Memory of chirality in rebound cyclizations of α-amide radicals

Aniruddha Sasmal, Tsuyoshi Taniguchi, Peter Wipf, and Dennis P. Curran

Abstract: Reduction of (*S*)-*N*-(2-bromoallyl)-*N*-(*tert*-butyl)-2-methyl-3-phenylpropanamide with tributyltin hydride provides (3*S*,4*S*)-3-benzyl-1-(*tert*-butyl)-3,4-dimethylpyrrolidin-2-one with about 80% retention of chirality at the stereocenter adjacent to the amide carbonyl group. This memory of chirality is suggested to occur by transfer of chirality from a stereocenter to an axis, then from the axis back to a new stereocenter.

Key words: memory of chirality, radical reactions, amides, stereochemistry.

Résumé : La réduction du (*S*)-*N*-(2-bromoallyl)-*N*-(*tert*-butyl)-2-méthyl-3-phénylpropanamide par l'hydrure de tributylétain conduit à la formation de la (3*S*,4*S*)-3-benzyl-1-(*tert*-butyl)-3,4-diméthylpyrrolidin-2-one avec 80 % de rétention de la chiralité au stéréocentre adjacent du groupe carbonyle de l'amide. Il est suggéré que ce souvenir de la chiralité résulte d'un transfert de chiralité du stéréocentre vers un axe, puis de cet axe vers un nouveau stéréocentre.

Mots-clés : souvenir de la chiralité, réactions radicalaires, amides, stéréochimie.

[Traduit par la Rédaction]

Radical reactions involve open-shell intermediates and therefore tend to occur much more rapidly than ionic and pericylic reactions involving closed-shell species.[1] Indeed, many radical reactions can occur on timescales comparable to or faster than common conformational changes of organic molecules, including simple bond rotations. This speed makes radicals attractive for reactions that involve transient conformational chirality.

Depending on the overall transformation, reactions with transiently chiral intermediates can exhibit transfer of chirality or memory of chirality (MOC).[2] An example of each reaction type is shown in Fig. 1. Cyclizations of *o*-haloanilides are typified by the reductive cyclization of **1** to give **3** via the intermediacy of axially chiral radical **2**.[3] Levels of transfer of axial chirality from **1** to the new stereocenter in **3** are high even when the ortho substituent R is hydrogen.[3b] Simple rotation of the anilide N–Ar bond is a racemization reaction that would erase the chirality transfer, so clearly cyclization of **2** is faster than this rotation.

Memory of chirality occurs at a stereocenter when a formal substitution reaction proceeds stereoselectively even though the reaction passes through a trigonal intermediate.[2a] Rychnovsky and co-workers[4] have shown that radical reactions can be faster than ring interconversions, while Giese and co-workers[5] and Bertrand and co-workers[6] have shown that onward reactions of diradicals (for example, coupling) can compete effectively with simple σ-bond rotations. Bonjoch and co-workers[7] discovered intriguing examples of MOC in monoradical reactions that involved hydrogen transfer and cyclization of α-aminyl radicals.

In an example from Bertrand and co-workers,[6b] heating of **4** provides **6** with a high degree of retention of configuration at the stereocenter bearing the carbomethoxy (CO_2Me) group. This reaction must involve an axially chiral intermediate like **5** that is generated by enediyne cyclization and 1,6-hydrogen atom transfer. Onward reaction of α-aminyl radical **5** to form the product must be faster than CH_2–N bond rotation. In other words, the MOC results from a back-to-back relay of chirality transfer reactions: from a stereocenter to an axis, then from the axis back to a new stereocenter.

We wondered whether the electron-donating nitrogen substituent is indispensible in such types of MOC reactions. Indeed, there is some old circumstantial evidence that it is not. In 1968, Heiba and Dessau[8] reported that the atom transfer addition of chloroform to enantioenriched **7** gave a lactone product (**8**) with a small residual optical rotation. The enantiomeric excesses (ees) were not known for either **7** or **8**, so the significance of the residual rotation is unclear.

This transformation presumably involves addition of $Cl_3C\bullet$ to **7** followed by ester C–O bond rotation to give **9** and radical translocation[9] by 1,5-hydrogen atom transfer to give **10**. MOC will occur if the 5-exo cyclization of **10** is faster than rotation of the σ bonds to the carbonyl carbon and net retention is expected. This sequence of translocation and rebound cyclization is reminiscent of both Bertrand and co-workers'[6] and Bonjoch and co-workers'[7] MOC processes.

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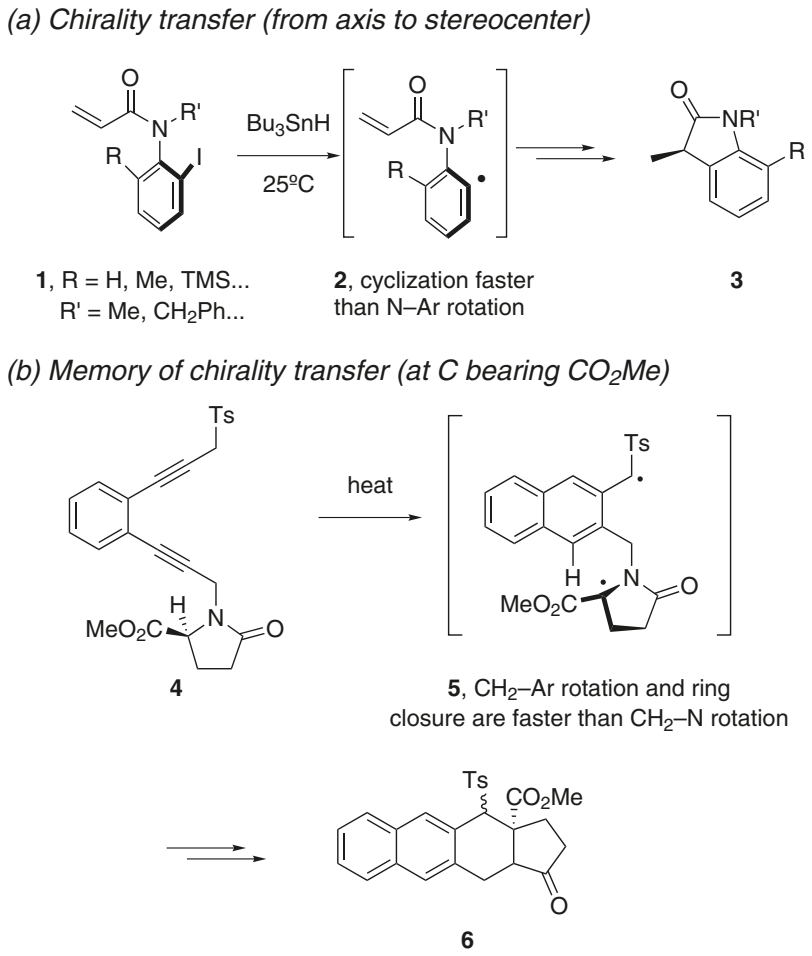
Fig. 1. Examples of radical intermediates in (*a*) transfer of chirality and (*b*) memory of chirality.



The memory effect can be spoiled by rotation of either the C–C bond to the carbonyl group of **10** (racemization results) or the C–O bond (an unfavorable geometry for cyclization results).

At the core of this postulate is the notion that ester-substituted radicals like **10** resemble α-substituted acrylates and related molecules.[10] Despite conjugation, their ground-state geometries are twisted owing to unfavorable steric interactions in the otherwise favored planar forms.[11] This is important because the planar form of **10** is achiral. In short, the assumption that **8** must inevitably be racemic (because a trigonal intermediate is involved) is not on solid footing.

To start, we reproduced the cyclization of enantiopure **7** and confirmed that the small rotation of **8** is not an artifact.[12] But we could not easily determine the enantiomeric composition of **8**. It decomposed on GC injection, and the use of shift reagents was complicated because **8** is already a mixture of diastereomers (Supplementary data).

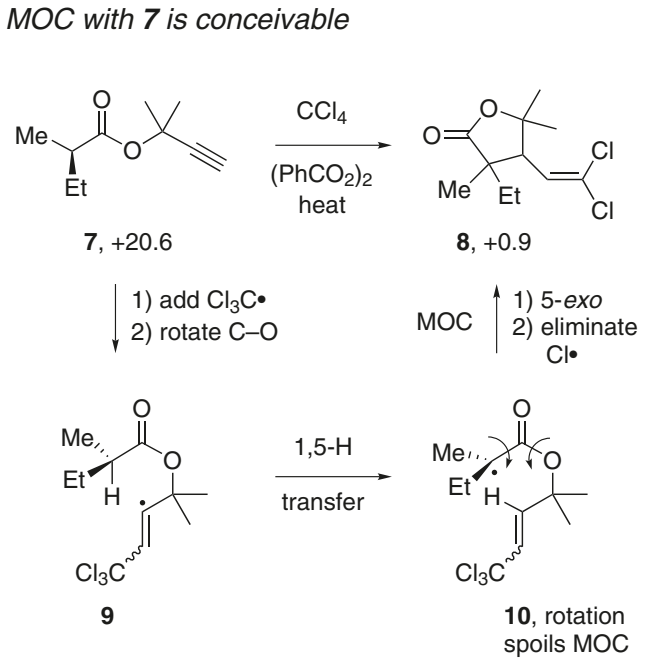
Instead of trying to solve the analytical problems with **8**, we retooled the precursor in three ways. First, we replaced the ester with an amide. One of the two amide substituents is always well-positioned for both 1,5-hydrogen transfer and subsequent cyclization. This eliminates the problem of the unfavorable rotation trans geometry at the ester C–O bond of **7**. Second, the addition reaction of $Cl_3C\bullet$ is not an essential component of the process, so we designed it out, leaving an alkenyl halide as a direct precursor of the alkenyl radical needed for 1,5-hydrogen abstraction. Third, we removed the geminal methyl groups of **7**. This gives precursors **11a**–**11c** shown in the lower part of Fig. 2.

The first substrate studied was amide **11a**, which exists as a roughly 1:1 mixture of *E*/*Z* amide rotamers[13] (structure **11a** shows the favorable rotamer for MOC chemistry). The study of this compound proved to be a wrong turn, though we prefer to regard it as a short scenic detour. Reduction of racemic **11a** with tributyltin hydride in refluxing toluene provided a crude product that did not apparently contain either the target MOC product or the directly reduced product. Instead, the major product was **12**, which was isolated in a 50% yield by flash chromatography.

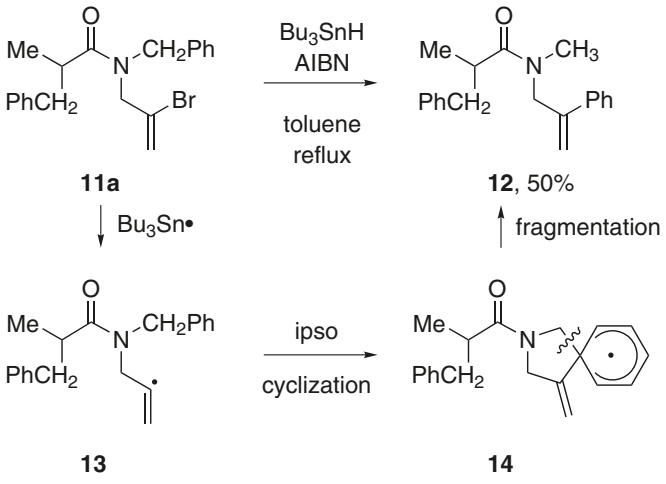
Compound **12** is a rearranged product of 1,4-phenyl transfer that presumably forms by ipso cyclization of **13** to give **14** followed by fragmentation, as shown in Scheme 1. The mechanism was supported by a reduction of **11a** with Bu_3SnD, which gave **12** with significant deuterium labeling on the $N–CH_3$ group. Related aryl transfer reactions are well-known,[14] although none apparently with this structural motif. With optimization, this reaction could be useful for preparing β-aryl allyl amides and related molecules.

To eliminate competing phenyl migration, we targeted precursors **11b** and **11c** bearing *N*-*tert*-butyl groups in place of the *N*-benzyl group of **11c**. Precursors **11b** and **11c** exist as one major rotamer in solution,[13b] which has the *tert*-butyl group

Fig. 2. Top: Could memory of chirality have occurred in this old reaction of an α-chiral ester? Bottom: A retooled amide **11** eliminates potential problems.



Scheme 1. An interesting phenyl transfer reaction provides a short scenic detour.



cis to the amide oxygen atom, as drawn in Scheme 2. These precursors were synthesized in racemic and enantiopure forms,[12] and the results of key reduction experiments are summarized in Scheme 2. Direct reductive debromination of these precursors was a consistent problem, and higher yields of the target cyclized products (**15**) were obtained at higher temperatures. We settled on standard conditions involving syringe pump addition of Bu_3SnH and 2,2′-azobisisobutyronitrile (AIBN) in toluene to a refluxing solution of the precursor in toluene. The target products were isolated by flash chromatography, then analyzed by spectroscopy and chiral GC.

The reduction of (*rac*)-**11b** in this way provided about a 1:1 mixture of diastereomers **15b** in a 39% isolated yield. We could not separate these diastereomers, nor could we make a clear cis/trans assignment. Nonetheless, the sample of (*rac*)-**15b** exhibited four peaks on chiral GC, showing that both pairs of enantiomers were resolved. Cyclization of (*S*)-**11b** (>99:1 enantiomeric ratio (er)) provided the same ratio of diastereomers **15b** in about the same isolated yield, but now both diastereomers were significantly enantioenriched to the extent of about 84:16.

While we learned the enantiomer ratios of **15b**, it was not easy to preparatively separate the diastereomers or to assign their configurations in the mixture. To simplify the assignment problem, we selected **11c** with the hypothesis that one diastereomeric radical resulting from cyclization would cyclize again, whereas the other would not.[15] Tin hydride reduction of (*rac*)-**11c** provided a mixture of products including the product of direct reductive debromination (about a 30% yield), a small amount of an isomeric cyclized product (<5%),[16] and the target products (*rac*)-**15c** and tricycle **16**. The products were partially resolved by chromatography; the reported yields (16% and 9%) are from pure fractions.

In contrast with **15b**, **15c** is a single diastereomer, which we assign as having the vicinal α-benzyl and β-methyl groups trans. The cis isomer was not detected in the crude product mixture. We believe that the cyclization of the translocated radical gives both isomers, one of which is reduced and the other of which cyclizes (see the following). This is why the yields of **15c** (trans only) are about half of the yields of **15b** (cis/trans mixture).

Reductions of (*S*)-**11c** and (*R*)-**11c** provided the products **15c** in similar yields to the racemate, but now significantly enantioenriched. The ratio of enantiomers (*S*)-**15c**/(*R*)-**15c** was 78:22 starting from (*S*)-**11c** and 21:79 starting from (*R*)-**11c**. These values of chirality transfer are comparable to those seen in the diastereomers of **15b**.

With a diastereopure sample now available, the assignment of absolute configuration was accomplished by experimental and computational rotation methods. The measured specific rotations of **15c** are +44.6 and −44.3 (*c* 0.25, $CHCl_3$). The specific rotation of (*S*,*S*)-**15c** was calculated by established techniques to be +125 in $CHCl_3$.[17] From the measured rotation of enantioenriched samples, the rotations of enantiopure samples of **15c** are about +77 and −77, respectively. While the values of measured and calculated rotations differ somewhat, it seems clear because of the large magnitudes involved that the dextrorotatory enantiomer has the (*S*,*S*) configuration. This means that the conversion of **11c** to **15c** (and by analogy **11b**

Scheme 2. Memory of chirality in reductions of **11b** and **11c**.

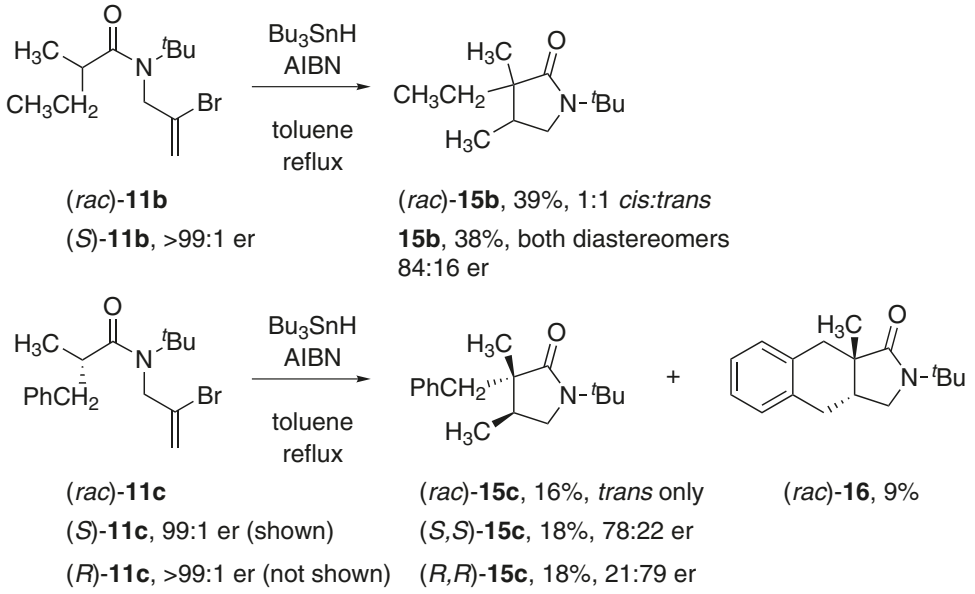
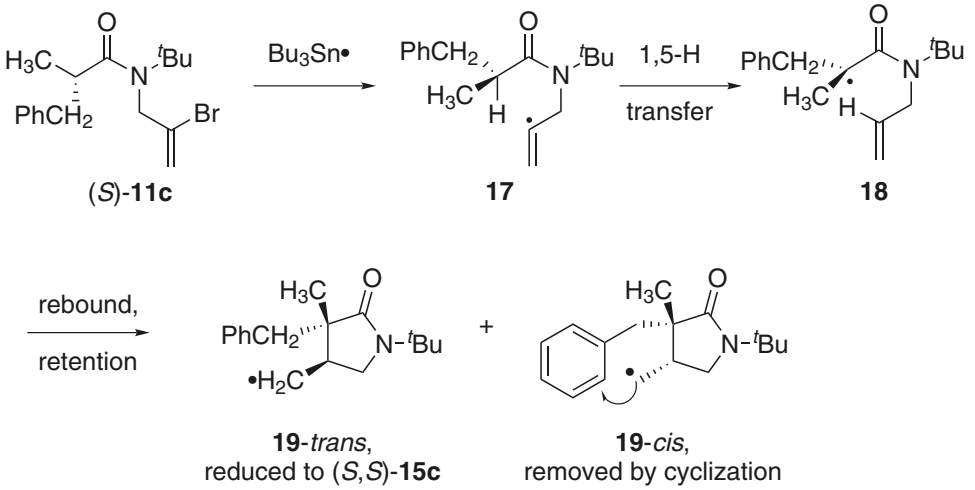


Fig. 3. Proposed pathways in the reduction of **11c**.



to **15b**) occurs predominately (about 80%) with the retention of configuration.

Figure 3 shows suggested pathways for the reduction of (*S*)-**11c**. Bromine abstraction provides alkenyl radical **17**, which in turn abstracts a hydrogen atom adjacent to the carbonyl group. Because of geometric requirements, the abstracted hydrogen is not aligned with the carbonyl π orbitals but is instead positioned roughly anti to the carbonyl group. This reaction erases the stereocenter but provides axially chiral radical **18**. Rebound cyclization of **18** to the alkene completes the MOC process, which must occur with retention. Now the diasteromeric products **19**-*trans* and **19**-*cis* take different pathways with **19**-*trans* being reduced as usual. However, **19**-*cis* is derailed by cyclization to the aryl ring, thereby simplifying the product analysis.

In summary, *N*-(2-bromo-2-propenyl)-*N*′-*tert*-butyl amides bearing a tertiary stereocenter adjacent to the amide carbonyl group undergo a sequence of radical reactions whose key steps are radical translocation (by 1,5-hydrogen transfer) and rebound 5-exo cyclization of the resulting α-amidyl radical to the resulting alkene. Even though a trigonal radical intermediate is formed, the γ-lactam product is produced with about 80% retention of configuration. This MOC is suggested to occur by transfer of chirality from a stereocenter to an axis, then from the axis back to a new stereocenter. The work suggests that generation of α-amide and related α-carbonyl (α-ester, α-keto, and so on) radicals by radical translocation might be a general route to reactions involving MOC of preformed tert-α-stereocenters in such precursors.

Supplementary data

Supplementary data are available with the article through the journal Web site http://nrcresearchpress.com/doi/suppl/10.1139/v2012-085.

Acknowledgements

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(12) Experimental, computational, and compound characterization data (except for compound **16**) can found in the thesis of A. Sasmal, University of Pittsburgh, 2011: open access at http://d-scholarship.pitt.edu/10754/ (see the Supplementary data). Data for **16**: IR (thin firm, cm^{-1}) ν_{max}: 1670;.^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.15 (9H, s), 1.24 (3H, s), 2.29−2.37 (1H, m), 2.43 (1H, d, J = 14.4 Hz), 2.54 (1H, dd, J = 14.4, 4.5 Hz), 2.74 (1H, dd, J = 9.9, 4.5 Hz), 2.83 (1H, dd, J = 14.4, 5.1 Hz), 2.93 (1H, d, J = 14.4 Hz), 3.54 (1H, t, J = 9.6 Hz), 7.11−7.15 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.6, 27.2, 33.7, 36.8, 38.3, 46.8, 49.0, 53.6, 126.2, 126.5, 127.5, 127.9, 136.4, 137.6, 178.4. HR-MS (ESI) calcd for $C_{17}H_{23}NONa$ ($[M + Na]^+$): 280.1677; found: 280.1681.

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