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Investigation of the asymmetric Birch reduction–alkylation of a chiral 5-arylbenzamide containing a carbamate group

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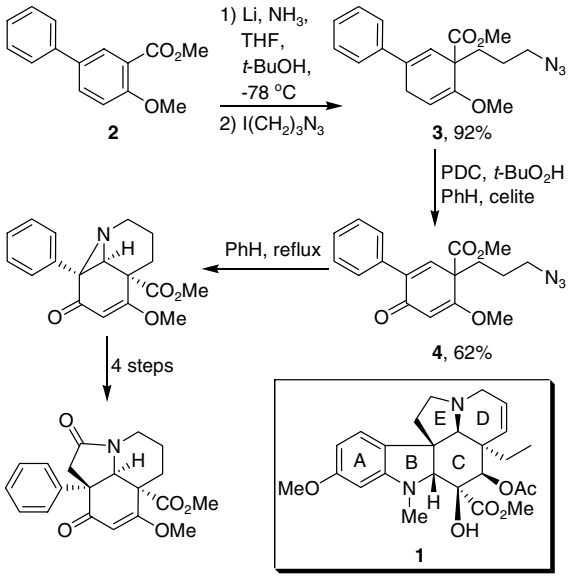
Abstract—The synthesis and asymmetric Birch reduction–alkylation of chiral benzamide **17** are described. Birch reductive alkylation of benzamide **17** was optimized to give the corresponding cyclohexa-1,4-diene products in 66–78% isolated yield and with high diastereoselectivity (dr: >98:2). The effects of performing the reduction in the presence and in the absence of *tert*-butyl alcohol are discussed.

The asymmetric Birch reductive alkylation of chiral nonracemic benzoic acid derivatives has demonstrated ample utility for the synthesis of a variety of natural products.[1] In these applications, chiral 2-alkoxy-, 2-alkyl-, 2-aryl-, and 2-trialkylsilyl-benzamides have been efficiently converted into a variety of optically active cyclohexa-1,4-diene derivatives. Our continuous interest in the application of the Birch reductive alkylation as the key strategic element in natural product synthesis has recently led us to investigate new synthetic methods toward vindoline (**1**). This highly functionalized alkaloid has important medicinal interest because of its biosynthetic and synthetic role as a precursor of the anticancer drugs vincristine and vinblastine.[2] In addition, vindoline has attracted the attention of numerous research groups, and both racemic[3] and asymmetric[4] total syntheses have been reported. Our initial work in this area consisted in the disclosure of an efficient racemic synthesis of the tricyclic core structure of vindoline.[5] Important features of this work include the elaboration of ring C of vindoline by means of a Birch reductive alkylation of 5-phenylbenzoic acid derivative **2** to cyclohexadiene **3** and an intramolecular 1,3-dipolar cycloaddition of azido dienone **4** that was used for the construction of ring D of **1** (Scheme 1).



Scheme 1. Racemic synthesis of tricylic core structure of vindoline.

As an extension to our initial studies, and with the aim of investigating conditions for the development of an asymmetric total synthesis of (+)-vindoline, the Birch reduction–alkylation of chiral benzamide **6** was planned (Scheme 2). Following the chemistry developed in our earlier studies, it was envisioned that Birch reduction of **6** and alkylation of the corresponding enolate with 3-azido-1-iodopropane would provide diene **5** that represents an advanced intermediate for the construction of

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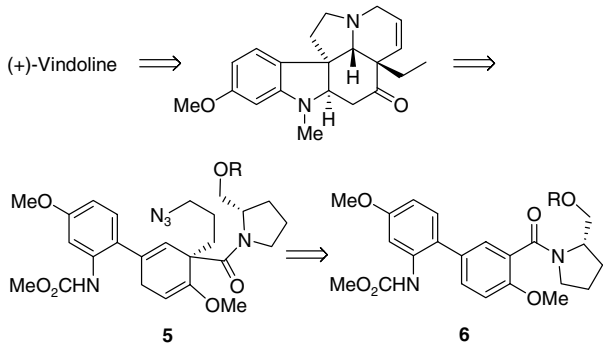
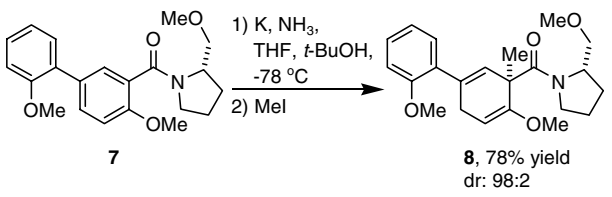


Scheme 2. Proposed disconnection of (+)-vindoline.

rings D and E of (+)-vindoline. The quaternary center created during the asymmetric Birch reduction–alkylation step would direct the stereochemistry in subsequent transformations en route to (+)-**1**. The selection of chiral benzamide **6** for this study was based on the opportunity to incorporate early a 5-aryl substituent that contains all the functionality required for the construction of the indole ring (rings A and B) of vindoline. The early incorporation of the aromatic substituent in the synthesis of aspidosperma alkaloids has received considerable attention from different groups.[6] There was limited information about the asymmetric Birch reduction–alkylation of highly substituted chiral benzamide derivatives like **6**. Previous studies carried out in our laboratories showed that Birch reduction–alkylation of benzamide **7** gave cyclohexadiene **8** in 78% isolated yield and with a diastereomer ratio of 98:2 (Scheme 3).[7] The reasonable asymmetric control established with this prototype model gave support to continue with the proposed study. The selection of the protecting group for the prolinol chiral auxiliary in benzamide **6** would be determined based on ease of synthesis and compatibility with subsequent steps. The effect of the carbamate group on the Birch reduction–alkylation was not completely known when this study was undertaken. Based on our previous experience with the Birch reduction–alkylation of anthranilic acid derivatives containing an ionizable NH group,[8] as is the case of benzamide **6**, the carbamate group was expected to serve as a potential proton donor for the protonation of the radical anion formed after the initial first electron transfer. In this communication, the results of our studies of the asymmetric Birch reductive alkylation are described.

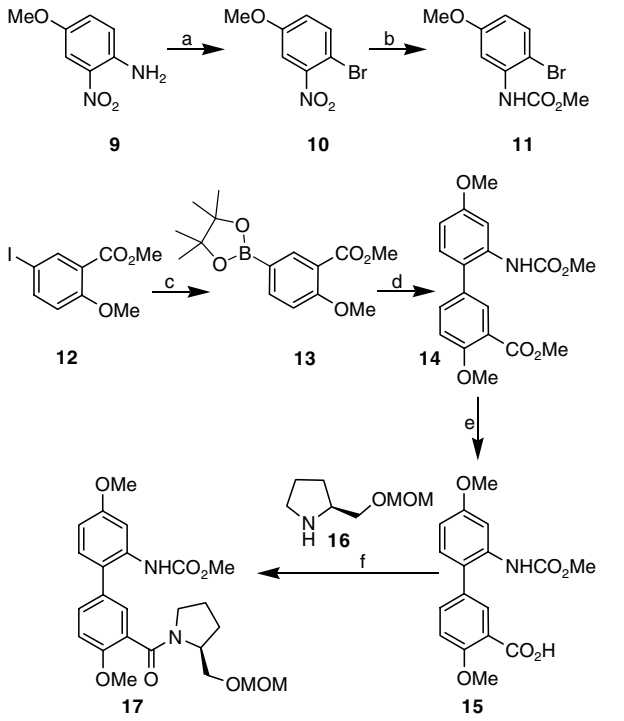
The initial efforts of this study were directed at developing an efficient synthesis of ester **14**. This intermediate would not only serve as a precursor of the desired chiral benzamide, but also Birch reductive alkylation of this



Scheme 3. Asymmetric Birch reductive alkylation of benzamide **7**.

intermediate would provide useful information about the feasibility of this step. After examination of a variety of biaryl coupling techniques, the Suzuki cross-coupling was selected as the most efficient alternative for the preparation of **14**.[9] The preferred synthetic route departs from 4-methoxy-2-nitroaniline (**9**) and iodosalicylate **12** (Scheme 4). Nitroaniline **9** is transformed into bromoanisole **10**[10] via a Sandmeyer reaction in 85% yield following conditions described by Stille and co-workers.[11] Iron–acetic acid reduction of nitroanisole **10** was followed by reaction of the aniline with methyl chloroformate in the presence of potassium carbonate to afford bromide **11** in 92% overall yield.

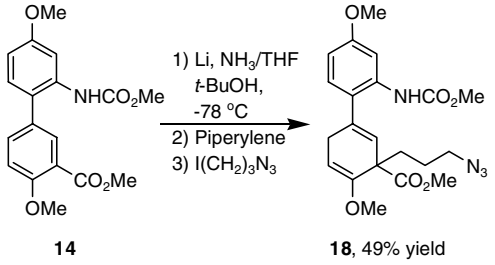
Evaluation of a variety of arylboronic acids and esters for the Suzuki coupling led to the selection of pinacolboronate ester **13** as the most suitable coupling partner. This compound was prepared using the methodology reported by Murata and Masuda.[12] Iodosalicylate **12**[13] was reacted with pinacolborane and triethylamine in the presence of $PdCl_2(PPh_3)_2$ to give boronate ester **13** in 84% yield. Cross-coupling between bromide **11** and **13** was achieved using $Pd(PPh_3)_4$ and 2 M Na_2CO_3 in DME at 80 °C to give ester **14** in 97% isolated yield. Potassium cyanide-catalyzed ester hydrolysis afforded carboxylic acid **15** in 92% yield. As discussed above, previous work with the asymmetric Birch reductive alkylation of chiral 5-arylbenzamides (e.g., benzamide **7**)



Scheme 4. Synthesis of benzamide **17**. Reagents and conditions: (a) (i) HBr, H_2O, 1,4-dioxane, reflux, (ii) $NaNO_2$, H_2O, 0 °C, (iii) CuBr, HBr, 0–60 °C, 85%; (b) (i) Fe, EtOH, AcOH, reflux, (ii) MeOCOCl, K_2CO_3, acetone, reflux, 92%; (c) pinacolborane, $PdCl_2(PPh_3)_2$, Et_3N, 1,4-dioxane, 80 °C, 84%; (d) **11**, $Pd(PPh_3)_4$, 2 M Na_2CO_3, DME, 80 °C, 97%; (e) K_2CO_3, KCN (0.2 equiv), THF-MeOH–H_2O, 80 °C, 36 h, 92%; (f) (i) $(COCl)_2$, cat. DMF, CH_2Cl_2, (ii) **16**, Et_3N, −70 °C to rt, 87%.

was performed using (*S*)-2-methoxymethyl-pyrrolidine as the chiral auxiliary. However, (*S*)-2-methoxymethoxymethyl-pyrrolidine **16**[14] was identified as the preferred chiral auxiliary for this study based on the simplicity for its removal and compatibility with later transformations.[15] In addition, the ratio of diastereomers obtained with these two chiral auxiliaries was identical when they were compared in the Birch reductive alkylation of benzamide derivatives.[16] The incorporation of the chiral auxiliary was accomplished by first reacting carboxylic acid **15** with oxalyl chloride and catalytic DMF to afford the corresponding acid chloride. Without isolation, the acid chloride was reacted with prolinol ether **16** and triethylamine at low temperature to give benzamide **17** in 87% isolated yield.

The Birch reduction–alkylation of ester **14** was investigated first (Scheme 5). Birch reduction of ester **14** with lithium (3.2 equiv) in the presence of *t*-BuOH (1 equiv) in NH_3–THF at −78 °C followed by addition of piperylene (1,3-pentadiene) to consume excess metal and alkylation with 3-azido-1-iodopropane[17] afforded cyclohexadiene **18** in 49% isolated yield. As previously discussed, Birch reduction–alkylation of 5-phenylbenzoic acid derivative **2** proceeded in high yield (92%). Therefore, it appears that the functionality present in the 5-aryl substituent has a strong effect on the yield of the cyclohexadiene product. No optimization of the Birch reductive alkylation of ester **14** was attempted.



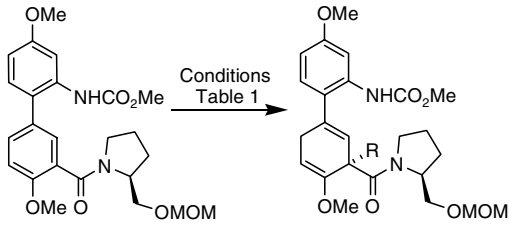
14 **18**, 49% yield

Scheme 5. Birch reductive alkylation of ester **14**.

The asymmetric Birch reduction–alkylation of benzamide **17** was explored next and the results are summarized in Table 1. This reaction was first performed using potassium (7 equiv) in the presence of *t*-BuOH (1 equiv) in NH_3–THF at −78 °C followed by quenching excess metal with piperylene. The enolate was reacted with 3-azido-1-iodopropane to afford **19** in only 30% yield (entry 1). Reducing the amount of potassium to 6.0 equiv furnished a modest improvement in the yield of **19** (entry 2). Further investigation of the Birch reduction conditions led to performing the reaction in the absence of *t*-BuOH (entry 3) and to our delight, a drastic increase in the yield of **19** (70%) was achieved while using a similar amount of potassium (5.2 equiv) for the reduction. The optimal conditions (entry 4) involved performing the reduction of **17** with 3.7 equiv of potassium, in the absence of *t*-BuOH, in THF/NH_3 at −78 °C for 3 h followed by addition of piperylene and then 3-azido-1-iodopropane to provide **19** in 78% yield. This reaction has been performed in multi-gram scale under these conditions to provide **19** in 74–78% isolated yield.

The asymmetric Birch reduction–alkylation of benzamide **17** to cyclohexadiene **20** was also investigated and a similar effect was observed when the reaction was carried out in the absence of *t*-BuOH. Reduction of **17** with potassium (4 equiv) in the presence of *t*-BuOH (1 equiv) followed by addition of piperylene and alkylation with iodoethane led to **20** in 46% yield (Table 1, entry 5). A modest, but noticeable increase in the yield of cyclohexadiene **20** (66%) was obtained by carrying out the reduction with 4.8 equiv of potassium in the absence of *t*-BuOH (entry 6). The results from these experiments indicate that the reduction of **17** is best performed in the absence of *tert*-butyl alcohol. Changes in the amount

Table 1. Asymmetric Birch reduction–alkylation of benzamide **17**

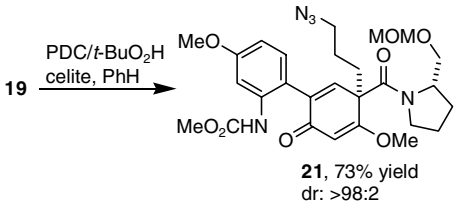


17

19 R = $CH_2CH_2CH_2N_3$
20 R = CH_2CH_3

Entry	RX	Conditions[a]		Product	Yield (%)
		Potassium (equiv)	*t*-BuOH (equiv)		
1	$I(CH_2)_3N_3$	7.0	1	19	30
2	$I(CH_2)_3N_3$	6.0	1	19	40
3	$I(CH_2)_3N_3$	5.2	0	19	70
4	$I(CH_2)_3N_3$	3.7	0	19	78
5	EtI	4.0	1	20	46
6	EtI	4.8	0	20	66

[a] General reaction conditions: Benzamide **17** in NH_3–THF was reacted with K (*n* equiv), *t*-BuOH (*n* equiv) at −78 °C for 3 h; piperylene was added followed by RX.



Scheme 6. Synthesis of cyclohexadienone **21**.

of potassium used for the reduction leads only to a modest improvement in the yield of the product. As discussed earlier, the acidic NH moiety of the carbamate group of **17** was expected to serve as the proton source for the protonation of the radical anion formed after the initial first electron transfer. The results of this study support this role. The dianion obtained after transfer of a second electron would undergo reaction with alkyl halides and protonation with NH_4Cl. The participation of the NH group of **17** in the protonation step is in agreement with our previous results with other substrates containing ionizable NH groups.[8] However, it is important to note that this is the first report of an asymmetric Birch reductive alkylation of a chiral benzamide performed in the absence of *t*-BuOH that provides synthetically useful yields of the cyclohexadiene product.[18]

The diastereoselectivity of the Birch reductive alkylation was determined after conversion of diene **19** to cyclohexadienone **21**. Bisallylic oxidation of **19** with PDC, *t*-BuO_2H, and celite gave **21** in 73% isolated yield (Scheme 6). The diastereomeric ratio of **21** was determined to be >98:2 by HPLC comparison to a 1:1 mixture of diastereomers prepared from the racemic ester **18**.

Acknowledgments

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Supplementary data

Experimental procedures and analytical data for new compounds. Supplementary data associated with this article can be found, in the online version, at doi: 10.1016/j.tetlet.2006.02.093.

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