

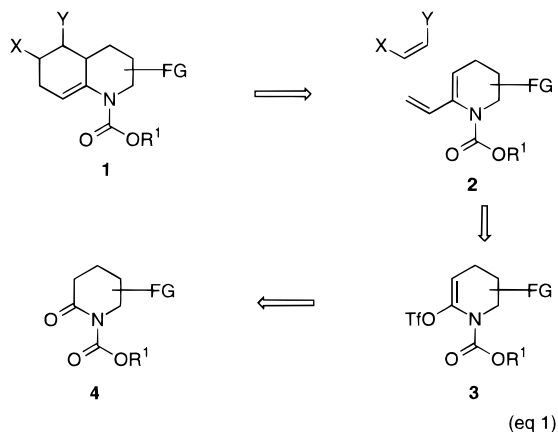
Diels–Alder Reactions of 2-(*N*-Acylamino)-1,3-dienes. Atypical Regioselectivity and Endo/Exo Selectivity

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Given the unparalleled synthetic utility of the Diels–Alder reaction in the formation of functionalized six-membered rings, it is hardly surprising that the large body of imaginative conceptual advances and synthetic applications continues to exploit the inherent control of regiochemistry and stereochemistry. Of particular importance is the development of the heteroatom-substituted dienes (e.g., those containing siloxy substituents), which provide the otherwise inaccessible functionality arrays, in addition to enhanced reactivity. Extension has also been made to use of amino-substituted dienes. For example, general synthetic utility of the Diels–Alder reaction of 1-(*N*-acylamino)-1,3-butadienes has been well demonstrated in the pioneering work by Overman and Oppolzer,^{1,2} which complements that of the corresponding (*N,N*-dialkylamino)diene.^{3,4} In contrast, regioisomeric *N,N*-dialkyl-2-amino-1,3-dienes have found scant use in the Diels–Alder reaction, and a recent theoretical study suggested that these cross-conjugated compounds would function as poor dienes in cycloadditions.⁵ In fact, only a few examples are known, and these are limited to use of β -nitrostyrenes as the dienophiles, for which a stepwise polar mechanism has been proposed.⁶ Little is known about the reactivity of the analogous 2-(*N*-acylamino)-1,3-dienes.⁷ Herein, we report the novel features of the Diels–Alder reactions of 1,3-dienes **2**, which afford an expeditious assembly of octahydroquinolines **1**.



For a preliminary study, the piperidine ring system and the benzyloxycarbonyl (Cbz) group were chosen as the 2-amino skeleton and protecting group ($R^1 = \text{benzyl}$), respectively, as part of our research program directed at the construction of suitably functionalized decahydroquinoline

rings.⁸ The starting dienes **2a–d** were readily prepared in 78–87% yield by the Pd(PPh₃)₄-mediated cross-coupling of tributyl(vinyl)tin and (*N*-acylamino)enol triflates **3** (eq 1). In turn, the requisite triflates **3** were prepared in excellent yield from *N*-acylated lactams **4** by the recently published procedure.^{9,10}

The Diels–Alder reactions of these dienecarbamates were then investigated. Relatively unreactive dienophiles such as ethyl (*E*)-crotonate or crotonaldehyde failed to undergo the thermal (up to 180 °C) Diels–Alder reaction. On the other hand, (*E*)-1-nitro-1-heptene afforded the cycloadducts, albeit in modest yields, at 180 °C (toluene, sealed tube). Ethyl acrylate and *N*-phenylmaleimide were found to react efficiently in refluxing benzene or toluene. The results are summarized in Table 1.¹¹ The observed product distributions given in Table 1 are kinetic in origin, since pure individual cycloadducts remain unchanged when subjected to the identical reaction conditions.

Structures for the cycloadducts were determined by ¹H NMR analysis (¹H, ¹H COSY and difference NOE measurements).¹² A characteristic feature is that the C-2 siloxymethyl substituent occupies the pseudoaxial position to minimize *A*^(1,2) and *A*^(1,3) strain as indicated by observation of a nuclear Overhauser effect on the siloxymethylene signal on irradiation of the H-4a proton.¹³

Most striking is the anomalous regiochemical preference in favor of the 1,3-regioisomers (with respect to the *N*-acylamino function). This unexpected meta regioselectivity (entries 2–7) is opposite to the prediction based on consideration of either the HOMO diene–LUMO dienophile interaction or a two-step process involving a 1,4-addition to the dienophile and subsequent closure of the vinyl acylimmonium ion. Also, conspicuously atypical is the unusual lack of endo selectivity. Moreover, it appears to be dependent on the dienophiles. For example, the Diels–Alder reactions with ethyl acrylate show no endo/exo selectivity (entries 3, 5, and 7), but those of (*E*)-1-nitro-1-heptene with the sterically more demanding dienes **2b,c** show the proclivity toward the exo products **8a** and **10a** (entries 4 and 6 vs entry 2). On the other hand, the reactions of *N*-phenylmaleimide display exclusive endo preference to afford **5a** and

(3) For example, see: (a) Hünig, S.; Kahane, H. *Chem. Ber.* **1957**, *90*, 238. (b) Dauben, W. G.; Kozikowski, A. P. *J. Am. Chem. Soc.* **1974**, *96*, 3664. (c) Snowden, R. L. *Tetrahedron Lett.* **1984**, *25*, 3835.

(4) For use of 1-amino-3-siloxy-1,3-dienes, see: (a) Smith, A. B., III; Wexler, B. A.; Tu, C.-Y.; Konopelski, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 1308. (b) Schlessinger, R. H.; Pettus, T. R. R.; Springer, J. P.; Hoogsteen, K. *J. Org. Chem.* **1994**, *59*, 3246. (c) Kozmin, S. A.; Rawal, V. H. *J. Org. Chem.* **1997**, *62*, 5252 and *J. Am. Chem. Soc.* **1997**, *119*, 7165.

(5) Koikov, L. N.; Terent'ev, P. B.; Gloriozov, I. P.; Bundel', Y. G. *J. Org. Chem. USSR* **1984**, *20*, 832.

(6) For reviews, see: (a) Enders, D.; Meyer, O. *Liebigs Ann.* **1996**, 1023. (b) Krohn, K. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1582.

(7) To our knowledge, to date only two reports have appeared on the Diels–Alder reaction of 2-(acylamino)-1,3-dienes: (a) Terada, A.; Murata, K. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 1644. (b) Reference 1b; no structure was given for the cycloadduct.

(8) Decahydroquinoline rings are present in several major classes of alkaloids, including dendrobatid alkaloids (such as pumiliotoxin C, *cis*-243A, and gephyrotoxin), *Lycopodium* alkaloids (lycodine, lycopodine, and lycodoline), luciduline, etc.

(9) Ha, J. D.; Lee, D.; Cha, J. K. *J. Org. Chem.* **1997**, *62*, 4550.

(10) (a) Foti, C. J.; Comins, D. J. *J. Org. Chem.* **1995**, *60*, 2656. (b) Okita, T.; Isobe, M. *Tetrahedron* **1995**, *51*, 3737. (c) Luker, T.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron Lett.* **1996**, *37*, 8257; *J. Org. Chem.* **1997**, *62*, 3592.

(11) Surprisingly, the Diels–Alder reaction of diene **2a** with ethyl acrylate gave an inseparable mixture of all four possible isomers (on the basis of ¹H and ¹³C NMR spectra). This lack of regiocontrol is in sharp contrast with that of dienes **2b–d**.

(12) The ¹H, ¹H COSY spectra of **5a**, **8a**, **9a,b**, **11a,b**, **14**, **15a,b**, and **16** are available in the Supporting Information.

(13) For numbering, see structure **8a** in Table 1.

(1) (a) Overman, L. E.; Jessup, P. J. *Tetrahedron Lett.* **1977**, 1253. (b) Overman, L. E.; Clizbe, L. A. *J. Am. Chem. Soc.* **1976**, *98*, 2352 and 8295. (c) Overman, L. E.; Jessup, P. J. *J. Am. Chem. Soc.* **1978**, *100*, 5179. (d) Overman, L. E.; Fukaya, C. *J. Am. Chem. Soc.* **1980**, *102*, 1454. (e) Jessup, P. J.; Petty, C. B.; Roos, J.; Overman, L. E. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, p 95.

(2) (a) Oppolzer, W.; Fröstl, W. *Helv. Chim. Acta* **1975**, *58*, 590. (b) Oppolzer, W.; Bieber, L.; Francotte, E. *Tetrahedron Lett.* **1979**, 4537.

Table 1

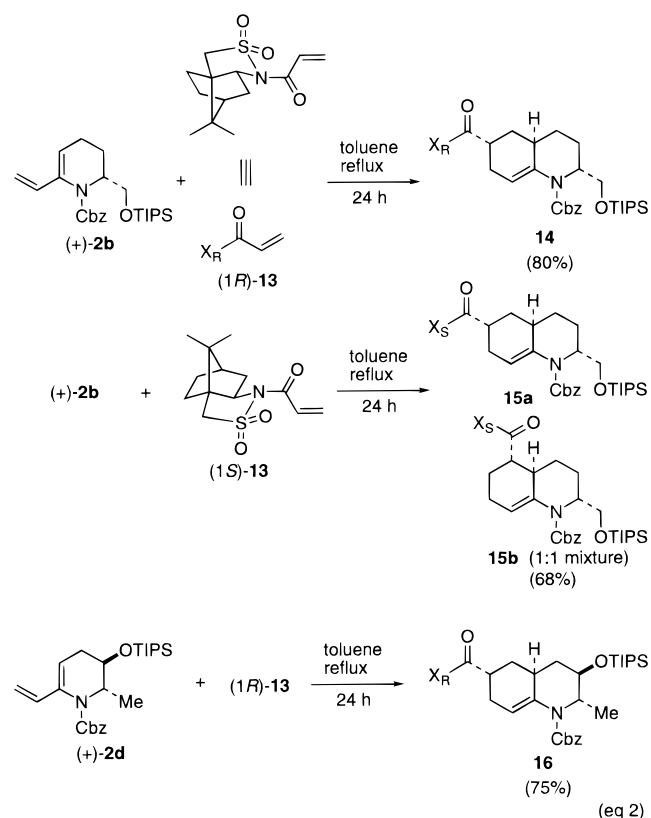
entry	1,3-diene	dienophile	cycloadduct(s) ^a
1			 5a (75%) 5b (20%)
2	2a	<i>n</i> -pentyl-	 6a 6b 49% (1 : 1)
3	2b		 7a: β -CO ₂ Et 7b: α -CO ₂ Et 88% (1 : 1)
4	2b	<i>n</i> -pentyl-	 8a 8b ^b 41% 8%
5	2c		 9a: β -CO ₂ Et 9b: α -CO ₂ Et 85% (1 : 1)
6	2c	<i>n</i> -pentyl-	 10a 10b ^b 28% 5%
7	2d		 11a: α -CO ₂ Et 11b: β -CO ₂ Et 79% (1 : 1)
8	2d		 12a: β -imide, α -H 12b: α -imide, β -H 76% (2 : 1) 12c ^c 18%

^a Reaction conditions: (for entries 1 and 8) benzene, reflux; (for entries 3, 5, and 7) toluene, reflux; (for entries 2, 4, and 6) toluene, 180 °C (sealed tube). ^b In entries 4 and 6, the respective minor isomers, **8b** and **10b**, were isolated in impure form, and their structures were not determined. ^c In entry 8, the double-bond-isomerized product **12c** was also obtained in 18% yield.

12a/12b (entries 1 and 8) [along with varying amounts of the (double bond) isomerized products **5b** and **12c**].

Excellent diastereofacial control exerted by a C-2 substituent is apparent (entries 3–7): addition of the dienophile takes place at the face of the diene opposite the C-2 substituent.¹³ The observed diastereofacial selectivity can be explained by consideration of the preferred half-chair

conformation with the C-2 substituent occupying the pseudo-axial position to avoid allylic strain and the preferential approach of a dienophile anti to the same substituent.



As suggested in the case of (sterically more encumbered) (*E*)-1-nitro-1-heptene, exo preference could be amplified by increasing steric effects which outweigh the marginal secondary orbital interactions with these cross-conjugated dienes.¹⁴ Indeed, the Diels–Alder reaction of the acrylate bearing (1*R*)-(+)-2,10-camphorsultam [(1*R*)-**13**] with (+)-**2b** and (+)-**2d** afforded the exo cycloadducts **14** and **16**, respectively, as a single isomer, in 75–80% yield (eq 2), where the observed π -facial selectivity from the C(α)-*Re*-face of the *N*-enoyl sultams is identical with that of the several known addition reactions.¹⁵ Another striking feature is the unexpected, complete reversal of regioselectivity! A mismatched double stereodifferentiation arising from use of (1*S*)-**13** with (+)-**2b** gave a 1:1 mixture of the regioisomers **15a,b**.

In summary, the Diels–Alder reaction of endocyclic “cross-conjugated” 2-(acylamino)-1,3-dienes allows rapid access to octahydroquinolines containing various functionalities for further elaboration. Stereoselective reactions are possible by taking advantage of excellent diastereofacial control exerted by a C-2 substituent.

Acknowledgment. We are grateful to the National Institutes of Health (GM35956) for generous financial support.

Supporting Information Available: Representative experimental procedures and spectroscopic data (47 pages).

JO980593K

(14) Highly exo-selective Diels–Alder reactions were achieved by use of a sterically demanding dienophile: (a) Yoon, T.; Danishefsky, S. J.; de Gala, S. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 853. (b) Maruoka, K.; Imoto, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 12115.

(15) Oppolzer, W. *Pure Appl. Chem.* **1990**, *62*, 1241.