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On the stereoselective bicyclization of aminodienes catalyzed by chelating diamide complexes of the group 3 metals. A direct comparison of Sc(III) and Y(III) bis(amide)s with an application to the synthesis of alkaloid 195F†

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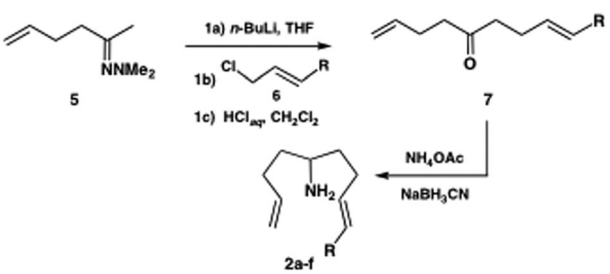
Highly diastereoselective bicyclizations of aminodienes catalyzed by chelating diamide complexes of Sc(III) and Y(III) that lead to pyrrolizidines and indolizidines are described. This bis(annulation) procedure has been utilized in a concise synthesis of the pyrrolizidine alkaloid 195F.

The catalytic hydroamination/cyclization of aminoalkenes constitutes a synthetic route to azacycles that is endowed with exceptional atom economy. Although main-group metal complexes have recently been used as catalysts for alkene hydroamination,[1a] the most general cases for the synthesis of amines and their derivatives involve transition metal catalysis using complexes of rhodium,[1b–d] ruthenium,[1e–f] nickel,[1g–i] palladium,[1j–p] and gold[1q–s] as well as the group 3[2a–o] and group 4[2p–z] metals. The group 3 metallocenes developed by Marks and coworkers[2] for this important reaction have more recently been supplemented by a variety of nonmetallocene complexes of the group 3 and group 4 metals as viable catalysts. We have previously disclosed that chelating diamido complexes of the group 3 metals (particularly Y, Nd, and Sc) are potent catalysts for intramolecular alkene hydroamination[2e] and, in certain instances, aminodiene bicyclizations.[2c,d] In this communication we present our most recent observations on the stereoselectivities and rates associated with the bicyclization of a series of *electronically differentiated* aminodienes catalyzed by chelating diamide complexes of the type **1a**,**b**.

We have previously shown[2j] that 5-amino-1,8-nonadiene (**2a**) undergoes efficient monocyclization to provide **3a** with 13 : 1 *trans*/*cis* selectivity in the presence of $Y[N(TMS)_2]_3$ (2.7 mol%) at 10 °C (18 h), and subsequent *stereospecific* bicyclization to **4a** at 70 °C (18 h), wherein the minor *cis*-isomer $\mathbf{3a}_{cis}$ remained unreacted. We subsequently demonstrated that catalyst **1b** is vastly more stereoselective, furnishing **3a** (*trans*/*cis* = 49 : 1) with ultimate conversion to pyrrolizidine **4a**.[2d] The stereospecific conversion of **3a** to **4a** is consistant with a mechanism involving *syn*-addition of the metal-nitrogen bond to the C=C π-bond (Scheme 2).[2a] The aminodienes **2a–e** that were utilized in this study were prepared as described previously[2c] by the sequential alkylation of 5-hexene-2-one-*N*,*N*-dimethylhydrazone (**5**) [(1a) *n*-BuLi, THF; (1b) RCH=CHCH$_2$Cl **6**] followed by hydrolysis (HCl/H$_2$O) and reductive amination (Scheme 1).

Exposure of **2a** to the more reactive and selective chelating diamide complex of yttrium **1a**[2e,3] (10 mol%) in toluene-D$_8$ at 23 °C gave rise to an exceptionally rapid monocyclization event (≤9 min) to provide $\mathbf{3}_{trans}$ and $\mathbf{3}_{cis}$ as an 18 : 1 mixture (by ^{1}H NMR spectroscopy). Subsequent heating of the reaction mixture to 60 °C (3 h) subsequently furnished **4a** (91%, NMR) with $\mathbf{3}_{cis}$ remaining unreacted. As previously reported, catalyst **1b** (10 mol%) proved exceptionally stereoselective, albeit less reactive, furnishing **3a** [*trans*/*cis* = 49 : 1, (10 °C, 12 h)] and ultimately pyrrolizidine **4a** (3 h, 60 °C). Aminodienes **2b–e** were subsequently subjected to bicyclization catalyzed by **1a** and **1b** respectively. The results of these studies are presented in Table 1.

As is evident from these results, and as would be expected, the rate and stereoselectivity of monocyclization to pyrrolidines **3b–f** is metal dependent, but invariant with respect to the structure of the 7-aryl(ethenyl) substituent. The stereochemical consequences of the subsequent bicyclizations of **3b–f** are stereospecific, in accord with our earlier observations for **3a**.[2j] Under the indicated reaction conditions using **1a**, $\mathbf{3b}_{cis}$–$\mathbf{3f}_{cis}$ (*ca.* 5.3%) were resistant toward further cyclization and only pyrrolidines $\mathbf{3b}_{trans}$–$\mathbf{3f}_{trans}$ underwent bicyclization. Gratifyingly, $\mathbf{3b}_{cis}$–$\mathbf{3f}_{cis}$ were easily separated from **4b–4f** by column chromatography. Cyclizations catalyzed by **1b** provided exclusively $\mathbf{3b}_{trans}$–$\mathbf{3f}_{trans}$ (as observed by ^{1}H NMR spectroscopy) which subsequently underwent stereospecific cyclization to provide pyrrolizidines **4b–4f**.



Scheme 1 Synthesis of aminodienes **2a–f**.

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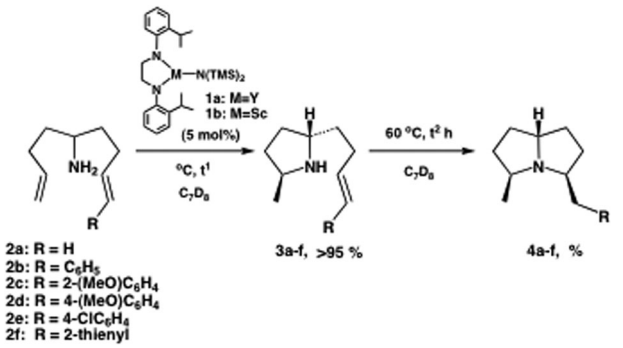


Scheme 2 Catalytic bicyclizations of aminodienes **2a–f**.

Table 1 Bicyclization of aminodienes **2a–2f**

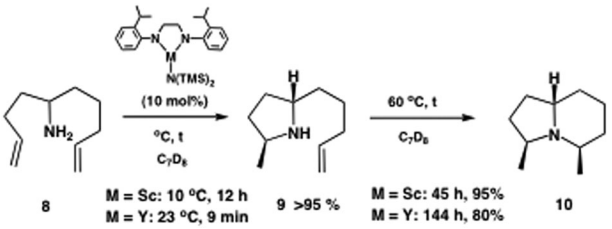
Complex	Substrate	°C	t^1	$\mathbf{3}_{trans}:\mathbf{3}_{cis}$	t^2 (h)	$\%_{NMR}$[c]	**4** ($\%_{isol.}$)
1a	**2a**	23	9 min[a]	18 : 1	3	95	(98)[d]
1b	**2a**	10	12 h	49 : 1	3	95	(98)[e]
1a	**2b**	23	9 min[a]	18 : 1	44	87	(73)
1b	**2b**	10	12 h	49 : 1	26	90	(85)
1a	**2c**	23	9 min[a]	18 : 1	11	91	(81)
1b	**2c**	10	12 h	49 : 1	6	90	(70)
1a	**2d**	23	9 min[a]	18 : 1	48[b]	70	(64)
1b	**2d**	10	12 h	49 : 1	36	86	(71)
1a	**2e**	23	9 min[a]	18 : 1	30	84	(75)
1b	**2e**	10	12 h	49 : 1	24	90	(84)
1a	**2f**	23	9 min[a]	18 : 1	60	82	(74)
1b	**2f**	10	12 h	49 : 1	17	91	(71)

[a] Time span from the addition of the aminodiene to aquisition of the ^{1}H NMR spectrum. [b] Reaction conducted at 120 °C. [c] Integration relative to *p*-xylene as an internal standard. [d] Isolated as the trifluoroacetate salt, contains 5.3% $\mathbf{3}_{cis}$·TFA. [e] Isolated as the trifluoroacetate salt.

In contrast, the relative rates for bicyclization were markedly influenced by the nature of the aryl(alkenyl) substituent. Marks and coworkers have shown that turnover numbers for representative cyclization/hydroaminations of aminoalkynes catalyzed by rare-earth metallocenes are strongly coupled to the electronic characteristics of the alkyne substituent.[3] In that study, electron-rich alkynes were found to facilitate ring closure involving the *electron-deficient* metallocene amide intermediates. As is evident from the results presented in Table 1, the relative rates of bicyclization *for both* **1a** *and* **1b** follow the trend **3c** (Ar = 2-(MeO)C_6H_4) > **3b** (Ar = Ph) ≈ **3e** (Ar = 4-ClC_6H_4) > **3f** (Ar = 2-thienyl) > **3d** (Ar = 4-(MeO)C_6H_4). Although it can be asserted that 7-aryl(ethenyl) substituent of **3c** benefits both from electron donation and a possible chelation effect [arising from the 2-(MeO) group] when compared to the simple phenyl of **3b**, the unusual lethargy of **3d** toward bicyclization was unexpected. It is also noteworthy that the rates for bicyclization of **3b–f** catalyzed by **1b** exceeded those exhibited by the corresponding yttrium complex **1a** in all instances. This is counter to typical reactivity trends observed for *primary* aminoalkenes.

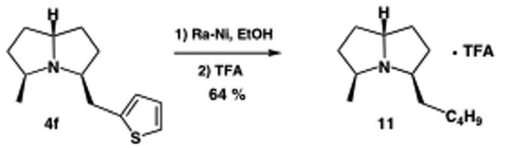
The indolizidine ring system is an essential subunit within numerous naturally occurring alkaloids. Accordingly, we undertook a brief study to ascertain the feasibility of extending the present methodology to the elaboration of fused 6/5 rings. Exposure of 5-amino-1,9-decadiene (**8**) to **1b** (10 mol%) led to efficient monocyclization (10 °C, 12 h) to give **9** [*trans* : *cis* = 49 : 1, 95% (NMR)]. Subsequent heating at 60 °C for 45 h induced stereospecific bicyclization to secure indolizidine **10** (95%). As expected, monocyclization catalyzed by **1a** (10 mol%) was very rapid (23 °C, ≤9 min) to furnish **9** (95%, *trans* : *cis* = 18 : 1), from which $\mathbf{9}_{trans}$ was lethargically converted to **10** [60 °C, 144 h, (80%)] (Scheme 3).

It is of preparative significance that aminodiene bicyclizations catalyzed by the more stereoselective scandium complex **1b** were readily achievable on ≥ 1 mmol scale with a catalyst loading of 2 mol%. To this end, aminodienes **2a**, **2b** and **8** were converted to azabicycles **4a**, **4b** and **10** in 98%, 74% and 98% isolated yields, respectively.[4]



Scheme 3 Catalytic bicyclizations leading to indolizidine **10**.

The pyrrolizidine defense alkaloid 195F (**11**) was isolated from the whole-body extract of the Madagascar arthropod *Paratrechina amblyops* in 2005.[5] Access to this natural product as its trifluoroacetate salt was readily achieved in 64% isolated yield by reductive desulfurization of **4f** *via* RANEY® Ni in EtOH and subsequent treatment with TFA. This represents the first total synthesis for this natural product (Scheme 4).[6]



Scheme 4 Synthesis of alkaloid 195F.

In conclusion, we have shown that the neutral Sc(III) chelating diamide complex **1b** is an unusually stereoselective precatalyst for intramolecular aminodiene bicyclization/hydroamination leading to pyrrolizidines and the indolizidine nucleus. Although the catalytic activity of the corresponding Y(III) complex **1a** is much higher for monocyclization, it is less stereoselective than **1b** and less effective at promoting bicyclization. Studies utilizing *chiral* chelating diamido and related complexes of the group 3 metals as catalysts for asymmetric intramolecular hydroamination are currently underway.

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4 Pyrrolizidine **4a** and indolizidine **10** were isolated as their trifluoroacetate salts.

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