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Dysprosium(III) catalyzed formation of hexahydrofuro[3,2-*c*]quinolines via 2:1 coupling of dihydrofuran with substituted anilines

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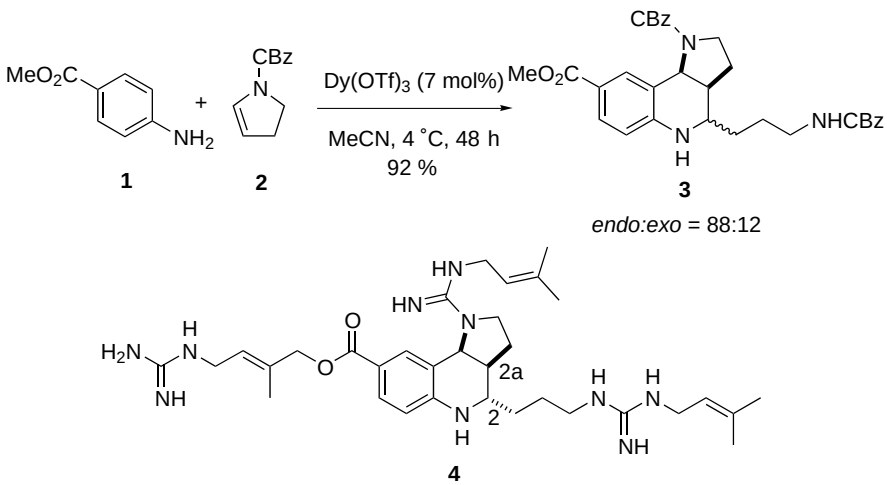
Abstract—A novel dysprosium(III) catalyzed 2:1 coupling reaction between substituted anilines and 2 equiv. of dihydrofuran that yields substituted hexahydrofuro[3,2-*c*]quinolines is described. The reaction proceeds via a formal Diels–Alder process between an in situ generated 2-azadiene with another equivalent of dihydrofuran and may proceed either through a stepwise or an asynchronous concerted mechanism. © 2001 Published by Elsevier Science Ltd.

The hetero Diels–Alder[1] reaction of 2-azadienes and electron rich olefins provides an efficient means for the synthesis of six-membered nitrogen containing heterocycles. The use of *N*-aryl imines as dienes in the Lewis or Brønsted acid promoted formal imino Diels–Alder cycloaddition with nucleophilic alkenes was first explored by Povarov and co-workers in the mid 1960s.[2] Since then numerous groups[3] have exploited this powerful methodology for the construction of functionalized quinolines[4,5] of various oxidation states. A major development in the field was the introduction by Kobayashi of lanthanide triflates as Lewis acid catalysts for the Povarov reaction.[6] Unlike most Lewis acids which are required in stoichiometric quantities, the lanthanide triflates can be used in catalytic amounts, and offer the additional advantage of being stable to air and water, alleviating the need for rigorous drying of solvents and reagents required with conventional Lewis acids.



Scheme 1.

Keywords: quinolines; hetero Diels–Alder; lanthanides; imines; oxonium ions; oxepins; multi-component coupling.

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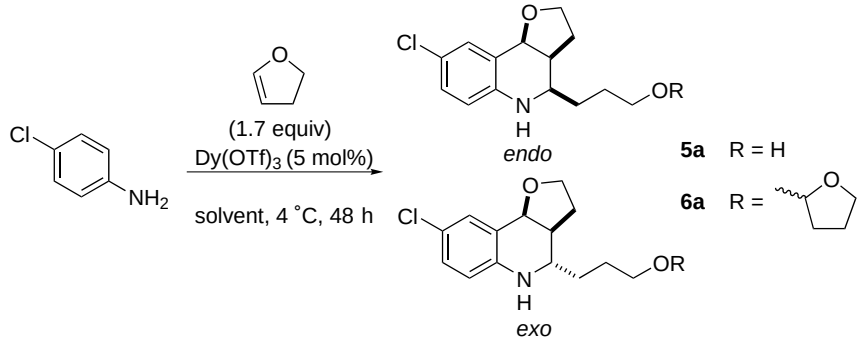
Table 1. Solvent effect on the formation of furoquinolines **5a** and **6a**



Solvent	Yield **5a** (%)[a]	Yield **6a** (%)[a]	*endo:exo*[b]
MeCN	81	<5[c]	76:24
Acetone	65	5	76:24
THF:H_2O (9:1)	<5[c,d]	–	–
THF	36	17	74:26
CH_2Cl_2	14	55	76:24
Toluene	65	14	92:8

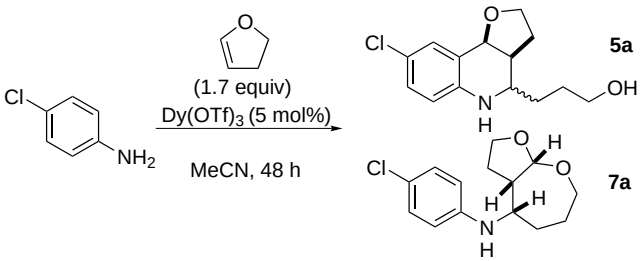
[a] Isolated yields based on DHF.
[b] Determined by ^{1}H NMR of crude reaction mixture for **5a**. Diastereoselectivities of **5a** and **6a** are identical within 5%.
[c] Only observed in the crude ^{1}H NMR.
[d] Unreacted aniline remains.

We recently reported the novel $Dy(OTf)_3$ catalyzed coupling reaction of methyl 4-aminobenzoate **1**, with 2 equiv. of an endocyclic enamine **2** to afford the substituted hexahydropyrrolo[3,2-*c*]quinoline **3** as a mixture of *endo* and *exo* diastereomers[7] (Scheme 1).[8] This methodology forms the basis of our continuing efforts towards a biomimetic synthesis of the natural product martinelline[9] **4**, as well as for combinatorial library synthesis using multi-component Povarov reactions (Scheme 1).

With the growing demand for facile and expedient syntheses of novel and adaptable scaffolds for pharmaceutical development, we elected to examine further the scope of this reaction. We were interested to establish whether other electron rich heteroatom analogues of **2** would also undergo this 2:1 coupling and our attention turned to cyclic enol ethers, particularly dihydrofuran (DHF) which is often utilized in the Povarov reaction.

To our delight the 2:1 coupling reaction proceeded as anticipated with $Dy(OTf)_3$ as a catalyst (Table 1). Thus, reaction between 4-chloroaniline and DHF (1.7 equiv.)[10] in the presence of 5 mol% $Dy(OTf)_3$ gave hexahydrofuro[3,2-*c*]quinoline **5a** as a mixture of *endo* and *exo* stereoisomers. The reaction proceeds well in polar aprotic solvents, such as acetone and MeCN, giving an approximately 3:1 mixture of *endo* and *exo* diastereomers. Reaction in less polar solvents such as THF and CH_2Cl_2 results in the formation of **5a** and protected adduct **6a**.[11] The diastereomeric ratios are similar in the various solvents examined, except for toluene, for which the *endo* diastereomer is favored over the *exo* 92:8. Relatively few reports have appeared on the use of lanthanide trichlorides as catalysts for C–C bond forming reactions,[12] however $GdCl_3$ has been used as a catalyst in the three component Povarov reaction.[13] We have also found that $DyCl_3{\cdot}6H_2O$[14] (5 mol%) catalyzes the reaction of 4-chloroaniline and DHF at 25°C for 48 h in MeCN to afford **5a** in 78% yield with an *endo*:*exo* ratio of 64:36.

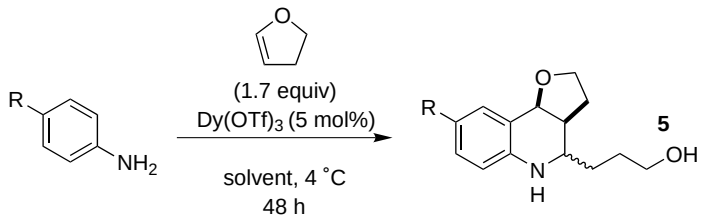
Table 2. Role of temperature on the diastereoselectivity of **5a** and emergence of **7a**



Temp (°C)	Yield **5a** (%)[a]	*endo:exo*[b]	Yield **7a** (%)[a]	Combined ratio
−60[c]	<5[d,e]	–	–	–
−30[f]	63	82:18	20	62:36
4	81	76:24	10	68:32
25	76	64:36	–	64:36
50	86	62:38	–	62:38
75	85	62:38	–	62:38

[a] Isolated yields based on DHF.
[b] Determined by ^{1}H NMR of the crude reaction mixture.
[c] Reacted for 6 days.
[d] Only observed in the crude ^{1}H NMR.
[e] Unreacted aniline remains.
[f] Reacted for 3 days.

Table 3. Formation of substituted tetrahydroquinolines via 2:1 coupling reaction



R	Solvent	Yield **5** (%)[a]	Product	*endo*:*exo*[b]
Cl	MeCN	81	**a**	76:22
	Toluene	65		92:8
Br	MeCN	81	**b**	66:34
	Toluene	76		92:8
I	MeCN	90	**c**	64:36
	Toluene	86		82:18
NO_2	MeCN	84	**d**	58:42
	Toluene	33		74:26
OMe	MeCN	86	**e**	76:24
	Toluene	64		76:24
COOMe	MeCN	76[c]	**f**	>98:2

[a] Isolated yields based on DHF.
[b] Determined by ^{1}H NMR of the crude reaction mixture.
[c] Oxepin **7f** was isolated in 4% yield along with 6% *endo* **6f**.

In an effort to improve the diastereoselectivity of the reaction, the role of temperature was examined (Table 2). From 25 to 75°C the yield and diastereoselectivity of the reaction varies very little. Upon cooling however, a noticeable effect on the diastereomeric ratio of **5a** takes place, accompanied by the emergence of a single diastereomer of a new product **7a**, a furo[2,3-*b*]oxepin, the stereochemistry of which was determined by 2D ^{1}H NOE studies. Importantly, when **7a** was reacted with 5 mol% $Dy(OTf)_3$ in MeCN at room temperature for 12 h the *exo* diastereomer **5a** was obtained exclusively and in quantitative yield, suggesting that formation of the oxepin is reversible and that *exo*-**5a** and **7a** arise from a common intermediate. With the inclusion of oxepin **7a** into the amount of *exo* adduct **5a** formed, the diastereomeric ratios in Table 2 now remain similar over the entire temperature range examined.

With an adequate set of conditions in hand,[15] a variety of substituted anilines were tested under the optimized reaction conditions (Table 3). The 4-halo substituted anilines were reacted with DHF and 5 mol% $Dy(OTf)_3$ at 4°C for 2 days giving good yields of the coupled products **5a**–**c**. A pronounced improvement in the stereoselectivity in favor of the *endo* diastereomer was observed upon switching from MeCN to toluene. Other electron poor (Table 3, **5d**, **5f**) and electron rich substrates (Table 3, **5e**) gave good yields of the coupled product **5** as a mixture of diastereomers, in all cases favoring the *endo* diastereomer. Once again, with substrate **5d**,[16] a change in the solvent from MeCN to toluene resulted in diastereoselection in favor of the *endo* adduct. Interestingly for the electron rich 4-anisidine substrate **5e** no such change was observed. Remarkably, methyl 4-aminobenzoate gave a greater than 98:2 diastereoselectivity for the *endo* adduct **5f, which** was obtained in 76% yield along with 6% of *endo*-**6f** and 4% of oxepin **7f**.

X-Ray crystallography[17] of **5f** (Fig. 1) confirmed this product to be the *endo* diastereomer and validated the stereochemical assignment for the other diastereomers of **5a**–**e**.

Oxepin **7f**, which was also analyzed by X-ray crystallography,[17] (Fig. 2) showed identical relative stereochemistry to oxepin **7a** which was assigned earlier based on 2D ^{1}H NOE studies.

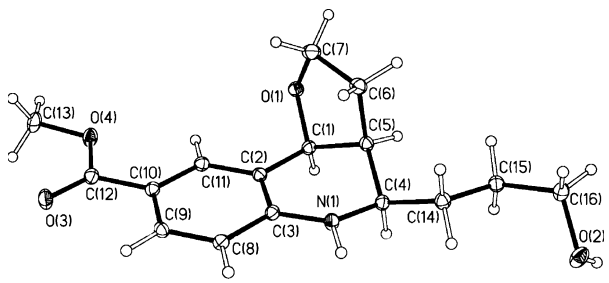


Figure 1. ORTEP drawing of **5f** with 30% thermal ellipsoids.

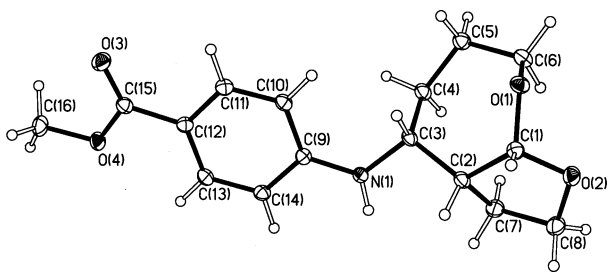


Figure 2. ORTEP drawing of **7f** with 30% thermal ellipsoids.

Mechanistically, the reaction presumably proceeds through a formal hetero Diels–Alder reaction between a 2-azadiene **8**, formed on condensation of the aniline with the in situ hydrolysis product of DHF,[18] with another equivalent of DHF. Several researchers have probed the mechanistic details of the reaction between benzilidene anilines and nucleophilic alkenes, and both concerted and stepwise mechanisms have been suggested.[3b,c,6b]

The diastereoselectivity of the reaction is controlled by the initial C–C bond formation between C-4 of DHF and the sp^2 carbon of the *N*-aryl imine **8** (i.e. bond *a*, Fig. 3). The second bond formation (i.e. bond *b*) between C-5 of DHF and C-2 of the aromatic ring, may be concerted with the first C–C bond forming step, or may occur in a stepwise manner. The concerted pathway may be favored in non-polar solvents, although it is still likely that the new C–C bonds are formed in an asynchronous manner. Formation of **7** indicates that a stepwise mechanism must also operate, via an oxonium ion intermediate **9**. The oxonium intermediate can react with the aromatic nucleophile or be trapped by the alcohol side chain, leading to the formation of **5** or **7**, respectively. An analogous process presumably occurs in the *endo* series, although it should be noted that no oxepins of this relative stereochemistry were isolated.

Whilst the formation of adducts **5** involves the reaction of just two different components, the reactions can be viewed as a special case of a multi-component coupling reaction, since the 2 equiv. of DHF serve very different roles. With the growing importance of multi-component and other coupling reactions, we propose the following nomenclature to distinguish reactions in which one of the components is incorporated more than once, as in the reaction of a molecule ***A*** with 2 equiv. of a molecule ***B***. Reactions in which each component reacts in a different manner, as above, can be categorized as ***ABB*** couplings. Whereas, an ***AB²*** coupling can be defined as those in which the 2 equiv. of molecule ***B*** react in a similar manner.

In conclusion, we have demonstrated the Dy(III) catalyzed formal hetero Diels–Alder reaction of substituted anilines with 2 equiv. of DHF to give hexahydrofuro[3,2-*c*]quinolines **5**. In view of the widespread use of DHF as an electron rich dienophile in the Povarov reaction it is surprising that these products have never been reported. The reaction is quite general and works for both electron rich and electron poor anilines. The formation of oxepins **7** suggest the reaction proceeds, at least in part, via a stepwise mechanism. Studies into other electron rich alkenes which can participate in this novel 2:1 coupling reaction, the use of chiral ligands for asymmetric synthesis, and further mechanistic studies are being actively pursued within our laboratories.

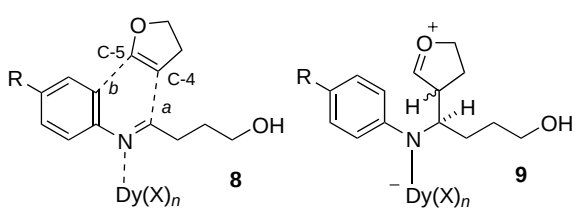


Figure 3.

Acknowledgements

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7. The *endo* and *exo* diastereomers are defined based on the Diels–Alder reaction, where H-2 and H-2a have a *cis* and *trans* relationship, respectively. (Numbering system based on **4**, Scheme 1).
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10. DHF was used as the limiting reagent in order to minimize the formation of protected adducts **6**.
11. Compound **6a** was characterized as a mixture of diastereomers.
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14. The more cost effective $Dy(OTf)_3$ ($1920/mol Dy) was initially chosen over the more commonly utilized $Yb(OTf)_3$ ($4768/mol Yb). $DyCl_3 \cdot 6H_2O$ ($326/mol Dy) however, is significantly cheaper than both of these catalysts. (Sigma-Aldrich 2001 $US)
15. *Representative procedure for the formation of* ***5***, ***6*** *or* ***7***: A solution of the substituted aniline (1.80 mmol) and $Dy(OTf)_3$ (47 mg, 0.08 mmol) in the corresponding solvent (5 mL) and temperature (see Tables 1–3) was treated with DHF (3.00 mmol, 227 μL). The reaction was stirred for 48 h then poured into a 5% aqueous solution of $NaHCO_3$ (25 mL) and extracted with EtOAc (3×10 mL). The organic layer was washed with brine (25 mL), dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel chromatography using hexanes/EtOAc. **(3a*S***,4*S***,9b*S***)-3-(8-Chloro-2,3,3a,4,5,9b-hexahydro-furo[3,2-*c*]quinolin-4-yl)-propan-1-ol (*endo* 5a).** Obtained as a clear oil 232 mg (58% yield). $R_f = 0.13$ (50:50 hexanes/EtOAc). IR (film) ν 3356, 2936, 1605, 1488, 1305 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.23 (1H, d, $J = 2.5$ Hz), 6.94 (1H, dd, $J = 8.5$, 2.5 Hz), 6.41 (1H, d, $J = 8.5$ Hz), 5.02 (1H, d, $J = 8.0$ Hz), 3.77 (2H, dd, $J = 8.5$, 3.0 Hz), 3.68 (2H, t, $J = 5.5$ Hz), 3.43–3.39 (1H, m), 2.62–2.54 (1H, m), 2.01–1.91 (1H, m), 1.88–1.80 (1H, m), 1.69–1.55 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.3, 129.5, 128.1, 124.0, 122.9, 115.6, 75.3, 66.7, 62.4, 52.2, 42.1, 30.7, 28.9, 23.7. MS (EI) m/e 267 (M^+, 53), 210 (45), 208 (100), 164 (24). HRMS (EI) m/e (M^+) calcd 267.1026, found 267.1035.
16. Diastereomers of **5d** and **5e** could not be separated by silica gel chromatography. As such they were converted to their TBDMS ethers followed by chromatography to give protected adducts of *endo* **5d**, *exo* **5d**, *endo* **5e** and *exo* **5e** in 39, 24, 69 and 20% yield, respectively.
17. Crystallographic data for the structure **5f** and **7f** have been deposited at the Cambridge Crystallographic Data Centre, deposition numbers 167030, 167031. Copies of the data can be obtained in application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. [fax +44(0)-1223-336033; e-mail: deposit@ccdc.cam.ac.uk).
18. Alternatively the 2-azadiene may form from direct addition of aniline to protonated DHF followed by ring opening.