Synthesis of Substituted Tetrahydropyrans via Intermolecular Reactions of δ-Halocarbanions with Aldehydes

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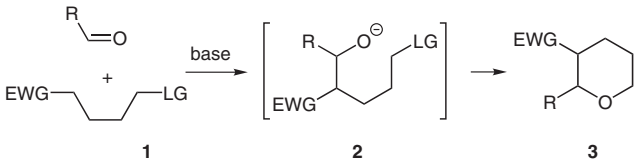
Abstract: Intramolecular substitution in δ-halocarbanions leading to cyclobutanes is a relatively slow process, thus they readily add to carbonyl groups; the thus-produced anionic adducts cyclize to tetrahydropyran derivatives. A simple mechanistic discussion, optimization of the reaction conditions, and scope of the reaction is presented.

Key words: aldol reactions, sulfones, halocarbanions, cyclizations, tetrahydropyrans



EWG = electron-withdrawing group
LG = leaving group

Scheme 1

In our preceding papers we have shown that although γ-halocarbanions undergo fast intramolecular 1,3-substitution they can be trapped by suitable electrophilic reagents. Aldol-type adducts from γ-halocarbanions and aldehydes undergo rapid intramolecular substitution reactions giving 2,3-disubstituted tetrahydrofurans.[1,2] A similar reaction of various γ-halocarbanions with electron-deficient imines and the Michael acceptors gave pyrrolidines[3] and cyclopentanes,[4] respectively. On the other hand, intramolecular 1,4-substitution in δ-halocarbanions, for enthalpic and entropic reasons, is a relatively slow process.[5,6] Such differences in the behavior of γ- and δ-halocarbanions can be, for example, observed during the alkylation of methylenic carbanions with 1,2- and 1,3-dihaloalkanes.[7] Alkylation of diethyl malonate, ethyl cyanoacetate, or phenylacetonitrile carbanions with 1,2-dibromoethane cannot be arrested at the 2-haloethyl derivative stage, because they cyclize immediately giving substituted cyclopropanes,[8] whereas in the reaction of these carbanions with 1,3-dibromopropane a number of products are formed; a 3-bromopropyl-substituted derivative is the major product.[9] We could, therefore, expect that δ-halocarbanions generated from 4-bromobutyl phenyl sulfone, alkyl 5-bromopentanoate, or 5-bromo-1-phenylpentan-1-one should form reasonably long-lived species that could be trapped by aldehydes and ketones, intramolecular substitution in the thus-produced intermediate aldol-type anions should give substituted tetrahydropyrans (Scheme 1).

In the literature, only few specific examples of intermolecular reactions of carbanions with leaving groups in the δ-position are reported.[10] 5-Chloropentanenitrile reacted with nonenolizable aldehydes in the presence of potassium *tert*-butoxide giving the expected cyanotetrahydropyrans,[11] Hassner and co-workers reported the synthesis of substituted cyclohexanes via the reaction of 4-bromobutyl phenyl sulfone carbanion with chiral α,β-unsaturated oxazolines.[12] In a similar reaction 5-bromo-1-phenylpentan-1-one reacted with highly electrophilic N-substituted isatine giving spiro derivatives of tetrahydropyrans.[13] On the basis of these precedents and our generalized scheme developed for the reactions of γ-halocarbanions, we commenced studies in the area of intermolecular reactions of δ-halocarbanions.[14]

In preliminary experiments,[15] conducted under conditions described by Fleming for the reactions of ω-haloalkanenitriles (*t*-BuOK, THF, 0 °C, 3 h, then to r.t.) we observed, that base-induced reaction of the model carbanion precursor 4-chlorobutyl phenyl sulfone (**1a**) with benzaldehyde gave 2-phenyl-3-(phenylsulfonyl)tetrahydro-2*H*-pyran (**3a**) with yields not exceeding 50%, probably due to the decomposition of this compound under the reaction conditions. On the other hand at lower temperatures (–25 °C, 1 h) we observed only traces of **3a** in the crude reaction mixture (^{1}H NMR), the uncyclized aldol-type adduct being the main product. To increase the rate of cyclization via intramolecular substitution at low temperature we changed the halogen and used 4-bromobutyl phenyl sulfone (**1b**). At –50 °C after a short reaction time (1 min) and subsequent quenching of the reaction mixture with aqueous ammonium chloride, we observed exclusive formation of the intermediate aldol-type adduct **2a** from the addition of the carbanion to the aldehyde as a mixture of two diastereomers (94%, ~2:1),[16] but only traces of the final cyclized tetrahydropyran derivative **3a** were formed. Extension of the reaction time to one hour and a slight increase in the temperature to –40 °C led to the formation of **3a** as single *trans*-diastereomer in high yield (89%) (Scheme 2).

The discrepancy between the observed diastereoselectivity of the initial aldol addition process and the composition

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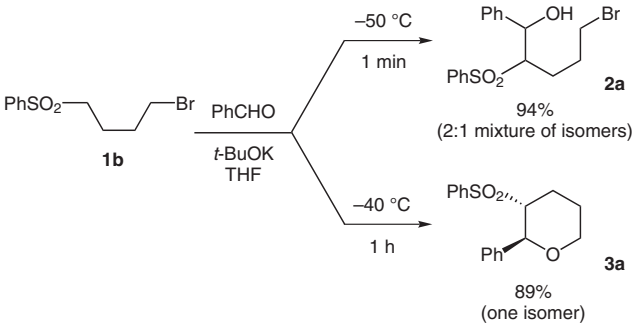
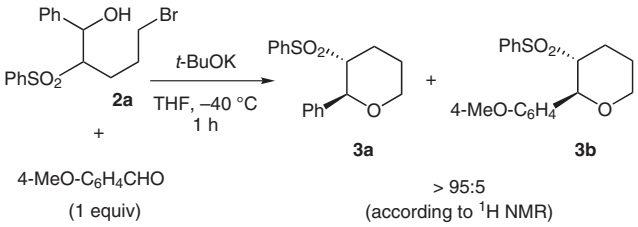


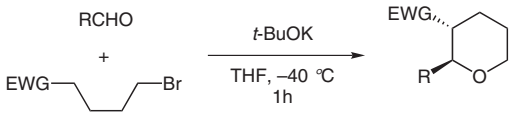
Scheme 2

of the product **3a** prompted us to investigated this matter further. For this purpose we isolated samples of the pure diastereomers of **2a** and introduced them into cross experiments with 4-methoxybenzaldehyde under the standard reaction conditions. Analysis of the crude reaction mixtures with ^{1}H NMR showed that only minor amounts (<5%)[17] of the 4-methoxyphenyl-substituted tetrahydropyran **3b** were formed. It appears, therefore, that the initially formed aldol-type adducts do not dissociate under these conditions, or they dissociate more slowly than they cyclize to give **3a** (Scheme 3).



Scheme 3

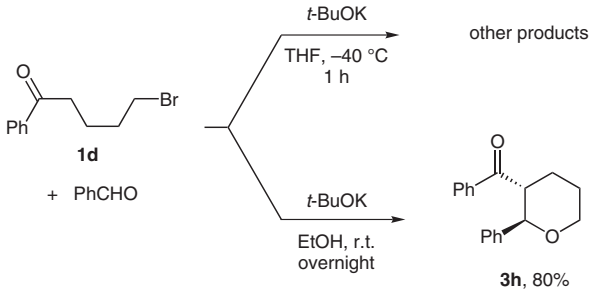
^{1}H NMR analysis of crude reaction mixtures when these experiments were halted before complete conversion (–40 °C, 10 min) showed also, that the diastereomers of **2a** do not interconvert via epimerization of their C–H acidic centers. Thus, we can conclude that the exclusive formation of the pure *trans*-isomer of **3a** is of thermodynamic nature, due to the epimerization of the initially formed mixture of *cis*- and *trans*-tetrahydropyran derivatives.[18]



Scheme 4

The scope and limitations of this addition–alkylation sequence under optimized conditions[19] (–40 °C, 1 h) were determined for reactions δ-halocarbanion precursors, **1b** and methyl 5-bromopentanoate (**1c**) with other nonenolizable aldehydes (Scheme 4, Table 1).

Under these conditions, reactions of **1b** and **1c** with nonenolizable aldehydes proceeded cleanly and in high yield. By contrast, the reaction of 5-bromo-1-phenylpentan-1-one (**1d**) with benzaldehyde under the same conditions failed to give the expected product (Scheme 5).[21]



Scheme 5

To overcome this problem, we successfully used a protic solvent, ethanol; the procedure was described by us earlier for reactions γ-haloenolates of ketones.[2] In all explored cases, formation of pure *trans*-diastereomers was observed (Schemes 4, 5).

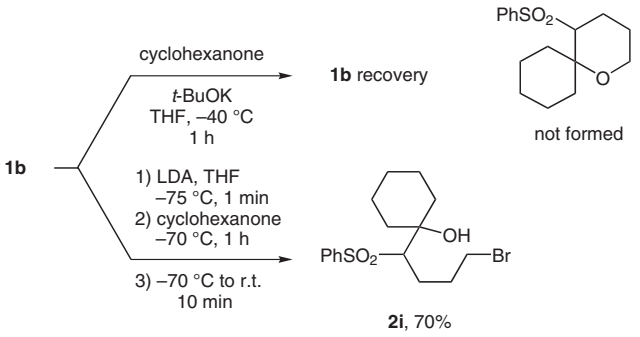
Finally, we investigated the reaction of **1b** with cyclohexanone. To avoid contact of the electrophile with the base, we generated the lithium salt of carbanion of **1b** with lithium diisopropylamide before addition of cyclohexanone to promote the addition–alkylation sequence.

Reaction of **1b** with cyclohexanone gave the aldol-type adduct **2i** as the only isolable product (Scheme 6). Under

Table 1 Reactions of δ-Halocarbanion Precursors with Nonenolizable Aldehydes

Entry	δ-Halocarbanion precursor	EWG	R	Product	Isolated Yield (%)
1	**1b**	SO_2Ph	Ph	**3a**	89
2	**1b**	SO_2Ph	4-$MeOC_6H_4$	**3b**	78
3	**1b**	SO_2Ph	4-ClC_6H_4	**3c**	80
4	**1b**	SO_2Ph	2-furyl	**3d**	58
5	**1b**	SO_2Ph	*t*-Bu	**3e**	83
6	**1c**	CO_2Me	Ph	**3f**	89[a]
7	**1c**	CO_2Me	4-BrC_6H_4	**3g**	81[a]

[a] Reaction was performed at –25 °C.[20]



Scheme 6

several conditions tested, we were unable to force the subsequent cyclization process, leading to tetrahydropyran derivatives.

In conclusion, we have shown, that δ-halocarbanions react with nonenolizable aldehydes with the formation of 2,3-disubstituted tetrahydropyrans in the course of a two-step addition–alkylation sequence.[1] This route represents simple, efficient, and general approach for the synthesis of cyclic compounds, but requires optimization of the reaction conditions in some cases.

All reagents were used as obtained from the commercial sources. All reactions were carried out under an atmosphere of argon in dried glassware using standard Schlenk techniques. THF was distilled from K/benzophenone ketyl and anhydrous grade EtOH was used. Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded with $CDCl_3$ as standard (δ = 7.26 and 77.0 ppm) on a Varian 200 spectrometer. IR data were recorded on an FT-IR Perkin-Elmer Spectrum 2000 using a film (for oils) or in KBr pellets (for solids). MS data were obtained by electron ionization on an AMD 604 GmbH spectrometer in EI mode or on a Mariner spectrometer in ESI mode. Microanalyses were performed at the Institute of Organic Chemistry, Polish Academy of Sciences.

Compounds **1a** and **1b** were obtained by the reaction of sodium benzenesulfinate with 1,4-dichlorobutane and 1,4-dibromobutane, respectively, according to the typical procedure. Compound **1c** was commercially available (Aldrich). Compound **1d** was obtained by the Friedel–Crafts reaction of benzene and 5-bromopentanoyl chloride according to the procedure described in literature.[22]

4-Bromobutyl Phenyl Sulfone (1b); Typical Procedure

A suspension of sodium benzenesulfinate (24.63 g, 0.15 mol, Fluka) and 1,4-dibromobutane (64.87 g, 0.30 mol) in polyethylene glycol (PEG-400, Merck, 80 mL) was stirred overnight at 80 °C. The mixture was poured into H_2O (500 mL), extracted with EtOAc (5 × 100 mL), washed with H_2O (3 × 100 mL), brine (500 mL), and dried ($MgSO_4$). The mixture was separated on a large chromatographic column (hexanes–EtOAc, 3:1 to 1:1) to give 4-bromobutyl phenyl sulfone (**1b**) (24.25 g, 58%) as a pale yellowish solidifying oil; mp 56–57 °C (Lit.[23] 58–59 °C) and 1,4-bis(phenylsulfonyl)butane (4.92 g, 19%) as white crystals; mp 120 °C (Lit.[24] 122–123 °C).

2-Phenyl-3-(phenylsulfonyl)tetrahydro-2*H*-pyran (3a); Typical Procedure

To a stirred soln of **1b** (277 mg, 1 mmol) and benzaldehyde (133 mg, 1.25 mmol) in THF (4 mL) at –40 °C under argon was added 1 M *t*-BuOK in THF (2.1 mL). After 1 h, aq NH_4Cl was added with vigorous stirring and the mixture was extracted with EtOAc, washed with brine, and dried ($MgSO_4$). Chromatographic separation (hexanes–EtOAc, 6:1 to 3:1) gave **3a** as white crystals; yield: 269 mg (89%); mp 134–135 °C.

IR (KBr): 2945, 2868, 1586, 1456, 1446, 1380, 1303, 1285, 1143, 1087, 1023, 947, 760, 720, 696, 684, 606, 550, 538, 519 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.32–7.44 (m, 3 H), 7.02–7.26 (m, 7 H), 4.55 (d, *J* = 9.7 Hz, 1 H), 3.99–4.11 (m, 1 H), 3.55–3.66 (m, 1 H), 3.43–3.55 (m, 1 H), 2.46–2.61 (m, 1 H), 2.06 (dd, *J* = 12, 4.7 Hz, 1 H), 1.70–2.00 (m, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 139.2, 137.7, 132.6, 128.7, 128.5, 128.3, 128.2, 127.8, 80.7, 68.2, 64.6, 25.5, 23.7.

MS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{18}NaO_3S$: 325.1; found: 325.1.

Anal. Calcd for $C_{17}H_{18}O_3S$: C, 67.52; H, 6.00; S, 10.60. Found: C, 67.54; H, 6.28; S, 10.30.

Similar conditions were applied to the experiments depicted in Schemes 3 and 4 and Table 1.

erythro-5-Bromo-1-phenyl-2-(phenylsulfonyl)pentan-1-ol (*erythro*-2a)

Oil.

IR (neat): 3516, 3064, 2963, 1968, 1816, 1603, 1585, 1495, 1448, 1401, 1304, 1148, 1084, 853, 759, 729, 689, 629, 585, 539 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.96–8.05 (m, 2 H), 7.58–7.79 (m, 3 H), 7.18–7.38 (m, 5 H), 5.38–5.43 (br s, 1 H), 3.38 (d, *J* = 2 Hz, 1 H), 3.10–3.17 (m, 1 H), 3.06 (t, *J* = 6.5 Hz, 2 H), 1.96–2.08 (m, 2 H), 1.22–1.55 (m, 1 H), 1.55–1.79 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 139.4, 137.4, 134.3, 129.6, 128.7, 128.6, 127.8, 125.3, 69.7, 69.4, 32.5, 31.3, 20.4.

MS (ESI): *m*/*z* [M(^{81}Br) + Na]$^+$ calcd for $C_{17}H_{19}{}^{81}BrO_3SNa$: 407.0; found: 407.0.

Anal. Calcd for $C_{17}H_{19}BrO_3S$: C, 53.27; H, 5.00; Br, 20.85; S, 8.37. Found: C, 53.09; H, 5.35; Br, 20.69; S, 8.98.

threo-5-Bromo-1-phenyl-2-(phenylsulfonyl)pentan-1-ol (*threo*-2a)

Mp 70–71 °C.

IR (KBr): 3483, 2930, 1446, 1280, 1136, 1079, 1052, 1023, 760, 731, 697, 644, 569, 537 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.98–8.06 (m, 2 H), 7.62–7.82 (m, 3 H), 7.34–7.43 (m, 5 H), 5.10 (dd, *J* = 8.9, 2.4 Hz, 1 H), 4.44 (d, *J* = 2.4 Hz, 1 H), 3.33–3.44 (m, 1 H), 2.96–3.15 (m, 2 H), 1.67–1.94 (m, 1 H), 1.30–1.60 (m, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 139.2, 137.8, 134.1, 129.3, 128.8, 128.7, 127.2, 73.4, 69.9, 32.5, 29.8, 25.5.

MS (ESI): *m*/*z* [M(^{81}Br) + Na]$^+$ calcd for $C_{17}H_{19}{}^{81}BrNaO_3S$: 407.0; found: 407.0.

Anal. Calcd for $C_{17}H_{19}BrO_3S$: C, 53.27; H, 5.00; Br, 20.85; S, 8.37. Found: C, 53.20; H, 5.19; Br, 21.08; S, 8.55.

2-(4-Methoxyphenyl)-3-(phenylsulfonyl)tetrahydro-2*H*-pyran (3b)

Oil.

IR (neat): 2959, 1613, 1515, 1446, 1307, 1247, 1145, 1084, 1071, 1021, 824, 753, 719, 690, 605, 547 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.40–7.54 (m, 3 H), 7.24–7.35 (m, 2 H), 7.07–7.16 (m, 2 H), 6.61–6.70 (m, 2 H), 4.56 (d, *J* = 9.7 Hz, 1 H), 4.05–4.17 (m, 1 H), 3.80 (s, 3 H), 3.48–3.71 (m, 2 H), 2.55–2.69 (m, 1 H), 2.12 (dd, *J* = 12.3, 4.7 Hz, 1 H), 1.78–2.04 (m, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 159.7, 139.4, 132.4, 130.0, 129.3, 128.4, 127.8, 113.6, 80.1, 68.2, 64.9, 55.2, 25.5, 23.7.

MS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{20}NaO_4S$: 355.1; found: 355.1.

Anal. Calcd for $C_{18}H_{20}O_4S$: C, 65.04; H, 6.06; S, 9.65. Found: C, 64.93; H, 6.08; S, 9.44.

2-(4-Chlorophenyl)-3-(phenylsulfonyl)tetrahydro-2*H*-pyran (3c)
Mp 123–124 °C.

IR (KBr): 2921, 2865, 1600, 1494, 1446, 1306, 1285, 1143, 1089, 1025, 952, 817, 745, 721, 682, 606, 552, 526 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.40–7.59 (m, 3 H), 7.28–7.39 (m, 2 H), 7.07–7.20 (m, 4 H), 4.60 (d, *J* = 9.6 Hz, 1 H), 4.07–4.18 (m, 1 H), 3.44–3.73 (m, 2 H), 2.52–2.66 (m, 1 H), 2.13 (dd, *J* = 12.7, 4.8 Hz, 1 H), 1.77–2.06 (m, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 139.1, 136.3, 134.5, 132.7, 129.6, 128.6, 128.4, 127.8, 79.9, 68.3, 65.0, 25.4, 23.7.

MS (ESI): *m*/*z* [M(^{35}Cl) + Na]$^+$ calcd for $C_{17}H_{17}{}^{35}ClNaO_3S$: 359.0; found: 359.0.

Anal. Calcd for $C_{17}H_{17}ClO_3S$: C, 60.62; H, 5.09; Cl, 10.53; S, 9.52. Found: C, 60.66; H, 5.09; Cl, 9.92; S, 9.81.

2-(2-Furyl)-3-(phenylsulfonyl)tetrahydro-2*H*-pyran (3d)
Mp 126–128 °C.

IR (KBr): 3145, 2971, 2882, 1585, 1503, 1448, 1346, 1305, 1284, 1142, 1075, 1025, 941, 919, 878, 850, 817, 758, 749, 721, 687, 605, 550 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.33–7.63 (m, 5 H), 6.93 (d, *J* = 1.9 Hz, 1 H), 6.29 (dd, *J* = 3.3, 0.6 Hz, 1 H), 6.11 (dd, *J* = 3.3, 1.9 Hz, 1 H), 4.64 (d, *J* = 9.7 Hz, 1 H), 3.96–4.08 (m, 1 H), 3.67–3.82 (m, 1 H), 3.46–3.61 (m, 1 H), 2.43–2.58 (m, 1 H), 1.67–2.13 (m, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 149.8, 142.8, 138.5, 132.9, 128.8, 128.1, 110.3, 71.9, 67.9, 62.1, 24.8, 23.2.

MS (EI): *m*/*z* (%) = 292 (1), 169 (2), 150 (100), 125 (22), 122 (19).

Anal. Calcd for $C_{15}H_{16}O_4S$: C, 61.63; H, 5.52; S, 10.97. Found: C, 61.37; H, 5.66; S, 11.26.

2-*tert*-Butyl-3-(phenylsulfonyl)tetrahydro-2*H*-pyran (3e)
Oil.

IR (neat): 2961, 2878, 1585, 1478, 1445, 1299, 1282, 1212, 1144, 1079, 930, 763, 738, 688, 589, 445 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.86–7.95 (m, 2 H), 7.52–7.71 (m, 3 H), 3.67–3.99 (m, 2 H), 3.83 (d, *J* = 3.3 Hz, 1 H), 3.16–3.24 (m, 1 H), 1.65–2.04 (m, 4 H), 0.86 (s, 9 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 138.6, 133.7, 129.2, 128.7, 78.7, 62.5, 60.5, 35.8, 25.6, 18.6, 17.9.

MS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{22}NaO_3S$: 305.1; found: 305.1.

Anal. Calcd for $C_{15}H_{22}O_3S$: C, 63.80; H, 7.85; S, 11.35. Found: C, 63.95; H, 8.06; S, 11.25.

Methyl 2-Phenyltetrahydro-2*H*-pyran-3-carboxylate (3f)
Oil.

IR (neat): 2950, 2852, 1733, 1495, 1454, 1436, 1368, 1317, 1261, 1162, 1094, 1028, 954, 759, 699, 537 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.28–7.45 (m, 5 H), 4.52 (d, *J* = 10.1 Hz, 1 H), 4.15–4.26 (m, 1 H), 3.65–3.79 (m, 1 H), 3.51 (s, 3 H), 2.69–2.84 (m, 1 H), 2.16–2.30 (m, 1 H), 1.8–2.16 (m, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.6, 140.2, 128.3, 128.0, 126.8, 81.4, 68.5, 51.3, 49.7, 27.7, 24.7.

MS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{16}NaO_3$: 243.1; found: 243.1.

Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.58; H, 7.22.

Methyl 2-(4-Bromophenyl)tetrahydro-2*H*-pyran-3-carboxylate (3g)
Oil.

IR (neat): 2950, 2851, 1734, 1593, 1490, 1435, 1365, 1317, 1258, 1162, 1096, 1012, 956, 815, 539 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.45–7.53 (m, 2 H), 7.16–7.24 (m, 2 H), 4.41 (d, *J* = 10.1 Hz, 1 H), 4.06–4.17 (m, 1 H), 3.54–3.69 (m, 1 H), 3.46 (s, 3 H), 2.53–2.67 (m, 1 H), 2.08–2.21 (m, 1 H), 1.64–2.00 (m, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.5, 139.4, 131.4, 128.6, 121.9, 80.6, 68.5, 51.5, 49.7, 27.7, 24.6.

MS (EI): *m*/*z* (%) = 300 (30), 298 (31), 240 (58), 238 (60), 185 (50), 183 (50), 114 (100).

Anal. Calcd for $C_{13}H_{15}BrO_3$: C, 52.19; H, 5.05; Br, 26.71. Found: C, 52.05; H, 5.31; Br, 26.86.

3-Benzoyl-2-phenyltetrahydro-2*H*-pyran (3h)
To a stirred soln of **1d** (241 mg, 1 mmol) and benzaldehyde (265 mg, 2.5 mmol) in EtOH (3 mL) at r.t. under argon was added a soln of *t*-BuOK (238 mg, 2.1 mmol) in EtOH (2 mL). The mixture was left overnight, then aq NH_4Cl was added with vigorous stirring and the product **3h** was isolated according to the typical procedure; mp 76–80 °C.

IR (KBr): 3062, 3033, 2947, 2850, 1674, 1596, 1449, 1365, 1299, 1260, 1197, 1088, 1033, 952, 928, 831, 756, 699, 665, 551 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.62–7.72 (m, 2 H), 7.06–7.50 (m, 8 H), 4.71 (d, *J* = 9.7 Hz, 1 H), 4.14–4.26 (m, 1 H), 3.65–3.81 (m, 2 H), 1.67–2.22 (m, 4 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 202.1, 140.6, 136.6, 132.9, 128.4, 128.2, 127.9, 127.8, 126.9, 81.8, 68.5, 50.8, 28.7, 25.2.

MS (EI): *m*/*z* (%) = 266 (37), 160 (66), 146 (23), 131 (7), 117 (5), 115 (4), 105 (100), 91 (8), 77 (42).

Anal. Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 80.86; H, 6.75.

1-[4-Bromo-1-(phenylsulfonyl)butyl]cyclohexan-1-ol (2i)
To a stirred soln of **1b** (277 mg, 1 mmol) in THF (2 mL) at –75 °C under argon, 2.0 M LDA in THF–heptane–ethylbenzene (0.5 mL, Fluka) was added dropwise. After 1 min, a soln of cyclohexanone (122 mg, 1.25 mmol) in THF (2 mL) was added dropwise and the mixture was kept at –70 °C for 1 h. Then the flask was warmed to 0 °C (~10 min), aq NH_4Cl was added with vigorous stirring and the product **2i** was isolated as an oil according to the typical procedure.

IR (neat): 3516, 3063, 2922, 2858, 1585, 1447, 1286, 1137, 1082, 973, 854, 729, 690, 652, 576 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.85–7.98 (m, 2 H), 7.50–7.72 (m, 3 H), 3.80 (s br, 1 H), 3.12 (t, *J* = 6.3 Hz, 2 H), 3.04 (t, *J* = 4.5 Hz, 1 H), 1.07–2.17 (m, 14 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 140.2, 133.8, 129.3, 128.2, 75.1, 73.2, 36.3, 33.7, 32.4, 32.3, 25.3, 25.2, 21.3.

MS (EI): *m*/*z* (%) = 376 (1), 374 (1), 278 (24), 276 (23), 235 (76), 233 (79), 217 (50), 215 (51), 197 (11), 169 (64), 165 (18), 163 (19), 137 (30), 135 (32), 99 (100).

HRMS (EI): *m*/*z* [M(^{79}Br)]$^+$ calcd for $C_{16}H_{23}{}^{79}BrO_3S$: 374.05513; found: 374.05434.

Anal. Calcd for $C_{16}H_{23}BrO_3S$: C, 51.20; H, 6.18; S, 8.54, Br, 21.29. Found: C, 51.19; H, 6.44; S, 8.11; Br, 20.62.

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(15) The behavior of **1a** and **1b** without an electrophile under basic conditions [*t*-BuOK (2 equiv), THF, –50 °C or 0 °C, 1 h] revealed that, in contrast to γ-halocarbanions, intramolecular substitution in δ-halocarbanions leading to cyclobutanes is a slow process disturbed by competitive elimination and oligomerization reactions.
(16) The ratio of the diastereomers of **2a** remains almost constant, in the range 1:0.55–1:0.70 (*erythro*/*threo*, according to ^{1}H NMR), during the course of the reaction.
(17) The *erythro*-isomer gave product **3a** exclusively, while the *threo*-isomer gave a mixture of **3a**/**3b** (9:1, according to ^{1}H NMR). This observation may lead to the conclusion, that *erythro*-isomer cyclizes relatively rapidly, while this process is slower for the *threo*-isomer and competitive retro-aldol reaction gives cross product **3b**. The conformational preference for the cyclization of diastereomers of analogous aldol-type adducts **2a** on the basis of their ^{1}H–^{1}H coupling constants and reactivity pattern were discussed in: (a) Mąkosza, M.; Barbasiewicz, M.; Krajewski, D. *Org. Lett.* **2005**, *7*, 2945. (b) Hassner, A.; Usak, D.; Kumareswaran, R.; Friedman, O. *Eur. J. Org. Chem.* **2004**, 2421.
(18) In an independent experiment we performed the reaction of PhCHO (1 mmol), 4-$MeOC_6H_4CHO$ (1 mmol), and **1b** (1 mmol) under standard conditions to evaluate the effect of the relative electrophilicity of aldehydes. This experiment gave an approximately 1: 1 mixture of **3a** and **3b** (according to ^{1}H NMR of the crude reaction mixture), leading to the conclusion that complete equilibration of adduct **2a** with 4-$MeOC_6H_4CHO$ in the aldol dissociation–addition sequence should lead to an equimolar mixture of **3a** and **3b**.
(19) During the optimization process, we observed that excess benzaldehyde (>1.25 equiv) inhibits the second step of the reaction(cyclization), which causes contamination of product **3a** with aldol-type adducts **2a** and decreases the reaction yield. We assume that this effect is based on interaction of the O-anion of **2a** with the carbonyl group of excess aldehyde and formation of a hemiacetal-type adduct. This type of equilibrium operates, for example, in the reaction of the anion of 2-chloroethanol with aldehydes: Barbasiewicz, M.; Mąkosza, M. *Org. Lett.* **2006**, *8*, 3745.
(20) Reaction of **1c** with benzaldehyde (–40 °C, 1 h) led to a mixture of the expected product **3f** and uncyclized aldol-type adduct **2f** (according to ^{1}H NMR analysis of the crude reaction mixture). To force the cyclization process the temperature was increased to –25 °C. Similar behavior was observed for analogous reactions of γ-halocarbanions: an aldol-type adduct of 3-chloropropyl phenyl sulfone carbanion and benzaldehyde cyclizes much faster to the tetrahydrofuran derivative than its ester or cyano congeners: Barbasiewicz M., Mąkosza M., unpublished results.
(21) Probably due to the less favorable equilibrium of addition of stabilized enolate of ketone to the carbonyl group under these conditions, as compared to other less stabilized carbanions, see ref. 2 for details. The only isolable compound was the product of reaction of the expected tetrahydropyran derivative with the second molecule of aldehyde and/or its subsequent transformations (yield ~20%).
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