3.81 (s, 3H), 3.48 (br s, 1H), 3.23–3.20 (comp, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 192.1, 161.5, 142.7, 128.5, 127.7, 125.7, 70.3, 52.3, 48.6; HRMS (FAB) for $C_{12}H_{11}ClN_2O_4$ $[M+Na]^+$ calcd: 305.0305; found 305.0322; HPLC (Chirapack-AD): hexanes: *i*PrOH 85:15, 1.0 mL/min; minor 16.1 min, major 18.9 min ($R_f = 0.4$ in 4:1 hexane and ethyl acetate).

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