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Diels-Alder Reaction of Chiral Acrylamide and a Convenient Synthesis of Optically Pure Methyl (3R, 4R, 6R)-Bicyclo[2. 2. 1]heptene-4-carboxylate

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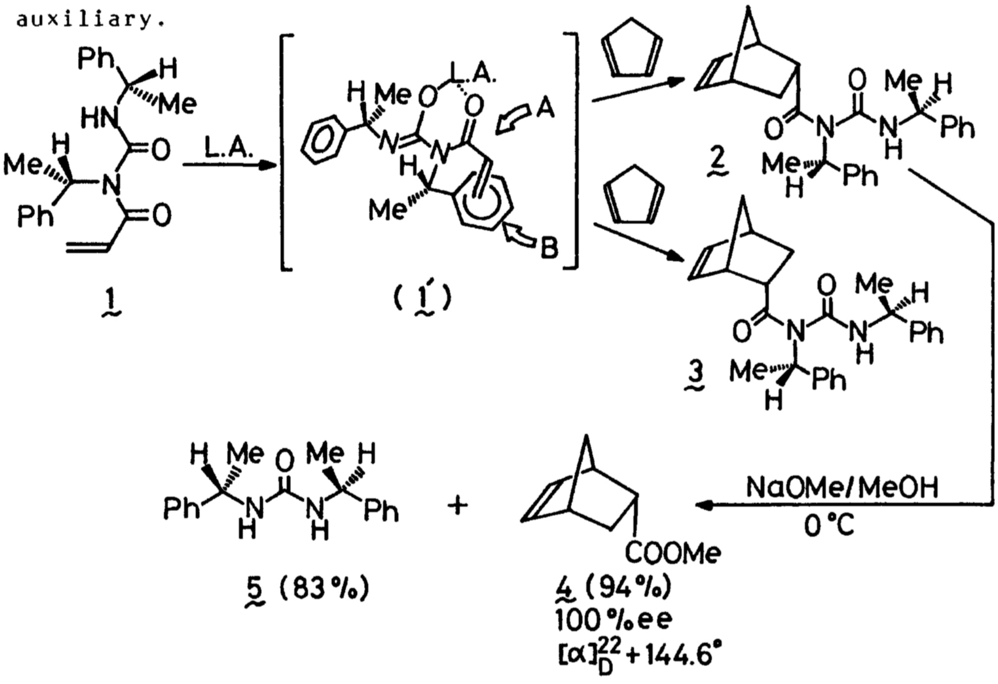
Asymmetric Diels-Alder reaction of the chiral acrylamide 1 proceeds highly diastereoselectively and methanolysis of the adduct 2 gives the optically pure (3R, 4R, 6R)-bicyclo[2. 2. 1]-heptene-4-carboxylate.

In recent studies of asymmetric Diels-Alder reactions[1)] some highly enantioselective reactions have been reported. However to isolate a pure enantiomer is often problematic. In our investigation of the asymmetric Diels-Alder reaction of acrylamide 1, we have established a very convenient method to synthesize optically pure (100% ee) methyl (3R, 4R, 6R)-bicyclo[2. 2. 1]heptene-4-carboxylate (4) in an excellent yield. The advantages of our method over others are the commercial availability of the chiral sources (both (R)- and (S)-1-phenylethylamine), a simple separation of the primary diastereomeric cycloadducts 2 and 3 by conventional column chromatography and methanolysis under mild condition to remove the chiral auxiliary.



Scheme 1.

Table 1. Diels-Alder Reaction of the Chiral Acrylamide 1 with Cyclopentadiene

No.	Lewis Acid	Temp/°C	Time/h	Yield/%[a]	endo/exo[b]	2/3[b]
1	no cat.	100	3	71	77:23	52:48
2	$SnCl_4$	-78	1	87	97: 3	64:36
3	Et_2AlCl	-115	1	60	97: 3	68:32
4	$TiCl_4$	-78	1	85	98: 2	81:19
5	$TiCl_4$	-115	1	93	98: 2	74:26

a) Combined yields of all four Diels-Alder adducts. b) The ratios were determined by HPLC (Merck Lichrosorb Si 60; hexane:ethyl acetate=4:1) and ^{1}H-NMR (270 MHz) analysis.[2)]

The acrylamide 1 was prepared from acrylic acid and N, N'-di-((S)-1-phenylethyl)urea.[3)] The Diels-Alder reaction of 1 (1 mmol) with cyclopentadiene (1.5 mmol) was performed in the presence of a Lewis acid (1.5 mmol) at 100 °C (in toluene), at -78 °C (in CH_2Cl_2) or at -115 °C (in EtCl). Without catalyst the endo/exo ratio was 77:23. However in the presence of Lewis acid the endo-selectivity was significantly improved (over 97%). Especially $TiCl_4$ promoted the reaction with high stereoselectivity.

The major bicyclic acylurea 2 was purified by column chromatography (silica gel, hexane-ethyl acetate) and treated with NaOMe (10 equiv.)/MeOH (0 °C, 8 h) to give the optically pure methyl ester 4[4)] (94%) and the chiral urea 5 (83%).

The observed high selectivity can be explained by considering the complex 1' depicted in Scheme 1. The π-π attractive interactions of the pendant vinyl group with the benzene ring must occur at the re-face of the olefine moiety due to the H-H repulsions between the olefin and the methyl group of the phenethyl moiety. Accordingly, the Diels-Alder reaction should occur stereoselectively at the si-face giving the bicyclic acylurea 4 as a major product.

These results indicate that it is also possible to obtain the optically pure (3S, 4S, 6S)-isomer from (R)-1-phenylethylamine. Further, both the chiral auxiliaries can be efficiently recycled.

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References

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2) The ratios (2/3) were determined based on the following signals. ^{1}H-NMR (δ, J in Hz, $CDCl_3$): 2: 6.08(dd, J=5.6, 2.8, 1H, H-C(2)), 3.18(s, 1H, H-C(3)), 3.31 (qi, J=7.0, 1H, H-C(4)), 3: 5.90(dd, J=5.8, 2.8, 1H, H-C(2)), 2.78(s, 1H, H-C(3)), 3.37(qi, J=4.2, 1H, H-C(4)).

3) K. Yamada, K. Kishikawa, S. Kohmoto, and M. Yamamoto, Chem. Lett., 1988, 351.

4) The value observed was $[\alpha]_D^{22}$ +144.6° (EtOH). (lit. $[\alpha]_D$ +141° (95% EtOH): J. A. Berson and D. A. Ben-Efraim, J. Am. Chem. Soc., 81, 4084 (1959).

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