ORGANIC LETTERS

2000
Vol. 2, No. 20
3241−3244

Investigation of a Dialkylation Approach for Enantioselective Construction of Vicinal Quaternary Stereocenters

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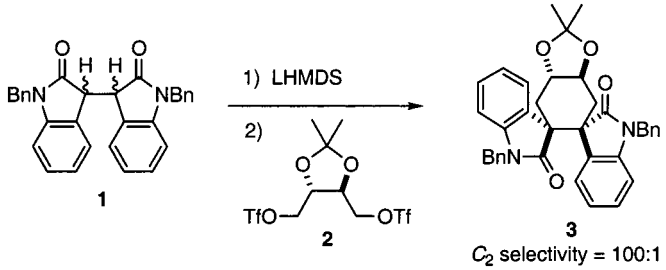
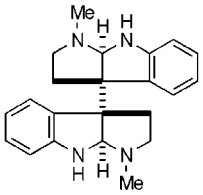
Received August 22, 2000

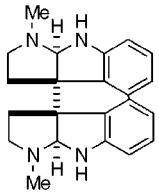
ABSTRACT



A detailed study of the dialkylation of dianions derived from dihydroisoindigo 1 with enantiopure ditriflate 2 is reported. The LHMDS-mediated process has been optimized to give C_2-symmetric product 3 with high selectivity (C_2 selectivity 3:5 = 100:1; C_2:C_1 selectivity = 8:1). Stereoselection in the C_2 manifold is determined in both the bimolecular and intramolecular alkylation steps.

In the context of total syntheses of polypyrroloindoline natural products, we recently disclosed two methods for enantioselective construction of vicinal stereogenic quaternary centers.[1−3] The more efficient of these sequences featured a dialkylation reaction that forged both quaternary stereocenters in a single step.[2] For example, treatment of dihydroisoindigo **1** with 2.1 equiv of either NaHMDS or KHMDS in THF generated an enolate species that reacted with enantiopure, tartrate-derived ditriflate **2** to give C_1-symmetric product **4** in 92% yield (Scheme 1). In contrast, sequential treatment of **1** with 2.0 equiv of LHMDS and **2** in 9:1 THF−DMPU delivered C_2-symmetric product **3** in 55% yield, together with 20% of **4** and 1% of the other C_2-symmetric adduct **5**. Further processing of **3** provided (+)-chimonanthine in 21% overall yield from commercially available oxindole and isatin; a similar sequence transformed **4** into *meso*-chimonanthine in 39% overall yield. The formation of essentially one C_2-symmetric product in the LHMDS-mediated dialkylation appears to be a rare example


(+)-chimonanthine


meso-chimonanthine

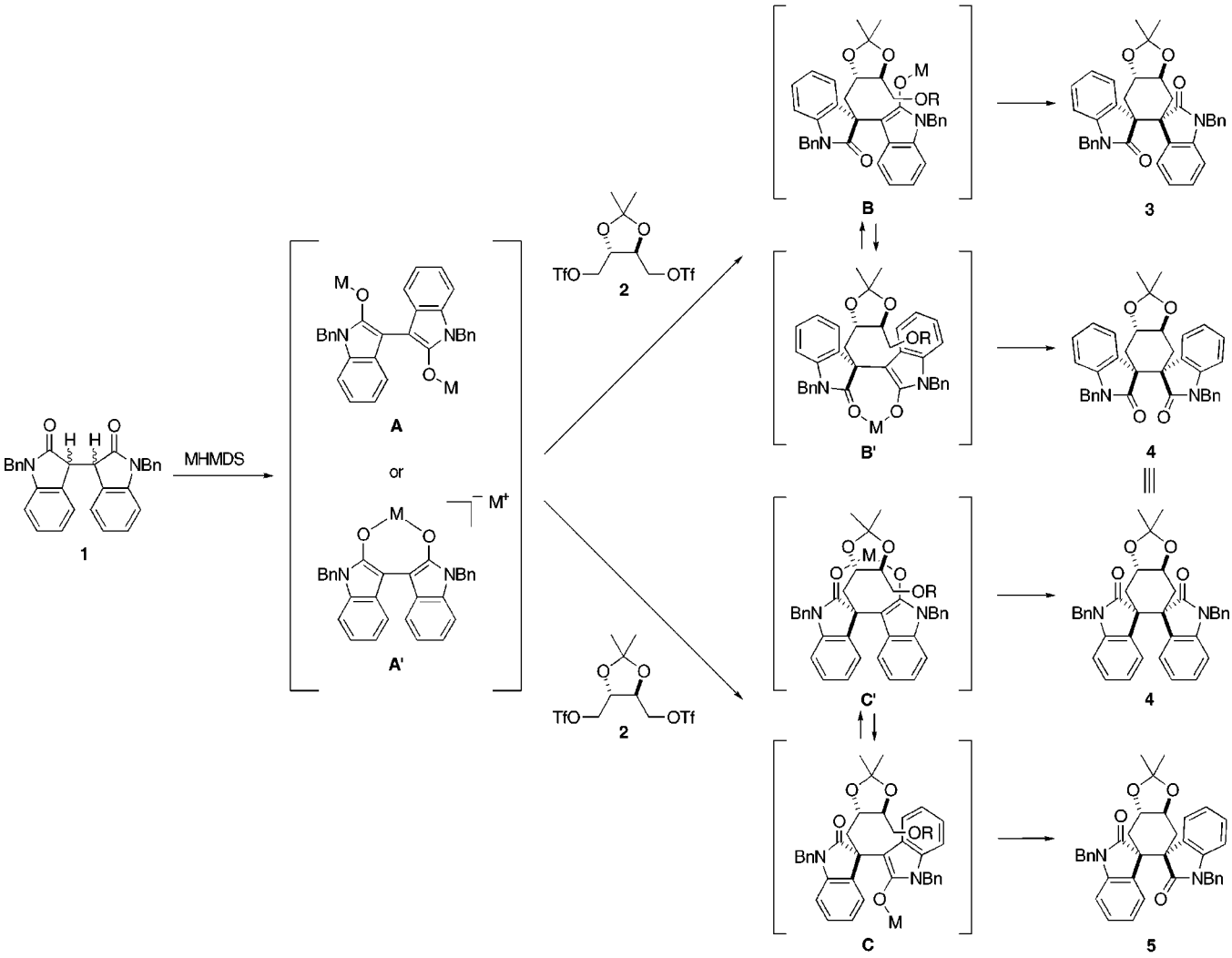
of high stereoselection resulting from the reaction of a prostereogenic enolate with a chiral, sp^3-hybridized electrophile. We report herein a detailed investigation of the dialkylation of dihydroisoindigo **1** with enantiopure ditriflate **2**. These studies have led to optimized reaction procedures and have defined some of the critical stereochemical control elements of this uncommon diastereoselective alkylation.

At the outset of the current investigation, the mechanistic details of the dialkylation reactions summarized in Scheme 1 were unknown. We were particularly interested in resolving three key issues: (1) Is the nucleophile in the initial bimolecular alkylation step a dienolate bearing no stereogenic centers, or is it a monoenolate containing a stereocenter that could influence the outcome of the initial alkylation?[4] (2) What factors account for the observed counterion-dependent distribution of C_2-symmetric and C_1-symmetric products? (3)

(1) Overman, L. E.; Paone, D. V.; Stearns, B. A. *J. Am. Chem. Soc.* **1999**, *121*, 7702−7703.
(2) Overman, L. E.; Larrow, J. F.; Stearns, B. A.; Vance, J. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 213-215.
(3) For recent reviews of asymmetric synthesis of quaternary carbon centers, see: (a) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388−401. (b) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037−2066.

10.1021/ol006494m CCC: $19.00
Published on Web 09/14/2000

Scheme 1. Stereoselective Dialkylation Reactions



What is the origin of the remarkable proclivity for generating essentially one C_2-symmetric product in the LHMDS-mediated process? To address these questions, we performed the following studies.

To determine whether a dienolate was fully formed prior to alkylation with the ditriflate, we monitored the reaction of **1** with **2** via in situ infrared spectroscopy. By observing the appearance and disappearance of enolate and carbonyl-related absorptions in the IR spectrum as a function of temperature, we were able to ascertain the temperatures at which dienolate formation was complete and alkylation began to take place (Figure 1). When our original reaction procedure was employed,[4] dienolate formation with LHMDS did not occur until the reaction had warmed from −78 °C to ca. −20 °C (internal temperature); under these relatively dilute conditions (0.13 M), alkylation occurred but could not be detected spectroscopically (Table 1, entry 1). When the reaction was conducted at higher concentration (0.31 M), the temperatures at which dienolate formation was complete and alkylation began to occur could both be determined for a variety of bases (Table 1, entries 2−4).

Armed with this information, we revised our reaction protocol to ensure that a dienolate was fully formed before the ditriflate was added. In the new procedure, base was

Table 1. In Situ IR Spectroscopic Analysis of Reaction of **1** and **2**[a]

entry	base	concn, M	dienolate formation, °C	alkylation, °C
1	LHMDS	0.13	−17	not detected
2	LHMDS	0.31	−45	−55
3	NaHMDS	0.31	−76	−52
4	KHMDS	0.31	−71	−60

[a] Reactions conducted in 9:1 THF−DMPU using 2.2 equiv of base and 1.2 equiv of **2**.

(4) The experimental procedure employed in our initial studies involved addition of an amide base to a solution of **1** and THF (with or without additive) at −78 °C; after 15 min, ditriflate **2** was added and the reaction was allowed to warm to room temperature.[2] As a result, it was unclear whether dienolate formation occurred faster than alkylation of a monoenolate.

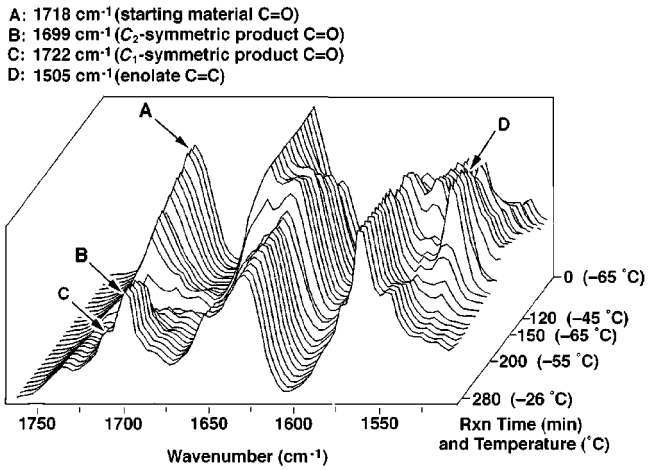


Figure 1. IR data from the LHMDS-mediated dialkylation. LHMDS was added at −65 °C and the reaction was warmed to −45 °C over 2 h. The reaction was then recooled to −65 °C, ditriflate **2** was added, and the reaction was slowly warmed to −26 °C.

added to a solution of **1** in THF (with or without additive) at −40 °C; after stirring for 1 h at −40 °C, ditriflate **2** was added. Unless otherwise noted, all of the following experiments were conducted using this modified procedure. This change ensures that the stereocenters present in dihydroisoindigo **1** are eliminated prior to coupling with ditriflate **2** and thus do not influence the stereochemical outcome of dialkylation.

We next sought to improve stereoselection in the LHMDS-mediated reaction. The alkylation process was carefully optimized with regard to temperature and cosolvent (Table 2). The results of these experiments indicated that while reaction stereoselectivity was relatively insensitive to temperature, it was profoundly sensitive to both the nature and amount of cosolvent employed. Optimal results were obtained when the reaction was run at −40 °C using a 7:3 mixture of THF−HMPA (Table 2, entry 8). Under these conditions, selectivity within the C_2-symmetric product manifold (**3**:**5**) was 100:1, while the preference for forming C_2-symmetric products (**3**:**4**) was 8:1.[5]

Table 2. Effect of Cosolvent on Stereoselectivity in the LHMDS-Promoted Reaction of **1** and **2**[a]

entry	solvent	**3**:**4**:**5**[b]	**3**:**5**
1	THF	6:10:1	6:1
2	9:1 THF−DMPU	41:28:1	41:1
3	8:2 THF−DMPU	47:24:1	47:1
4	7:3 THF−DMPU	53:18:1	53:1
5	1:1 THF−DMPU	22:8:1	22:1
6[c]	DMPU	5:2:1	5:1
7[d]	8:2 THF−HMPA	100:19:nd[e]	100:nd
8[d]	7:3 THF−HMPA	100:12:1	100:1
9	1:1 THF−HMPA	11:1.4:1	11:1
10[f]	HMPA	5:1:1	5:1

[a] Reactions conducted at −40 °C, 0.3 M in **1** except as noted. [b] Determined by HPLC. [c] At 0 °C. [d] Mean product ratio reported. [e] None detected. [f] At room temperature.

Our next goal was to determine why the LHMDS-mediated dialkylation afforded a different product distribution than the NaHMDS- and KHMDS-mediated reactions. We had previously postulated that monoalkylated sodium or potassium enolates underwent the second, intramolecular alkylation via chelated intermediates **B′** and **C′** en route to **4**.[2,6] The second alkylation step of the LHMDS-mediated process, on the other hand, was believed to proceed primarily through nonchelated intermediate **B** en route to major product **3**. To test this hypothesis, we performed the reaction in the presence and absence of various crown ethers. The results of these experiments are summarized in Table 3. The KHMDS-mediated reaction provided a 44:1 ratio of **4**:**3** in THF, which was degraded to 3:1 in the presence of 5 equiv of 18-crown-6 (Table 3, entries 1 and 3). Similarly, the NaHMDS-mediated reaction produced a 56:1 ratio of **4**:**3** in THF and a diminished 11:1 ratio of **4**:**3** in THF containing 5 equiv of 15-crown-5 (entries 4 and 6). These results are in accord with the intervention of chelated intermediates **B′** and **C′** in the intramolecular alkylation step when the counterion is potassium or sodium. In contrast, when run under conditions optimized for the formation of C_2-symmetric product **3**, the LHMDS-mediated reaction afforded strikingly similar product distributions in the presence or absence of 12-crown-4 (Table 3, entries 7 and 8).

Table 3. Effects of Crown Ethers on Stereoselectivity in the Reaction of **1** and **2**[a]

entry	base	conditions	**4**:**3**[b]
1	KHMDS	THF	44:1
2	KHMDS	THF, 3 equiv of 18-C-6	4:1
3	KHMDS	THF, 5 equiv of 18-C-6	3:1
4	NaHMDS	THF	56:1
5	NaHMDS	THF, 3 equiv of 15-C-5	16:1
6	NaHMDS	THF, 5 equiv of 15-C-5	11:1
7	LHMDS	7:3 THF−HMPA	1:8
8	LHMDS	7:3 THF−HMPA, 5 equiv of 12-C-4	1:9

[a] Reactions conducted at −40 °C, 0.3 M in **1**. [b] By HPLC analysis. In each case, C_2-symmetric product **5** was detected as a minor component.

Our final task was to elucidate the basis of selectivity within the C_2 manifold (**3**:**5** = 100:1) in the LHMDS-mediated process. We envisioned two limiting scenarios that could account for the observed result. In the first, stereoselectivity is determined largely during the initial bimolecular alkylation event. Thus, reaction with **2** takes place selectively from one face of either a chelated (**A′**) or nonchelated (**A**) dienolate species to yield largely one monoalkylated intermediate; two rotamers of this species, **B** and **B′**, are depicted in Scheme 1, as are two rotamers, **C** and **C′**, of the other possible diastereomeric monoalkylated intermediate. Sub-

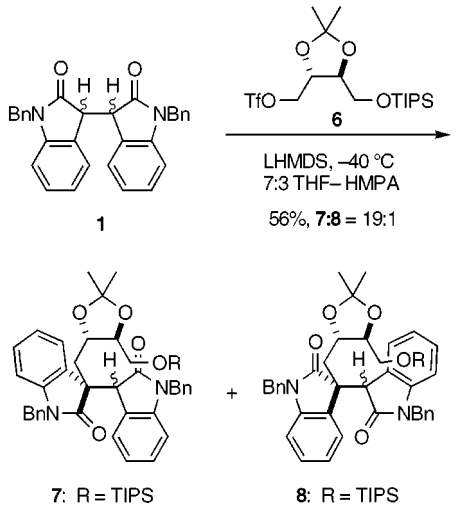
(5) Product ratios were determined by HPLC analysis using an Alltima silica column.

(6) Link, J. T.; Overman, L. E. *J. Am. Chem. Soc.* **1996**, *118*, 8166−8167.

sequent intramolecular alkylation of the major diastereomer is less selective, with **B** and **B′** providing major products **3** and **4**, respectively. Intramolecular alkylation of the minor monoalkylation intermediate (**C** and **C′**) yields additional **4** as well as traces of product **5**. Alternatively, the high stereoselectivity observed within the C_2 manifold derives largely from diastereoselective partitioning of the monoalkylated intermediates in the intramolecular alkylation step. In this scenario, the initial bimolecular alkylation generates a slight predominance of **B**/**B′** relative to **C**/**C′**. The high selectivity for forming C_2-symmetric product **3** then arises because **B**/**B′** partitions preferentially to form **3** rather than **4**, while **C**/**C′** partitions with high selectivity to form **4** rather than **5**.

To discriminate between these two limiting cases, we needed to determine the stereoselectivity of the initial intermolecular alkylation. Unfortunately, monoalkylated intermediates could not be trapped or detected under our optimized conditions, consistent with the first alkylation step being rate-limiting. To estimate diastereoselection in the initial alkylation step, the reaction of **1** with triflate **6** was investigated.[7] Formation of the dilithium dienolate of **1** under optimized conditions followed by treatment with 0.35 equiv of **6** provided four products which could be separated by careful column chromatography on silica gel (Scheme 2).[8]

Scheme 2. Estimating Stereoselection in the First Alkylation Step



Epimerization experiments run under basic conditions (3 equiv of DBU, THF, rt) revealed that the four products were, in fact, two pairs of lactam epimers, **7** and **8**; the configurations of **7** and **8** were then secured by correlation of the major epimer of **7** with **3**.[9] HPLC analysis of the crude reaction mixture showed that **7** and **8** were produced in a 19:1 ratio.

To the extent that **6** is a good model for **2**, the results summarized in Scheme 2 indicate that the initial bimolecular alkylation step of the LHMDS-mediated reaction of **1** and **2** in 7:3 THF−HMPA occurs with a facial selectivity of ca. 19:1. Comparison of this ratio with the final product ratio (**3**:**4**:**5** = 100:12:1) reveals that the major monoalkylated intermediate **B**/**B′** partitions in the second alkylation step to generate predominantly the C_2-symmetric product **3** (**B** → **3**:**B′** → **4** = 12:1) while the minor monoalkylated intermediate **C**/**C′** partitions in the opposite sense to generate largely the C_1-symmetric product **4** (**C′** → **4**:**C** → **5** = 5:1).[10]

In conclusion, the previously reported dialkylation of **1** with **2** has been optimized to provide either C_2-symmetric product **3** or C_1-symmetric product **4** in a highly stereoselective manner. IR data collected in situ demonstrate that the reaction proceeds via initial formation of a dienolate species. Results obtained using crown ether additives support the hypothesis that sodium and potassium enolates of monoalkylated intermediates undergo subsequent intramolecular alkylation in THF largely through chelated transition structures, while the corresponding lithium enolates react in 7:3 THF−HMPA predominantly via nonchelated transition structures. The 100:1 stereoselectivity observed in the formation of C_2-symmetric products in the LHMDS-mediated process is determined both in the initial intermolecular alkylation and in the subsequent partitioning of monoalkylated intermediates. Notably, the prostereogenic dilithium dienolate of **2** reacts with enantiopure, tartrate-derived electrophile **6** with a facial selectivity of 19:1. This result challenges the conventional wisdom that the combination of prostereogenic enolates with chiral, sp^3-hybridized electrophiles is not a useful tactic for stereocontrolled C−C bond construction.[11,12] Experiments aimed at defining the structural features of **1** and **2** responsible for high alkylation stereoselection are currently underway, as are studies geared toward expanding the scope of this uncommon class of diastereoselective alkylation reactions.

Acknowledgment. This research was supported by NIH Grant GM-12389 and a postdoctoral fellowship to S.B.H. from NIGMS (GN-19820). NMR and mass spectra were determined with instrumentation purchased with the assistance of NSF and NIH shared instruments programs.

Supporting Information Available: IR data for the KHMDS- and NaHMDS-promoted reactions reported in Table 1, experimental procedures for the alkylation reactions reported in Tables 2 and 3, and characterization data for new compounds reported in Scheme 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Prepared in standard fashion by triflating the corresponding known alcohol: Taunton, J.; Collins, J. L.; Schreiber, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 10412−10422.

(8) Reactions conducted using 0.5−1.0 equiv of **6** gave undesired dialkylated side products.

(9) The TIPS group was removed with TBAF in THF/HOAc, the resulting alcohol was converted to the corresponding triflate, and this latter intermediate was cyclized in the presence of LHMDS to yield **3**.

(10) The thermodynamic stabilities of the hexacyclic stereoisomers appear to be reflected in the transition state energies of the intramolecular alkylation step under these conditions: E_{rel}(MM2) kcal/mol **3** (0.0), **4** (3.0), **5** (4.8).

(11) A recent survey of stereoselective C−C bond formation cites no examples in sections dealing with alkylation reactions with chiral electrophiles, see: *Methoden Org. Chem. (Houben-Weyl, Workbook Edition)*, 4th ed.; 1996; Vol. E21/2, pp 1077−1118.

(12) Examples of selectivity in the range of 7−10:1 using lactate triflates were recently reported: Vedejs, E.; Daugulis, O. *J. Am. Chem. Soc.* **1999**, *121*, 5813−5814.