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Directed Heterodimerization: Stereocontrolled Assembly via Solvent-Caged Unsymmetrical Diazene Fragmentation

Mohammad Movassaghi,* Omar K. Ahmad, and Stephen P. Lathrop

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States

Supporting Information

ABSTRACT: A general strategy for the directed and stereocontrolled assembly of carbon−carbon linked heterodimeric hexahydropyrroloindoles is described. The stepwise union of complex amines in the form of mixed diazenes followed by photoexpulsion of dinitrogen in a solvent cage provides completely guided assembly at challenging $C_{sp^3}-C_{sp^3}$ and $C_{sp^3}-C_{sp^2}$ connections.

Dimeric and oligomeric cyclotryptamine and cyclotryptophan alkaloids constitute a large family of natural products with diverse molecular architectures and a wide range of biological activities.[1] Nature can access an array of these alkaloids containing quaternary stereocenters at C3a through the amalgamation of various monomers. In 2007, we reported a versatile strategy for the concise and enantioselective synthesis of homodimeric cyclotryptamine substructures.[2] However, to date, there are no reported methods for selective $C-C^3$ bond construction at the C3a quaternary stereocenter of two dissimilar cyclotryptamine subunits, a synthetically challenging structural motif found in many heterodimeric alkaloids (Figure 1).[4] Herein we report a strategy for completely stereoselective and directed union of complex fragments at these sterically crowded linkages. We demonstrate the utility of this chemistry in adjoining differing monomers at C−C fusions common to this family of natural products.

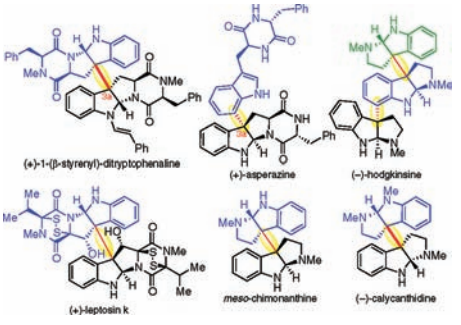
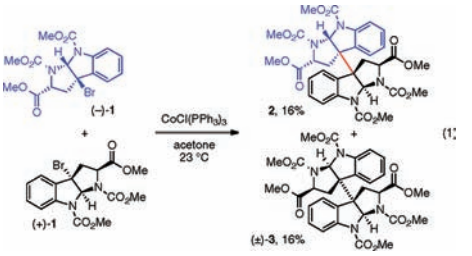


Figure 1. Representative heterodimeric cyclotryptamine alkaloids.

Our laboratory seeks effective methodology for controlled union of complex fragments for application in natural products synthesis. While our Co(I)-promoted homodimerization of cyclotryptamine derivatives has enabled concise total syntheses,[2,5] we found its extension to heterodimerization problematic. For example, uncontrolled dimerization of tricyclic bromides (+)-**1** and (−)-**1** using our Co-promoted strategy provides the desired heterodimeric *meso*-**2** in only 16% isolated yield (eq 1). The near-statistical product mixture of **2** and **3** also contains the corresponding disproportionation and related byproducts which hampers the isolation of pure heterodimer **2**.[6] The low yield of the desired product along with complications associated with side product formation restricts the use of this chemistry in preparative heterodimeric assembly. A maximally convergent solution to heterodimeric molecules requires a method that provides a single product with minimal influence of substrate bias in the planned union.



Inspired by the work of Bartlett, Engel, and Naumann,[7] we considered the possibility of using diazenes as traceless linkers[8] and radical precursors for our desired heterodimerization chemistry. Dialkyl diazenes are known to undergo expulsion of dinitrogen upon photoexcitation to generate two radical species. However, in these cases,[7b] radical combination is accompanied by varying amounts of disproportionation. Furthermore, photoexcitation of unsymmetrical diazenes is often complicated by cross-over products due to out-of-cage coupling,[7f,l,m] thus limiting their utility in fragment assembly and complex molecule synthesis.

We envisioned the expulsion of dinitrogen from an unsymmetrical diazene **5** (Scheme 1) to form a pair of carbon-centered radicals whose directed union in a solvent cage[9] would result in selective formation of the desired heterodimer **4**. The use of the mixed sulfamide **6** as the precursor[10] to the unsymmetrical diazene **5** would provide a platform for the directed assembly of the two monomeric amines, **7** and **7′**. Implementation of this strategy in complex synthesis would require: (a) synthesis of cyclotryptamine-based mixed sulfamides,[11] (b) mild conditions for their conversion to the corresponding unsymmetrical diazenes followed by fragmentation,[12] (c) solvent-cage-controlled radical pair combination,[9] and (d) minimization of out-of-cage coupling (homodimerization) and disproportionation.[7]

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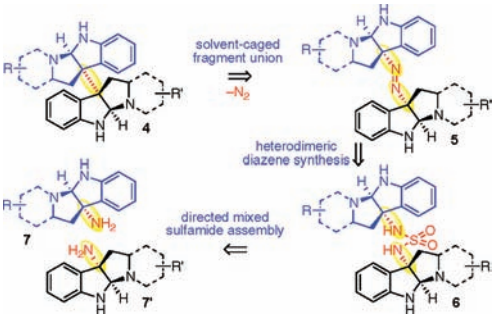
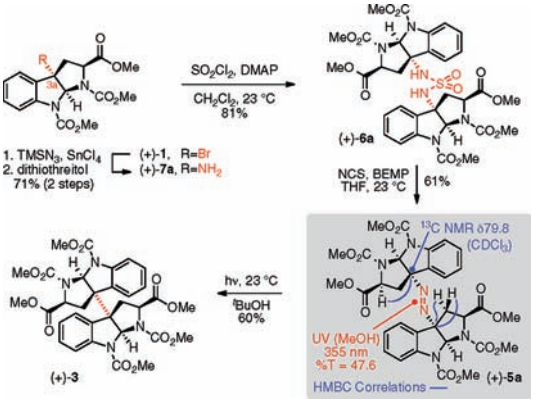
Scheme 1. Directed Heterodimerization



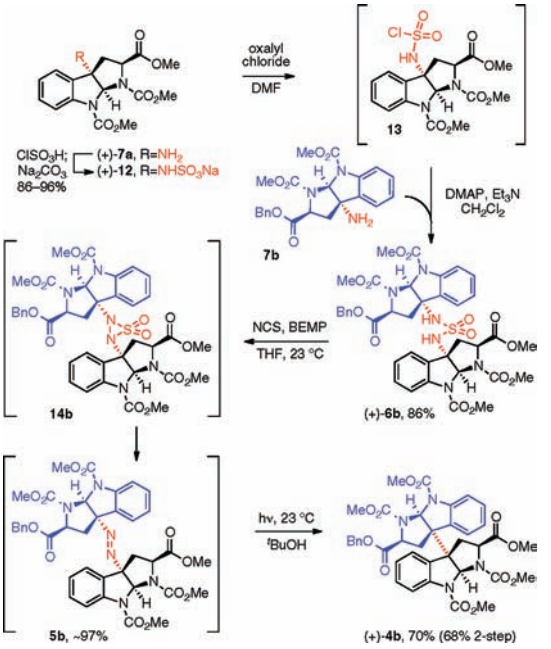
Scheme 2. Homodimer Synthesis



Our initial studies focused on the evaluation of the use of dialkyl diazenes in the context of homodimerization. We began with the development of a diazene-based synthetic route to homodimer (+)-**3** (Scheme 2). We developed a versatile entry to the necessary amines **7** (Scheme 1) by derivatization of the corresponding benzylic bromides that had been utilized in our Co-promoted dimerization studies. As illustrated in Scheme 2, exposure of the bromide (+)-**1**[6] to tin tetrachloride and trimethylsilyl azide followed by reduction of the corresponding azide[13] provided the desired hexahydropyrroloindolyl amine[14] (+)-**7a** (71%). Exposure of (+)-**7a** to sulfuryl chloride provided the sulfamide (+)-**6a** in 81% yield. Under optimal conditions, subsequent oxidation of sulfamide (+)-**6a** with *N*-chlorosuccinimide in the presence of 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine on polystyrene resin (BEMP) generated the desired diazene (+)-**5a** in 61% isolated yield.[15] The UV absorption at 355 nm and the ^{13}C NMR resonance of the C3a of (+)-**5a** were in accord with previously reported data for dialkyl diazenes.[16] Photoexcitation[17] of (+)-**5a** led to expulsion of dinitrogen and formation of the desired dimeric hexacycle (+)-**3** in 60% yield. The overall efficiency of the process is increased (48% over two steps) when the freshly prepared crude diazene (~99%, based on ^{1}H NMR with internal standard) is used in the following step without chromatographic purification.

Having established the viability of using the sulfamide (+)-**6a** as a precursor to homodimer (+)-**3**, we turned our attention to the development of a general method for directed heterodimerization. Stepwise sulfonylation of different hexahydropyrroloindolyl amines was expected to provide a means for assembly of a heterodimeric structure as the prelude to the construction of the desired linkage. The selective synthesis of mixed sulfamide (+)-**6b** is illustrated in Scheme 3. Treatment of amine (+)-**7a** with chlorosulfonic acid followed by addition of sodium carbonate afforded the corresponding sodium sulfamate salt (+)-**12**.[11a] In situ activation of **12** to form the sulfamoyl chloride **13** followed by direct union with complex amine **7b** provided the unsymmetrical sulfamide (+)-**6b** (86% based on **7b**). Exposure of (+)-**6b** to *N*-chlorosuccinimide provided the corresponding unsymmetrical diazene **5b**, likely via the transient thiadiaziridine dioxide **14b**. The crude diazene **5b** was subjected to photoinduced expulsion of dinitrogen to *exclusively* afford the desired heterodimer (+)-**4b** in 68% yield from (+)-**6b**. The optimal conditions involved irradiation using a medium-pressure mercury vapor lamp in *tert*-butanol as solvent

Scheme 3. Directed Assembly and Heterodimer Synthesis



in a Pyrex reaction vessel. Importantly, neither of the two possible homodimeric products was observed by HPLC analysis of the crude product mixture. Notably, the formation of heterodimer (+)-**4b** constitutes the first example of *directed and stereoselective C−C bond construction fusing two different cyclotryptamine fragments at vicinal quaternary stereocenters.*

The exclusive formation of heterodimeric product (+)-**4b** suggests exquisite control in the solvent-caged coupling of the radical pair formed upon dinitrogen expulsion from the dialkyl diazene **5b**. We sought opportunities to probe the level of control exerted by this strategy in the guided unification of complex monomers. Exposure of an equal mixture of symmetrical sulfamides **6a** and **6c** to the two-step sequence for oxidation and fragmentation afforded only an equal mixture of the respective homodimeric products **3** and **15** (55% and 51% yield, respectively, eq 2). Notably, HPLC analysis of the crude product mixture against authentic

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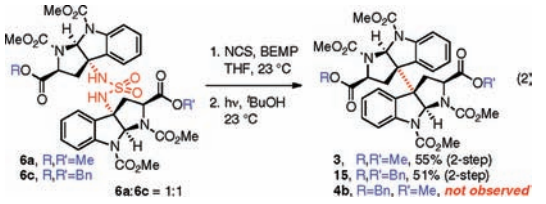
samples of **3**, **4b**, and **15** did not reveal any of the heterodimeric product **4b**.[6]



Furthermore, photoexpulsion of dinitrogen from (+)-**5a** in the presence of 1,4-cyclohexadiene (5.0 equiv), a H-atom donor, resulted in an almost equal mixture of the desired dimeric product (+)-**3** (45% yield) and the corresponding monomeric C3a-H reduction product (21% yield, ~1:1 molar ratio).[6] An increase in the amount of H-atom donor (20 equiv) afforded a similar molar ratio of product (+)-**3** (41% yield) to monomeric C3a-H reduction product (20% yield). For comparison, under our reported Co-mediated dimerization conditions,[2] bromide (+)-**1** exclusively provided the monomeric C3a-H reduction product in the presence of 1,4-cyclohexadiene (5.0 equiv, 54%; 20 equiv, 82%).[6] The formation of the dimer as the major product, even in the presence of excess H-atom donor and at higher dilution under our photochemical conditions, is consistent with solvent-cage-directed radical-pair combination.

Having found conditions for the synthesis of the desired heterodimeric product, we sought to further examine the scope of this process. Gratifyingly, mixed sulfamides **6d**−**6i** (Table 1) were readily prepared using the optimal conditions described above (Scheme 3). In each case, the more readily available amine was converted to the corresponding sulfamoyl chloride, allowing for the directed assembly of the heterodimeric sulfamides. Exposure of mixed sulfamides **6d**−**6i** to the optimized oxidative diazene synthesis afforded the heterodimeric diazenes **5d**−**5i** (Table 1). The crude diazenes were subjected to photochemical expulsion of dinitrogen and gave the desired dimeric products (+)-**4d**−**4i** and *meso*-**2**.

Notably, this strategy allows access to complex heterodimers such as products (+)-**4e** and (+)-**4f**. Specifically, heterodimer (+)-**4f** results from the fusion of a tetracyclic diketopiperazine with a cyclotryptamine moiety. Thus, the chemistry described here offers the first solution for directed and exclusive heterodimeric union of requisite dissimilar cyclotryptamine precursors. Coupling the enantiomeric amines (+)-**7a** and (−)-**7a** afforded the *meso*-sulfamide **6g** (Table 1, entry 4), which upon oxidation and photolysis provided cleanly and exclusively the corresponding *meso*-dimer **2** (56% over two steps), a structural core found in *meso*-chimonanthine,[4a] (+)-leptosin K,[4d] and many other cyclotryptamine natural products.[18] The exclusive formation of *meso*-**2** in 28% overall yield from tricyclic bromides (+)-**1** and (−)-**1** can be directly compared to the example described in eq 1.

Furthermore, we wanted to explore the applicability of this methodology to the synthesis of C3a-aryl-substituted quaternary stereocenters. The C_{sp^3}−C_{sp^2} connectivity between cyclotryptamine substructures is found in many natural alkaloids (Figure 1).[1] Notably, our Co-promoted dimerization chemistry is not applicable to such unions. We were delighted to find that replacement of one of the amine components with an aniline derivative provided access to mixed aryl−cyclotryptamine sulfamides (Table 1, entries 5 and 6).[6] Oxidation and photolysis provided the corresponding arylated hexahydropyrroloindoles

Table 1. Directed Heterodimer Synthesis

Entry	Unsymmetrical Sulfamide[a]	Diazene[b]	Heterodimeric Product[c]
1	**6d**, 72	**5d**, (80)	(+)-**4d**, 72 [60% 2-steps]
2	**6e**, 79	**5e**, (88)	(+)-**4e**, 59 [52% 2-steps]
3	**6f**, 57	**5f**, (83)	(+)-**4f**, 59 [47% 2-steps]
4	**6g**, 81	**5g**, (99)	**2**, 57 [56% 2-steps]
5	R = H, **6h**, 91	**5h**, (91)[d]	(+)-**4h**, 53[e] [50% 2-steps]
6	R = CF_3, **6i**, 57	**5i**, (99)	(+)-**4i**, 61 [60% 2-steps]

[a] Mixed sulfamide synthesis: **7**, **13**, DMAP, Et_3N, CH_2Cl_2, 0 → 23 °C. Isolated % yield of **6** after chromatography. [b] Diazene synthesis: BEMP, NCS, THF, 23 °C. Crude % yield of sensitive diazene **5** in parentheses. [c] Heterodimer synthesis: *t*-BuOH, *hν* >280 nm, 23 °C, 5 h. Isolated % yield of **4** after chromatography. Yield of **4** from **6** in brackets. [d] DBU, NCS, MeOH, 0 → 23 °C. [e] *hν* 300 nm, 12 h.

(+)-**4h** and (+)-**4i**. The efficiency of the dinitrogen expulsion from *N*-aryl-*N*′-cyclotryptaminyl diazenes **5h**[19] and **5i** was on par with that of mixed diazenes **5d**−**5g**. Current efforts are directed at broadening the scope of this methodology by developing milder methods for converting complex mixed aryl−alkyl sulfamides to the corresponding diazenes.

We have developed a general strategy for the stereoselective directed synthesis of dimeric substructures found in hexahydropyrroloindole alkaloids. Our findings constitute the first controlled coupling of different cyclotryptamine monomers at quaternary carbons and is distinct from prior strategies based on desymmetrization chemistry.[20] The described protocol allows for the synthesis of heterodimeric products with exquisite selectivity in four operations from the corresponding amines while only requiring purification of the mixed sulfamides and final products after photolysis. This chemistry allows directed heterodimerization at important substructure linkages, particularly the challenging C_{sp^3}−C_{sp^3} connections, found in this family of heterodimeric complex alkaloids. This completely stereocontrolled

and directed fragment coupling draws on the versatility of diazene chemistry[7,21] and holds great potential for complex molecule assembly.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, spectroscopic data, and related mechanistic studies. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
movassag@mit.edu

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(16) Key spectroscopic data for representative diazenes: α,α′-azocumene, λ_{max} = 367 nm,[7b] ^{13}C NMR ($CDCl_3$) δ 71.32 (α-carbon);[12d] *trans-N,N′*-di(1-adamantyl)diazene, λ_{max}(octane) = 368 nm.[7k]

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