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Intramolecular Nitrogen Assistance in the Nickel-Promoted Tandem Cyclization−Capture of Amino-Tethered Vinyl Bromides and Alkenes

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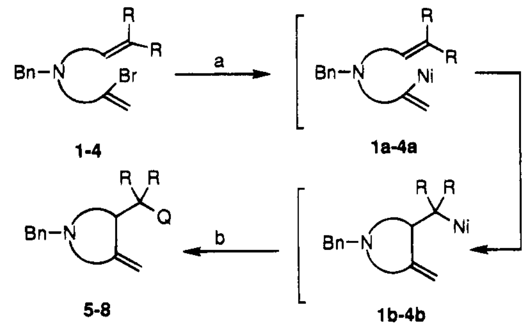
Over the last years, tandem processes, and particularly transition-metal-based methods, are gaining importance in organic synthesis since they allow the simultaneous formation of more than one bond in a single synthetic operation with high selectivity.[1,2] As a part of our ongoing research on nickel-induced C−C bond formation leading to carbo- and heterocyclic compounds,[3−5] we became interested in the synthesis of functionalized nitrogen-containing systems as key precursors for the elaboration of natural and nonnatural products. Herein we describe the results obtained in the reaction of amino-tethered halodienes of type **1−4** with $Ni(COD)_2$ followed by trapping of the presumably formed σ-alkylmetal intermediates with different reagents to give compounds **5−8**[6] according to the sequence shown in Scheme 1.

The reaction takes place by addition of the substrate to a solution of $Ni(COD)_2$ in acetonitrile at room temperature followed by quenching with the trapping reagent.[7,8] Under these mild conditions, methyl esters, nitriles, or reduced products were obtained (see Table 1). Pyrrolidines and piperidines were obtained in good to excellent yields, and the reaction proceeded with complete diastereoselectivity for the synthesis of substituted perhydroindoles (Table 1, entries 6−10).

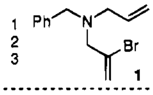
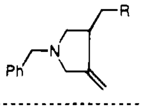
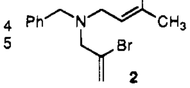
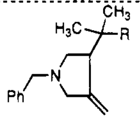
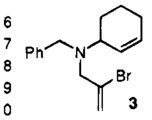
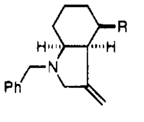
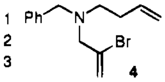
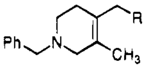
In contrast with our previous work on the formation of carbo- and heterocycles,[3−5] based on $Ni(CO)_4$ as the metal source, use of stoichiometric $Ni(COD)_2$ allows the disassembling of the initial oxidative addition of the starting halodienes to the nickel complex from the ultimate carbonylation step. In this way, CO is introduced into the reaction mixture once ring closure has been accomplished, thus avoiding the formation of open chain esters arising from the premature interception of the σ-vinylmetal intermediates by the quencher. On the other hand, this protocol allows one to sensibly widen the scope of the reaction by using different quenchers as reaction terminators.

Scheme 1[a]



[a] (a) $Ni(COD)_2$, (1−2 equiv), CH_3CN, 3−10 min; (b) quencher (Q); R: H, alkyl.

Table 1

entry	substrate	quencher[(a)]	product		R	% isolated yield
1	 1	A		**5a**	$COOCH_3$	70
2		B		**5b**	CN	99
3		C		**5c**	H	45
4	 2	A		**6a**	$COOCH_3$	50
5		B		**6b**	CN	61
6	 3	A		**7a**	$COOCH_3$	95[(b)]
7		B		**7b**	CN	99[(b)]
8		C		**7c**	H	70[(b)]
9		D		**7c**	H	77[(b)]
10		E		**7d**	OH	45[(b,c)]
11	 4	A		**8a**	$COOCH_3$	40
12		B		**8b**	CN	60[(d)]
13		C		**8c**	H	41[(e)]

[a] A: addition of MeOH (3 equiv) and bubbling of CO through the reaction mixture. B: TMSCN (neat, 2.5 equiv). C: $NaBH_4$ (16 equiv) in MeOH (6 equiv). D: Et_3SiH (neat, 2.5 equiv). E: O_2 bubbling through the reaction mixture. [b] Stereochemistry based on ^1H and ^{13}C NMR. [c] **9** (40%) was also obtained (see footnote 12). [d] A 9:1 mixture of **8b** and the isomer *N*-benzyl-4-(cyanomethyl)-3-methylenepiperidine was also isolated. [e] A 8:2 mixture of **8c** and the isomer *N*-benzyl-4-methyl-3-methylenepiperidine.

The success of this sequential strategy relies on the apparent high stability of the presumed alkylnickel intermediates **1b−4b** arising from oxidative addition and further alkene insertion (Scheme 1). The enhanced stability of the above intermediates can be explained as being due to the presence of the amino function which would coordinate the metal and avoid a subsequent β-elimination prior to the addition of the trapping reagent (Figure 1).[9,10] Assistance by the distal nitrogen atom could also be the reason for the high stereoselectivity displayed by the reaction (entries 6−10, Table 1).

In agreement with this explanation, when the amino group is absent (compounds **12** and **13**) or its coordinating ability is reduced by incorporation into an amide function (compounds **10** and **11**), cyclization proceeds in a different way. Thus, in

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(1) Hok, T. L. *Tandem Organic Reactions*; Wiley Interscience: New York, 1992.

(2) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131−163.

(3) Llebaria, A.; Camps, F.; Moretó, J. M. *Tetrahedron Lett.* **1992**, *33*, 3683−3686.

(4) Llebaria, A.; Delgado, A.; Camps, F.; Moretó, J. M. *Organometallics* **1993**, *12*, 2825−2831.

(5) Delgado, A.; Llebaria, A.; Camps, F.; Moretó, J. M. *Tetrahedron Lett.* **1994**, *23*, 4011−4014.

(6) All new compounds were characterized by elemental analysis and/or spectroscopic data.

(7) A typical experimental procedure is as follows: To a solution of $Ni(COD)_2$ (1−2 mmol) in dry acetonitrile (5 mL), at room temperature and under an Ar atmosphere, was added a solution of the vinyl bromide **1−4** (1 mmol) and Et_3N (3 mmol) in dry acetonitrile. The reaction mixture, which turned from yellow to red, was stirred at room temperature. When all starting material had been consumed (2.5−30 min, checked by TLC), the quencher was added (see footnote *a*, Table 1) and the mixture was stirred at room temperature for an additional 3 h. After filtration through Celite and careful washings with CH_2Cl_2, the mixture was partitioned between CH_2Cl_2 and saturated Na_2CO_3. Drying of the organic phases, followed by filtration and evaporation, afforded the desired cycloadduct.

(8) Disappearance of the starting material must be carefully controlled, since the presumed alkylnickel intermediates **1b−4b** afford β-elimination products or complex mixtures after long periods of time.

(9) Prevention of β-elimination in products arising from aminopalladation of terminal olefins has been reported. The resulting σ-(β-aminoethyl)-palladium was susceptible to quenching by different nucleophiles; for a review on this topic, see: Hegedus, L. S. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds; Pergamon Press: Oxford, 1991; Vol. 4.

(10) For a related example of directed insertion by intramolecular nitrogen−Ni coordination, see: Tamao, K.; Ito, Y. *Synlett* **1992**, 539−546.

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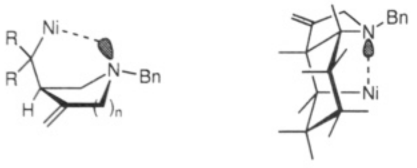
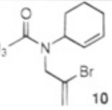
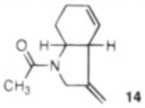
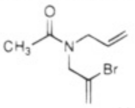
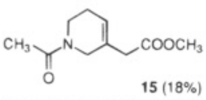
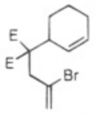
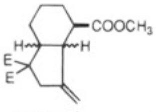
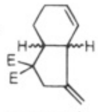
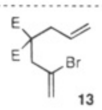
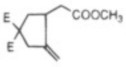
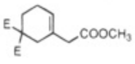
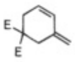


1b,2b,4b **3b**

Figure 1.

Table 2

entry	substrate	quencher[(a)]	products (%isolated yield)
1	 **10**	B	 **14** (38%)[b]
2	 **11**	A	 **15** (18%)
3[c]	 **12**	A	 **16** (28%)[d]  **17** (30%)[d]
4[e]	 **13**	A	 **18** (14%)  **19** (39%)  **20** (24%)

[a] See Table 1. [b] Single isomer. [c] E = $COOCH_3$. [d] A 1:1 mixture by ^{1}H-NMR. [e] E = $COOCH_2CH_3$.

the monocyclic series (Table 2, entries 2 and 4), the reaction followed a preferent 6-endo cyclization course,[11] whereas in the fused 6 + 5 bicyclic series (Table 2, entries 1 and 3), major or exclusive β-elimination cycloadducts were obtained.

Starting from **3**, when the trapping reagent is oxygen, the corresponding alcohol **7d** is obtained together with the β-elimination bicyclic diene **9**.[12] This side reaction indicates that a delicate balance between the stability of the alkylnickel intermediates **1b**–**4b** and the rate of the trapping step is necessary to obtain good yields of the desired coupling products.

The process here described is related to some palladium-catalyzed intramolecular processes, in particular, to the Heck reaction,[13] where a transient σ-alkyl palladium species, similar to **1b**–**4b**, would suffer β-hydride elimination or cyclopropanation followed by subsequent ring expansion.[11] To our knowledge, although there are several examples in the literature on the trapping of σ-alkyl palladium species,[14–16] examples of capture processes in substrates where β-elimination is possible are scarce.[17–20]

An example of the low tendency toward β-elimination exhibited by substrates **1**–**4** in our reaction system is shown in entries 4 and 5 (Table 1). In these cases, the presumed intermediate **2b** (Scheme 1) can be efficiently trapped by either CO or CN without formation of the "Heck-type" adduct despite having seven hydrogen atoms available for β-elimination.

In summary, the stoichiometric use of $Ni(COD)_2$ in a mild tandem cyclization–capture process starting from some nitrogen-tethered halodienes is reported. The amino function seems essential for the diversion of the presumed σ-alkylnickel intermediates from the β-elimination to the trapping by a terminating agent and to efficiently control the relative stereochemistry of the resulting stereogenic centers . Further studies directed toward additional effects that may be brought about by an amino function in these and related ring-forming processes are currently underway.

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Supplementary Material Available: Characterization data for **5a**–**c**, **6a,b**, **7a**–**d**, **8a**–**c**, and **14**–**20** (58 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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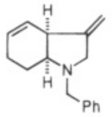
(11) Owczarczyk, Z.; Lamaty, F.; Vawter, E. J.; Negishi, E. *J. Am. Chem. Soc.* **1992**, *114*, 10091–10092.

(12) The origin of the hydroxyl functionality to give **7d** still remains intriguing. We have obtained similar results with N_2O (Matsunaga, P. T.; Hillhouse, G. L. *J. Am. Chem. Soc.* **1993**, *115*, 2075–2077) and H_2O_2, while *t*-BuOOH, another "oxidizing quencher", afforded only the β-elimination adduct **9**. Mixtures of **7d** and **9** have been obtained by using a "protic quencher" such as H_2O (for a related example, see: Horino, H.; Arai, M.; Inoue, N. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 1683–1686).



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(13) Heck, R. F. *Org. React. (N.Y.)* **1982**, *27*, 345–390.

(14) Burns, B.; Grigg, R.; Santhakumar, V.; Sridharan, V.; Stevenson, P.; Worakun, T. *Tetrahedron* **1992**, *48*, 7297–7320.

(15) Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.* **1993**, *115*, 12491–12509.

(16) Negishi, E. *Pure Appl. Chem.* **1992**, *64*, 323–334.

(17) Trost, B. M. *Acc. Chem. Res.* **1990**, *23*, 34–42.

(18) Oppolzer, W.; Ruiz Montes, J. *Helv. Chim. Acta* **1993**, *76*, 1266–1274.

(19) Balme, G.; Bouyssi, D. *Tetrahedron* **1994**, *50*, 403–414.

(20) For a conceptually related cyclization–capture process, see: Stadtmuller, H.; Tucker, C. E.; Vaupel, A.; Knochel, P. *Tetrahedron Lett.* **1993**, *34*, 7911–7914.