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Anion Relay Chemistry: Development of an Effective Diastereoselective [3+2] Annulation Tactic Exploiting an Aldol/Brook Rearrangement/Cyclization Cascade

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Abstract

An effective [3+2] annulation tactic for the construction of diverse bicyclic compounds possessing highly functionalized cyclopentane rings has been developed employing soft ketone enolates as the initial nucleophile for Anion-Relay-Chemistry (ARC). The protocol entails a highly diastereoselective Aldol/Brook rearrangement/cyclization cascade.

Graphical Abstract

Keywords

anion relay chemistry; aldol reaction; Brook rearrangement; [3+2] annulation

The development of effective tactics to access architecturally complex, stereochemically defined molecular scaffolds comprises one of the most important aspects of organic chemistry especially in the area of drug development. To this end, we have developed and validated Anion Relay Chemistry (ARC) (a.k.a., charge relay chemistry),^{[1],[2]} a versatile “one-pot” multi-component union tactic to elaborate complex structures (Figure 1). These tactics in turn have been exploited in both a number of total syntheses,^[3] and in Diversity Oriented Synthesis (DOS).^[2e,f] Central to this effort has been the design and validation of diverse bifunctional linchpins (I–VII; Figure 1).

We recognize however that to date most of our efforts on the development and extension of the ARC tactic have focused on the generation of linear tri-component adducts, wherein the initiating nucleophiles involve highly basic, hard anions (i.e., alkyl/aryl lithiums and/or alkyl cuprates) with the derived Brook anion also comprising a hard highly basic nucleophile,

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both limiting the potential structural diversity of the three component tactic. Notwithstanding this shortfall in functional diversity, early on we had developed three protocols that lead to cyclic compounds in a “single pot” (Scheme 1, A–C). Inspired by the successful annulation of α -disubstituted enolates with a thiophene aldehyde linchpin (Scheme 1A), we recently turned to the possibility of a more robust and potentially diastereoselective two component [3+2] annulation tactic (Scheme 1D) exploiting the reaction of “soft” ketone enolates (**1**) with an aldehyde linchpin (**2**) to construct highly functionalized cyclic systems such as **3**. Assuming success with different-sized cyclic ketones, this tactic would hold promise of accessing diverse [*n*.3.0] bicyclic building blocks with multiple functional handles required to construct biologically active natural products such as the capnellenes, lucinone, africanol and rhodomollein XIV and/or their analogues.^[4]

Based on our understanding of the ARC tactic,^[2b] we anticipated that the proposed reaction cascade (Scheme 1) could easily result in a number of issues: complex mixtures due to possible competing retro-aldol reactions and/or the formation of undesired elimination or quenched products generated under the reaction conditions required to trigger the critical Brook rearrangement.^[5] Moreover, if the retro-aldol reaction competes with the Brook rearrangement, the annulation process would likely result in low stereoselectivity. Thus to achieve success with the envisioned diastereoselective [3+2] annulation tactic, precise stereocontrol of the initial aldol reaction, in conjunction with the discovery of effective reaction conditions to trigger the Brook/cyclization sequence over retro-aldol and/or elimination/quenching processes would be required.

We began this study by exploring the aldol reaction between cyclohexanone and aldehyde linchpin **2**, testing various combinations of bases, solvents and Brook triggers (i.e., polar solvents, cation exchange and temperature elevation) (Table 1).

The initial aldol reaction between cyclohexanone and linchpin **2** at $-78\text{ }^{\circ}\text{C}$ in THF or Et₂O was highly diastereoselective generating exclusively **4-anti** (*anti:syn*>15:1) compared to the reported results (*anti:syn*=6:1).^[6] To trigger the Brook rearrangement, we first examined the polar solvent HMPA (entries 1 & 2) at $-78\text{ }^{\circ}\text{C}$, with the expectation of a fast rearrangement relative to a retro-aldol reaction. Initially, we obtained a single diastereomeric hydrindane (**5-anti**), albeit in low yield (15%). The observed low yield suggested that the retro-aldol process dominates the Brook rearrangement, when the counter cation (i.e., Li⁺) is remote from the aldol adduct. We turned to the use of K⁺ ions, known to trigger Brook rearrangements.^[1b] To this end, after initiating the lithium aldol reaction at $-78\text{ }^{\circ}\text{C}$, addition of ^tBuOK (1 equiv.) in Et₂O with slow temperature elevation ($-78\text{ }^{\circ}\text{C}$ to rt) led to hydrindane **5-anti** in 35% yield. Recognizing that the initial intermediate upon cyclization is also a tertiary alkoxide, which can serve to trigger the Brook rearrangement (i.e., autocatalysis), we reduced the amount of ^tBuOK. Pleasingly, when 0.1 equiv. of ^tBuOK in THF was added to the initial lithium aldol adduct, the cyclization cascade proceeded more effectively as the reaction temperature was slowly/continuously elevated to rt, again to furnish the hydrindane **5-anti** now in 55% (entry 5). Even more surprising, just continuous elevation of the reaction temperature to rt after lithium aldol formation in THF *without addition of ^tBuOK* improved the yield to 74% (entry 6), again with excellent diastereoselectivity (16:1). We also discovered that the cascade process completed within 0.5

h at $-78\text{ }^{\circ}\text{C}$ in THF when the counter cation is exchanged for sodium (Na^+), although both the yield and stereoselectivity were reduced (entry 8). Finally, we explored the migratory effect of the silyl group. Surprisingly, the stereoselectivity in the aldol reaction was not retained for TMS-linchpin and TES-linchpin, which suggests aldol/retro-aldol reactions are under equilibrium control below the reaction temperature for the Brook rearrangement to occur (entries 8–10).

Having optimized the reaction conditions, the [3+2] ARC/cascade sequence was examined with diverse enolates generated from a series of cyclic ketones and enones employing LiHMDS (Table 2). Simple cyclic ketones with different ring sizes (entries 1–4) underwent the ARC-cascade in moderate to good yield (59–80%). Cycloheptanone and cyclooctanone furnished the hydroazulene and bicyclo[6.3.0]undecane congeners **6c** and **6d**, albeit yielding diastereomeric mixtures (7:1 and 15:1:1). Pleasingly, 3-phenylcycobutanone (entry 5) also undergoes the annulation process with TMS-linchpin **2** in 60% to generate the [3.2.0]carbobicycle **7** with four contiguous stereogenic centers.

Next, a series of heterocyclic and fused cyclic ketones participated well under the standard reaction conditions in good yield with high diastereoselectivity (entries 6–11). Notably, 8-azabicyclo-[3.2.1]octan-3-one and norcamphor underwent the desired ARC cascade smoothly to provide the architecturally interesting tricyclic alcohol **9** and **10** respectively (entry 8, 9). Of interest, the sodium enolates of indanone/ α -tetralone (entries 10 and 11) undergo the ARC-cascade effectively to provide fused cyclic products also in good yields. Equally important, the monoethylene ketal of 1,4-cyclohexadione (entry 12), as well as cyclic enones and vinylogous ester (entries 13–15) participate effectively in this annulation process to furnish highly functionalized bicyclic building blocks **12–14**; (*S*)-carvone (entry 16) also underwent the cascade process with TMS-linchpin **2** to furnish complex hydrindane (+)-**15** and the diastereomer, which can be easily separated by flash chromatography (1.4:1, 87%). Finally, lactones, such as butyrolactone and dihydrocumarine (entries 17 and 18) participate in the ARC cascade; in this case however ring-opening and elimination occur to yield [3+2] annulation alcohol **16** and phenol **17**, respectively.

Encouraged with the outcome of cyclic enolates, we next explored acyclic ketones and enones with linchpin **2** (Table 3).^[7] Here a variety of methyl ketones were found to undergo the [3+2] annulation smoothly to furnish the functionalized cyclopentane scaffolds **18–23** in moderate to good yield, albeit with lower diastereoselectivity (ca. 1:1 ~ 3:1). When NaHMDS, known to trigger the Brook rearrangement at lower temperature^[1b] was used, acyclic ketones/enones underwent the ARC cascade with higher yields and slightly better diastereoselectivity. Finally, known (*2R*)-2-(benzoyloxy)pentan-3-one underwent the ARC cascade generating the highly substituted cyclopentane (–)-**24a**. Notably, the stereoselectivity was reversed when LiHMDS was used as the base; presumably the Brook rearrangement for the kinetic lithium *syn*-aldolate^[8a] is less favored than *anti*-aldolate and vice versa for sodium aldolate under Curtin-Hammett control.^[8b]

We have also briefly explored this ARC tactic with linchpin (–)-**2a** possessing an α -methyl group (Scheme 2). Pleasingly, the cascade proceeded at $-78\text{ }^{\circ}\text{C}$ in THF maintaining the stereoselectivity of the initial aldol reaction to provide the desired product (+)-**25** in good

yield (83%) without loss of stereogeneity; the structure of (+)-**25** was confirmed by X-Ray analysis.

To demonstrate further the potential synthetic utility of this [3+2] annulation process, we carried out the annulation on preparative scale; 1.2 mmol of ketone and 1.0 mmol of linchpin **2** or (–)-**2a**: **6b** (83%), **8b** (66%), **12** (65%), **24a** (53%) and (+)-**25** (74%). In addition, we explored the versatility of the functionalities delivered in the products as illustrated by the transformations outlined in Scheme 3.

Assignment of the reported stereochemical outcome in the ARC [3+2] annulation cascades was initially based on analysis of the aldol intermediates obtained upon quenching the reaction prior to Brook rearrangement (Scheme 4), and confirmed via a number of X-Ray structures (i.e., **6d**, **8b**, **10**, **13a** and (+)-**15**; see supporting information). For example, the initial aldol condensation between cyclohexanone and TBS-linchpin **2** preferentially furnishes *anti* aldol adduct (**4-anti**) over the *syn* congener (**4-syn**) by chelation control (the Zimmerman-Traxler model).^[10] As the reaction temperature goes up, the aldol products undergo the Brook rearrangement. Subsequent stereoselective cyclization from the more accessible *Si* face furnishes the *cis*-fused bicyclic system. In the case of acyclic methyl ketones however both **Major** and **Minor**-cyclization products are generated with low facial selectivity via conformers **A** and **B** respectively; the **A** conformer is slightly enhanced in case of larger R groups due to a pseudo-A^{1,3} diaxial interaction that occurs during the cyclization (Table 3, entry 3–6).

In summary, we have developed and validated an effective new diastereoselective [3+2] annulation tactic with aldehyde linchpin **2** and the α-methyl congener (–)-**2a**, employing a series of enolates as the initial nucleophile, which after addition and Brook rearrangement serve as latent nucleophiles to provide access to diverse functionalized cyclopentane scaffolds generated in a “single flask” from two components. Precise control of charge migration during the course of the Aldol/Brook rearrangement/cyclization cascade permits the annulation tactic to be effective with a broad range of readily accessible ketone enolates. Studies to explore diverse aldehyde linchpins are currently underway. Taken together, this [3+2] annulation tactic extends the ARC protocol from generating multi-component linear carbon frameworks to diverse highly functionalized cyclopentane and bicyclic building blocks.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Anion Relay Chemistry (ARC) and categorized ARC linchpins, based on the reactivity of each carbon in the reaction.

A. Thiophene linchpin (Linchpin IV) with α -disubstituted ester enolates (2009) **B. 2-TMS-5-OTf-benzaldehyde (Linchpin VII) with arynophile (2011)** **C. Amide linchpin (Linchpin III) with epoxide (2016)** **D. Aldehyde linchpin (Linchpin III) with enolates (this work)** **Scheme 1.**

(A–C) Previous ARC tactics yielding cyclic scaffolds, (D) Envisioned strategy.

Scheme 2.
[3+2] annulation with α -methyl linchpin.

Scheme 3.
Transformations of the annulation products.

A. Cyclic Ketone to Bicyclic System

B. Acyclic Ketone to Cyclopentane System

Scheme 4.
Mechanism of the ARC cascade.

Table 1

Optimization of ARC Cascade.

Entry	Base	R	Solvent	Additive	4- <i>anti</i> : 4- <i>syn</i> ^a	5- <i>anti</i> : 5- <i>syn</i> ^b	Yield ^c (%)
1	LiHMDS	TBS	THF	HMPA	15 : 1	20 > 1	15
2	LiHMDS	TBS	Et ₂ O	KO ^t Bu (1.0 equiv)	8 : 1	20 > 1	35
3	LiHMDS	TBS	Et ₂ O	KO ^t Bu (0.25 equiv)	8 : 1	20 > 1	41/45 ^d
4	LiHMDS	TBS	Et ₂ O	KO ^t Bu (0.1 equiv)	8 : 1	20 > 1	51
5	LiHMDS	TBS	THF	KO ^t Bu (0.1 equiv)	15 : 1	20 > 1	55
6	LiHMDS	TBS	THF	None	15 : 1	16 : 1	74
7	NaHMDS	TBS	THF	None	-	7 : 1	63/61 ^e
8	LiHMDS	TMS	THF	None	20 > 1	5 : 1	73
9	NaHMDS	TMS	Et ₂ O	None	-	2 : 1	54
10	LiHMDS	TES	THF	None	20 > 1	2 : 1	56 ^f

^aRatio was determined by ¹H-NMR of crude aldol adducts after 0.5 h at -78 °C.^bRatio was determined by ¹H-NMR of crude products.^cIsolated yield of 5-*anti*.^dLDA was used as base.^eReaction was quenched after 0.5 h at -78 °C.^fCombined yield of 5-*anti* and 5-*syn*.

Table 2

Substrate Scope: Cyclic Ketones, Enones and Lactones.

Substrate (Entry)	Product ^a	Yield ^b (d.r.) ^c	Substrate (Entry)	Product ^a	Yield ^b (d.r.) ^c
(1) n=1, (2) n=2 (3) n=3, (4) n=4		6a n=1, 60% (d.r. 20>1) 6b n=2, 74% (d.r. 16:1) 6c n=3, 77% ^d (d.r. 7:1) 6d n=4, 75% (d.r. 15:1:1)	(12)		12 , 73% (d.r. 20>1)
(5)		7a R=TBS, 35% (d.r. 20>1) 7b R=TMS, 60% (d.r. 20>1)	(13) ^e R=H (14) R=Me		13a R=H, 71% (d.r. 20>1) 13b R=Me, 58% (d.r. 20>1)
(6) X=O (7) X=NBn		8a X=O, 73% (d.r. 20>1) 8b X=NBn, 70% (d.r. 20>1)	(14)		14 , 40% (55%) ^f (d.r. 20>1)
(8)		9 , 64% (d.r. 20>1)	(16)		(+)-15 , 87% ^d (d.r. 1.4:1)

Substrate (Entry)	Product ^a	Yield ^b (d.r.) ^c	Substrate (Entry)	Product ^a	Yield ^b (d.r.) ^c
(9)		10 , 81% (d.r. 20>1)	(17)		16 , 70%
(10) ^e n=0 (11) ^e n=1		11a n=0, 73% 11b n=1, 67%	(18)		17 , 55%

^aRelative stereochemistry of major diastereomer is illustrated.

^bIsolated yield of major diastereomer.

^cThe d.r. values were determined by ¹H NMR.

^dCombined yield of two diastereomers.

^eNaHMDS was used as base.

^fCombined yield of further elimination product (See supporting information).

Table 3

Substrate Scope: Acyclic Ketones and Enones.^a

Substrate (Entry)	Product	Yield ^b (d.r.) ^c	Substrate (Entry)	Product	Yield ^b (d.r.) ^c
		18a n=1, 67% (d.r. 1.6:1) 18b n=2, 72% (d.r. 1.2:1)			22 79% (d.r. 3:1)
		19 73% (d.r. 1.2:1)			23 58% (d.r. 1:1)
		20 74% (d.r. 2:1)			(-)-24a 53% ^e
		21 62% (d.r. 2.5:1)			(-)-24b 48% ^e

^aNaHMDS was used as base.^bCombined yield of both diastereomers.

The d.r. values were determined by ^1H NMR.

d_{LHMDS} was used as base.

Isolated yield of major isomer.

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