



Lanthanide(III)-catalyzed multi-component aza-Diels–Alder reaction of aliphatic *N*-aryaldimines with cyclopentadiene[☆]

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This paper is dedicated to our friend and colleague, Professor William F. Reynolds, on the occasion of his 65th Birthday

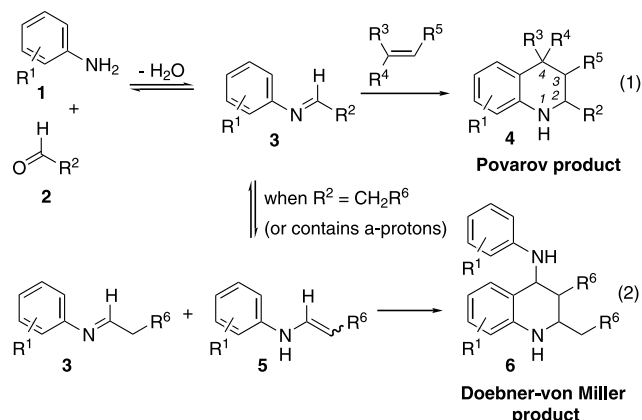
Abstract—The Ln(OTf)₃-catalyzed formal aza-Diels–Alder (or Povarov) reaction of cyclopentadiene with in situ generated *N*-arylimines containing enolizable protons is described. This three-component Povarov reaction generates highly functionalized C-2 aliphatic substituted tetrahydroquinolines, heterocycles that were previously inaccessible using the Povarov reaction, because of the instability of the intermediate aliphatic *N*-aryaldimine.

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The formal aza-Diels–Alder reaction¹ of electron rich olefins with *N*-arylimines (the Povarov reaction²) is a powerful and efficient means for the construction of substituted tetrahydroquinolines.³ This reaction has been extensively exploited by the synthetic community for the synthesis of quinolines of varying oxidation states,⁴ with numerous advances having been made since its initial disclosure over 40 years ago. The most notable advance has been the use of mild and water tolerant Lewis acid and protic acid catalysts, for the three-component coupling reaction,⁵ wherein an aniline **1** and aldehyde **2**, serve to generate an intermediate *N*-arylimine **3** in situ, which is then converted into tetrahydroquinoline **4** (Scheme 1).^{3,6}

Despite the utility of the Povarov reaction, there remain some limitations in the type of substrates that are amenable to the reaction, particularly with respect to the aldehyde component. Traditionally, aromatic aldehydes and those aldehydes that do not contain α -protons (**2**, R²=aryl, H, CO₂R, etc.) have been used as coupling partners for the synthesis of Povarov product **4**.⁷ The use of aliphatic aldehydes with enolizable protons in the Povarov reaction (**2**, R²=CH₂R⁶) has been severely limited due to the problems associated with the

synthesis, isolation and stability of the aliphatic *N*-arylimine **3** intermediates. Competitive isomerization of the aliphatic imine **3** to an enamine **5**, and self-condensation of this electron-rich dienophile with another equivalent of the *N*-arylimine leads to the formation of Doebner–von Miller type intermediates **6**,^{8–10} which can also be considered to arise from a formal aza-Diels–Alder process (Scheme 1). Consequently, only a handful of examples of Povarov reactions utilizing aliphatic aldehydes have appeared in the literature. For example, Kobayashi described two examples in which 2-cyclohexane carboxaldehyde was used as the aldehyde component in the three-component Povarov reaction.⁶ Recently, Beaton has coupled aliphatic aldehydes in the

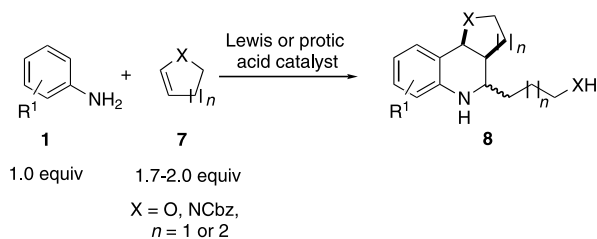


Scheme 1.

Keywords: quinolines; aza-Diels–Alder; Povarov reaction; lanthanides; multi-component coupling.

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Scheme 2. 2:1 Povarov reaction.

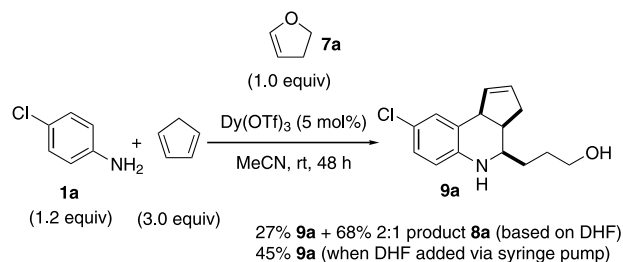
three-component Povarov reaction using a ketene dithioacetal dienophile; however the reaction required the use of stoichiometric amounts of $\text{Sc}(\text{OTf})_3$ and high temperatures (65°C).³ⁱ There is a need, therefore, for the development of a mild and general protocol for the coupling of aliphatic aldehydes in the Povarov reaction. This would significantly increase the range of compounds accessible through the Povarov reaction, beyond the already well-established C-2 aryl substituted tetrahydroquinolines. Herein we describe our efforts towards this goal using aliphatic aldehydes containing enolizable protons, and their synthetic equivalents.

Our interest in Povarov reactions using aliphatic aldehydes containing enolizable protons area was sparked by our discovery of a 2:1 Povarov reaction of aniline **1** with 2 equiv. of a cyclic enol/protected enamine **7** for the synthesis of 2,3,4-trisubstituted tetrahydroquinolines **8** (Scheme 2).¹¹ The products **8** result from an *ABB'* coupling in which one component, **7**, fulfills two different roles in the reaction. The incorporation of a C-2 aliphatic moiety onto the tetrahydroquinoline core prompted us to examine the use of aliphatic aldehydes in the *ABC* Povarov reaction. In particular, we envisaged that use of a masked aldehyde such as **7** may minimize the formation of the otherwise expected Doebner–von Miller type intermediates **6** (i.e. *AA'BB'* coupling products), thereby allowing access to C-2 aliphatic substituted tetrahydroquinolines, structures that are difficult to obtain using existing Povarov methodologies.

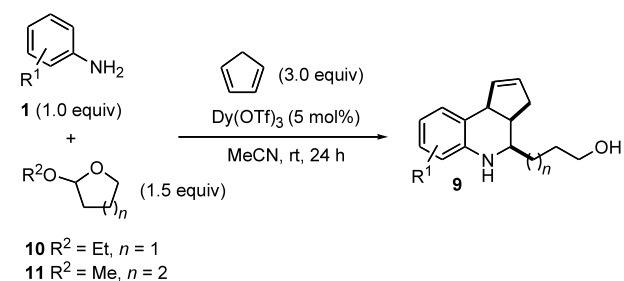
To probe conditions suitable for the coupling of aliphatic aldehydes in the Povarov reaction, we began by examining the three-component coupling reaction between anilines, cyclopentadiene and dihydrofuran **7a** (DHF). Our previous work on the 2:1 Povarov reaction had already demonstrated the ability of DHF to act as aldehyde equivalents (Scheme 2).^{11b} Air and water stable lanthanide triflates¹² were chosen as mild Lewis acid catalysts, in order to minimize protic acid-catalyzed isomerization of **3** to enamine **5**. This is a critical feature, since enamines such as **5** are amongst some of the most reactive dienophiles in the Povarov reaction and upon formation react rapidly with *N*-arylimines **3** to give the undesired Doebner–von Miller type products **6**, even in the presence of a large excess of another dienophile. $\text{Dy}(\text{OTf})_3$, was chosen as a representative lanthanide triflate catalyst, having already been demonstrated to display high catalytic activity in other Povarov reactions. Thus, reaction of 4-chloroaniline **1a**,

DHF and cyclopentadiene in MeCN, in the presence of $\text{Dy}(\text{OTf})_3$ (5 mol%), gave the three-component coupling product **9a** in 27% yield along with 68% of the 2:1 type coupling product **8a** ($\text{R}^1 = \text{Cl}$, $\text{X} = \text{O}$, $n = 1$) (Scheme 3). The cycloaddition product **9a** was obtained as a single, all *cis*, diastereomer, arising from *endo* addition (assuming a formal Diels–Alder reaction mechanism). This diastereomer was assigned based on comparison to similar compounds¹¹ and the H2–H3 and H3–H4 coupling constants (typically $J_{\text{H2-H3}} = 2\text{--}3$ Hz and $J_{\text{H3-H4}} = 8\text{--}9$ Hz). An excess of cyclopentadiene is required in order to obtain sufficient quantities of adduct **9a**; however, the yields for this product remain low, due to competitive trapping of the in situ generated *N*-arylimine with the DHF dienophile. To combat this side reaction, DHF was added slowly, via syringe pump, to a solution of cyclopentadiene and aniline in MeCN. Under this protocol the corresponding three-component coupling product **9a** was obtained in 45% yield, with only a small amount (<10%) of **8a** observed in the ^1H NMR spectra of the crude reaction mixture (Scheme 3).

We rationalized that in order to further minimize the competitive formation of 2:1 Povarov adduct **8**, the propensity of DHF to act as a dienophile would need to be reduced. As such, we chose to use 2-ethoxytetrahydrofuran **10**, as a masked equivalent of DHF, since although it does act as a competent reactant for 2:1 Povarov reactions, its reaction with anilines to generate an intermediate *N*-arylimine should occur faster than elimination of ethanol to generate DHF, thus enhancing the selectivity of **9** over **8**. As envisaged, $\text{Dy}(\text{OTf})_3$ (5 mol%) catalyzed reaction of 4-chloroaniline, cyclopentadiene and 2-ethoxytetrahydrofuran **10** (added slowly via syringe pump over 8–10 h), exclusively generated the all *cis* (*endo*) diastereomer **9a** in 63% yield (Table 1).¹³ Reaction of 2-methoxytetrahydropyran **11** was far more sluggish, giving the three-component coupling product **9b** in only 18% yield (Table 1). The reaction with **10** proceeds well for most substituted anilines, in all cases giving **9** as a single diastereomer (Table 1, **9c–9h**). Exceptions to this occurred using either 2-aminophenol or 4-methoxyaniline, which both failed to give significant yields of product. This result is perhaps not too surprising, given that electron-donating groups raise the LUMO of the *N*-arylimine and reduce the rate of the inverse electron demand Diels–Alder reaction.



Scheme 3. Three-component coupling reaction of 4-chloroaniline with cyclopentadiene and DHF.

Table 1. Formation of tetrahydroquinolines **9** from the three-component coupling reaction of anilines **1**, cyclopentadiene and masked aldehydes **10** and **11**

R^1	n	Product	d.r. ^a	Yield (%) ^b
4-Cl	1	9a	>95:5	63
4-Cl	2	9b	>95:5	18
2-Cl	1	9c	>95:5	67
4-Br	1	9d	>95:5	71
H	1	9e	>95:5	52
4-CO ₂ Me	1	9f	>95:5	65
4-Ph	1	9g	>95:5	61
4-CF ₃	1	9h	>95:5	51
2-OH	1	—	n.d.	<20% ^c
4-OCH ₃	1	—	—	no rxn

^a Determined by ¹H NMR ($\pm 5\%$). ^b Isolated yield after column chromatography. ^c Observed in the ¹H NMR spectra of the crude reaction mixture.

The success of the slow addition protocol using masked aldehydes **10**, prompted us to consider whether this methodology could be directly applied to aliphatic aldehydes **2** containing enolizable protons. These aldehydes were indeed found to be suitable coupling partners in the three-component Povarov reaction with cyclopentadiene, leading to the formation of tetrahydroquinolines **12** (Table 2). In order to minimize self-condensation of the intermediate aliphatic *N*-arylimines into Doebner–von Miller type products, the concentration of the *N*-aryl aliphatic aldimine should be kept low. As such, the aza-Diels–Alder reaction was carried out by the *slow* addition of the aldehyde **2** (1.5 equiv.), via syringe pump (over 6–8 h), to a solution of aniline **1** (1.0 equiv.), cyclopentadiene (3.0 equiv.) and Dy(OTf)₃ (5 mol%) in MeCN. Several aliphatic aldehydes were successfully utilized in this manner, giving the desired tetrahydroquinoline products **12** in good to excellent yields. In each case the *endo* diastereomer was isolated almost exclusively.

A small amount (<10%) of the Doebner–von Miller side-product **6** was observed by TLC and in the ¹H NMR of the crude reaction mixtures for most of the reactions described in Table 2. Analysis of these side products was complicated on account of the number of possible diastereomers of **6** and the difficulty in distinguishing the ring protons from the other aliphatic protons. Analysis was however possible for the reaction utilizing phenylacetaldehyde (**2**, $\text{R}^2 = \text{CH}_2\text{C}_6\text{H}_5$), where

Table 2. Formation of tetrahydroquinolines **12** from the three-component coupling reaction of anilines **1**, cyclopentadiene and aliphatic aldehydes **2**

R^1	Aldehyde 2	Product	d.r. ^a	Yield (%) ^b
Br		12a	>95:5	58
Br		12b	>95:5	64
Br		12c	>95:5	72
Br		12d	>95:5	59 (+ 8% 6a)
Br		12e	>95:5	82
CO ₂ Me	"	12f	>95:5	92
NHAc	"	12g	>95:5	60
Br		12h	1:1	54
Br	"	12h	4.8:1	81 ^c

^a Determined by ¹H NMR ($\pm 5\%$). ^b Isolated yield after column chromatography. ^c Reaction was carried out using Sc(OTf)₃ (7 mol%) in CH₂Cl₂ at -30 °C in the presence of powdered 4 Å MS.

compound **6a** ($\text{R}^1 = \text{Br}$, $\text{R}^6 = \text{C}_6\text{H}_5$) was isolated and characterized. A single diastereomer was isolated and assigned as 2,3-*trans*-2,4-*cis* on the basis of the H-3 proton which appeared as a triplet with a coupling constant of 10.0 Hz, indicative of protons H-2, H-3, and H-4 all occupying pseudo-axial positions. A small amount of the other diastereomers may have been present, but were not isolated during chromatography.¹⁴

The use of a chiral aldehyde in the three-component Povarov reaction was also examined. Treatment of a mixture of 4-bromoaniline, cyclopentadiene and Dy(OTf)₃ (5 mol%) in MeCN with the dimethylacetone of (*R*)-glyceraldehyde gave a 1:1 mixture of *endo* diastereomers in 54% combined yield (Table 2, **12h**). The diastereoselectivity could be improved to 4.8:1 by carrying out the reaction in CH₂Cl₂ at lower temperatures (-30°C) in the presence of powdered 4 Å molecu-

lar sieves and using a more reactive $\text{Sc}(\text{OTf})_3$ catalyst (7 mol%). The absolute stereochemistry of the major diastereomer, assigned on the basis of X-ray crystallography, was determined to be 3a*S*,4*R*,9*bR*. This result is in accord with reaction occurring through a 6-membered chelate between the arylaldimine nitrogen, scandium(III) catalyst and the distal ketal oxygen.

In summary, we have accomplished a three-component Povarov reaction using aliphatic aldehydes, or cyclic acetals with enolizable protons, substrates that under previous conditions have resulted in the formation of Doebner–von Miller type products. A key finding in these reactions is that the concentration of the in situ generated *N*-arylimine be kept low through slow addition of the aldehyde component. In addition, the use of mildly Lewis acidic lanthanide catalysts minimizes competitive side reactions of these intermediates. In this manner, C-2 aliphatic substituted tetrahydroquinolines can be obtained in good to excellent yield and high diastereoselectivity.

Acknowledgements

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- General procedure for the $\text{Dy}(\text{OTf})_3$ -catalyzed three-component Povarov reaction of anilines with cyclopentadiene and cyclic acetals/aliphatic aldehydes.** Freshly distilled aldehyde or cyclic acetal (1.50 mmol) was dissolved in MeCN (1 mL) and added, via syringe pump, over a period of 6–10 h to a solution of aniline (1.00 mmol), freshly distilled cyclopentadiene (198 mg, 3.00 mmol) and $\text{Dy}(\text{OTf})_3$ (31 mg, 0.05 mmol) in dry MeCN (4 mL). The reaction was stirred at room temperature for 24 h and then poured into a separatory funnel containing H_2O (25 mL) and extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine (20 mL), dried over MgSO_4 , filtered and concentrated in vacuo. The diastereoselectivity of the reaction was determined by ^1H NMR spectroscopic analysis of a small sample of the crude reaction mixture, following filtration through a short plug of silica gel. The crude reaction mixture was purified by silica gel chromatography using hexanes/ Et_3O containing 2% Et_3N (the use of base treated silica gel

ensures reproducible yields and minimizes acid promoted oxidation to quinolines).

14. In a preliminary experiment, we have found that Dy(OTf)₃-catalyzed reaction of 4-bromoaniline with

phenylacetaldehyde results in a 70:30 mixture of 2,3-*trans*-2,4-*cis* and 2,3-*cis*-2,4-*cis* diastereomers **6a** (R¹=Br, R⁶=C₆H₅) in 88% yield. These results mirror those of Fang and co-workers (Ref. 10a).