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Chiral Brønsted Acid-Promoted Enantioselective Desymmetrization in an Intramolecular Schmidt Reaction of Symmetric Azido 1,3-Hexanediones: Asymmetric Synthesis of Azaquaternary Pyrroloazepine Skeletons

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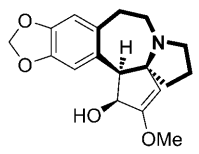
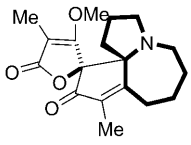
Alkaloids containing azaquaternary pyrroloazepine skeletons including cephalotaxine[1] and stemonamine[2] are an important class of bioactive molecules in nature. How to directly and enantioselectively construct the azaquaternary



cephalotaxine



stemonamine

pyrroloazepine skeleton remains a challenge. Desymmetrization reactions, which are used to synthesize chiral molecules, are proving to be a powerful method, and variations of this type of reaction have been well developed.[3] For example, the proline catalyzed enantioselective desymmetrization of *meso*-1,3-diones that yield Hajos–Parrish[4] and Wieland–Miescher[5] ketones is widely known. When coupled with an intramolecular Schmidt reaction,[6] which has proven to be a useful tool in the synthesis of alkaloids,[7] it could allow facile construction of optically active lactams from readily available starting materials. The combined desymmetrization and Schmidt reaction of ketones and chiral azido alcohols in an intermolecular fashion was first developed by Aubé and co-workers, wherein the products did not contain an azaquaternary center.[8] However, an intramolecular Schmidt reaction of prochiral azido 1,3-diketones could concisely construct azaquaternary pyrroloazepine and indolizine compounds. Recent efforts to achieve enantioselective symmetry breaking of azido 1,3-diketones using this reaction failed when chiral Lewis acids were used.[9] Herein, we report the first successful enantioselective desymmetrization in an intramolecular Schmidt reaction of prochiral azido 1,3-hexanediones; this reaction was promoted by 1,1′-bi-2-naphthal (BINOL)-derived *N*-triflylphosphoramides and yielded chiral azaquaternary pyrroloazepine skeletons.

A difficulty in the enantioselective desymmetrization in the intramolecular Schmidt reaction of azido 1,3-diketones might be the requirement for rather strong Brønsted acid promoters. In recent years, BINOL-derived phosphoric acids have been widely used in enantioselective catalysis as strong Brønsted acids.[10] However, they were not effective for the intramolecular Schmidt reaction of azido 1,3-hexanediones because of their relatively low acidity ($pK_a \approx 1$ in water).[11a] In 2006, Yamamoto et al. introduced a triflate moiety, which is a strong electron-withdrawing group, into BINOL-based phosphates, and they successfully used the corresponding BINOL-derived *N*-triflylphosphoramides in an asymmetric Diels–Alder reaction of ethyl vinyl ketone with siloxydienes.[12a] The higher acidity of BINOL-derived *N*-triflylphosphoramides ($pK_a \approx -3$ in water)[11a] compared with the corresponding phosphoric acids means they can effectively activate carbonyl groups and have been frequently used for asymmetric catalysis.[12] Because trifluoroacetic acid ($pK_a \approx 0.23$ in water)[11b] can efficiently induce an intramolecular Schmidt reaction of an azidopropyl-substituted 1,3-diketone,[6b] we proposed that BINOL-derived *N*-triflylphosphoramides might promote enantioselective desymmetrization in the intramolecular Schmidt reaction of azido 1,3-hexanediones.

In an initial screening of chiral BINOL-derived *N*-triflylphosphoramides for the reaction of **1a**, **2a–f** can effectively induce the reaction, with only **2e** and **2f** giving low enantioselectivity (Table 1, entries 1–6). When **1b** was used as the substrate and **2e** or **2f** as the inducer, better enantioselectivity was obtained (Table 1, entries 7 and 8). The reaction be-

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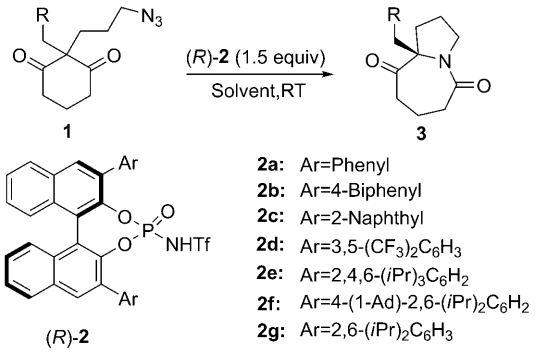
Table 1. Optimization of the reaction conditions.[a]



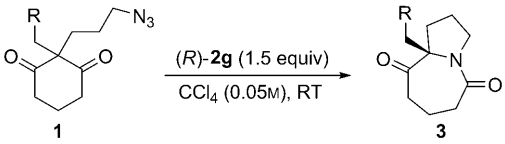
Entry	R	2	Solvent	*t* [d]	Yield [%][b]	*ee* [%][c]
1	H(**1a**)	**2a**	CH_2Cl_2	1	66	6
2	H(**1a**)	**2b**	CH_2Cl_2	1	55	7
3	H(**1a**)	**2c**	CH_2Cl_2	1	58	5
4	H(**1a**)	**2d**	CH_2Cl_2	1	69	4
5	H(**1a**)	**2e**	CH_2Cl_2	3	52	25
6	H(**1a**)	**2f**	CH_2Cl_2	3	50	23
7	Ph(**1b**)	**2e**	CH_2Cl_2	5	68	30
8	Ph(**1b**)	**2f**	CH_2Cl_2	6	39	30
9	Ph(**1b**)	**2e**	$CHCl_3$	6	27	20
10	Ph(**1b**)	**2e**	$ClCH_2CH_2Cl$	5	61	31
11	Ph(**1b**)	**2e**	toluene	5	40	28
12	Ph(**1b**)	**2e**	benzene	6	46	37
13	Ph(**1b**)	**2e**	CCl_4	6	43	49
14	Ph(**1b**)	**2g**	CCl_4	2	63	46
15[d]	Ph(**1b**)	**2g**	CCl_4	4	62	56

[a] Reactions were carried out using 0.1 M **1** of unless otherwise noted. [b] Yield of isolated product. [c] Determined by chiral HPLC on a Chiralpak IC column. [d] The reaction was carried out in CCl_4 (0.05 M).

tween **1b** and **2e** was then chosen for use as a model reaction to screen the solvent;[13] carbon tetrachloride was found to be the best solvent for this reaction. Although an enantiomeric excess (*ee*) of 49% was obtained, the long reaction time and low yield required optimization. Comparing entry 7 with entry 8, the reaction of **1b** with **2f** was slower than that with **2e**, but a similar enantioselectivity was obtained. An 1-adamantyl substituent at the *para*-position of the aromatic ring in **2f** is sterically more bulky than the isopropyl group at the *para*-position of the aromatic ring in **2e**. Therefore, we considered that a bulky substituent at the *para*-position of the aromatic ring in **2e** and **2f** might not be necessary. Next, we synthesized *N*-triflyl phosphoramide **2g** without a substituent at the *para*-position of the aromatic ring. To our delight, when **1b** was treated with **2g** in carbon tetrachloride under the conditions described above, a 63% yield and 46% enantioselectivity were obtained within two days. Although there was a minor decrease in enantioselectivity, the reaction rate was much faster (Table 1, entry 14). When the concentration of **1b** was decreased to 0.05 M, a 62% yield and 56% enantioselectivity were obtained within four days (Table 1, entry 15).

With the optimal reaction conditions in hand, a series of 2-substituted-2-azidopropyl 1,3-hexanediones were prepared to examine their reactivity toward enantioselective desymmetrization in the intramolecular Schmidt reaction

Table 2. Chiral Brønsted acid-promoted asymmetric intramolecular Schmidt reaction for desymmetrization of 2-substituted-2-azidopropyl 1,3-hexanediones.

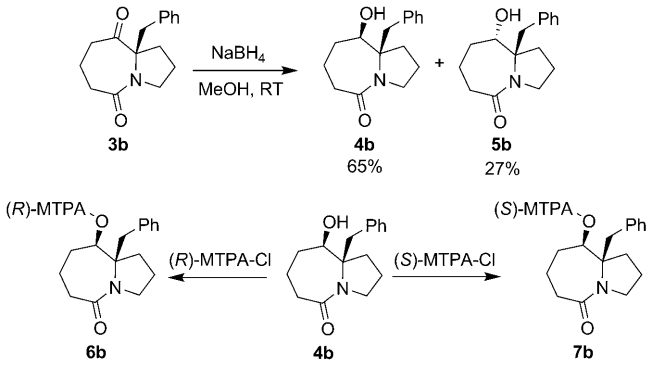


Entry	R	*t* [d]	Yield [%][a]	*ee* [%][b]
1	H(**1a**)	1	54	41
2	Ph(**1b**)	4	62	56
3	Cyclohexyl(**1c**)	2	53	39
4	$PhCH_2$(**1d**)	4	88	55
5	4-BrC_6H_4(**1e**)	4	58	53
6	3-BrC_6H_4(**1f**)	4	58	54
7	2-BrC_6H_4(**1g**)	3	33	57
8	2-FC_6H_4(**1h**)	4	65	58
9	2-MeC_6H_4(**1i**)	4	44	58
10	1-naphthyl(**1j**)	4	51	50
11	2-$CF_3C_6H_4$(**1k**)	3	16	47
12	3,5-Cl_2 C_6H_3(**1l**)	3	18	59

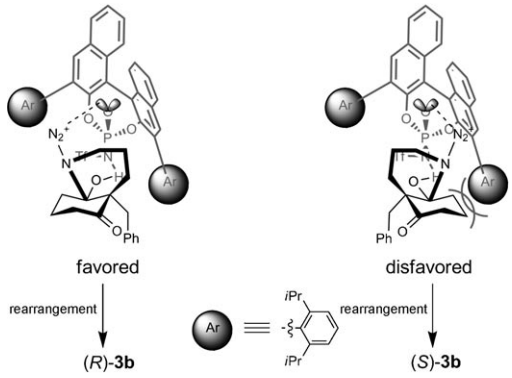
[a] Yield of isolated product. [b] Determined by HPLC on Chiralpak IC or Chiralcel OD-H column.

(Table 2). Substrates bearing an aryl substituent exhibited better enantioselectivity than substrates without an aryl substituent (Table 2, entries 1 and 3 compared with entries 2 and 4–12). The enantioselectivity depended slightly on the substitution of the aryl substituent of the azido 1,3-hexanediones. For example, substrates **1g–1i**, which contained bromine, fluorine, or methyl groups at the *ortho*-position of the aryl substituent, gave slightly better enantioselectivity (Table 2, entries 7–9). In contrast, lower enantioselectivity was obtained for aryl substituents possessing an electron-withdrawing group at the *ortho*-position (Table 2, entry 11). A bulky substituent at the *ortho*-position of the aryl substituent caused a dramatic decrease in the yield of the Schmidt reaction because of decomposition of the substrate (Table 2, entries 7, 9, 11, and 12). The highest enantioselectivity was achieved for substrate **1l**, albeit in low yield (Table 2, entry 12). Although a stoichiometric amount of chiral acid **2g** was used in the reaction, about 80% of the acid could be recovered afterwards. After acidification, the recovered chiral acid **2g** exhibited similar reactivity and enantioselectivity in the Schmidt reaction.

The absolute configuration of product (*R*)-**3b** was determined by Mosher's method using ^{19}F NMR spectroscopy.[14] As shown in Scheme 1, first, chemoselective reduction of **3b** with sodium borohydride gave diastereomeric alcohols **4b** and **5b**, and the major product was confirmed to be the *cis*-isomer by analysis of the X-ray crystal structure (Figure 1).[15] Then, the *cis*-isomer (**4b**) was esterified with (*R*)-α-methoxy-α-trifluoromethylphenylacetyl chloride ((*R*)-MTPA-Cl) and (*S*)-MTPA-Cl to give the corresponding Mosher esters **6b** and **7b**. The ^{19}F signal of the major isomer of **6b** appeared at 5.357 ppm, while in the spectrum of **7b** it appeared at 5.312 ppm.[16] The configuration-correlation models of the Mosher esters are shown in Figure 2. These



Scheme 1. Chemoselective reduction of **3b** and esterification of the *cis*-isomer with Mosher's reagent.



Scheme 2. Proposed models of chiral Brønsted acid-promoted enantioselective desymmetrization through the intramolecular Schmidt reaction.

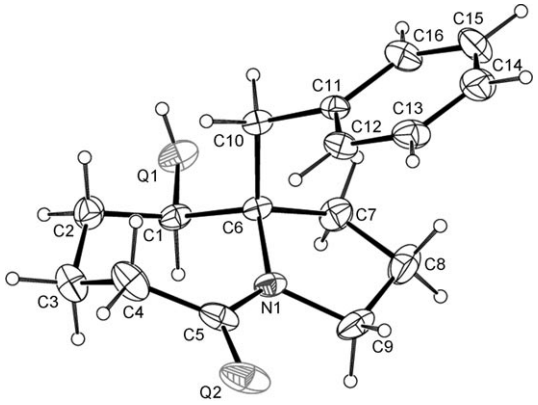


Figure 1. X-ray structure of (±)-**4b.**

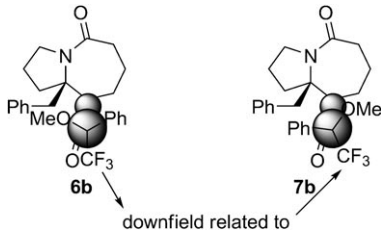


Figure 2. Configuration-correlation model of **6b** and **7b**.

observations are in agreement with an (*R*)-configuration for **4b** at the secondary alcohol position, thereby indicating that the absolute configuration of **3b** is (*R*). The absolute configuration could be explained by the proposed reaction models shown in Scheme 2, which were devised from models of chiral phosphoric acid-catalyzed desymmetrization of *meso*-1,3-diones calculated by Akiyama et al.[17] In the reaction models, on one hand, the acidic proton of the chiral phosphoramide activated one of the carbonyl groups of the substrate; on the other, an n→π* interaction may exist between an oxygen lone pair (highest occupied molecular orbital) of the chiral phosphoramide and π* (lowest unoccupied molecular orbital) of the N≡N bond. These interactions could stabilize the transition state and the favored one would lead to the formation of the (*R*)-configuration of **3b**.

In conclusion, we have synthesized chiral phosphoramide **2g** and found that it was an effective promoter for enantioselective desymmetrization in the intramolecular Schmidt reaction of symmetric azido 1,3-hexanediones to yield chiral azaquaternary pyrroloazepine skeletons. Although only moderate enantioselectivity was obtained, it successfully demonstrates for the first time that enantioselective desymmetrization of symmetric azido 1,3-diketones through an intramolecular Schmidt reaction is a viable process using a chiral Brønsted acid. Further investigation into other effective chiral inducers for this reaction to improve the enantioselectivity, range of substrates, and the use of chiral acid **2g** as a catalyst in other reactions are ongoing.

Experimental Section

A typical procedure for the intramolecular Schmidt reaction is as follows

An azido 1,3-hexanedione substrate (**1a–l**; 0.1 mmol, 1.0 equiv) was dissolved in dry CCl_4 (2 mL) in a flame-dried flask, and then phosphoramide **2g** (0.15 mmol, 1.5 equiv) was added under argon. The reaction mixture was stirred at room temperature. After completion of the reaction, the crude reaction mixture was evaporated, preabsorbed on silica gel, and then purified by column chromatography on silica gel (eluent of petroleum ether/ethyl acetate (4:1–1:1)) to recover phosphoramide **2g** and afford the product mixed with a small quantity of **2g**. The crude product was subjected to further column chromatography on basic alumina and eluted with petroleum ether/ethyl acetate (1:1) to afford the desired product in high purity.

Acknowledgements

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Keywords: alkaloids · asymmetric synthesis · desymmetrization · enantioselectivity · intramolecular Schmidt reaction

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[15] CCDC 804165 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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