Synthetic Methods

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Synthesis of 3,4-Dihydroisoquinolines by a C(sp^3)–H Activation/Electrocyclization Strategy: Total Synthesis of Coralydine**

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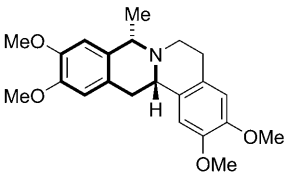
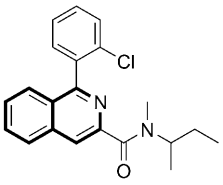
In memory of Christian Marazano

Isoquinolines, in various oxidation states (for example, isoquinolines, dihydro- and tetrahydroisoquinolines), are found in numerous natural products[1] and bioactive molecules, such as the tetrahydroprotoberberine alkaloid coralydine[2] and the peripheral benzodiazepine receptor ligand PK11195 (see below).[3]

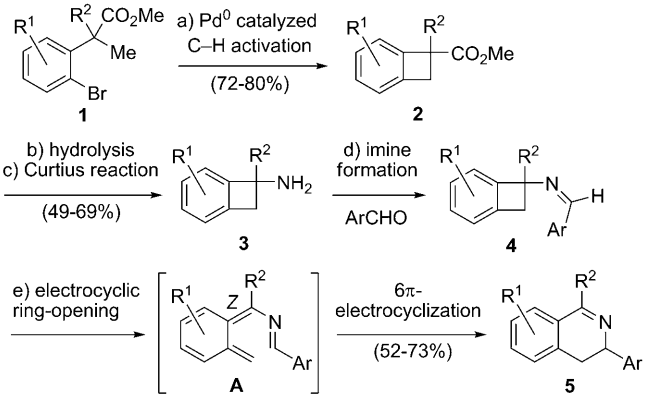


coralydine



PK11195

Dihydroisoquinolines (DHIQ) constitute synthetically strategic molecules in this context, since they are precursors to both isoquinolines and tetrahydroisoquinolines. Whereas a range of new methods have been developed for the synthesis of 1,2-DHIQ,[4] efforts have focused on the parent 3,4-DHIQ to a much lesser extent. Classical syntheses of 3,4-DHIQ involve Bischler-Napieralski-type reactions that rely on an electrophilic aromatic substitution (S_EAr) step.[5] However, for the purpose of introducing broader structural diversity onto this motif, the development of conceptually different synthetic alternatives is of great interest. We envisioned the construction of a variety of 3-aryl-3,4-DHIQ **5** from imino-BCB **4** (BCB = benzocyclobutene) by thermal tandem electrocyclic ring-opening/6π-electrocyclization via *o*-xylylene intermediate **A** (Scheme 1).[6,7] In turn, imines **4** would arise from amino-BCB **3**, which should be accessible from BCB-esters **2** by hydrolysis and Curtius rearrangement. BCB **2** can be readily synthesized from bromobenzenes **1** by the palladium-catalyzed C–H activation of methyl groups that was developed recently in our group.[8]



Scheme 1. Overall strategy for the synthesis of dihydroisoquinolines. Reagents and conditions: a) $Pd(OAc)_2$ (10 mol%), $P(tBu)_3$ (20 mol%), K_2CO_3, DMF, 140°C; b) NaOH, $MeOH/H_2O$, reflux; c) diphenylphosphoryl azide (DPPA), Et_3N, toluene, reflux, then aq. HCl, 80°C; d) ArCHO (1 equiv), $MgSO_4$, CH_2Cl_2, reflux; e) DMF, 160°C.

Amino-BCB **3a–d** (Table 1) were synthesized from the corresponding aryl bromides **1**. The construction of the cyclobutene ring by Pd-catalyzed C–H activation/intramolecular C–C coupling was carried out in good yield as described earlier (Scheme 1, step a).[8b] After ester hydrolysis (Scheme 1, step b), the corresponding carboxylic acids underwent a Curtius rearrangement in the presence of diphenylphosphoryl azide (DPPA, Scheme 1, step c).[9] Amino-BCB **3e** (Table 1, entry 12) was obtained from the corresponding BCB-nitrile by hydrolysis to the primary amide and PhI-$(OCOCF_3)_2$-mediated Hofmann rearrangement[10] (see the Supporting Information). Amino-BCBs, such as **3**, have limited thermal stability when $R^2 = H$, and therefore they have very rarely been isolated and employed in synthesis.[11] In this case, the presence of a quaternary benzylic carbon ($R^2 \neq H$), which is also necessary for the C–H activation step (a),[8b] stabilized the molecule, probably by raising the energy barrier for the cyclobutene ring-opening, which allowed us to isolate the free amines **3** and to engage them in the next step. Thus amino-BCB **3** was treated with one equivalent of an aromatic aldehyde (Scheme 1, step d) and the corresponding imines **4** underwent the thermal tandem electrocyclic ring-opening/ring-closing process (Scheme 1, step e). It was anticipated that the presence of the R^2 alkyl substituent would favor inward rotation of the imine group to give the *Z* isomer of the *o*-xylylene intermediate (Scheme 1, **A**) that was

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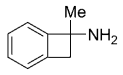
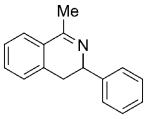
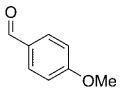
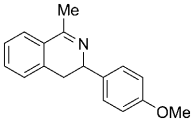
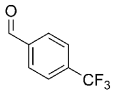
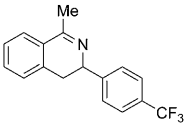
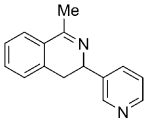
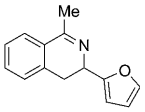
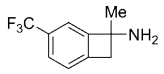
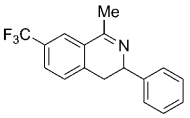
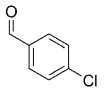
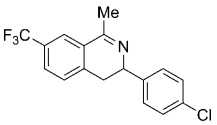
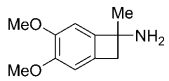
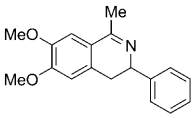
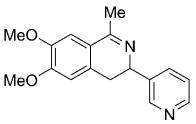
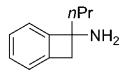
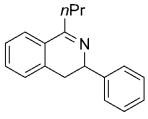
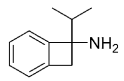
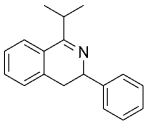
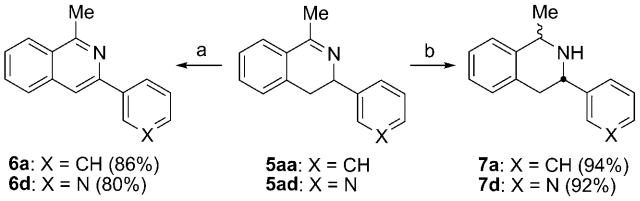
Table 1: Synthesis of 3,4-dihydroisoquinolines **5** from amino-BCB **3**.

Entry	BCB-amine[a]	ArCHO	Product	Yield [%][b]
1	 **3a**		 **5aa**	73
2	**3a**		 **5ab**	65
3	**3a**		 **5ac**	52
4	**3a**		 **5ad**	68
5	**3a**		 **5ae**	60
6	 **3b**		 **5ba**	60
7	**3b**		 **5bb**	59
8	 **3c**		 **5ca**	61
9	**3c**		 **5cb**	60
10	 **3d**		 **5d**	61
11	 **3e**		 **5e**	61

[a] See Supporting Information for detailed preparative procedures. [b] Yield of the isolated product, calculated from **3**.

required for the subsequent 6π-electrocyclization.[12] Indeed, the thermolysis of imine **4a** ($R^1 = H$, $R^2 = Me$, $Ar = Ph$), derived from amine **3a** and benzaldehyde, in DMF at 160 °C produced 3,4-DHIQ **5aa** in 73 % yield (Table 1, entry 1). The reaction in DMF was found to be superior to that in more conventional apolar solvents. Using these conditions, a variety of amino-BCB **3a–e** and aromatic aldehydes were combined to give the corresponding 3,4-DHIQ **5** in satisfactory overall yields (Table 1, entries 2–11). In particular the method seemed compatible with various substituents R^1 (Table 1, entries 6-9) and R^2 (Table 1, entries 10–11) on amino-BCB **3**, and with a variety of aromatic and heteroaromatic (Table 1, entries 4, 5, 9) aldehydes.[13]

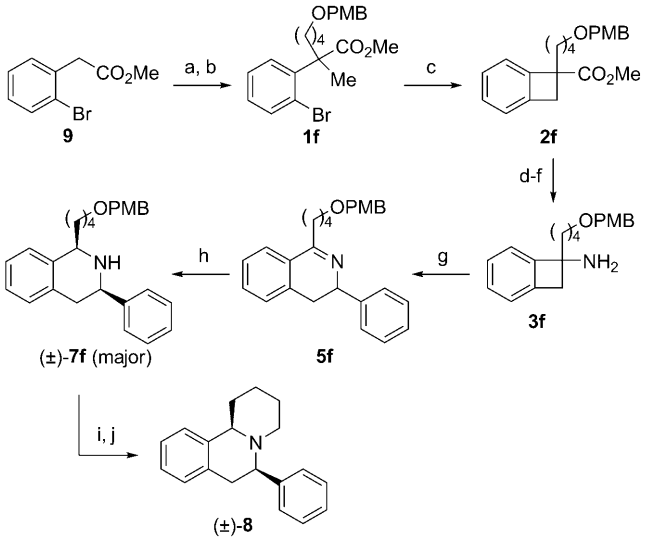
To demonstrate the synthetic utility of the synthesized 3,4-DHIQ, compounds, **5aa** and **5ad** were converted to the corresponding isoquinolines **6a** and **6d** by aromatization in the presence of Pd/C, and to tetrahydroisoquinolines **7a** and **7d** by reduction with sodium borohydride (Scheme 2).



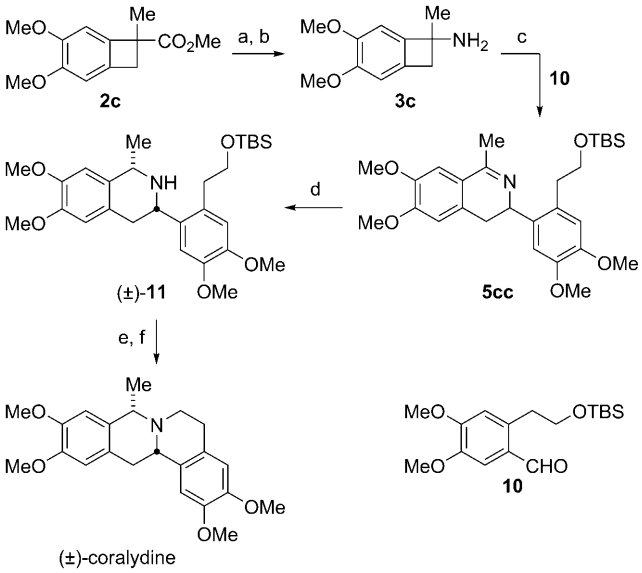
Scheme 2. Aromatization and reduction of 3,4-DHIQ. Reagents and conditions: a) 10 % Pd/C, decaline, reflux; b) $NaBH_4$, MeOH, 20 °C.

In the latter case, an approximate 7:3 ratio of diastereoisomers was detected, the major diastereoisomer having the expected *cis* configuration.

As a second illustration of this strategy , we synthesized the fused heterocycle **8**, which is of potential medicinal interest (Scheme 3).[14] To this end, the novel BCB-ester **2f**, incorporating a *p*-methoxybenzyl (PMB)-protected terminal alcohol was first synthesized in three steps from bromide **9** by sequential alkylations and palladium-catalyzed C–H activation. As reported for other substrates,[8b] the C–H activation step occurred, completely regioselectively, on the methyl group without affecting the other alkyl chain (Scheme 3, step c, 73 % yield). After ester hydrolysis (Scheme 3, step d), we first attempted the direct conversion of the corresponding carboxylic acid to amine **3f** by Curtius rearrangement and HCl-mediated hydrolysis of the isocyanate intermediate, as before (Scheme 1), but the concomitant cleavage of the PMB protecting group could not be avoided. As the unprotected alcohol proved unsatisfactory in the subsequent steps, we opted for a two-step procedure (Scheme 3, steps e, f). Thus the Curtius isocyanate intermediate was quenched with allyl alcohol, to give the corresponding allylcarbamate, which was converted to amino-BCB **3f** under palladium catalysis.[15] Imine formation from **3f** and benzaldehyde and subsequent thermolysis furnished 3,4-DHIQ **5f** in 63 % yield (Scheme 3, step g). The $NaBH_4$-mediated reduction of **5f** gave tetrahydroisoquinoline *cis*-**7f** as the isolated major diastereoisomer in 74 % yield (Scheme 3, step h). Finally, removal of the PMB group using cerium(IV) ammonium nitrate (CAN), followed



Scheme 3. Synthesis of fused heterocycle **8**. Reagents and conditions: a) NaHMDS (HMDS = hexamethyldisilazide), $PMBO(CH_2)_4I$ (PMB = *p*-methoxybenzyl), THF, 20 °C, 76%; b) NaHMDS, MeI, THF, 74%; c) $Pd(OAc)_2$ (10 mol%), $P(tBu)_3$ (20 mol%), K_2CO_3, DMF, 140 °C, 73%; d) NaOH, $MeOH/H_2O$, reflux, 85%; e) DPPA, Et_3N, toluene, reflux, then allyl alcohol, 80 °C, 83%; f) $[Pd(PPh_3)_4]$ (2 mol%), PPh_3 (9 mol%), 2-ethylhexanoic acid, CH_2Cl_2, 20 °C, 68%; g) benzaldehyde, $MgSO_4$, CH_2Cl_2, reflux, then DMF, 160 °C, 63%; h) $NaBH_4$, MeOH, 20 °C (d.r. = 7:1), 74%; i) $[Ce(NH_4)_2(NO_3)_6]$ (CAN), $MeCN/H_2O$, 20 °C, 78%; j) HBF_4, then PPh_3, diisopropyl azodicarboxylate (DIAD), THF, reflux, 67%.



Scheme 4. Synthesis of (±)-coralydine. Reagents and conditions: a) NaOH, $MeOH/H_2O$, reflux, 90%; b) DPPA, Et_3N, toluene, reflux, then aq. HCl, 80 °C, 69%; c) **10**, CH_2Cl_2, 20 °C, then DMF, 160 °C, 52%; d) $NaBH_4$, MeOH, 20 °C (d.r. = 6:1), 68%; e) nBu_4NF, THF, 20 °C, 86%; f) HBF_4, then PPh_3, DIAD, THF, reflux, 63%.

by the Mitsunobu reaction in the presence of HBF_4[16] furnished target compound **8** in 52% yield for the final two steps.

As a final demonstration of this strategy, the convergent synthesis of the tetrahydroprotoberberine alkaloid coralydine was undertaken (Scheme 4). BCB-ester **2c** was synthesized in three steps from commercially available starting materials according to our C–H activation method.[8b] It was then converted to amino-BCB **3c** by hydrolysis and Curtius rearrangement (as described in Scheme 1). Imine formation, from amino-BCB **3c** and the known aldehyde **10**,[17] and subsequent thermolysis provided 3,4-DHIQ **5cc** in 52% yield from **3c**. This somewhat lower yield might be imputable to the presence of an *ortho* substituent on the arylaldehyde. The reduction of the imine gave a 7:1 mixture of diasteroisomers (96% combined yield), from which the major *cis* diastereoisomer **11** was isolated (68% yield). Desilylation and HBF_4-mediated Mitsunobu reaction (as in Scheme 3) furnished racemic coralydine (54% yield from **11**), which had identical physical properties to those reported for the natural product.[2] This total synthesis gives an overall yield of 6.2% for a nine-step linear sequence.

In conclusion, we have developed a novel strategy for the synthesis of 3-aryl-3,4-dihydroisoquinolines via amino-benzocyclobutenes. Key steps include a palladium-catalyzed $C(sp^3)$-H activation and a tandem electrocyclic ring-opening/6π-electrocyclization. The synthetic utility of this approach was demonstrated by the synthesis of various isoquinoline-containing molecules, including the tetrahydroprotoberberine alkaloid coralydine.

Experimental Section

General procedure for the synthesis of 3,4-DHIQ **5**: The aldehyde (0.2–0.6 mmol) and $MgSO_4$ (5 equivalents) were added at 20 °C to a solution of amino-BCB **3** (1 equivalent) in CH_2Cl_2 (0.1–0.2 M concentration) under argon. The mixture was heated at reflux until completion of the reaction (monitored by ^1H NMR spectroscopy). After cooling, the reaction mixture was filtered under argon through syringe filter, to remove undissolved material, and the solvent removed under reduced pressure to give the crude imine **4**. The crude imine was dissolved in degassed anhydrous DMF (0.01 M solution based on total conversion) was heated to 160 °C for 2.5–3.5 h to form the corresponding 3,4-DHIQ **5**. After completion of the reaction (monitored by ^1H NMR spectroscopy), the solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel using ethyl acetate and heptanes as the eluent.

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Keywords: alkaloids · C–H activation · electrocyclic reactions · heterocycles · natural products

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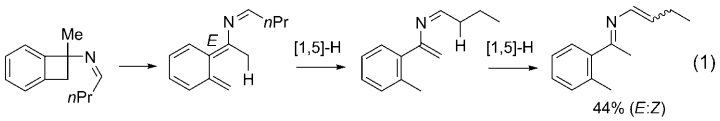

(1)

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