ORGANIC LETTERS

2009
Vol. 11, No. 19
4346−4349

# Asymmetric Intermolecular Pauson−Khand Reaction of Symmetrically Substituted Alkynes

**Yining Ji, Antoni Riera,* and Xavier Verdaguer***

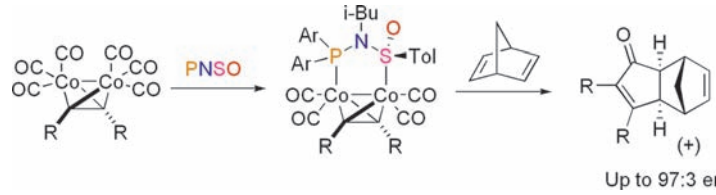
*Unitat de Recerca en Síntesi Asimètrica (URSA-PCB), Institute for Research in Biomedicine (IRB) and Departament de Química Orgànica, Universitat de Barcelona, c/Baldiri Reixac, 10. E-08028 Barcelona, Spain*

*antoni.riera@irbbarcelona.org; xavier.verdaguer@irbbarcelona.org*

**Received July 28, 2009**



## ABSTRACT




**The asymmetric intermolecular Pauson−Khand reaction of symmetric alkynes has been accomplished for the first time. *N*-Phosphino-*p*-tolylsulfinamide (PNSO) ligands have been indentified as efficient ligands in this process. The chirality of the cobalt S-bonded sulfinyl moiety was found to direct olefin insertion into one of the two possible cobalt−carbon bonds in the alkyne complex. Reaction of symmetric alkynes allows for a simplified experimental protocol since there is no need for separation of diastereomeric complexes.**

Since its discovery, the Pauson−Khand reaction (PKR) has attracted the interest of the community of chemists because it provides the most simple and attractive access to cyclopentenone compounds, which in turn are valuable synthetic intermediates.[1,2] The use of cobalt,[3,4] rhodium,[5] iridium,[6] and titanium[7] complexes has allowed the development of efficient asymmetric intramolecular versions of this process. Although great advances have been made in this field, one major challenge remains,[8] namely the use of symmetrically substituted alkynes in an enantioselective intermolecular process. From the synthetic point of view, an intermolecular reaction offers a clear advantage over an intramolecular one: from three simple components (alkene, alkyne, CO) it provides high added-value molecules in a single step.

The standard methodology used in the asymmetric cobalt-mediated intermolecular PKR relies on the use of chiral phosphines and terminal alkynes.[9] The reaction of a chiral phosphine with a terminal dicobalt−alkyne complex provides two diastereomers. Once these are separated, olefin reaction with each diastereomer usually leads to the corresponding PKR product in high optical purity. The success of this approach depends on two

(1) Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E.; Foreman, M. I. *J. Chem. Soc., Perkin Trans. 1* **1973**, 977.
(2) Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E. *J. Chem. Soc., Chem. Commun.* **1971**, 36.
(3) Gibson, S. E.; Lewis, S. E.; Loch, J. A.; Steed, J. W.; Tozer, M. J. *Organometallics* **2003**, *22*, 5382.
(4) Hiroi, K.; Watanabe, T.; Kawagishi, R.; Abe, I. *Tetrahedron: Asymmetry* **2000**, *11*, 797.
(5) Jeong, N.; Sung, B. K.; Choi, Y. K. *J. Am. Chem. Soc.* **2000**, *122*, 6771.
(6) Shibata, T.; Takagi, K. *J. Am. Chem. Soc.* **2000**, *122*, 9852.
(7) Hicks, F. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 7026.
(8) For selected reviews on the PKR, see: (a) Shibata, T. *Adv. Synth. Catal.* **2006**, *348*, 2328. (b) Gibson, S. E.; Mainolfi, N. *Angew. Chem., Int. Ed.* **2005**, *44*, 3022. (c) Laschat, S.; Becheanu, A.; Bell, T.; Baro, A. *Synlett* **2005**, 2547. (d) Bonaga, L. V. R.; Krafft, M. E. *Tetrahedron* **2004**, *60*, 9795. (e) Blanco-Urgoiti, J.; Anorbe, L.; Pérez-Serrano, L.; Dominguez, G.; Pérez-Castells, J. *Chem. Soc. Rev.* **2004**, *33*, 32. (f) Gibson, S. E.; Stevenazzi, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1800. (g) Brummond, K. M.; Kent, J. L. *Tetrahedron* **2000**, *56*, 3263. (h) Pericàs, M. A.; Balsells, J.; Castro, J.; Marchueta, I.; Moyano, A.; Riera, A.; Vazquez, J.; Verdaguer, X. *Pure Appl. Chem.* **2002**, *74*, 167.
(9) (a) Bladon, P.; Pauson, P. L.; Brunner, H.; Eder, R. *J. Organomet. Chem.* **1988**, *355*, 449. (b) Hay, A. M.; Kerr, W. J.; Kirk, G. G.; Middlemiss, D. *Organometallics* **1995**, *14*, 4986. (c) Castro, J.; Moyano, A.; Pericàs, M. A.; Riera, A.; Alvarez-Larena, A.; Piniella, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 7944.

10.1021/ol901728r CCC: $40.75 
**Published on Web 09/09/2009**

crucial chemical events: (a) olefin coordination to the phosphine-free cobalt atom and (b) olefin insertion on the Co−C(terminal) bond, as illustrated in Figure 1.

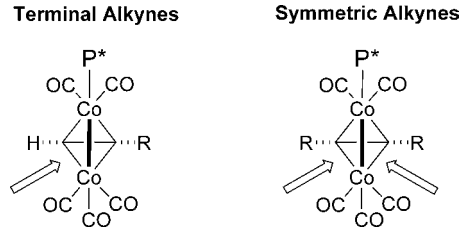
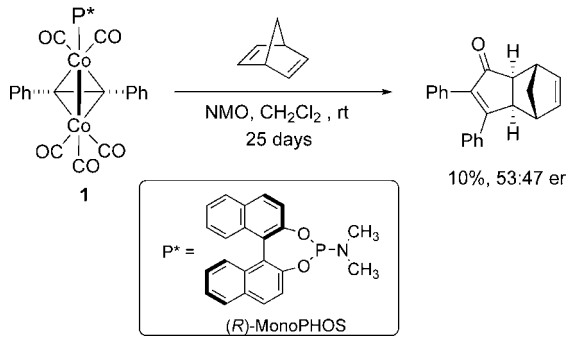



**Figure 1.** Olefin insertion in phosphine−alkyne complexes.

Several factors hamper the use of internal symmetric alkynes in the asymmetric PKR. First, these compounds are intrinsically less reactive than terminal ones. In addition, once a phosphine is bound to the alkyne−$Co_2$ complex, the structural element containing the chiral information is too far away to direct olefin insertion. Consequently, olefin is inserted indistinctively on either side of the alkyne, which leads to a racemic product (Figure 1). To illustrate this behavior, we synthesized the corresponding (*R*)-MonoPHOS−$Co_2(CO)_5$−$C_2Ph_2$ complex **1** (Scheme 1). When **1** was reacted with

**Scheme 1.** PKR of Diphenylacetylene Complex with MonoPHOS




norbornadiene in the presence of *N*-methylmorpholine *N*-oxide (NMO), the corresponding PKR cyclopentenone was produced in only 10% yield and a 53:47 enantiomeric ratio. This observation confirmed that when the chiral information is placed away from the olefin insertion it does not induce any relevant selectivity.[10]

Over the past decade, we have developed hemilabile chiral bidentate P,S ligands for the intermolecular PKR of terminal alkynes.[11−14] We have recently introduced *N*-phosphinosulfinamides (PNSO) ligands as novel and efficient chiral controllers for the intermolecular PKR (Figure 2).[15,16] When

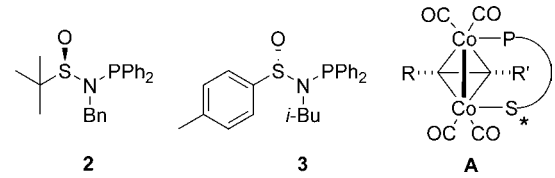
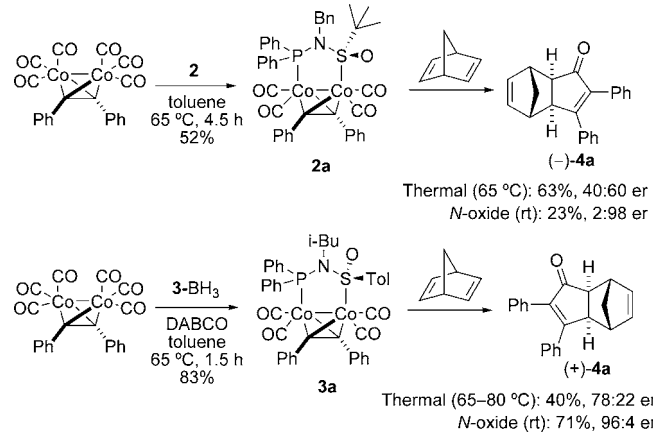


**Figure 2.** *N*-Phosphine−sulfinamide (PNSO) ligands and their $Co_2$−alkyne complexes.

coordinated to $Co_2$−alkyne complexes (R′ = H), ligands **2** and **3** function as bridged P,S ligands. The main feature of the resulting complexes (**A**) is that the chiral sulfur atom is directly bound to one of the cobalt atoms. We consider that the chirality of the sulfinyl group is ideally suited to direct the insertion of the olefin in type **A** complexes derived from symmetric alkynes (R = R′). Here we provide the first report on a highly enantioselective intermolecular asymmetric PKR with internal symmetric alkynes.

For exploratory purposes, we began using diphenylacetylene as a benchmark internal symmetric alkyne (Scheme 2).

**Scheme 2.** Asymmetric Intermolecular Pauson−Khand Reactions of Diphenylethyne




Ligand-exchange reaction of the corresponding dicobalt hexacarbonyl complex with PNSO ligand **2**, bearing a *tert*-butylsulfinyl group, provided the desired bridged single enantiopure complex (**2a**) in 52% yield. Reaction of **2a** with

(10) An attractive alternative could be the use of chiral $C_2$ diphosphines. However, double phosphorus coordination turns the resulting complexes completely unreactive; see: Derdau, V.; Laschat, S.; Dix, I.; Jones, P. G. *Organometallics* **1999**, *18*, 3859.

(11) Verdaguer, X.; Moyano, A.; Pericàs, M. A.; Riera, A.; Maestro, M. A.; Mahia, J. *J. Am. Chem. Soc.* **2000**, *122*, 10242.

(12) Verdaguer, X.; Pericàs, M. A.; Riera, A.; Maestro, M. A.; Mahía, J. *Organometallics* **2003**, *22*, 1868.

(13) Verdaguer, X.; Lledó, A.; López-Mosquera, C.; Maestro, M. A.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **2004**, *69*, 8053.

(14) Solà, J.; Riera, A.; Verdaguer, X.; Maestro, M. A. *J. Am. Chem. Soc.* **2005**, *127*, 13629.

(15) Solà, J.; Revés, M.; Riera, A.; Verdaguer, X. *Angew. Chem., Int. Ed.* **2007**, *46*, 5020.

(16) Revés, M.; Achard, T.; Solà, J.; Riera, A.; Verdaguer, X. *J. Org. Chem.* **2008**, *73*, 7080.

norbornadiene for 2 days at 65 °C provided the corresponding levorotatory product **4a** in good yield but low enantioselectivity (40:60 er). When the same reaction was performed under *N*-oxide-promoted conditions (NMO, $CH_2Cl_2$, rt), the reaction time increased to 17 days and the yield was only 23%; however, the product showed excellent optical purity (2:98 er). We subsequently explored the *p*-tolylsulfinyl PNSO ligand **3** in the same process (Figure 2, Scheme 2). For reasons of stability, ligand **3** is better stored as its borane complex.[16] This is not an inconvenience since borane removal and ligand exchange reaction can be performed in a one-pot procedure. Complex **3a** was obtained from diphenylacetylene in an improved 83% yield. Gratifyingly, *N*-oxide-promoted reaction led to **4a** in good yield (71%) and excellent enantiomeric excess (96:4 er). Again, thermal conditions provided the PKR product in lower enantiomeric purity (78:22 er) than the *N*-oxide-mediated reaction.

Most interestingly, the stereochemistry of the sulfinyl moiety in ligands **2** and **3** determined the absolute configuration of the PKR adducts. Thus, $R_S$ ligand **2** provided levorotatory cyclopentenones, while $S_S$ ligand **3** afforded dextrorotatory ones. The absolute configuration of the disubstituted adducts was determined by means of X-ray crystallography of a dichloro analogue (Figure 3).[17]

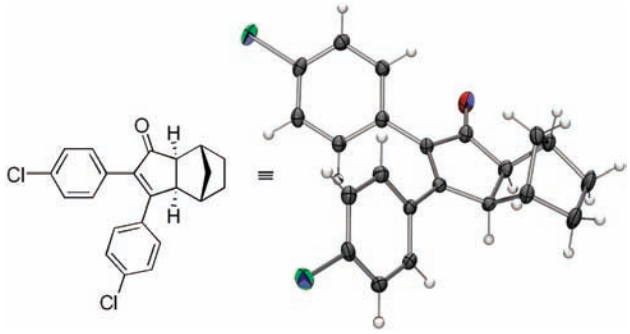



**Figure 3.** Dihydro derivative of (+)-**4d** and its X-ray structure.

Despite a slightly lower selectivity, overall, the *p*-tolyl ligand **3** was more effective than the *tert*-butyl analogue since it afforded higher yields in the ligand exchange and cycloaddition steps. At this point, in an attempt to improve selectivity, we undertook the optimization of the phosphine moiety in ligand **3**. For this purpose, ligands **5**−**8** were synthesized from the corresponding *N*-isobutyl-*p*-tolylsulfinamide. Reaction of lithium sulfinamide with the corresponding $Ar_2PCl$ reagent followed by treatment with $BH_3-SMe_2$ in a one-pot procedure afforded the desired borane-protected ligands in good to excellent yield (Figure 4). In the case of ligand **7**, increased steric hindrance around the phosphorus atom prevented borane protection allowing the isolation of **7** as a free phosphine.

(17) Compound (+)-**4d** was partially hydrogenated ($H_2$, Pd/C, MeOH). The dihydro derivative provided single crystals suitable for X-ray analysis. The absolute configuration was determined by the anomalous dispersion method.

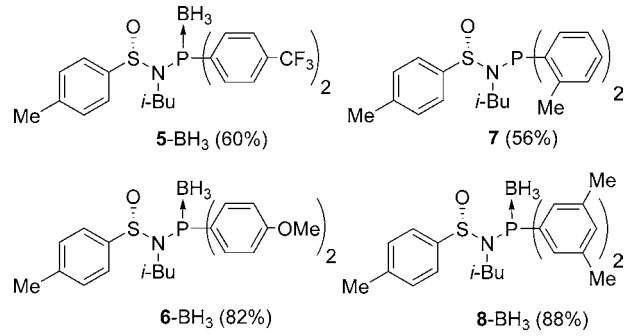



**Figure 4.** Novel PNSO ligands with a range of diarylphosphine groups. Yield in parentheses corresponds to the one-pot phosphinylation−borane protection of the corresponding *N*-isobutyl-*p*-tolylsulfinamide (*n*-BuLi, THF, −78 °C, $Ar_2PCl$, then $BH_3-SMe_2$ at −30 °C).

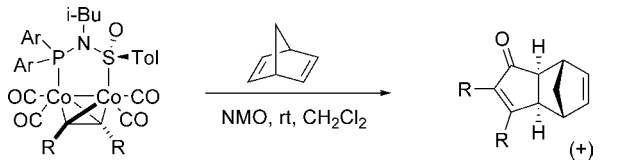
With the novel ligands in hand, we proceeded to check their efficiency toward the PKR of diphenylacetylene (Table 1, entries 2−5). While ligands **3**, **6**, and **8** afforded the corresponding bridged complexes in excellent yield, the PNSO ligand **7** failed to produce the desired complex **7a**. Again, it is highly probable that the steric encumbrance caused by the *ortho* substituents on the phosphine moiety obstructed the ligand-exchange reaction. The novel PNSO ligands exhibited small differences in selectivity, all of them giving higher than 95:5 er. Among these, compound **6**, holding a bis(*p*-methoxyphenyl)phosphine group, afforded the final PKR adduct in an enhanced 97:3 enantiomeric ratio (Table 1, entry 3). We then proceeded to explore the scope of the reaction with respect to the nature of the alkyne component. We found that neither electron-releasing nor electron-withdrawing groups on the aromatic rings attached to the alkyne have any effect on the outcome of the reaction (Table 1, entries 6−10). Again, for both methoxy- and fluorine-substituted substrates, ligand **6** provided a better enantiomeric ratio than ligand **3**. Alkynes with nonaromatic substituents were also studied. Triisopropylsilyl (TIPS)-protected 2-butyne-1,4-diol provided a good yield of the bridged complex and an enantiomeric ratio of 93:7 (Table 1, entry 12). Finally, complex **6f** derived from 4-octyne provided the cyclization product in low yield (27%) but excellent enantioselectivity (94:6 er).

Previous research on intermolecular PKR of terminal alkynes has shown that directing olefin insertion to a specific Co−C bond is essential to accomplish stereoselective cyclization.[9] With this in mind, a feasible mechanistic scenario that would account for the observed results is that in the presence of *N*-oxide the PNSO ligand works mainly as a

(18) For a review on sulfoxide−metal bonding, see: Calligaris, M. *Coord. Chem. Rev.* **2004**, *248*, 351.

(19) (a) Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Tetrahedron Lett.* **1990**, *31*, 5289. (b) Verdaguer, X.; Moyano, A.; Pericàs, M. A.; Riera, A.; Bernardes, V.; Greene, A. E.; Alvarez-Larena, A.; Piniella, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 2153. (c) Montenegro, E.; Poch, M.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron Lett.* **1998**, *39*, 335. (d) Verdaguer, X.; Vazquez, J.; Fuster, G.; Bernardes-Genisson, V.; Greene, A. E.; Moyano, A.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **1998**, *63*, 7037.

**Table 1.** Pauson−Khand Reaction of the PNSO−dicobalt Complexes with Norbornadiene




| entry | R | ligand | complex (yield %)[a] | time (days) | yield (%)[b] | er (%)[c] | enone |
|---|---|---|---|---|---|---|---|
| 1 | Ph | **3** | **3a** (83) | 20 | 71 | 96:4 | **4a** |
| 2 | Ph | **5** | **5a** (88) | 25 | 73 | 95:5 | **4a** |
| 3 | Ph | **6** | **6a** (90) | 17 | 77 | 97:3 | **4a** |
| 4 | Ph | **7** | **7a** | | | | |
| 5 | Ph | **8** | **8a** (80) | 19 | 64 | 94:6 | **4a** |
| 6 | 4-MeO-Ph | **3** | **3b** (86) | 22 | 73 | 95:5 | **4b** |
| 7 | 4-MeO-Ph | **6** | **6b** (78) | 26 | 73 | 96:4 | **4b** |
| 8 | 4-F-Ph | **3** | **3c** (82) | 17 | 82 | 95:5 | **4c** |
| 9 | 4-F-Ph | **6** | **6c** (85) | 26 | 85 | 97:3 | **4c** |
| 10 | 4-Cl-Ph | **6** | **6d** (88) | 26 | 85 | 97:3 | **4d** |
| 11 | $TIPSOCH_2$ | **3** | **3e** (78) | 19 | 80 | 90:10 | **4e** |
| 12 | $TIPSOCH_2$ | **6** | **6e** (74) | 24 | 57 | 93:7 | **4e** |
| 13 | *n*-Pr | **3** | **3f** (43) | 25 | 6 | 94:6 | **4f** |
| 14 | *n*-Pr | **6** | **6f** (66) | 26 | 27 | 94:6 | **4f** |

[a] Yields of isolated complexes after flash chromatography. Reaction conditions: 1,4-diazabicyclo[2.2.2]octane (DABCO), toluene, 65 °C. [b] Yields of isolated products after flash chromatography. Reaction conditions: *N*-methylmorpholine *N*-oxide (NMO), $CH_2Cl_2$, rt. [c] Enantiomeric ratio determined by chiral HPLC.

solid bridging ligand and that olefin insertion occurs on the cobalt center where the sulfinyl group is bound, as depicted in **I** (Figure 5). Steric factors and the higher $\pi$-acidity of the sulfinyl ligand would favor olefin coordination at this cobalt center rather than to the one where the phosphine is bonded.[18] Once the olefin is bonded to cobalt, sulfur chirality would direct olefin insertion toward one of the two Co−C bonds. In contrast to terminal alkynes, a hemilabile ligand cannot explain the selectivity observed in an internal symmetric substrate since sulfur chirality would be too far away to direct olefin insertion, as depicted in **II** (Figure 5). Several experimental findings support the above mechanistic hypothesis. First, the stereochemistry of the sulfinyl moiety efficiently determines the configuration of the final product.

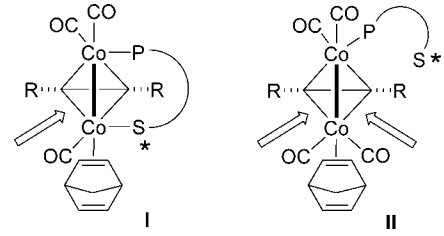



**Figure 5.** Olefin insertion hypotheses for $Co_2$−alkyne−PNSO complexes.

This observation indicates that olefin insertion takes place close to the chiral sulfur center. Second, better selectivities were accomplished under *N*-oxide conditions, thereby indicating that the PNSO ligand works as a solid bridging ligand rather than a hemilabile one. *N*-Oxides favor depletion of carbon monoxide in the reaction media, thus favoring closed bridged species rather than open ones like **II**.[19]

In summary, we have developed for the first time an asymmetric intermolecular PKR for internal symmetric alkynes. *N*-phosphino-*p*-tolylsulfinamide ligands that function as bridged P,S ligands were the most effective in this process. Extended reactions times, mostly due to the intrinsic low reactivity of internal alkynes, are not overly problematic since reactions were performed at room temperature. From a practical point of view, the use of symmetric alkynes prevents the formation of diastereomeric complexes and their separation. We propose a novel mechanism in which the sulfinyl group remains attached to cobalt and directs olefin insertion.

**Acknowledgment.** This work was supported by MICINN (CTQ2008-00763/BQU). Y.J. thanks the MEC for a fellowship.

**Supporting Information Available:** Experimetnal procedures; spectral and analytical data for all new compounds. Crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

OL901728R