ORGANOMETALLICS

What Controls Stereoselectivity and Reactivity in the Synthesis of a *trans*-Decalin with a Quaternary Chiral Center via the Intramolecular Pauson–Khand Reaction: A Theoretical Study

Song Liu,[†] Hongjuan Shen,[‡] Zhaoyuan Yu,[†] Lili Shi,[‡] Zhen Yang,^{*,‡} and Yu Lan^{*,†}

[†]School of Chemistry and Chemical Engineering, Chongqing University, Chongqing 400030, People's Republic of China

[‡]Laboratory of Chemical Genomics, School of Chemical Biology and Biotechnology, Peking University Shenzhen Graduate School, Shenzhen 518055, People's Republic of China

Supporting Information

ABSTRACT: The $Co_2(CO)_8$ -mediated intramolecular Pauson–Khand reaction is an efficient approach to the *trans*-decalin subunit with a defined C1 quaternary chiral center. The newly developed density functional theory method M11-L was employed to study the mechanism, reactivity, and stereoselectivity for this reaction. The rate- and stereoselectivity-determining step is the intramolecular alkene insertion into the carbon–cobalt bond. Insertion of the alkene by the *re*- and *si*-face was studied to explain the stereoselectivity. The effects of varying the substituent on the acetylene and the C3 chirality were investigated experimentally and theoretically.

T he Pauson–Khand reaction (PKR) was first reported in 1971.¹ It is a cycloaddition with an alkyne, an alkene, and carbon monoxide, used to generate synthetically useful cyclopentenones.² The PKR is normally catalyzed by cobalt,³ but other transition metal catalysts, such as titanium,⁴ zirconium,^{4b,5} nickel,⁶ molybdenum,⁷ ruthenium,⁸ rhodium,⁹ iridium,¹⁰ and palladium¹¹ can also be used. Recently, some of us reported a cobalt-mediated PKR using enynes to construct 6,6,5-tricyclic and 6,6-bicyclic skeletons.¹² This could be used in the synthesis of natural products containing *trans*-decalin subunits. Cyclopentanaphthalenone **2** was prepared via a PKR from enyne **1** (see SI for the synthesis of enyne **1**) with a stoichiometric amount of Co₂(CO)₈ at 110 °C under nitrogen in yields of up to 80% (Scheme 1).¹³ In this PKR,



toluene is used as solvent, while the trimethylamine *N*-oxide (TMANO) is additive. It has been well known that amine *N*-oxides could be employed to remove carbon monoxide ligands from transition metal complexes by oxidation to carbon dioxide.¹⁴ We have found that TMANO is the most effective promoter for this PKR.¹⁵ The *trans*-decalin has a defined C1



quaternary chiral center and was formed stereoselectively under these conditions. Enynes with a TMS (trimethylsilyl)-protected C5-hydroxyl group gave a better yield of product than those protected with (t-butyldimethylsilyl) or MOM (methoxymethyl). The reactivity of enyne 1 is controlled by the stereochemistry at C3. An *S* configuration gave a higher yield of product than those with an *R* configuration. Mechanistic studies are needed to understand these experimental observations.

The accepted mechanism of the cobalt-mediated PKR was proposed by Magnus in 1985.¹⁶ This involves reversible ligand exchange of carbon monoxide and an alkene on a $Co_2(CO)_8$ complex, followed by olefin insertion to form a five-membered metallocycle. Subsequently, carbonyl insertion and reductive elimination afford a cyclopentenone complex.¹⁷ This mechanism could also be applied to other metal-catalyzed PKRs,¹⁸ except those with palladium.¹⁹ The first density functional theory (DFT) study on the mechanism of cobalt-mediated intermolecular PKR was reported by Nakamura in 2001²⁰ and supported Magnus's mechanism. C-C bond formation leading to the cobaltacycle is the rate-determining step. Theoretical studies for intermolecular PKR indicated that the regioselectivity of the alkyne is controlled by both steric and electronic effects in the alkene insertion step.^{20,21} However, there are relatively few high-level theoretical studies on the stereoselectivity of the intramolecular PKR.²² Herein we report DFT calculations used to study the mechanism of the newly reported

Received: August 18, 2014 Published: November 5, 2014



Figure 1. Free-energy profiles and geometric information for the reaction pathway of $Co_2(CO)_8$ -mediated PKR. The values given by kcal/mol are the relative free energies and enthalpies calculated by the M11-L method in toluene solvent.

cobalt-mediated PKR to clarify the reactivity and stereo-selectivity.

All DFT calculations were carried out with the GAUSSIAN 09 series of programs.²³ DFT method B3LYP²⁴ with a standard 6-31G(d) basis set (SDD basis set for cobalt atoms) was used for geometry optimizations. Harmonic frequency calculations were performed for all stationary points to confirm them as local minima or transition state structures and to derive the thermochemical corrections for the enthalpies and free energies. The newly developed M11-L²⁵ functional with a standard 6-311+G(d) basis set (SDD for cobalt atoms), proposed by the Truhlar group, was used to calculate singlepoint energies in toluene with the conductor-like polarizable continuum model (CPCM), which could give more accurate energy information.²⁶ All values are given in kcal/mol. The M11-L-calculated free energy profiles of this intramolecular PKR in toluene are shown in Figure 1. Compound 3 was used initially to study the mechanism, which is set to the relative zero with a $Co_2(CO)_8$ molecule. Compound 3 reacted with $Co_2(CO)_8$ to form $Co_2/acetylene$ complex 4 with the release of two molecules of CO, with a 6.7 kcal/mol exotherm. The intramolecular coordination of the re-face of the alkene goes via coordinatively unsaturated complex 5 to give thermodynamically unfavorable complex 6 with the release of one molecule of CO. The re-face of the coordinated alkenyl group then inserts into the Co-C bond via transition state 7-ts with an activation free energy of 27.0 kcal/mol. These values indicate that insertion of this alkenyl group is the rate-determining step for the PKR. Complex 8, which contains a 6,6-bicyclic skeleton, coordinates with CO to give 9. A further CO insertion goes via 10-ts with a barrier of 10.9 kcal/mol with reversible formation of intermediate 11. Further CO coordination (11 to 12) is followed by reductive elimination to irreversibly give complex 14 via 13-ts. The activation energy for this step is 16.2 kcal/

mol. Product 15 is then generated with the formation of $Co_2(CO)_6$ from 14 with a 14.5 kcal/mol exotherm.

Another case is indicated by red lines in Figure 1. The cobalt in **5** coordinates with the *si*-face of the alkene to give **16** with a 2.9 kcal/mol endotherm. The relative free energy of **16** is 4.2 kcal/mol higher than that of **6**. This insertion could take place via **17-ts** with an activation energy of 30.3 kcal/mol, which is 3.3 kcal/mol higher than for the *re*-face. The competing insertion steps indicate that only complex **15** forms and the *re*face alkene insertion is observed experimentally.

The geometry information on important intermediates and transition states is shown in Figure 1, in which most hydrogen atoms are omitted for clarity. Complex 6 is formed with the coordination of an alkenyl group with the re-face, in which the configuration of the newly formed metal-containing sevenmembered ring is chair type. In complex 16, the si-face of the alkene coordinates to cobalt, resulting in the change in configuration, which leads to the higher relative free energy of 16 compared with 6. In transition state 17-ts, the inserting alkenyl group is closed with CO coordinated to cobalt (Figure 1). The distances between the inserting alkenyl group hydrogens and coordinated CO carbons (H1…C11 and H2… C12) are 2.63 and 2.65 Å, respectively. This is because the configuration of the inserting alkene and the corresponding $Co(CO)_2$ is eclipsed in 17-ts. In 7-ts, the staggered configuration of the two groups leads to longer distances (H1…C11 and H2…C12) of 2.78 and 2.68 Å, respectively, to reduce steric repulsion. Therefore, the relative free energy of 17-ts is higher than that of 7-ts.

The effect of varying the R group in complex **20** was studied (Table 1). When R is an alkyl group, a lower yield was observed (entries 1, 2). With an *S* configuration at C3 (entries 1, 2) higher yields were observed than for enynes with an *R* configuration (entries 3, 4).



^aTMS: trimethylsilyl; TBS: t-butyldimethylsilyl.

Complex **20a**, with a terminal methyl on the acetylene, was used to study the substituent effect (Figure 2). Coordination of



Figure 2. Free energy profiles and geometry information for the alkene insertion step of the PKR with **20a**. The values given in kcal/mol are the relative free energies and enthalpies calculated by the M11-L method in toluene solvent.

20a to $Co_2(CO)_8$ with the release of two molecules of CO leads to a 1.3 kcal/mol free energy decrease (5.4 kcal/mol higher than for unsubstituted 3). This is because of the steric repulsion of the terminal methyl group from the CO on the cobalt. The alkene insertion takes place via **23-ts** with a barrier of 28.0 kcal/mol (1.0 kcal/mol higher than for unsubstituted 3). This theoretical result indicates that insertion of the alkene

into 20a is harder than for 3, which is consistent with experimental observations. The steric repulsion between the terminal methyl group on acetylene and the CO coordinated with cobalt leads to the CO moving close to the inserting alkenyl group. The distances between the hydrogen atoms in the inserting alkenyl group and carbon atoms in the coordinated CO (H1…C11 and H2…C12) are 2.73 and 2.59 Å, respectively, which are about 0.05-0.09 Å shorter than those in 7-ts.

Enyne 20c was used to study the effect of C3 chirality on the PKR (Figure 3). The reaction of enyne 20c with $Co_2(CO)_8$



Figure 3. Free energy profiles and geometry information for the alkene insertion step of the PKR with **20c**. The values given in kcal/mol are the relative free energies and enthalpies calculated by the M11-L method in toluene solvent.

resulted in a 4.2 kcal/mol exotherm with the release of two molecules of CO. The alkene inserted into the carbon—cobalt bond via 27-ts with a barrier of 29.2 kcal/mol, which is 1.2 kcal/mol higher than the corresponding step for 20a via 23-ts. The calculations indicate that the insertion step for enyne 20c with the *R* configuration at C3 is harder than that for enyne 20a with the *S* configuration. This is consistent with lower yields for 20c and 20d. In the newly formed six-membered ring, both the methyl group on the alkene and the OTBS are axial. The 1,3-repulsion between the two groups leads to a higher relative energy for 27-ts. The distance of H5…O1 is 2.29 Å, which also indicates 1,3-repulsion.

In summary, the newly reported DFT method, M11-L, has been used to study the mechanism of the $Co_2(CO)_8$ -mediated PKR in the stereoselective synthesis of the trans-decalin subunit with a defined C1 quaternary chiral center. The rate- and stereoselectivity-determining steps are the intramolecular alkene insertion into the carbon-cobalt bond. Theoretical calculations indicate that re-face insertion of the alkene is favorable, leading to the R configuration at C1. Experimental results showed that the alkyl group on the acetylene gives a lower yield, which can be explained theoretically by steric repulsion leading to higher activation energy. The R configuration at the C3 causes 1,3-repulsion in the formation of the six-membered ring and increases the activation energy of the alkene insertion transition state. Therefore, the S configuration at the C3 is better, which is consistent with experimental observations.

ASSOCIATED CONTENT

S Supporting Information

Cartesian coordinates and energies of all reported structures and full authorship of Gaussian 09. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Authors

*(Y. Lan) Tel: +86-18680805840. Fax: +86-023-65111067. Email: lanyu@cqu.edu.cn.

*(Z. Yang) Tel: +86-10-62759105. Fax: +86-10-62759105. Email: zyang@pku.edu.cn.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This project was supported by the National Science Foundation of China (Grants 21372266 and 51302327), the 973 Program (Grant No. 2012CB722602), and the Foundation of Bairenjihua Chongqing University (Project 0903005203191).

REFERENCES

(1) (a) Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E. J. Chem. Soc., Perkin Trans. 1 1973, 975–977. (b) Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E.; Foreman, M. I. J. Chem. Soc., Perkin Trans. 1 1973, 977–981.

(2) (a) Frühauf, H.-W. Chem. Rev. 1997, 97, 523-596. (b) Geis, O.;
Schmalz, H.-G. Angew. Chem., Int. Ed. 1998, 37, 911-914.
(c) Brummond, K. M.; Kent, J. L. Tetrahedron 2000, 56, 3263-3283. (d) Boñaga, L. V. R.; Krafft, M. E. Tetrahedron 2004, 60, 9795-9833. (e) Gibson, S. E.; Mainolfi, N. Angew. Chem., Int. Ed. 2005, 44, 3022-3037. (f) Xie, X.-J.; Yang, G.-S.; Zhao, G. Chin. J. Org. Chem. 2002, 22, 610-616.

(3) (a) Muller, J.-L.; Rickers, A.; Leitner, W. Adv. Synth. Catal. 2007, 349, 287–291. (b) Gibson, S. E.; Stevenazzi, A. Angew. Chem., Int. Ed. 2003, 42, 1800–1810. (c) Fletcher, A. J.; Christie, S. D. R. J. Chem. Soc., Perkin Trans. 1 2000, 1657–1668.

(4) (a) Hicks, F. A.; Kablaoui, N. M.; Buchwald, S. L. J. Am. Chem. Soc. 1996, 118, 9450–9451. (b) Hicks, F. A.; Berk, S. C.; Buchwald, S. L. J. Org. Chem. 1996, 61, 2713–2718. (c) Hicks, F. A.; Buchwald, S. L. J. Am. Chem. Soc. 1996, 118, 11688–11689. (d) Hicks, F. A.; Buchwald, S. L. J. Am. Chem. Soc. 1999, 121, 7026–7033. (e) Hicks, F. A.; Kablaoui, N. M.; Buchwald, S. L. J. Am. Chem. Soc. 1999, 121, 5881–5898. (f) Zhao, Z.; Ding, Y.; Zhao, G. J. Org. Chem. 1998, 63, 9285–9291.

(5) (a) Negishi, E.-I.; Holmes, S. J.; Tour, J. M.; Miller, J. A. J. Am. Chem. Soc. 1985, 107, 2568–2569. (b) Agnel, G.; Negishi, E.-I. J. Am. Chem. Soc. 1991, 113, 7424–7426.

(6) (a) Tamao, K.; Kobayashi, K.; Ito, Y. J. Am. Chem. Soc. **1988**, 110, 1286–1288. (b) Zhang, M.; Buchwald, S. L. J. Org. Chem. **1996**, 61, 4498–4499.

(7) (a) Mukai, C.; Uchiyama, M.; Hanaoka, M. J. Chem. Soc., Chem. Commun. 1992, 1014–1015. (b) Jeong, N.; Lee, S. L.; Lee, B. Y.; Chung, Y. K. Tetrahedron Lett. 1993, 34, 4027–4030. (c) Kent, J. L.; Wan, H.; Brummond, K. M. Tetrahedron Lett. 1995, 36, 2407–2410.
(d) Adrio, J.; Rivero, M. R.; Carretero, J. C. Org. Lett. 2005, 7, 431– 434. (e) Adrio, J.; Carretero, J. C. J. Am. Chem. Soc. 2007, 129, 778– 779.

(8) (a) Morimoto, T.; Chatani, N.; Fukumoto, Y.; Murai, S. J. Org. Chem. **1997**, 62, 3762–3765. (b) Kondo, T.; Suzuki, N.; Okada, T.; Mitsudo, T.-A. J. Am. Chem. Soc. **1997**, 119, 6187–6188. (c) Koga, Y.; Kobayashi, T.; Narasaka, K. Chem. Lett. **1998**, 27, 249–250.

(9) (a) Jeong, N.; Lee, S.; Sung, B. K. Organometallics **1998**, *17*, 3642–3644. (b) Jeong, N.; Sung, B. K.; Choi, Y. K. J. Am. Chem. Soc. **2000**, *122*, 6771–6772. (c) Fan, B. M.; Xie, J.-H.; Li, S.; Tu, Y.-Q.; Zhou, Q.-L. Adv. Syn. Catal. **2005**, *347*, 759–762. (d) Fan, B.; Li, S.;

Xie, J.; Wang, L.; Tu, Y.; Zhou, Q. Science in China, Ser. B: Chem. 2006, 49, 81–87. (e) Fan, B. M.; Li, S.; Xie, J. H.; Wang, L. X.; Tu, Y. Q.; Zhou, Q. L. Sci. China, Ser. B 2005, 35, 390–395.

(10) (a) Shibata, T.; Takagi, K. J. Am. Chem. Soc. 2000, 122, 9852– 9853. (b) Shibata, T.; Toshida, N.; Yamasaki, M.; Maekawa, S.; Takagi, K. Tetrahedron 2005, 61, 9974–9979.

(11) (a) Tang, Y.; Deng, L.; Zhang, Y.; Dong, G.; Chen, J.; Yang, Z. *Org. Lett.* **2005**, *7*, 1657–1659. (b) Deng, L.-J.; Liu, J.; Huang, J.-Q.; Hu, Y.; Chen, M.; Lan, Y.; Chen, J.-H.; Lei, A.; Yang, Z. *Synthesis* **2007**, *16*, 2565–2570.

(12) (a) Tang, Y.; Deng, L.; Zhang, Y.; Dong, G.; Chen, J.; Yang, Z. Org. Lett. 2005, 7, 593–595. (b) Jiang, B.; Xu, M. Angew. Chem., Int. Ed. 2004, 43, 2543–2546. (c) Bolton, G. L.; Hodges, J. C.; Rubin, J. R. Tetrahedron 1997, 53, 6611–6634.

(13) Shi, L.-L.; Shen, H.-J.; Fang, L.-C.; Huang, J.; Li, C.-C.; Yang, Z. Chem. Commun. 2013, 49, 8806–8808.

(14) (a) Alper, H.; Edward, J. T. Can. J. Chem. 1970, 48, 1543-1549.

(b) Shvo, Y.; Hazum, E. J. Chem. Soc., Chem. Commun. 1974, 336-337.

(c) Shen, J.-K.; Gao, Y.-C.; Shi, Q.-Z.; Basolo, F. Organometallics 1989, 8, 2144–2147.

(15) Jeong, N.; Chung, Y. K.; Lee, B. Y.; Lee, S. H.; Yoo, S.-E. Synlett. **1991**, 204–206.

(16) Magnus, P.; Principle, L. M. Tetrahedron Lett. **1985**, 26, 4851–4854.

(17) Torres, R. R. The Pauson–Khand Reaction: Scope, Variations, and Applications; Wiley: Weinheim, 2012; pp 23–48.

(18) (a) Lee, H.-W.; Kwong, F.-Y. Eur. J. Org. Chem. 2010, 789-811.
(b) Jeong, N.; Sung, B. K.; Choi, Y. K. J. Am. Chem. Soc. 2000, 122, 6771-6772.
(c) Kondo, T.; Nomura, M.; Ura, Y.; Wada, K.; Mitsudo, T.-A. J. Am. Chem. Soc. 2006, 128, 14816-14817.

(19) Lan, Y.; Deng, L.; Liu, J.; Wang, C.; Wiest, O.; Yang, Z.; Wu, Y.-D. J. Org. Chem. **2009**, 74, 5049–5058.

(20) Yamanaka, M.; Nakamura, E. J. Am. Chem. Soc. 2001, 123, 1703–1708.

(21) (a) Robert, F.; Milet, A.; Gimbert, Y.; Konya, D.; Greene, A. E. *J. Am. Chem. Soc.* **2001**, *123*, 5396–5400. (b) Fager-Jokela, E.; Muuronen, M.; Patzschke, M.; Helaja, J. J. Org. Chem. **2012**, *77*, 9134–9147.

(22) (a) Vázquez, J.; Fonquerna, S.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron: Asymmetry* **2001**, *12*, 1837–1850. (b) Fjermestad, T.; Pericàs, M. A.; Maseras, F. J. Mol. Catal. A: Chem. **2010**, *324*, 127–132. (c) Fjermestad, T.; Pericàs, M. A.; Maseras, F. Chem. Eur. J. **2011**, *17*, 10050–10057.

(23) Frisch, M. J.; et al. *Gaussian 09*; Gaussian, Inc.: Wallingford, CT, 2009.

(24) (a) Becke, A. D. J. Chem. Phys. **1993**, 98, 5648-5652. (b) Lee, C.; Yang, W.; Parr, R. G. Phys. Rev. B **1988**, 37, 785-789.

(25) Peverati, R.; Truhlar, D. G. J. Phys. Chem. Lett. 2011, 2, 2810-2817.

(26) (a) Peverati, R.; Truhlar, D. G. Phys. Chem. Chem. Phys. 2012, 14, 11363–11370. (b) Lin, Y.-S.; Tsai, C.-W.; Li, G.-D.; Chai, J.-D. J. Chem. Phys. 2012, 136, 154109. (c) Steckel, J. A. J. Phys. Chem. A 2012, 116, 11643–11650. (d) Zhao, Y.; Ng, H. T.; Peverati, R.; Truhlar, D. G. J. Chem. Theory Comput. 2012, 8, 2824–2834. (e) Yu, Z.; Lan, Y. J. Org. Chem. 2013, 78, 11501–11507.