

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

Stefano Crotti, Ferruccio Bertolini, Franco Macchia and Mauro Pineschi*

Received (in Cambridge, UK) 4th March 2008, Accepted 7th April 2008

First published as an Advance Article on the web 8th May 2008

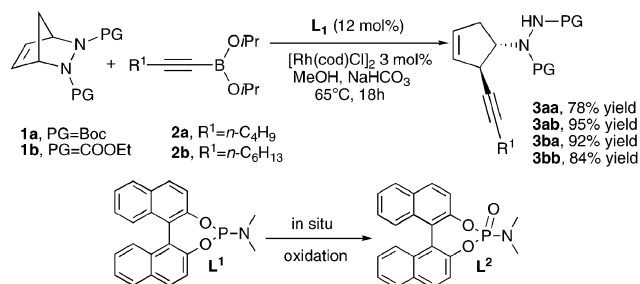
DOI: 10.1039/b803693d

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 alkylation 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 alkylation of bicyclic hydrazines, which constitutes the first successful asymmetric alkylation of a symmetrical strained alkene.⁴

Symmetrical bicyclic hydrazines are attractive substrates because they are stable and can easily be obtained in multi-gram 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 NaHCO₃ 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 **L**¹ was oxidized to the corresponding phosphoric amide **L**², as determined by ¹H and ³¹P 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 alkylation 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 alkylation 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).

Dipartimento di Chimica Bioorganica e Biofarmacia, Università di Pisa, Via Bonanno 33, 56126 Pisa, Italy.

E-mail: pineschi@farm.unipi.it; Fax: +390502219660

† Electronic supplementary information (ESI) available: Experimental details and spectral data. See DOI: 10.1039/b803693d

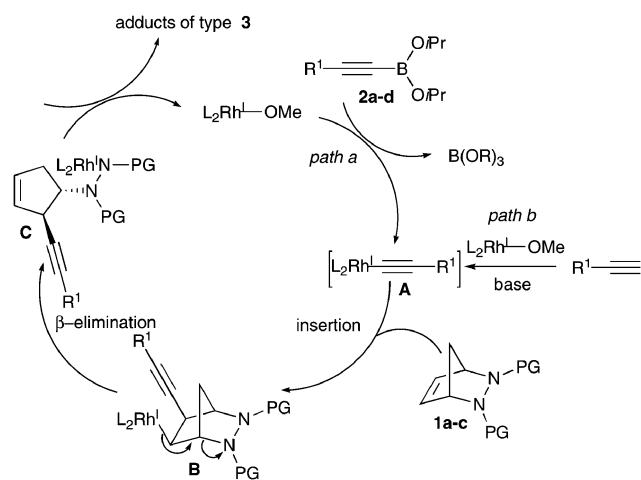
Table 1 Lewis-acid performance in the direct rhodium–Monophos catalyzed ring-opening of diazabicyclo **1a** with 1-hexyne^a

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(<i>i</i> PrO) 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 alkylation 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(C₂H₄)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).

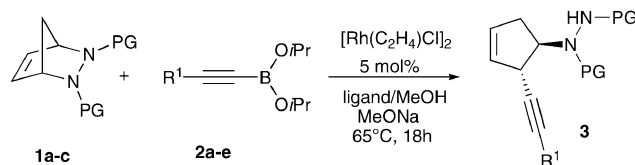
The direct use of terminal alkynes was also examined in the enantioselective ring opening (entries 3, 8, 12). Even if the

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

enantioselectivity of the corresponding adducts of type **3** was of the same level, the conversions and yields were remarkably lower.

Therefore, the experimental data indicate that the basic reaction conditions activate the terminal C(sp)³–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 carboration 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-demetalation

Table 2 Rhodium-catalyzed enantioselective alkylation of diazabicycles **1a–c**^a

Entry	PG	R ¹	Ligand	Conv. ^b (%)	Ee ^c (%)
1	COOBn (1c)	<i>n</i> -C ₄ H ₉ (2a)	Tol-Binap	81 (54) 3ca	52
2	COOBn (1c)	<i>n</i> -C ₄ H ₉ (2a)	Xylyl-Binap	66 (43) 3ca	60
3	COOBn (1c)	<i>n</i> -C ₆ H ₁₀ ^d	Tol-Binap	25	38
4	COOBn (1c)	Ph (2c)	Xylyl-Binap	85 (67) 3cc	66
5 ^c	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)	<i>t</i> -Bu (2d)	Tol-Binap	55 (40) 3cd	48
10	COOBn (1c)	<i>t</i> -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 (SiO₂) 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(C₂H₄)₂Cl]₂ (5 mol%), ligand (12 mol%), B(*O*iPr)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 synthesized 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 transmetalation 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 diazabicyclic, avoiding alkyne dimerization, which is often an inherent problem when dealing with alkynyl–rhodium intermediates.

This work was supported by the Ministero dell'Università e della Ricerca (PRIN 2006, *Catalysts, methodologies and new regio- and stereoselective processes in organic synthesis*) and by the University of Pisa.

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(C₂H₄)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 NaHCO₃ after 18 h. After extraction with Et₂O (2 × 10 ml) and CH₂Cl₂ (10 ml), the organic phase was dried with MgSO₄, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography.

- Palladium: (a) L. Chen and C.-J. Li, *Chem. Commun.*, 2004, 2362; ruthenium: (b) S. Chang, Y. Na, E. Choi and S. Kim, *Org. Lett.*, 2001, **3**, 2089; copper: (c) T. F. Knöpfel and E. M. Carreira, *J. Am. Chem. Soc.*, 2004, **125**, 6054; (d) T. F. Knöpfel, P. Zarotti, T. Ichikawa and E. M. Carreira, *J. Am. Chem. Soc.*, 2005, **127**, 9682; (e) S. Fujimori and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2007, **46**, 4964; rhodium: (f) G. I. Nikishin and I. P. Kovalev, *Tetrahedron Lett.*, 1990, **31**, 7063; (g) R. V. Lerum and J. D. Chisholm, *Tetrahedron Lett.*, 2004, **45**, 6591.
- (a) K. Yoshida and T. Hayashi, in *Modern Rhodium-Catalyzed Reactions*, ed. P. A. Evans, Wiley-VCH, Weinheim, 2005, pp. 55–77. For highly enantioselective rhodium-catalyzed

- ring opening of strained alkenes with aryl- and alkenylboronic acids, see: (b) M. Lautens, C. Dockendorff, K. Fagnou and A. Malicki, *Org. Lett.*, 2002, **4**, 1311; (c) H. A. McManus, M. J. Fleming and M. Lautens, *Angew. Chem., Int. Ed.*, 2007, **46**, 433.
- While this manuscript was being prepared, a highly enantioselective conjugate addition of (triisopropylsilyl)acetylene to α,β -unsaturated ketones was reported: T. Nishimura, X.-X. Gua, N. Uchiyama, T. Katoh and T. Hayashi, *J. Am. Chem. Soc.*, 2008, **130**, 1576.
- To the best of our knowledge, the only ring-opening addition of terminal acetylenes to bicyclic olefins was catalyzed by nickel complexes and afforded the corresponding *cis*-alkynylated dihydronaphthalene derivatives in a racemic form: (a) D. K. Rayabarapu, C.-F. Chiou and C.-H. Cheng, *Org. Lett.*, 2002, **4**, 1679; For the addition of terminal alkynes to norbornadiene, see: (b) A. Tenaglia, L. Giordano and G. Buono, *Org. Lett.*, 2006, **8**, 4315.
- O. Diels, J. H. Blom and W. Knoll, *Justus Liebigs Ann. Chem.*, 1925, **443**, 242–262.
- Racemic: (a) M.-L. Yao, G. Adiwidjaja and D. E. Kaufmann, *Angew. Chem., Int. Ed.*, 2002, **41**, 3375; (b) K. V. Radhakrishnan, V. S. Sajisha, S. Anas and K. S. Krishnan, *Synlett*, 2005, 2273; (c) J. John, V. S. Sajisha, S. Mohanlal and K. V. Radhakrishnan, *Chem. Commun.*, 2006, 3510; (d) F. Menard, C. F. Weise and M. Lautens, *Org. Lett.*, 2007, **9**, 5365; (e) C. Bournard, D. Robic, M. Bonin and L. Micouin, *J. Org. Chem.*, 2005, **70**, 3316. Asymmetric: (f) A. Pérez. Luna, M. Cesario, M. Bonin and L. Micouin, *Org. Lett.*, 2003, **5**, 4771; (g) M. Pineschi, F. Del Moro, P. Crotti and F. Macchia, *Org. Lett.*, 2005, **7**, 3605; (h) C. Bournard, C. Falciola, C. Lecourt, S. Rosset, A. Alexakis and L. Micouin, *Org. Lett.*, 2006, **8**, 3581; (i) F. Bertolini, F. Macchia and M. Pineschi, *Tetrahedron Lett.*, 2006, **47**, 9173; (j) F. Menard and M. Lautens, *Angew. Chem., Int. Ed.*, 2008, **47**, 2085.
- H. C. Brown, N. G. Bhat and M. Srebnik, *Tetrahedron Lett.*, 1988, **29**, 2631.
- T. R. Wu and J. M. Chong, *J. Am. Chem. Soc.*, 2005, **127**, 3244.
- For a review, see: P. W. N. M. van Leeuwen, *Appl. Catal. A: General*, 2001, **212**, 61.
- For a copper-catalyzed partial oxidation of a phosphoramidite, see: M. G. Pizzuti, A. J. Minnaard and B. L. Feringa, *J. Org. Chem.*, 2008, **73**, 940. Control experiments carried out with newly synthesized Monophos oxide **L**² (from Monophos and H₂O₂ in CH₂Cl₂), showed a lower activity of this ligand compared with the phosphoramidite, which probably undergoes a slow oxidation under the reaction conditions.
- Other bases used were MeONa, CsF, K₂CO₃, NaHCO₃, *t*BuOK, *i*PrONa.
- Determined by ¹³C NMR spectra of boronate **2a** performed in CD₃OD at 65 °C.
- For recent examples, see: (a) J.-i. Ito, M. Kitase and H. Nishiyama, *Organometallics*, 2007, **26**, 6412; (b) J. M. Joo, Y. Yuan and C. Lee, *J. Am. Chem. Soc.*, 2007, **129**, 14818.
- T. B. Marder, D. Zargarian, J. C. Calabrese, T. H. Herskovitz and D. Milstein, *J. Chem. Soc., Chem. Commun.*, 1987, 1484.
- For a very recent mechanistic study on the transmetalation from boron to rhodium by β -elimination, see: P. Zhao, C. D. Incarvito and J. F. Hartwig, *J. Am. Chem. Soc.*, 2007, **129**, 1876.
- M. Ge, E. Cline and L. Yang, *Tetrahedron Lett.*, 2006, **47**, 5797.
- R. Kuang, A. K. Ganguly, T.-M. Chan, B. N. Pramanik, D. J. Blythin, A. T. Maphail and A. K. Saksena, *Tetrahedron Lett.*, 2000, **41**, 9575.
- L. A. Trimble and J. C. Vederas, *J. Am. Chem. Soc.*, 1986, **108**, 6397.
- For a recent review, see: V. D. Bock, H. Hiemstra and J. H. van Maarseveen, *Eur. J. Org. Chem.*, 2006, 51–56.