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A new diastereoselective intramolecular electroreductive coupling of unsaturated β-ketoesters and β-ketoamides in ionic liquids at a tin cathode

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ABSTRACT

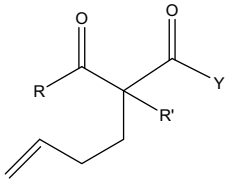
The diastereoselective intramolecular electroreductive coupling of several β-ketoesters and β-ketoamides has been accomplished at a tin cathode in ionic liquids and isopropanol (9:1). The ionic liquids used are 1-butyl-3-methylimidazolium bromide [BMIM]Br, 1-butyl-3-methylimidazolium tetrafluoroborate [BMIM]BF_4, 1-methoxyethyl-3-methylimidazolium trifluoroacetate [MOEMIM]CF_3COO and 1-methoxyethyl-3-methylimidazolium mesylate [MOEMIM]Ms. This methodology offers a clean and green process for the synthesis of functionalized carbocycles in good yields with excellent stereochemical control at three stereogenic centres.

A survey of the literature reveals that the ketyl radicals generated photochemically,[1–3] electrochemically[4–8] or chemically[9–13] from organic compounds possessing keto-olefin/keto-alkyne functionality, offer an attractive synthetic method for achieving regioselectivity and stereoselectivity in their reactions. Kariv-Miller et al.[6,13–15] reported that *N*,*N*-dimethylpyrrolidinium (DMP^+), *N*-methylquinuclidinium (MQ^+) at the cathodic potentials of Hg and Pb yielded R_4N-$Metal_5$ complexes that are capable of heterogeneous electron transfer leading to reduction/reductive cyclization products. We have reported earlier enantioselective[16] syntheses of (*S*)-alcohols from ketones at a mercury cathode in DMF–water (90:10) using a catalytic amount of (1*R*,2*S*)-(−)-*N*,*N*-dimethylephedrinium tetrafluoroborate. The reductive cyclization of several unconjugated ketones, for example, 6-heptan-2-one, was accomplished with excellent regio- and stereochemical control[1,2,4,5,8] leading to the formation of (1*R*,2*S*)-1,2-dimethylcyclopentanol.

These reactions involve hazardous chemicals, for example, solvents such as dimethylformamide and tetrahydrofuran and mercury as the cathode. The development of ecofriendly 'green' alternatives to common organic solvents has attracted enormous interest worldwide and ionic liquids (ILs)[17] fall into this domain. Their interesting properties, viz., negligible vapour pressure, unprecedented ability to dissolve a wide range of organic/organometallic/inorganic compounds, high thermal stability and recyclability, make ILs attractive environmentally benign solvents. One key reason for considering ILs, as better reaction media in electrosynthesis, is their unique ability to pass current without much resistance, thus making ILs excellent conducting media in non-aqueous electrochemistry.

In the present Letter, we report for the first time the diastereoselective intramolecular electroreductive coupling of unsaturated β-keto esters/amides at a tin cathode in the ILs, 1-butyl-3-methylimidazolium bromide [BMIM]Br, 1-butyl-3-methylimidazolium tetrafluoroborate [BMIM]BF_4, 1-methoxyethyl-3-methylimidazolium trifluoroacetate [MOEMIM]CF_3COO and 1-methoxyethyl-3-methylimidazolium mesylate [MOEMIM]Ms in the presence of isopropanol (9:1) to afford carbocycles regio- and stereoselectively. Thus, several unsaturated β-keto esters/amides were synthesized by a reported method[18] as model compounds (Scheme 1). We initially investigated the solubility of **1a** in [BMIM]Br, [BMIM]BF_4, [MOEMIM]CF_3COO, [MOEMIM]Ms and observe it to be 40, 55, 300 and 320 mg mL^{-1}, respectively.

A test electroreductive coupling of **1a** was carried out in [MOEMIM]Ms and isopropanol (9:1) at a tin cathode.[19] A similar method was followed for compound **1a** using the other ILs and the yields of



1a -h

Scheme 1. R and R′ = alkyl and Y = OR, NH_2.

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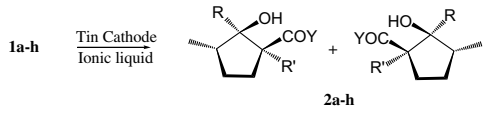
the product **2a**, so obtained, were found to be 65%, 70%, 80% and 90% in [BMIM]Br, [BMIM]BF_4, [MOEMIM]CF_3COO and [MOEMIM]Ms, respectively, using isopropanol as co-solvent in each case. We found after performing several experiments that the optimum yield of **2a** was obtained upon transfer of a charge corresponding to 3.0 F mol^{-1}. Next, we carried out the electroreductive coupling of compounds **1b–h** at a tin cathode in [MOEMIM]Ms and obtained products **2b–h** with excellent diastereoselectivity (Scheme 2, Table 1).

These compounds were purified by distillation/column chromatography and characterized by ^{1}H NMR, ^{13}C NMR and IR.[20] The diastereoselectivity was determined by fused silica capillary GC analysis of the reaction mixture on a 25 m × 320 μm 5% phenyl SE-54 fused silica/or 10% fused silica carbowax column.

The relative stereochemistry of the products was determined by ^{1}H NMR and IR combined with chemical derivatization. For example, the carboxylate and hydroxyl group in compound **2a** were assigned with cis stererochemistry on the basis of the fact that saponification of **2a** gave the corresponding β-hydroxy acid, which on treatment with benzenesulfonyl chloride yielded a β-lactone.[21] This observation is also consistent with an earlier literature report[22] that *trans*-2-hydroxycycloalkanecarboxylic acids do not give β-lactones under these conditions. An NOE difference ^{1}H NMR experiment[23] on **2a** revealed that the three methyl groups were oriented on the same face of the molecule, thereby confirming the relative stereochemistry of **2a**.

A typical cyclic voltammogram of compound **1a** in [MOEMIM]Ms at a tin cathode (at 100 mV s^{-1}) showed a reduction peak at E_p −2.4 V versus Ag/AgCl due to keto group and a second reduction peak appeared at −2.5 V versus Ag/AgCl, apparently due to the reduction of –COOEt. The same observation in [MOEMIM]Ms–isopropanol (9:1) showed a reduction peak of E_p −2.4 V versus Ag/AgCl and the co-solvent isopropanol was found to decompose at E_p −2.45 V versus Ag/AgCl. More detail investigations will be carried out by manipulating co-solvent to clinch this issue and the mechanism of the process will be addressed in a later publication.

The observed diastereoselectivity in compounds **2a–h** appears to be due to formation of a transition state between the negatively charged oxygen of the ketyl radical and the cation of the ionic liquid. The lone pair on the oxygen of the second keto group may also show weak interactions with the IL. Under these circumstances, the empty π^* molecular orbital (LUMO) of the olefin and

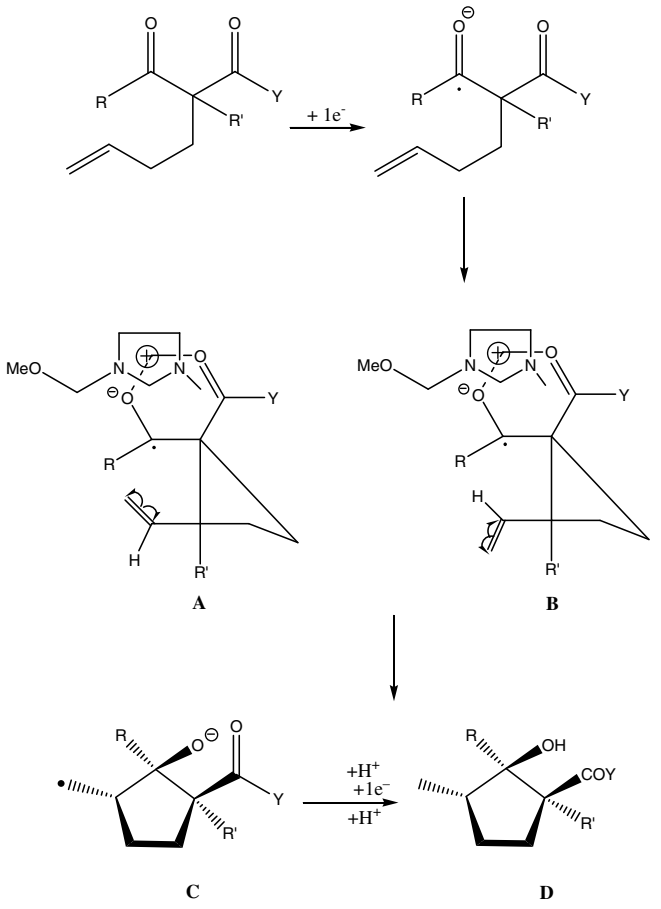


Scheme 2. Electroreductive coupling of compounds **1a–h** at a tin cathode in various ILs.

Table 1
Electroreductive coupling of compounds **1a–h** at a tin cathode in [MOEMIM]Ms–isopropanol (9:1), current density 0.19 mA cm^{-2} with a platinum foil anode wrapped with Nafion fibre

Substrate	Y	R	R′	Yield[a] **2** (%)	Diastereoselectivity[b]
1a	OEt	Me	Me	90	80:1
1b	OEt	Et	Me	70	85:1
1c	OEt	*i*-Pr	Me	80	90:1
1d	OEt	Me	Et	75	200:1
1e	OEt	Me	H	78	200:1
1f	NMe_2	Me	Et	89	>200:1
1g	NMe_2	Et	Me	75	>130:1
1h	NMe_2	*i*-Pr	Me	79	>140:1

Charge transfer = 3.0 F mol^{-1}.
[a] Isolated yield.
[b] Determined by GC analysis.



Scheme 3. A plausible mechanism.

the semi occupied molecular orbital (SOMO) of the ketyl radical align to acquire an appropriate angle maximizing the overlap. As a result, an intermediate is expected to form in which, the hydroxyl group and carboxyl group are located in cis position **(D)**.

The transition structure leading to the other diastereoisomer with trans stereochemistry about the hydroxyl and carboxylate groups is less favoured, owing to the inherent limitation of the C4-carbon of the olefinic side chain, which cannot attain correct orbital alignment without distortion.

The third stereocentre is expected to form via favourable electrostatic and secondary orbital interactions in the transition states shown in **A** or **B**. It must be noted that steric interactions further reinforce this stereochemical outcome thus directing the methylene group away from the face of the molecule in the transition state during ring formation (Scheme 3). The intermediate **C** upon protonation and electron transfer followed by a further proton transfer affords the desired product in good to excellent yield.

In this Letter, we describe an ecofriendly intramolecular electroreductive coupling of unsaturated β-ketoesters and β-ketoamides. This method provides a convenient process for the synthesis of highly functionalized five-membered carbocycles in good to excellent yield with high diastereoselectivity. This approach avoids the use of organic solvents with low volatility and the use of toxic reagents.

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18. Starting materials **Ia–e** were synthesized by condensation of ethyl propanoate with various aldehydes. The resultant products upon Swern oxidation, followed by alkylation with 4-bromo-1-butene gave the desired products, for example, Smith, A. B., III; Levenberg, P. A. *Synthesis* **1981**, 567. **1f–h** were prepared by refluxing β-ketoesters and dimethylamine.
19. Typical experimental procedure for preparative scale electrolysis: 0.01 mol of **1a–h** were added to 20 mL of IL–isopropanol (9:1). Tin foil (2 × 2 cm) was used as the cathode and a platinum foil (2 × 2 cm) wrapped with Nafion fibre served as the anode. The electrolyte cell was magnetically stirred. A constant current of 200 mA (current density 19 mA cm^{-2}) was passed until the charge transferred corresponded to 3 F mol^{-1}. The organic compound was extracted with water–ethyl acetate (1:9) (3 × 20 mL). The combined layer of ethyl acetate upon distillation, afforded the desired products **2a–h**. These products were purified by distillation/column chromatography over silica gel.
20. Details on the purification of compounds **2a–h** and their analytical data are presented below:
    Compound **2a**: Ethyl (1*R*,2*S*,3*S*)-2-hydroxy-1,2,3-trimethylcyclopentanecarboxylate: purified by chromatography on neutral alumina (activity III) with *n*-hexane–EtOAc (8:1), pale yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.18 (q, *J* = 7.0 Hz, 2H), 3.55 (br, s, 1H), 2.30 (m, 1H), 2.08–1.85 (m, 2H), 1.58 (m, 1H), 1.28 (t, *J* = 7.0 Hz, 3H), 1.20 (s, 3H), 1.18–1.12 (m, 1H), 1.08 (s, 3H), 0.95 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (75MHz, $CDCl_3$) δ 175.00, 82.02, 60.18, 54.70, 43.00, 32.40, 28.50, 19.60, 17.20, 14.85, 13.33. IR (neat, cm^{-1}) 3460 (br, s), 2980 (s), 2922 (s), 2878, 1702 (s), 1492, 1390, 1252 (s), 950 (m). Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.95; H, 10.07. Found: C, 66.03; H, 10.12.
    Compound **2b**: Ethyl (1*R*,2*S*,3*R*)-2-ethyl-2-hydroxy-1,3-dimethylcyclopentanecarboxylate: purified by distillation, bp 40 °C (0.05 mmHg). ^{1} H NMR (300 MHz, $CDCl_3$) δ 4.12 (q, *J* = 7.2 Hz, 2H), 2.40–2.32 (m, 1H), 2.18–2.06 (m, 2H), 1.80–1.62 (m, 3H), 1.50 (q, *J* = 7.2 Hz, 2H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.18 (s, 3H), 0.98 (d, *J* = 7.2 Hz, 3H), 0.90 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75MHz, $CDCl_3$) δ 178.84, 85.68, 60.80, 56.00, 43.70, 32.28, 30.34, 25.45, 20.68, 18.98, 14.10, 8.29. IR (neat, cm^{-1}) 3400 (br), 3000, 2900 (s) 2880, 1690 (s) 1450, 1390, 1340, 1250, 1110, 975. Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.24; H, 10.35. Found: C, 67.30; H, 10.38.
    Compound **2c**: Ethyl (1*R*,2*S*,3*S*)-2-hydroxy-2-isopropyl-1,3-dimethylcyclopentanecarboxylate: purified by distillation, bp 56–63 °C (0.05 mmHg). ^{1}H NMR(300 MHz, $CDCl_3$) δ 5.05 (s, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 2.30–2.22 (m, 2H), 2.15–2.0 (m, 1H), 1.97–1.82 (Sept. *J* = 6.4 Hz, 1H), 1.65–1.54 (m, 1H), 1.48–1.38 (m, 1H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.19 (s, 3H), 1.06 (d, *J* = 7.2 Hz, 3H), 0.92 (d, *J* = 6.4 Hz, 3H), 0.76 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.00, 89.00 61.06, 53.90, 44.15, 38.50, 30.83, .29.85, 20.24, 18.59, 18.15, 17.35, 13.86. IR (neat, cm^{-1}) 3430 (br, s), 3300 (w), 2980 (s), 2880 (m), 1690 (s), 1490, 1410, 1235, 1100, 1020. Anal. Calcd for $C_{13}H_{24}O_3$: C, 68.37; H, 10.60. Found: C, 68.40; H, 10.64.
    Compound **2d**: Ethyl (1*R*,2*S*,3*R*)-1-ethyl-2-hydroxy-2,3-dimethylcyclopentanecarboxylate: purified by column chromatography on silica gel with *n*-hexane–EtOAc (5:1), colourless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.2 (q, *J* = 7.2 Hz, 2H), 3.46 (s, 1H), 2.52–2.0 (m, 5H), 1.71–1.42 (m, 3H), 1.22 (q, *J* = 7.0 Hz, 2H), 1.14 (s, 3H), 1.0–0.9 (t, *J* = 7.0 Hz, 3H), 0.89 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.60, 80.64, 59.24, 58.20, 41.95, 28.25, 26.20, 25.45, 16.05, 13.20, 12.75, 8.48. IR (neat, cm^{-1}) 3500 (br), 2900 (s), 2855 (m), 1680 (s), 1480 (m), 1250 (s), 1200 (s), 1145 (s), 1030 (s), 980. Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.24; H, 10.35. Found: C, 67.30; H, 10.40.
    Compound **2e**: Ethyl (1*R*,2*S*,3*R*)-2-hydroxy-2,3-dimethylcyclopentanecarboxylate: purified by column chromatography on silica gel by *n*-hexane–EtOAc (5:1), followed by column chromatography on neutral alumina (activity III) by *n*-hexane–EtOAc (5:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.15 (q, *J* = 7.2 Hz, 2H), 3.10 (br, s, 1H), 2.60 (t, *J* = 7.2 Hz, 1H), 2.12–1.82 (m, 5H), 1.22 (s, 3H), 1.0 (t, *J* = 7.0 Hz, 3H), 0.88 (d, *J* = 7. 2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ .174.60, 80.10, 50.50, 50.02, 43.00, 29.56, 24.90, 21.90, 18.20, 15.22. IR (neat, cm^{-1}) 3500 (br), 3000 (m), 2960 (s), 2880 (m), 1710 (s), 1350 (s), 1180 (s), 930 (m). Anal. Calcd. for $C_{10}H_{18}O_3$: C, 64.47; H, 9.74. Found: C, 64.49; H, 9.78.
    Compound **2f**: (1*R*,2*S*,3*R*)-*N*,*N*-Dimethyl-1-ethyl-2-hydroxy-2,3-dimethylcyclopentanecarboxamide: purified by column chromatography on silica gel by *n*-hexane–EtOAc (1:1), pale yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.57 (s, 1H), 3.05 (s, 3H), 2.95 (s, 3H), 2.41–2.10 (m, 5H), 2.0–1.7 (q, *J* = 7.2 Hz, 2H), 1.18–1.10 (t, *J* = 7.2 Hz, 3H), 1.10 (s, 3H), 0.80 (d, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.00, 80.00, 46.25, .44.50, 42.50, 40.30, 32.28, 28.50, 22.30, 16.28, 13.50, 12.50. IR (neat, cm^{-1}) 3380 (br), 3000 (s), 2960; 2850, 1620 (s), 1450, 1380, 1225, 1150, 978. Anal. Calcd for $C_{12}H_{23}NO_2$: C, 67.55; H, 10.87; N, 6.56. Found: C, 67.59; H, 10.90; N, 6.59.
    Compound **2g**: (1*R*,2*S*,3*R*)-*N*,*N* -Dimethyl-2-ethyl-2-hydroxy-1,3-diemthylcyclopentanecarboxamide: purified by column chromatography on silica gel by *n*-hexane–EtOAc (1:1), pale yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.57 (s, 1H), 2.99 (s, 3H), 2.92 (s, 3H), 2.4–2.1 (m, 3H), 1.50–1.15 (m, 4H), 1.10 (s, 3H), 0.87 (t, *J* = 7.5 Hz, 3H), 0.80 (d, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.00, 80.00, 46.25, 44.50, 42.50, 40.30, .32.28, 28.50, 22.30, 16.30, 13.50, 12.50. IR (neat, cm^{-1}) 3380 (br), 3000 (s), 2960, 2850, 1650, 1620 (s), 1450, 1380, 1225, 1150, 978. Anal. Calcd for $C_{12}H_{23}NO_2$: C, 67.55; H, 10.87; N, 6.56. Found: C, 67.60; H, 10.91, N, 6.60.
    Compound **2h**: (1*R*,2*S*,3*R*)-*N*,*N*-Dimethyl-2-hydroxy-2-isopropyl-1,3-dimethylcyclopentane carboxamide: purified by column chromatography on silica gel by *n*-hexane–EtOAc (1:1), a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.50 (s, 1H), 3.05 (s, 3H), 2.90 (s, 3H), 2.5–1.5 (m, 6H), 1.18–1.0 (s, 3H), 0.88 (d, *J* = 6.75 Hz, 3H), 0.85 (d, *J* = 6.75 Hz, 3H), 0.75 (d, *J* = 6.50 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.00, 85.70, 42.20, 40.50, 35.90, 34.00, 32.10, 29.60, 26.30, 16.35, 16.20, 15.70, 13.40. IR (KBr pellet, cm^{-1}) 3360 (br), 3010 (s), 2950, 2870 (m), 2800, 1620 (s), 1475, 1400 (s), 1390 (s), 1250, 1140 (m), 980 (s). Anal. Calcd for $C_{13}H_{25}NO_2$: C, 68.66; H, 11.09; N, 6.16. Found: C, 68.70; H, 11.12; N, 6.18.
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