Rhodium-catalyzed enantioselective desymmetrization of bicyclic hydrazines with alkynylboronic esters†

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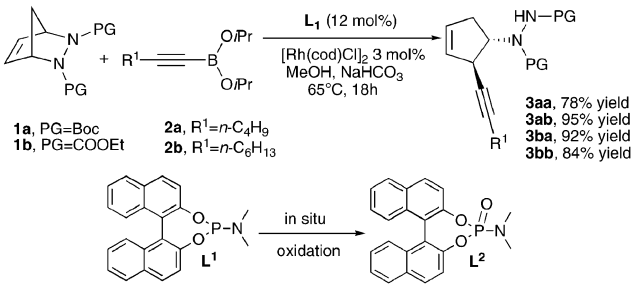
The first successful asymmetric transfer of rhodium–alkynyl species to symmetrical strained alkenes has been realized starting from bicyclic hydrazines and alkynylboronic esters.

The transition metal-catalyzed alkynylation of activated double bonds starting from terminal alkynes is a powerful strategy for C–C bond formation.[1] The rhodium-catalyzed asymmetric introduction of aryl and alkenyl moieties into activated alkenes has shown spectacular advances in recent years,[2] but the corresponding enantioselective addition of alkynyl organometallic reagents has remained elusive.[3] We here report a simple and synthetically useful rhodium-catalyzed alkynylation of bicyclic hydrazines, which constitutes the first successful asymmetric alkynylation of a symmetrical strained alkene.[4]

Symmetrical bicyclic hydrazines are attractive substrates because they are stable and can easily be obtained in multigram amounts from the hetero-Diels–Alder reaction of cyclopentadiene with azodicarboxylates.[5] Interest in the desymmetrization by ring-opening reactions of these systems has grown significantly in recent years, because the disubstituted cyclopentenes obtained are versatile intermediates for the synthesis of biologically interesting molecules.[6]

In a preliminary screening for reactivity, we chose 1-alkynyltriisopropylboronates as the alkynylating agents. These compounds are readily available from the corresponding terminal alkynes,[7] and they have rarely been used in an asymmetric addition to activated alkenes.[8] A number of rhodium sources, solvents and phosphorus-containing chiral ligands were evaluated as catalysts in the reaction. While THF, dichloromethane and toluene proved to be ineffective solvents, the use of $[Rh(cod)Cl]_2$ as the rhodium catalyst precursor, in combination with ligands containing an electron-poor phosphorus in alcoholic solvents gave a clean alkynylative ring-opening reaction. For example, when bicyclic hydrazines **1a** (Boc = *tert*-butyloxycarbonyl) and **1b** were allowed to react with 2.0 equiv. of 1-hexynyl diisopropylboronate (**2a**) or 1-octynyl diisopropylboronate (**2b**) in the presence of $[Rh(cod)Cl]_2$ (6 mol% Rh, cod = cycloocta-1,5-diene), racemic Monophos (12 mol%) and 2.0 equiv. of $NaHCO_3$ in refluxing MeOH, the corresponding *trans*-3-alkynyl-4-hydrazino cyclopentenes of type **3** were isolated in good yields after chromatographic purification (Scheme 1).



Scheme 1 Preliminary experiments of the rhodium-catalyzed desymmetrization of bicyclic hydrazines with alkynylboronic esters.

Interestingly, it was observed that the Monophos ligand $\mathbf{L^1}$ was oxidized to the corresponding phosphoric amide $\mathbf{L^2}$, as determined by ^1H and ^{31}P NMR analysis of the ligand formed at the end of the reaction. Redox processes between phosphorus-based ligand and transition metals had previously been reported,[9] but to the best of our knowledge, no precedents for the Rh-catalyzed oxidation of phosphoramidite ligands have been described.[10]

It was also noticed that, in sharp contrast with the rhodium-catalyzed reaction performed with arylboronic acids,[6h] the ring-opening alkynylation of bicyclic hydrazines occurred only in the presence of stoichiometric amounts of a base.[11] As the alkynyl–boron bond is gradually protonated in the protic reaction medium thus regenerating the corresponding alkyne,[12] the direct use of terminal alkynes was also considered. The formation of rhodium acetylides with rhodium–phosphine complexes has been observed several times in organometallic literature,[13] and it is known that rhodium acetylides are stable in polar protic solvents.[14] Indeed, the alkynylation reaction starting from 1-hexyne was feasible, but it was found that the use of stoichiometric or catalytic amounts of an external Lewis acid was necessary to realize the ring-opening of bicyclic hydrazine **1a** up to a synthetically useful extent (Table 1).

Among the Lewis acids screened in catalytic amounts, $Yb(OTf)_3$ gave cleanly adduct **3aa** with a satisfactory conversion in 18 h (entry 2). A number of other rhodium sources, bases and solvents were also examined, but inferior results were obtained (see ESI†). It is quite remarkable that even using the forcing reaction conditions reported in Table 1, the reaction carried out directly from the terminal alkynes never reached the efficiency obtained with the use of alkynylboronates. The use of 5.0 equiv. of $B(OiPr)_3$, which is actually a Lewis acid closely related to that obtained after protonation of boronate **2a**, did not show an increased activity, either (entry 6).

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Table 1 Lewis-acid performance in the direct rhodium–Monophos catalyzed ring-opening of diazabicycle **1a** with 1-hexyne[a]

Entry	Lewis acid (mol%)	Conversion[b]
1	None	18
2	$Yb(OTf)_3$ (10)	68
3	$In(OTf)_3$ (10)	50
4	$Sc(OTf)_3$ (10)	82[c]
5	$Cu(OTf)_2$ (10)	45
6	$B(iPrO)_3$ (500)	64

[a] *Reagents and conditions*: 1-hexyne (5.0 equiv.), MeONa (5.0 equiv.), $[Rh(cod)Cl]_2$ (5 mol%), Monophos (24 mol%), MeOH (2.0 ml), 65 °C, 18 h. [b] Percentage conversions were determined by ^1H NMR examination of the crude reaction mixture. [c] A complex reaction mixture was obtained.

Subsequently, our efforts were devoted to developing an asymmetric alkynylation of bicyclic hydrazines. After an extensive ligand screening, significant levels of enantioselectivity were obtained only when chiral Binol-derived diphosphines, such as (*R*)-Tol-Binap and (*R*)-Xylyl-Binap, were used in combination with $[Rh(C_2H_4)_2Cl]_2$ as the chiral catalysts (see Table 2).‡ However, despite the higher catalyst loading, in these reaction conditions the ring-opening desymmetrization never matched the complete conversion obtained using catalytic amounts of $[Rh(cod)Cl]_2$/Monophos (Scheme 1). As reported in Table 2, alkyl-, trimethylsilyl- and phenyl-substituted alkynyl boronic esters can be used in the enantioselective desymmetrization of differently protected bicyclic hydrazines to give products with significant values of enantiomeric enrichment. However, it was noticed that the use of hindered alkynyl boronates **2d** and **2e** in the same reaction conditions gave lower yields of the corresponding adducts (entries 9–11).

The direct use of terminal alkynes was also examined in the enantioselective ring opening (entries 3, 8, 12). Even if the enantioselectivity of the corresponding adducts of type **3** was of the same level, the conversions and yields were remarkably lower.

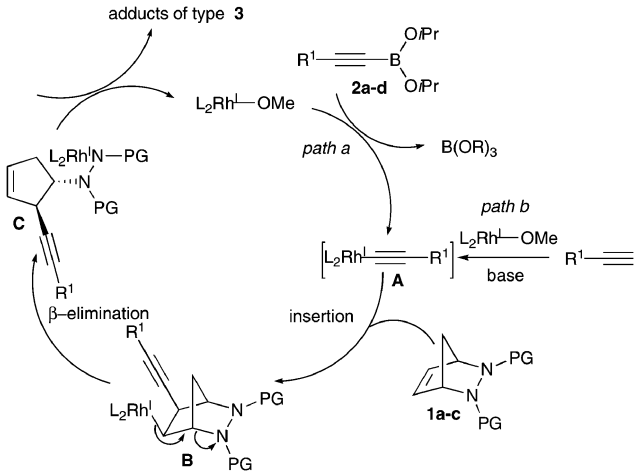
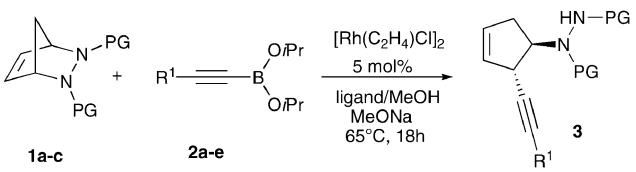


Fig. 1 Proposed catalytic cycle for the alkynylative desymmetrization of bicyclic hydrazines of type **1**.

Therefore, the experimental data indicate that the basic reaction conditions activate the terminal C(sp)–H bond of an alkyne, to generate an acetylide–Rh(I) species **A** (*path b*, Fig. 1), but that this catalytically key intermediate is better obtained by the corresponding boronate (*path a*).[15]

Reasonably, in the catalytic cycle a stereo- and enantioselective carborhodation at the enantiotopic reaction sites of the strained double bond occurs at the more accessible *exo*-face, thus generating the key intermediate carbometalated intermediate **B**.[6j] Subsequent β-elimination of the hydrazide leaving groups assisted by the Lewis acid would afford the ring-opened intermediate **C**, followed by proto-demetallation

Table 2 Rhodium-catalyzed enantioselective alkynylative desymmetrization of diazabicycles **1a–c**[a]



Entry	PG	R^1	Ligand	Conv.[b] (%)	Ee[c] (%)
1	COOBn (**1c**)	*n*-C_4H_9 (**2a**)	Tol-Binap	81 (54) **3ca**	52
2	COOBn (**1c**)	*n*-C_4H_9 (**2a**)	Xylyl-Binap	66 (43) **3ca**	60
3	COOBn (**1c**)	*n*-C_6H_{10}[d]	Tol-Binap	25	38
4	COOBn (**1c**)	Ph (**2c**)	Xylyl-Binap	85 (67) **3cc**	66
5[e]	COOEt (**1b**)	Ph (**2c**)	Tol-Binap	75 (58) **3bc**	21
6	Boc (**1a**)	Ph (**2c**)	Xylyl-Binap	83 (48) **3ac**	52
7	Boc (**1a**)	Ph (**2c**)	Tol-Binap	80 (45) **3ac**	32
8	Boc (**1a**)	PhCCH[d]	Tol-Binap	25	33
9	COOBn (**1c**)	*t*-Bu (**2d**)	Tol-Binap	55 (40) **3cd**	48
10	COOBn (**1c**)	*t*-Bu (**2d**)	Xylyl-Binap	43 (36) **3cd**	54
11	COOBn (**1c**)	TMS (**2e**)	Tol-Binap	38 (18) **3ce**	58
12	COOBn (**1c**)	TMSCCH[d]	Tol-Binap	No ring opening	

[a] *Conditions*: Reactions were run in accordance with the General procedure,‡ unless stated otherwise. [b] Conversion was determined by ^1H NMR examination of the crude reaction mixture. Isolated yields after chromatographic purification (SiO_2) of the indicated pure products are reported in parentheses. [c] Determined by HPLC on Daicel Chiralcel OD-H or AD-H columns. [d] Reactions carried out with the corresponding terminal alkyne (5.0 equiv.), MeONa (5.0 equiv.), $[Rh(C_2H_4)_2Cl]_2$ (5 mol%), ligand (12 mol%), $B(OiPr)_3$ (5.0 equiv.), MeOH (2.0 ml), 65 °C, 18 h. [e] CsF was used as base.

by the protic solvent to give *trans*-3,4-disubstituted cyclopentene adducts of type **3**.

It should be noted that alkynyl cyclopentenic hydrazines synthetized by means of our protocol in a completely regio- and stereocontrolled fashion, are very difficult to access by other routes. Moreover, considering that the versatile Boc and Cbz protecting groups used in our procedure can easily be cleaved to the corresponding free hydrazines, these products are versatile building blocks with multiple points of functionalization. For example, the hydrazine moiety can be converted into pyrazole derivatives,[16] 1,2,4-triazolo derivatives,[17] or into the corresponding amine.[18] Moreover, the alkynyl triple bond can easily be manipulated by "click chemistry" procedures to give 1,2,3-triazolines.[19]

In conclusion, an unprecedented asymmetric alkynylation of a strained alkene has been achieved. This protocol offers a new and a straightforward regio- and stereoselective entry to valuable alkynyl cyclopentenic hydrazines, which can be conveniently elaborated by standard procedures into valuable scaffolds for medicinal chemistry. The experimental evidence seems to indicate a probable transmetallation from an alkynyl–boron bond to give an intermediate Rh(I)-acetylide species. The particular nature of [2.2.1]diazabicyclic alkenes makes possible the insertion into the double bond of the strained diazabicycle, avoiding alkyne dimerization, which is often an inherent problem when dealing with alkynyl–rhodium intermediates.

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Notes and references

‡ *General procedure* for the Rh(I)-catalyzed asymmetric alkynylation of bicyclic hydrazines with 1-alkynyltriisopropylboronic esters: under argon protection, a solution of $[Rh(C_2H_4)_2Cl]_2$ (3.9 mg, 0.01 mmol), chiral ligand (0.024 mmol) in HPLC grade MeOH (1.0 ml) were stirred at room temperature in a Schlenk tube. After 30 min at 25 °C, a solution of **1** (0.2 mmol) in MeOH (1.0 ml) was added, followed by the addition of 1-alkynyl diisopropylboronic ester **2** (0.4–0.6 mmol) and MeONa (0.4–0.6 mmol). The reaction was gradually warmed at 65 °C and quenched with saturated aqueous $NaHCO_3$ after 18 h. After extraction with Et_2O (2 × 10 ml) and CH_2Cl_2 (10 ml), the organic phase was dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography.

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