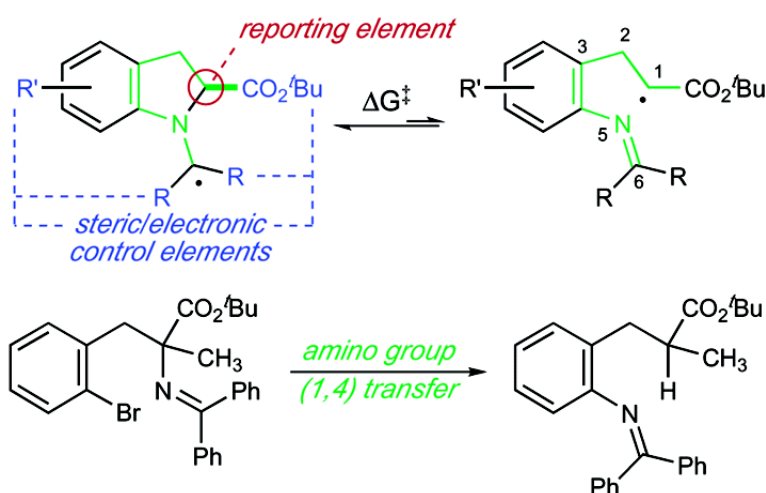Article

The First Azacyclopentenyl Carbinyl Radical Isomerizations (ACCRI): Independent Use of Steric and Electronic (Polarization) Effects as Gating Elements

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The First Azacyclopentenyl Carbinyl Radical Isomerizations (ACCRI): Independent Use of Steric and Electronic (Polarization) Effects as Gating Elements

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Abstract: The first examples of the azacyclopentenyl carbinyl radical isomerization are described within a series of enantiomerically enriched 2-substituted indolines, a substructure found extensively in both heterocyclic and natural product chemistry. The isomerization was identified by the varying loss of enantiomeric enrichment (ee) of imines during aryl radical cyclizations to azomethine nitrogen. Independent modification of the steric and electronic nature of the ring substituents revealed the full spectrum of sensitivity to these variables and ultimately defined the use of these effects as gating elements. An example is also given in which a 1,4-amino group transfer is effected via the isomerization mechanism. Analogies are drawn between the title isomerization and the azacyclopropyl carbinyl radical isomerization that has been studied in both chemical and biological contexts.

Introduction

The importance of radical isomerization reactions (e.g., eq 1) has been widely realized by chemistry and its allied areas.

$$\text{(1)}$$
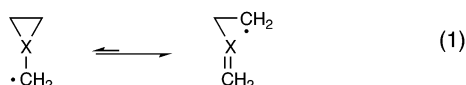
For example, ingenious designs that incorporate a radical fragmentation as the initial or terminal reaction of a cascade provide unique opportunities to generate structural complexity in a guided manner.[1,9l] Strategies that employ both directional steps of an isomerization in order to achieve a change of structure and/or functionality have also been exploited.[2] Indeed, a frequently quoted advantage of radical processes over their ionic variants, aside from their pH-neutral conditions, is the potential for development of elaborate unimolecular reaction cascades involving unactivated olefins.[3] These schemes often provide considerable increases in structural complexity by formation of multiple carbon–carbon σ-bonds.

Isomerizations involving ring–chain tautomerization are particularly prominent and include the "radical clocks" for which absolute rate constants have been measured.[4] The more rapid cyclopropyl carbinyl radical fragmentations (eq 1, X = CH) that favor the chain isomer have been frequently used as probes to investigate questions in enzymology.[5] Isomerizations in which a heteroatom plays a direct role[6] include oxiranyl carbinyl radical fragmentations.[7] These are among the fastest reactions known with absolute rate constants estimated at 10^{10} s^{-1}.[8] Although generally slower to fragment, several members of the aziridinyl carbinyl radical isomerization class have received substantial attention.[9] A notable variant involves carbon radical addition to an azomethine nitrogen in the chain form to provide an aziridine ring (eq 1, X = N). This aziridinyl carbinyl radical isomerization has been implicated as the mechanism utilized

(1) (a) Lange, G. L.; Gottardo, C.; Merica, A. *J. Org. Chem.* **1999**, *64*, 6738. (b) Crimmins, M. T.; Huang, S.; Guise-Zawacki, L. E. *Tetrahedron Lett.* **1996**, *37*, 6519.

(2) For example, formation and fragmentation of alkoxyl radicals: (a) Suarez, E.; Rodriguez, M. S. In *Radicals in Organic Synthesis*; Renaud, P.; Sibi, M., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 2, pp 440–454. (b) Dowd, P.; Zhang, W. *Chem. Rev.* **1993**, *93*, 2091–2115.

(3) (a) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 4, Chapter 4, pp 779–831. (b) Curran, D. P. *Synthesis* **1988**, 417. (c) Malacria, M. *Chem. Rev.* **1996**, *96*, 289.

(4) (a) Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 317–323. (b) Newcomb, M. *Tetrahedron* **1993**, *49*, 1151–1176. (c) Newcomb, M. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 1, pp 317–336.

(5) (a) Samano, V.; Robins, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 4007–4008. (b) Beckwith, A. L.; Ingold, K. U. In *Rearrangements in Ground and Excited States*; De Mayo, P., Ed.; Academic Press: New York, 1980; Vol. I, pp 227–237. (c) Suckling, C. J. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 537–552. (d) Auclair, K.; Hu, Z.; Little, D. M.; Ortiz de Montellano, P. R.; Groves, J. T. *J. Am. Chem. Soc.* **2002**, *124*, 6020–6027.

(6) *Direct* is defined as a ring–chain isomerization in which the heteroatom is directly involved as one of the three atoms undergoing a change in bonding.

(7) (a) Krosley, K. W.; Gleicher, G. J. *J. Phys. Org. Chem.* **1993**, *6*, 228–232. (b) Grossi, L.; Strazzari, S. *J. Chem. Soc., Chem. Commun.* **1997**, 917–918.

(8) Krishnamurthy, V.; Rawal, V. H. *J. Org. Chem.* **1997**, *62*, 1572–1573.

(9) (a) Stamm, H.; Sommer, A.; Woderer, A.; Wiesert, W.; Mall, T.; Assithianakis, P. *J. Org. Chem.* **1985**, *50*, 4946–4955. (b) Werry, J.; Stamm, H.; Lin, P.-Y.; Falkenstein, R.; Gries, S.; Irngartinger, H. *Tetrahedron* **1989**, *45*, 5015–5028. (c) Bellos, K.; Stamm, H.; Speth, D. *J. Org. Chem.* **1991**, *56*, 6846–6849. (d) Dickinson, J. M.; Murphy, J. A. *J. Chem. Soc., Chem. Commun.* **1990**, 434–436. (e) Dickinson, J. M.; Murphy, J. A. *Tetrahedron* **1992**, *48*, 1317–1326. (f) Schwan, A. L.; Refvik, M. D. *Tetrahedron Lett.* **1993**, *34*, 4901–4904. (g) De Kimpe, N.; De Smaele, D.; Bogaert, P. *Synlett* **1994**, 287–288. (h) DeKimpe, N.; Jolie, R.; De Smaele, D. *J. Chem. Soc., Chem. Commun.* **1994**, 1221–1222. (i) Pasto, D. J. *J. Org. Chem.* **1996**, *61*, 252–256. (j) DeSmaele, D.; Bogaert, P.; DeKimpe, N. *Tetrahedron Lett.* **1998**, *39*, 9797–9800. (k) Marples, B. A.; Toon, R. C. *Tetrahedron Lett.* **1999**, *40*, 4873–4876. (l) Prévost, N.; Shipman, M. *Org. Lett.* **2001**, *3*, 2383–2385. (m) Danen, W. C.; West, C. T. *J. Am. Chem. Soc.* **1974**, *96*, 2447–2453.
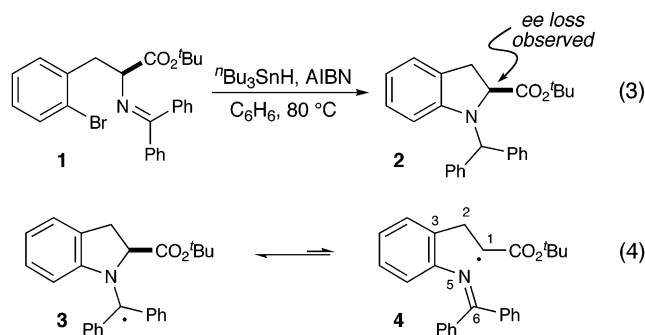
by lysine 2,3-aminomutase (Frey)[10] and potentially others.[11] In these pyridoxal phosphate (PLP) dependent isomerizations, a sequence of Schiff base formation from lysine and PLP, γ-hydrogen atom abstraction, azacyclopropyl carbinyl radical isomerization, hydrogen atom quench at the α-carbon, and hydrolysis results in the amino group isomerization necessary to metabolize lysine. An elegant and convincing chemical model was reported by Frey and Han in 1990 (eq 2),[10a] and has since
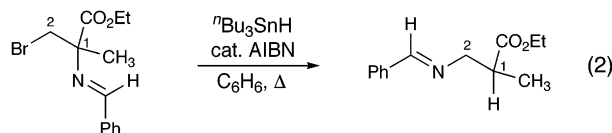
been the object of computational attention.[12] It is also apparent that Nature uses radical-mediated isomerizations of this kind for a variety of biochemical purposes.[13]

Three-membered-ring carbinyl radical isomerizations are normally easily detected since they often favor the chain form. The opposite is true for five-membered-ring carbinyl radical isomerizations.[14-16] Additionally, some members of the three-membered-ring carbinyl radical isomerizations differ mechanistically from their higher homologues by the availability of a radical cation pathway. The α-acyloxy radical rearrangement (eq 1, X = OC(O)R) is an example of a 1,2-shift that accesses a radical cation pair intermediate not available to a homologous rearrangement.[17] Hence, caution should be exercised when making a direct mechanistic comparison between 1,2-atom (or group) shifts and their 1,n-homologues.

We report here the identification of a new member of the carbinyl radical isomerizations, the *az*acyclopentenyl *c*arbinyl *r*adical *i*somerization (ACCRI) (eqs 3 and 4). We also demon-

strate the use of steric and electronic (polarization) effects

(10) (a) Han, O.; Frey, P. A. *J. Am. Chem. Soc.* **1990**, *112*, 8982–8983. (b) Frey, P. A.; Reed, G. H. *Arch. Biochem. Biophys.* **2000**, *382*, 6–14. (c) Cosper, N. J.; Booker, S. J.; Ruzicka, F.; Frey, P. A.; Scott, R. A. *Biochemistry* **2000**, *39*, 15668–15673. (d) Frey, P. A.; Booker, S. *Adv. Free Rad. Chem.* **1999**, *2*, 1–43.
(11) He, X. M.; Liu, H. *Annu. Rev. Biochem.* **2002**, *71*, 701–54.
(12) Wetmore, S. D.; Smith, D. M.; Radom, L. *J. Am. Chem. Soc.* **2001**, *123*, 8678–8689.
(13) For leading references, see: (a) Choi, S.-C.; Dowd, P. *J. Am. Chem. Soc.* **1989**, *111*, 2313–2314. (b) Dowd, P.; Choi, S.-C.; Duah, F.; Kaufman, C. *Tetrahedron* **1988**, *44*, 2137–2148. (c) Wollowitz, S.; Halpern, J. *J. Am. Chem. Soc.* **1988**, *110*, 3112–3120.
(14) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073–3100.
(15) Cyclopropyl carbinyl radical isomerizations (5-hexenyl radical cyclizations): (a) Beckwith, A. L. J. *Chem. Soc. Rev.* **1993**, 143. (b) RajanBabu, T. V. *Acc. Chem. Res.* **1991**, *24*, 139. (c) Beckwith, A. L. *Tetrahedron* **1981**, *37*, 3073. (d) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 753. (e) Julia, M. *Acc. Chem. Res.* **1971**, *4*, 386.
(16) Cyclopentyloxy radical fragmentations, although not carbinyl radicals, are similar and favor the chain form: ref 2.
(17) Crich, D. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 2, pp 188–206.

Table 1. Steric and Concentration Dependence of Azacyclopentenyl Carbinyl Radical Isomerization (eq 5)[a]
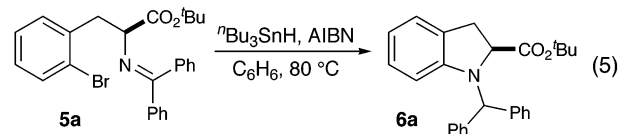
| entry | [5] (M) | % ee[b] | | % ee loss | yield[c] (%) |
		5	6	5 → 6	
1	0.01	96	63	33	85
2	0.05	96	80	16	74
3	0.1	96	96	0	70
4	0.01[d]	96	89	7	—[e]

[a] All reactions used 2.2 equiv of ^{n}Bu$_3$SnH. See Supporting Information for complete details. [b] Measured by HPLC using a Chiralcel AD column. [c] Isolated yield. [d] (PhSe)$_2$ used as additive (20 mol %). [e] Not determined.

independently to gate, or modulate, the isomerization process. An example is also provided in which equilibrium control is exerted over the isomerization by effecting a 1,4-amino group transfer reaction as part of an aryl amination.

Results

Carbinyl radical **3** was accessed by free radical-mediated aryl amination in which an aryl radical adds to the nitrogen of an azomethine π-bond. *o*-Bromophenethyl benzophenone imine precursors were conveniently synthesized as previously described.[18] In the experiments described here, the degree of enantiomeric excess (ee) retention from **5** to **6** was used to identify and measure the extent of ring fragmentation.

The effect of stannane concentration on the reaction was first determined (Table 1, entries 1−3). Importantly, it was unnecessary to add the stannane slowly in any of the transformations described; only when 8 equiv of ^{n}Bu$_3$SnH and a concentration of 0.1 M were used did the product of direct aryl radical reduction (ArH) become significant (∼10%). In the case of **5a**, a steady erosion of enantiopurity was observed at lower concentrations of ketimine, but no racemization was observable at 0.1 M in **5a**. It was also possible to use the Crich protocol (Table 1, entry 4) in which in situ generated benzene selenol serves as a more effective hydrogen atom transfer agent to curtail isomerization at concentrations that otherwise produced **6a** of diminished ee.[19]

A key experiment in which the conditions in entry 1 were implemented but the reaction stopped at 50% conversion removed from consideration the possibility that either **5a** or **6a** was racemized by the reaction conditions. In this experiment, **5a** and **6a** were recovered in 96% and 63% ee, respectively, indicating that *isomerization must occur after aryl radical formation yet prior to chain-propagating hydrogen atom transfer from stannane*. The possibility that **6a** was epimerized by ^{n}Bu$_3$SnBr formed during the reaction was further eliminated by appropriate control experiments.[20]

(18) (a) Johnston, J. N.; Plotkin, M. A.; Viswanathan, R.; Prabhakaran, E. N. *Org. Lett.* **2001**, *3*, 1009–1011. (b) Viswanathan, R.; Plotkin, M. A.; Prabhakaran, E. N.; Johnston, J. N. *J. Am. Chem. Soc.* **2003**, *125*, 163–168. (c) Prabhakaran, E. N.; Cox, A. L.; Nugent, B. M.; Nailor, K. E.; Johnston, J. N. *Org. Lett.* **2002**, *4*, 4197–4200.
(19) Crich, D.; Mo, X.-S. *J. Org. Chem.* **1997**, *62*, 8624.
(20) Evidence of the Lewis acidity of stannyl halides is somewhat contradictory. For example: (a) Yoder, C. H.; Otter, J. C.; Grushow, A.; Ganunis, T. F.; Enders, B. G.; Zafar, A. I.; Spencer, J. N. *J. Organomet. Chem.* **1990**, *385*, 33–37. (b) Sibi, M. P.; Ji, J. *J. Am. Chem. Soc.* **1996**, *118*, 3063 and references therein.
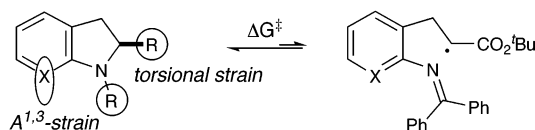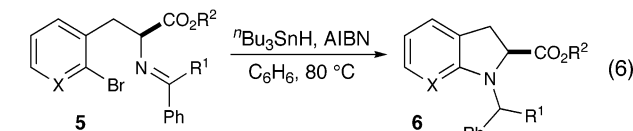
Figure 1.

Table 2. Steric Effect of α-Aminomethyl and Ester Substituents on Azacyclopentenyl Carbinyl Radical Isomerization[a]


entry	5/6	X	R^1	R^2	% ee[b] 5	% ee[b] 6	% ee loss 5 → 6	yield[c] (%)
1	b	N	Ph	^tBu	96	96	0	50
2	a	CH	Ph	^tBu	96	63	33	85
3	c	CCH_3	Ph	^tBu	88	0	88	15
4	d	CH	CH_3	^tBu	99	57[d]	42	76
5	e	CH	H	^tBu	95	81	14	6[e]
6	f	CH	Ph	allyl	76	38	38	75

[a] All examples used 2.2 equiv of $^nBu_3SnH$ and were 0.01 M in **5a,b,d−f**, and 0.1 M for **5c**. [b] Determined by HPLC; see Supporting Information for complete details. [c] Isolated yield. [d] ee of major diastereomer. Diastereoselectivity = 5:1 (65% ee for minor diastereomer). [e] Major product is the tetrahydroisoquinoline (67%, 95% ee); see refs 18 and 21.

We hypothesized that the rather large steric demands along the southern periphery of the ring might affect the propensity for racemization (Figure 1) by increasing the resident strain. Indeed, along the series **5b**, **5a**, and **5c** (X = N, CH, CCH_3, respectively) an increasing degree of racemization was observed (Table 2, entries 1, 2, 3). The relative ease of isomerization is also reflected by the higher concentration implemented to discourage isomerization ([**5c**] = 0.1 M) in the case of **5c**, albeit unsuccessfully.
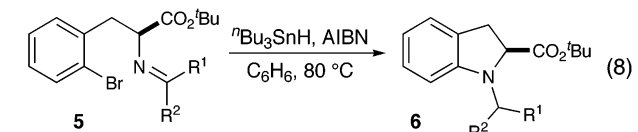
A significant, but less pronounced effect was observed by variation of the nitrogen substituent. For example, replacement of one ketimine phenyl by methyl (Table 2, entry 4) has no significant impact on the degree of isomerization. However, when replacement is made by a hydrogen, the degree of isomerization is only half that observed when R^1 = Ph or Me (Table 2, entries 2, 4, 5). The low yield of indoline product in aryl radical cyclization to an aldimine is due to the known preference for aldimines to furnish isoquinoline products (regioselective for carbon−carbon bond formation).[21] The size of the ester appears to be less significant since *tert*-butyl and allyl esters isomerized to a similar degree (Table 2, entries 2, 6).

Variation of the electronic nature of the aryl halide did not adversely affect the efficiency of *cyclization*, but did reveal an effect on the racemization at the remote C2 substituent (Table 3). Increasing epimerization was observed as a function of aryl bromide substitution by groups capable of increasing electron density (Cl, OCH_3), but not an associated steric effect. The effect appears to be additive as well, with a second methoxy substituent

(21) (a) Takano, S.; Suzuki, M.; Kijima, A.; Ogasawara, K. *Chem. Lett.* **1990**, 315. (b) Tomaszewski, M. J.; Warkentin, J. *Tetrahedron Lett.* **1992**, *33*, 2123. (c) Bowman, W. R.; Stephenson, P. T.; Terrett, N. K.; Young, A. R. *Tetrahedron Lett.* **1994**, *35*, 6369. (d) Ryu, I.; Ogura, S.; Minakata, S.; Komatsu, M. *Tetrahedron Lett.* **1999**, *40*, 1515. Reviews: (e) Friestad, G. K. *Tetrahedron* **2001**, *57*, 5461−5496. (f) Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *57*, 17543−17594.

Table 3. Remote Electronic Effect on the Azacyclopentenyl Carbinyl Radical Isomerization (eq 7)[a]
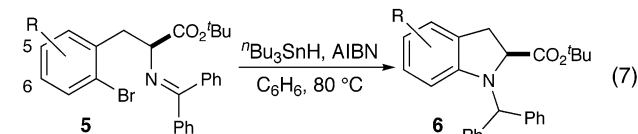
entry	5/6	R	% ee[b] 5	% ee[b] 6	% ee loss 5 → 6	yield[c] (%)
1	a	H	96	96	0	70
2	g	5-Cl	94	91	3	55
3	h	5-OMe	94	86	8	45
4	i	5,6-OMe	97	81	16	50

[a] All reactions used 0.1 M for [**5**] and 2.5 equiv (entries 1−3) or 3.0 equiv (entry 4) of $^nBu_3SnH$; see Supporting Information for complete details. [b] Measured by HPLC. [c] Isolated yield.

Table 4. Ketimine Electronic Dependence of Azacyclopentenyl Carbinyl Radical Isomerization (eq 8)[a]

entry	5/6	R^1	R^2	% ee[b] 5	% ee[b] 6	% ee loss 5 → 6	yield[c] (%)
1	a	C_6H_5	C_6H_5	96	63	33	85
2	j	CH_3	4-$MeOC_6H_4$	87	20[d]	67	50
3	k	4-$MeOC_6H_4$	4-$MeOC_6H_4$	99	47	52	71
4	d	CH_3	C_6H_5	99	57[e]	42	76
5	l	CH_3	2,4,5-$F_3C_6H_2$	87	80[f]	7	67

[a] All reactions used 2.2 equiv of $^nBu_3SnH$ and [**5**] = 0.01 M; see Supporting Information. [b] Measured by HPLC. [c] Isolated yield. [d] ee of major diastereomer. Diastereoselectivity = 2.6:1. [e] Major diastereomer. Diastereoselectivity = 5:1 (65% ee, minor diastereomer). [f] Major diastereomer. Diastereoselectivity = 4.9:1.

doubling the amount of epimerization observed with one methoxy group. An electronic effect was also observed when either electron-donating or electron-withdrawing groups were resident in the ketimine aryl radical acceptor (Table 4): electron-rich ketimines furnished products with greater loss of enantiomeric enrichment (Table 4, entries 2, 3), whereas electron-deficient ketimines gave indolines with significantly less racemization (Table 4, entry 4).
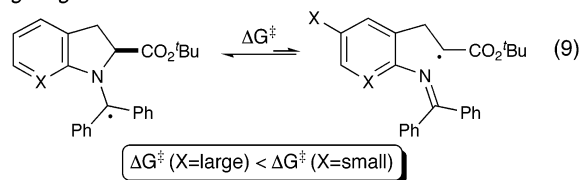
Discussion

Tables 1−4 identify a number of factors that directly impact conservation of enantiopurity: effective stannane concentration, the steric demands of substituents at N1, C2, and C7, and the electronic nature of substituents at N1 (both aryl and alkyl) and C2.[22] Importantly, the most easily modified variable, the effective stannane concentration, was used in nearly all cases to produce indoline product with complete conservation of ee in moderate to good yield. However, the conditions used to investigate the isomerization process were necessarily executed in a regime that revealed quantifiable differences. These experiments directly point to the operation of a ring−chain isomerization that competes with hydrogen atom transfer. According to this hypothesis, it is necessary for the intermediate

(22) No epimerization during formation of *cis*- or *trans*-2,3-dimethylindolines was observed (ref 18a).

steric gating

$$\Delta G^{\ddagger}\ (X = \text{large}) < \Delta G^{\ddagger}\ (X = \text{small})$$

(9)

electronic gating

$$\Delta G^{\ddagger}\ (X = EDG) < \Delta G^{\ddagger}\ (X = EWG)$$
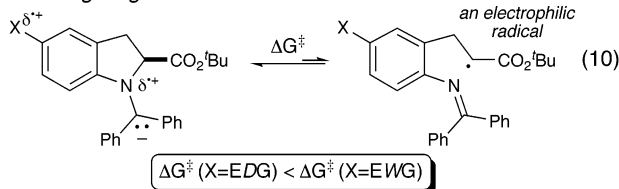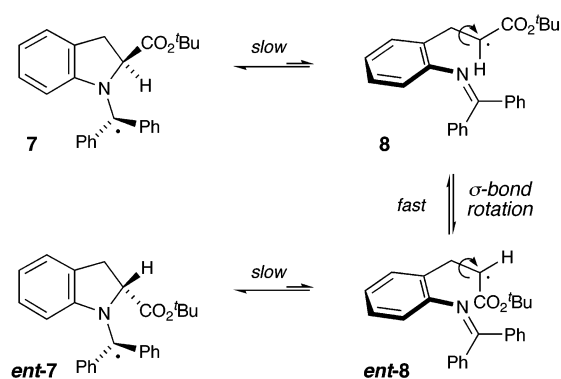
(10)

Figure 2.

Scheme 1

radical to undergo σ-bond rotation prior to ring closure (Scheme 1).

Steric Gating. A decreasing degree of isomerization is observed when varying the aminobenzyl radical substituent in the order phenyl ≈ methyl > hydrogen (Figure 2, eq 9). This observation details two important aspects of the fragmentation energy barrier: (1) the presence of one large substituent (the unchanged phenyl substituent) is sufficient to destabilize the ring form and override potentially stabilizing effects of the second substituent; (2) differences in propagation efficiency alone do not overtake the rate of ring-opening among these examples. A priori, thermodynamic arguments of torsional[23] and ring strain, and electronic stabilization of the chain isomer predicted a greater degree of isomerization for **5a** over **5d** in this series. However, only a change in size from phenyl or methyl to hydrogen resulted in noticeable attenuation of the isomerization process.

A more pronounced effect on the degree of isomerization was observed as a function of the steric demands at C7 (indoline numbering). Using conditions that normally promote the isomerization, azaindoline α-amino acid **6b** retained its enantiopurity.[24] However, at the benchmark concentration of 0.01 M, indoline **6a** was produced with 33% ee loss. Complete racemization was unavoidable with **6c** even at concentrations as high as 0.1 M. The progressively greater racemization is attributed to increased allylic strain between the substituents at

(23) Including a possible analogy to Fuson-type enols: Suter, C. M.; Truce, W. E. *J. Am. Chem. Soc.* **1944**, *66*, 1109.
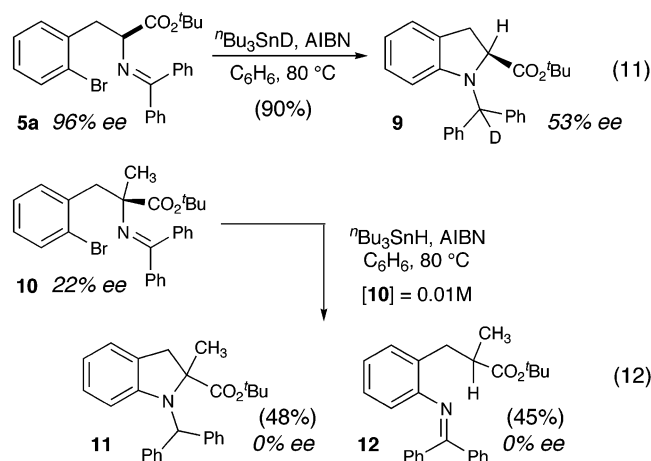(24) We cannot completely dismiss a possible electronic effect in this case as well.

C7 and N1 (indoline numbering). This congestion is then translated into increased torsional strain between the N1 and C1 substituents that ultimately lowers the activation barrier to ring fragmentation by ground state destabilization. It is important to recognize that despite the use of steric strain to promote ring opening, the equilibrium preference for the ring form is not substantially altered so as to allow isolation of the ring-opened product.

Electronic Gating. The isomerization was considerably more sensitive to the electronic nature of the indoline nitrogen (Figure 2, eq 10). Such an effect was not unexpected since polarization effects have been noted for reactions involving the electrophilic alkoxycarbonyl methyl radical.[25] The nitrogen is suitably positioned among the six atoms involved in the isomerization to have maximal electronic effect (eq 10). Specifically, an electron of the nitrogen lone pair can be moved to the carbinyl radical orbital to form the charge-separated resonance structure. Any aromatic ring substituent that stabilizes this resonance form would thereby increase the nucleophilic polar character of radical **7**, and promote fragmentation by lowering the activation barrier.[25,26] Such an effect is clearly observed: as the electron density of the aminoaryl ring increases, the degree of racemization increases (eq 10). Conversely, electron-withdrawing substituents attached to the aminoaryl ring are expected to minimize the isomerization. The resistance to racemization exhibited by **5b** might also be attributed to its electron-deficient nature.

A similar electronic effect might then be expected upon modification of the imine aromatic rings. We were unable to prepare appropriate electron-deficient symmetric benzophenone imine derivatives of varying electronic density. However, a variety of sufficiently diverse benzophenone and acetophenone imines (**5j**−**5l**) were obtained. At a substrate concentration of 0.1 M, a decrease by 67% ee was observed in the major diastereomer resulting from cyclization of the electron-rich *p*-methoxyacetophenone imine (Table 4, entry 2). Conversely, only a 7% ee loss occurred with the trifluoroacetophenone derivative **5l** (Table 4, entry 5). Both systems are capable of affecting the electron density at the benzylic carbon, through inductive (F) or resonance (OCH_3) effects, but in opposite direction. The intermediate benzylic radical will be significantly more nucleophilic in the latter case, thereby lowering the activation barrier toward production of the electrophilic alkoxycarbonyl methyl radical.

Other Considerations. We considered the possibility that racemization might occur through a 1,3-hydrogen atom direct (intramolecular) or formal (intermolecular) transfer.[27] The intramolecular hydrogen atom transfer mechanism is unlikely on the basis of previous studies. In the present case, such a transfer would not be exothermic, and the 1,3 nature of the transfer would require a transition state that deviates substantially from the optimal 180 °C−H−C bond angle. Notwithstanding, the cyclization of **5a** to **9** was effected with $^{n}Bu_3SnD$ under

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(26) Polar effects in radical reactions: review−Tedder, J. M. *Tetrahedron* **1982**, *38*, 313−329. Recent examples: (a) Della, E. W.; Kostakis, C.; Smith, P. A. *Org. Lett.* **1999**, *1*, 363−366.
(27) 1,4-Hydrogen atom transfers appear to be the lowest observed homologue: Viskolcz, B.; Lendvay, G.; Kortvelyesi, T.; Seres, L. *J. Am. Chem. Soc.* **1996**, *118*, 3006−3009. Lomas, J. S. Briand, S. *J. Chem. Soc., Perkin Trans. 2* **1992**, 191−200. Gulea, M.; Lopez-Romero, J. M.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2000**, *2*, 2591−2594.

Scheme 2

(11)

(12)

Figure 3. Known (**A**) and proposed (**B**) intermediates during α-amino acid epimerization.

conditions that allow partial racemization (Scheme 2, eq 11). Deuterium incorporation was observed only at the diphenyl aminomethyl carbon. Several attempts were also made to trap the putative electrophilic radical **8** with a variety of nucleophilic reagents, including allyl tri-*n*-butylstannane. However, only the usual indoline product was observed. Definitive evidence that neither intra- nor intermolecular hydrogen atom transfer from C2 was responsible was obtained by cyclization of scalemic **10** with complete racemization; the cyclized radical intermediate from **10** has no opportunity to epimerize at C2 without invoking ring fragmentation. Significantly, the isolation of 1,4-imino group transfer product **12** from tertiary imine **10** also provided insight into a means to shift the characteristic equilibrium (eq 4) toward the chain isomer of the intermediate radical.[28]

Considered together, these experiments are consistent with an azacyclopentenyl carbinyl radical isomerization that can be gated through independent use of steric (eq 9) and electronic effects (eq 10) (Figure 2). The latter, at least as defined through these experiments, is enabled by the acyl substituent at C1.

Broader Implications. The ACCRI complements the homologous azacyclopropyl carbinyl radical isomerization studied extensively by Frey (eq 2). Indeed, all features except substrate chain length are shared by both processes. The key functional difference of the ACCRI is its ability to effect a stereochemical change (racemization) without attendant structural change (1,2-migration). This behavior results from the equilibrium differences characteristic of each isomerization; whereas cyclopropyl carbinyl radicals favor the chain form, cyclopentyl carbinyl radicals generally favor the ring form. It then follows that the title isomerization establishes an alternative α-amino acid epimerization pathway and intermediate (Figure 3, via **B**) to the known ionic mechanism involving deprotonation/reprotonation (Figure 3, via **A** or its conjugate base).[29,30] Such a
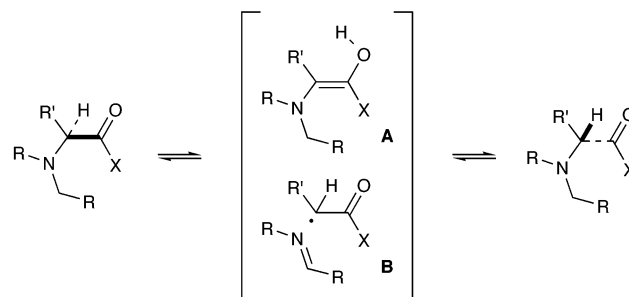
mechanism could be directly relevant to the occurrence of D-amino acids in peptides,[31] particularly in cases where peptidal D-amino acids are known to be formed via posttranslational epimerization and in cases where the deprotonation/reprotonation mechanism is less attractive.[32,33] Substantiation of these propositions awaits the proper investigations.[34]

Conclusion

This study details control of all aspects of the azacyclopentenyl carbinyl radical isomerization. This is synthetically attractive since it ultimately results in a 1,4-amino group transfer (**10** → **12**). Alternative variants that might improve upon this goal can be envisioned on the basis of the design principles outlined here. While some mechanistic divergence is apparent in radical-mediated 1,2-group migrations, it is clear that those involving a cyclization/fragmentation sequence benefit from rapid rates of cyclization characteristic of 3-exo processes. The 5-exo cyclizations reported here are undoubtedly several orders of magnitude slower in rate, but our results suggest that the higher homologues might be more prevalent than originally thought. The cases outlined here illustrate that, aside from steric and electronic effects, the detection method is critical to discovery.

Provocatively, we hypothesize that these isomerizations might be relevant to biochemistry and suggest a direction in which to begin investigation. Alternatively the title isomerization could serve as a chemical model for engineering of a nonnatural variant, thereby offering a new chemical tool for their study or manipulation. The yield for **12** is in accord with chemical mimicry of other enzyme-catalyzed rearrangements.[35]

Experimental Section[36]

General Procedure for Cyclizations Using Chiral Nonracemic Schiff Base Substrates. A benzene solution of the ketimine (1 equiv) and *n*Bu3SnH (2.2 equiv) was warmed to 85 °C followed by slow

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(36) General experimental details can be found in the Supporting Information.

addition of AIBN (1.2 equiv) using a syringe pump over 4−5 h. The solution was refluxed for an additional hour before concentration. The residue was treated with a 1:1 (by volume) solution of Et_2O and saturated aqueous KF, and the mixture was stirred vigorously until a white solid precipitated. The organic layer was washed with water, and concentrated prior to purification by silica gel chromatography to give the target indoline.

1-[Bis(4-methoxyphenyl)methyl]-2,3-dihydro-1*H*-indole-2-carboxylic Acid *tert*-Butyl Ester (6k). According to the general procedure, use of **5k** (31.1 mg, 59.5 μmol), $^{n}Bu_3SnH$ (35 μL, 130 μmol), and AIBN (7.8 mg, 47.6 μmol) provided the desired indoline after flash chromatography (SiO$_2$, 2% ethyl acetate in hexanes) as a colorless oil (18.7 mg, 71%). R_f = 0.18 (10% ethyl acetate in hexanes); IR (film) 2929, 1735, 1510 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.36 (d, J = 8.7 Hz, 2H), 7.23 (d, J = 8.6 Hz, 2H), 7.00 (d, J = 6.6 Hz, 1H), 6.83 (m, 5H), 6.61 (dd, J = 13.9, 7.0 Hz, 1H), 6.01 (d, J = 7.8 Hz, 1H), 5.54 (s, 1H), 4.08 (dd, J = 10.5, 5.9 Hz, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.38 (dd, J = 15.8, 10.5 Hz, 1H), 2.98 (dd, J = 15.8, 5.8 Hz, 1H), 1.34 (s, 9H); ^{13}C NMR (100 MHz) ppm 173.0, 158.9, 151.5, 133.8, 133.6, 130.3, 129.8, 128.0, 127.6, 124.0, 118.0, 114.0, 109.5, 81.1, 66.1, 65.2, 55.5, 34.3, 30.0, 28.2; HRMS (EI): Exact mass calcd for $C_{28}H_{31}NO_4$ [M]$^+$, 445.2253. Found 445.2263. Anal. Calcd for $C_{28}H_{31}$-NO_4: C, 75.48; H, 7.11; N, 3.17. Found: C, 75.19; H, 7.11; N, 3.17. HPLC: Chiralcel AD (2% ^{i}PrOH/hexanes, 1 mL/min, 254 nm), t_r (peak 1) 12.9 min, t_r (peak 2) 17.8 min; 83.9% ee: $[\alpha]_D^{21}$ −12.2° (c 0.8, CDCl$_3$).

Supporting Information Available: Experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JA029426Z