Communication

Stereospecific Photochemical Ring Expansion of Lithiated Benzamides

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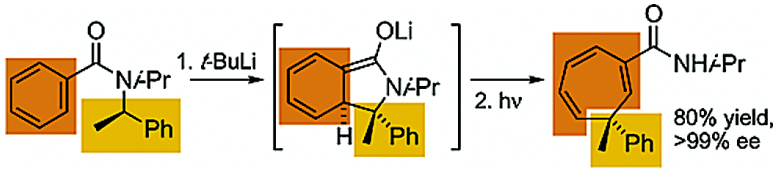

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Stereospecific Photochemical Ring Expansion of Lithiated Benzamides

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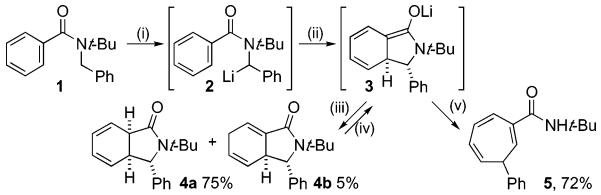
The six carbon atoms of a benzenoid aromatic ring can be a valuable resource for constructing more complex, nonaromatic targets,[1] and photochemistry[2] has a good track record as a tool for breaking open the aromatic sextet. In this Communication, we reveal a mild new photochemical reaction which, by means of base and a simple halogen spotlamp, achieves the stereospecific transformation of tertiary benzamides into a range of seven-membered cyclic trienes and dienones, or their norcaradiene analogues.

As we have previously shown, the extended enolate **3** may be made by lithiating **1** to form organolithium **2** in the presence of HMPA.[3] Protonation of **3** yields the dearomatized tetrahydroisoindolinones **4** in 80% yield (Scheme 1). However, when the enolate

Scheme 1. A Cycloheptatriene from a Benzamide[a]

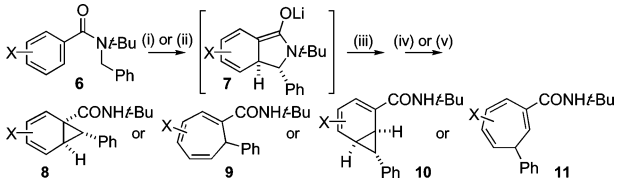


[a] Reagents: (i) *t*-BuLi, HMPA, −78 °C; (ii) −78 °C, 16 h; (iii) NH_4Cl; (iv) LDA, THF, 0 °C; (v) *hν*, >500 nm, 500 W, 3 h.

3 (which can be re-formed from **4** with LDA) was cooled to −78 °C and the resulting red solution was placed under a 500 W tungsten-filament halogen lamp, a rearrangement took place over a period of 3 h. Workup gave the cycloheptatriene **5** in 72% yield, an overall insertion of the *N*-benzyl group of **1** between the ortho and meta carbons of its aromatic ring.

Similar treatment of other *N*-benzylbenzamides **6**[4] led to related, but not always identical, rearrangements (Scheme 2). A range of

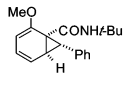
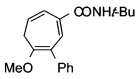
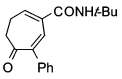
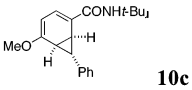
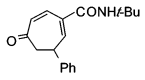
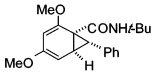
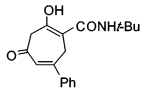
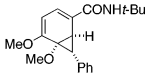
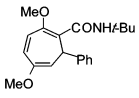
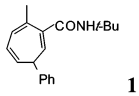
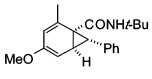
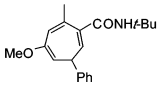
Scheme 2. Rearrangement of Lithiated Benzamides[a]



[a] Reagents: (i) LDA, THF, 0−20 °C, 2 h; (ii) *t*-BuLi, HMPA, THF, −78 °C, 16 h; (iii) *hν*, 500 nm, 500 W, −78 °C, 3 h; (iv) NH_4Cl (aq); (v) HCl (aq).

enolates **7** were irradiated, and the outcomes are collected in Table 1. The four classes of products **8**−**11** fall into two pairs of regioisomers, each pair related by a disrotatory thermal electrocyclization. Presumably, the lithium salts of norcaradienes **8** or **10** are the initial products in all cases, but ring opening on workup or before may give the cycloheptatrienes **9** or **11**. Aqueous acid, which hydrolyzes enol ether products to ketones, can promote formation of cycloheptatrienones. Whether the isolated product has the regiochemistry of **8** or **10** also depends on workup conditions (acid gives **11** not only from **10** but from **8** as well) but principally on ortho substitution in the starting amide (thus **6a**, **6d**, and **6h** give **8**, while **6c** and **6e** give **10**).

Table 1. Dearomatizing Ring Expansions of Benzamides

Entry	S.M.	X =.	Protocol	Product	Yield
1	**6a**	2-MeO	(i), (iii), (iv)	 **8a**	80
2	**6b**	3-MeO	(ii), (iii), (iv)	 **11b**	63
3	**6b**	3-MeO	(ii), (iii), (v)	 **11b'**	54
4	**6c**	4-MeO	(i), (iii), (iv)	 **10c**	73[a] 69[b]
5	**6c**	4-MeO	(i), (iii), (v)	 **11c**	73
6	**6d**	2,4-di-MeO	(ii), (iii), (iv)	 **8d**	33
7	**6d**	2,4-di-MeO	(ii), (iii), (v)	 **11d**	21
8	**6e**	3,4-di-MeO	(i), (iii), (iv)	 **10e**	75
9	**6f**	2,5-di-MeO	(ii), (iii), (iv)	 **9f**	24
10	**6g**	2-Me	(i), (iii), (iv)	 **11g**	72
11	**6h**	2-Me-4-MeO	(ii), (iii), (iv)	 **8h**	48
12	**6h**	2-Me-4-MeO	(ii), (iii), (v)	 **11h**	47

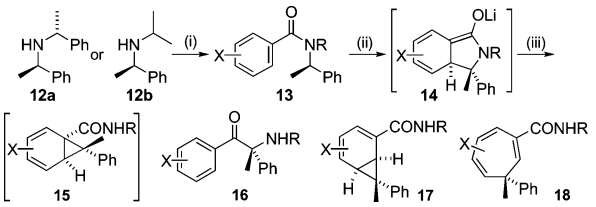
[a] Structure proved by X-ray diffraction. [b] With **12**Li as base (78% ee).

Introducing chirality into the starting materials or producing the enolate intermediates of the rearrangements enantioselectively both offered new opportunities for the asymmetric synthesis of chiral 6,3- and 7-ring systems and illuminated some features of the rearrangement's mechanism. Enantiomerically enriched (78% ee[5]) enolate **7c** (formed by cyclization of **6c** with lithiated **12b**) rearranged to the norcaradiene **10c** in 69% yield and with 74% ee, showing that the photochemical rearrangement of **7** to **9** can be stereospecific. Stereospecificity is also evident in the rearrangement

10.1021/ja035827i CCC: $25.00

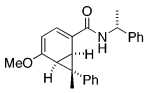
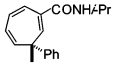
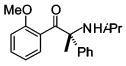
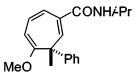
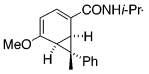
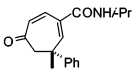
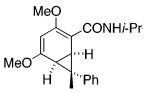
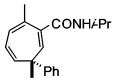
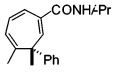
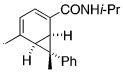
of amides derived from chiral amines **12a** and **12b** (Scheme 3 and Table 2). **17a** is formed as a single diastereoisomer from **13a**, and

Scheme 3. Rearrangement of Chiral Benzamides[a]



[a] Reagents: (i) ArCOCl, Et_3N, CH_2Cl_2; (ii) *t*-BuLi, DMPU, −78 to +20 °C; (iii) *hν*, >500 nm, 500 W, −78 °C, 3 h, then NH_4Cl.

Table 2. Stereospecific Ring Expansions of Chiral Benzamides

Entry	S.M.	R =	X =.	Product	Yield	ee
1	**13a**		4-MeO	 **17a**	52	>98[a]
2	**13b**	*i*-Pr	–	 **18b**	80	>99
3	**13c**	*i*-Pr	2-MeO	 **16c**	55	n/d
4	**13d**	*i*-Pr	3-MeO	 **18d**	20	90
5	**13e**	*i*-Pr	4-MeO	 **17e**	94	>99
6	**13e**	*i*-Pr	4-MeO	 **18e**	94	n/d
7	**13f**	*i*-Pr	2,4-di-MeO	 **17f**	53	92
8	**13g**	*i*-Pr	2-Me	 **18g**	49	80
9	**13h**	*i*-Pr	3-Me	 **18h**	40	92
10	**13i**	*i*-Pr	4-Me	 **17i**	85	86

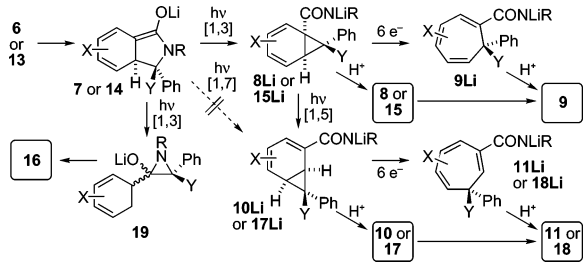
[a] Diastereoisomeric excess.

the enantiomeric purity of amides formed by acylation of **12a** is also largely preserved throughout the cyclization−rearrangement sequence. Norcaradienes **17** or cycloheptatrienes **18** were formed in up to 94% yield, but in no case was **15** or its cycloheptatriene isomer (analogous to **8** and **9**) isolated, even from ortho-substituted amides **13c** and **13f**. A rearrangement not seen with **6**, giving the ketone **16c**, was observed with **13c**.

The lowest measured product ee was 80%: stereospecificity persists through the deprotonation, cyclization,[6] and rearrangement steps. Overall, transformation of **13** to **17** or **18** amounts to a remarkable stereospecific insertion of a chiral carbenoid into the aromatic structure of the benzene ring.

The relative stereochemistry of the products[7] was proved by a combination of X-ray crystallography and NOE studies and, in most cases,[8] is consistent with rearrangement via stereospecific photochemical sigmatropic rearrangements of the enolates **7** and **14**, whose UV−visible spectra show absorptions in the region of 550 nm. Scheme 4 shows a proposed mechanistic pathway. Photochemical [1,3]-sigmatropic rearrangement (suprafacial and retentive)[9] of **7** or **14** gives norcaradiene **8**Li or **15**Li, or aziridine **19** whose protonation with ring opening yields **16**. From **8**Li or **15**Li, rearrangement may continue, forming **10**Li or **17**Li by 1,5-sigmatropic rearrangement,[10] presumably photochemical, because this then allows the observed stereochemistry to be formed by an invertive suprafacial migration.[11] Protonation of **8**Li, **10**Li, **15**Li, or **17**Li yields norcaradienes **8**, **10**, **15**, or **17**; six-electron disrotatory ring opening and protonation or hydrolysis (in either order) yields cycloheptatrienes **9**, **11**, or **18**.

Scheme 4. Mechanism of the Rearrangements



We are currently applying this reaction of extreme practical simplicity ((1) base, (2) halogen lamp) to the synthesis of further cyclopropane and cycloheptenone targets.

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Supporting Information Available: Characterization data for rearrangement products; X-ray crystallographic data for **10c** (PDF and CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) Clayden, J.; Knowles, F. E.; Menet, C. J. *Tetrahedron Lett.* **2003**, *44*, 3397.
(7) The absolute stereochemistry of **16**−**18** is deduced from the retentive stereospecificity of the cyclization of **13e**: see ref 6.
(8) Protonation of the enolate **7** derived by cyclization of **6a** indicates that it is formed as a mixture of diastereoisomers, so at least in this case the rearrangement must be stereoselective and not simply stereospecific.
(9) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: New York, 1976, Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Academic Press: New York, 1970. This rearrangement can be viewed as a reverse aza-vinylcyclopropane rearrangement (Hudlicky, T.; Reed, J. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 899. Cloke, J. B. *J. Am. Chem. Soc.* **1929**, *51*, 1174. Cloke, J. B.; Maginnity, P. M. *J. Am. Chem. Soc.* **1951**, *73*, 49. Ellis, M. C.; Stevens, R. V. *Tetrahedron Lett.* **1967**, 5185). For other photochemical N → C rearrangements, see: Archier-Jay, D.; Besbes, N.; Laurent, A.; Laurent, E.; Lesniak, S.; Tardivel, R. *Bull. Soc. Chim. Fr.* **1989**, 537. Amougay, A.; Letsch, O.; Pete, J.-P.; Piva, O. *Tetrahedron* **1996**, *52*, 2405. Becker, H.-D.; Skelton, B. W.; White, A. H. *Aust. J. Chem.* **1983**, *36*, 2073.
(10) Berson, J. A. *Acc. Chem. Res.* **1972**, *5*, 406.
(11) Such rearrangements are notoriously disrespectful of the Woodward−Hoffmann rules, see: Klärner, F.-G. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 268. Baldwin, J. E.; Broline, B. M. *J. Am. Chem. Soc.* **1974**, *96*, 2857.

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