Tetrahedron Letters 56 (2015) 5324–5327

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Cyclization of an alkene-bearing cyclopentanone: The role of rhodium and Brønsted acid

Xin Jiang, Zhongda Pan, Christopher J. Douglas *

Department of Chemistry, University of Minnesota—Twin Cities, 207 Pleasant St. SE, Minneapolis, MN 55455, USA

ARTICLE INFO

Article history:
Received 15 June 2015
Revised 23 July 2015
Accepted 27 July 2015
Available online 3 August 2015

Keywords:
Cyclopentanone
Rhodium
Acid-mediated
Rearrangement

ABSTRACT

The cyclization of an alkene-bearing cyclopentanone to a [2.2.1]-norcamphor ring system is described. The reaction is catalyzed by a combination of rhodium and Brønsted acid. Control experiments indicate that both are needed for acceptable yield. Control experiments with bulky base additives show that rhodium promotes alkene isomerization, likely the first step of this cascade reaction, and that rhodium alone does not promote cyclization. Cyclization is promoted by Brønsted acid in a Prins-type cyclization and carbocation rearrangement process. Trace Brønsted acid present in commercial samples of $Rh(cod)_2OTf$ is likely responsible for the observed reaction. Indeed, the norcamphor product can be obtained simply with strong acid, presumably initiated by acid-promoted alkene isomerization. Since our initial motivation for this work was the development of rhodium catalysts for the activation of C–C bonds adjacent to ketones, this communication serves to identify other, perhaps less obvious, pathways for the reactions of unsaturated ketone compounds by the action of rhodium catalysts.

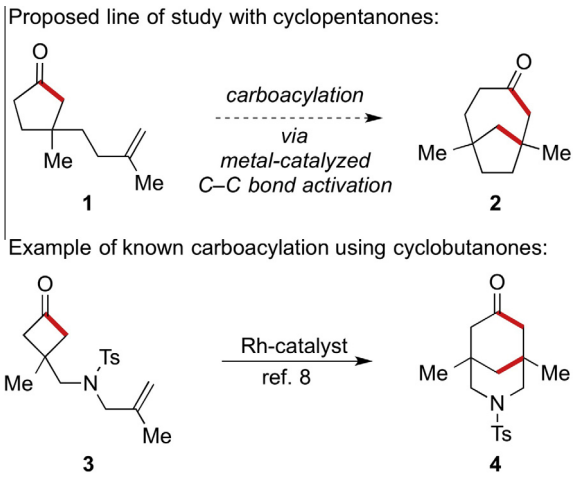
Carbon–carbon sigma (C–C) bond activation is a growing area of research for organic synthesis.[1] Our group has developed alkene carboacylation reactions based on the insertion of rhodium adjacent to unstrained ketones.[2,3] The general mechanistic strategy is to couple the activation of the C–C bond between a carbonyl carbon and the α-carbon with the insertion of an alkene.[4,5] In our prior work, we placed a nitrogen five atoms away from the carbonyl carbon to provide a chelate for C–C activation and prevent decarbonylation prior to an alkene engaging the activated bond in a productive capturing event.[6,7] Others have developed related alkene carboacylation reactions (sometimes termed 'cut-and-sew') without the judiciously placed heteroatom within the substrate, but this work is largely limited to strained ring ketones for starting materials, most often cyclobutanones.[8–12] Our goal at the outset of this work was to investigate similar chemistry of cyclopentanones, which have substantially less ring strain than the corresponding cyclobutanones. Herein, we report an unexpected cyclization encountered in our study. We show that a combination of alkene isomerization and a likely acid-mediated Prins-type cyclization and semi-pinacol rearrangement can account for the formation of this unexpected product. Our purpose in communicating this work is to demonstrate the need for an appropriate control experiment to rule out classic reaction pathways when developing C–C bond activation approaches to alkene carboacylation reactions.

We designed cyclopentanone **1** with the notion that rhodium might reversibly insert adjacent to the carbonyl. The tethered alkene could then coordinate to the metal center to promote carboacylation potentially generating the bridged compound **2** via alkene carboacylation (Scheme 1). This mechanistic thinking is in line with the documented cyclobutanone carboacylation reactions, exemplified by the transformation of cyclobutanone **3** to [3.3.1]bicyclo ring system in **4** (Scheme 1).

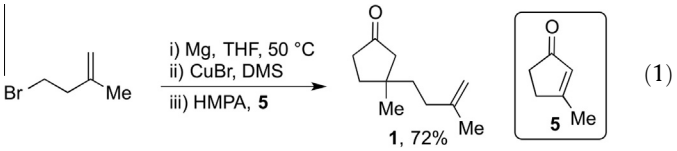
We expected that the insertion might be possible with a cyclopentanone system for the following reasons: (1) cyclopentanones are substantially more electrophilic than cyclohexanones or acyclic dialkyl ketones and (2) Jun has demonstrated that cycloalkanones can participate in metal-organic cooperative catalysis to activate C–C bonds.[13] Though cyclopentanone **1** is a known compound, the prior synthesis relied on a preparative gas chromatography procedure for purification that was impractical for our purposes.[14] We prepared **1** via organocopper conjugate addition into 3-methyl-2-cyclopentenone (**5**), which itself was easily prepared by intramolecular aldol condensation of hexane-2,5-dione.[15] The organocopper reagent derived from 4-bromo-2-methyl-1-butene underwent conjugate addition, providing **1** in 72% yield (Eq. (1)).[16,17] The synthesis was conducted on gram-scale.

* Corresponding author. Tel.: +1 612 625 0922; fax: +1 612 626 7541.
E-mail address: cdouglas@umn.edu (C.J. Douglas).

http://dx.doi.org/10.1016/j.tetlet.2015.07.086
0040-4039/



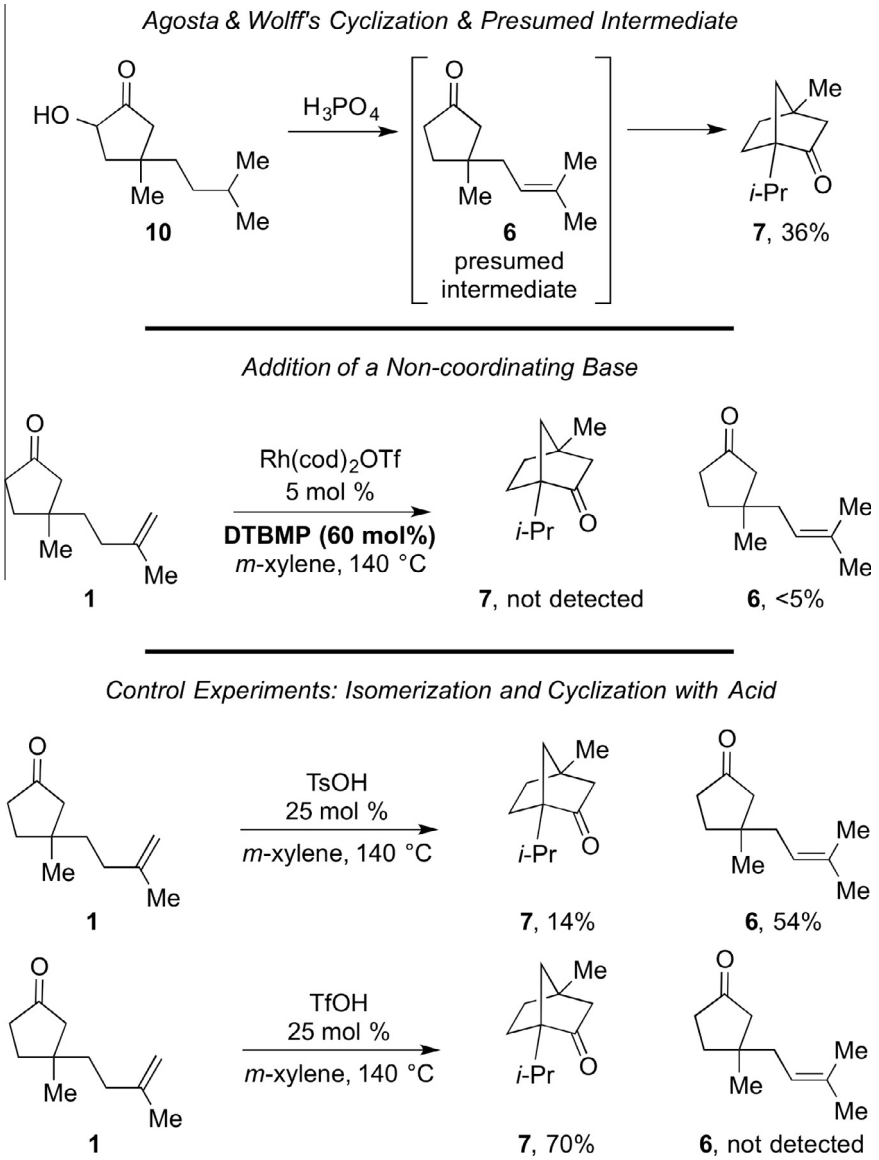
Scheme 1. Proposed and known carboacylation reactions.



(1)

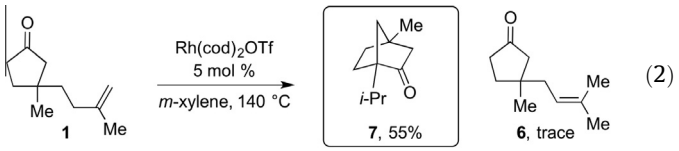
We investigated various rhodium complexes as potential precatalysts for our proposed carboacylation reaction, examining a variety of counterions for Rh(I) complexes, with or without phosphine ligands (not shown). In nearly all conditions we examined, the only detectable products by ^{1}H NMR resulted from alkene isomerization. Alkene isomer **6** was identified by the alkene chemical shift, δ 5.16 ppm (m, 1H), reported in prior work.[14] When **1** was allowed to react with Rh(cod)$_2$OTf at 140 °C, however, we identified a new product that was isolated by chromatography in 55% yield (Eq. (2)).

Our structural assignment of this new product as norcamphor **7** was largely in agreement with the previously reported data, but several key signals showed minor variation.[18] We observed that ^{13}C NMR signal for the carbonyl carbon was Δ0.2 ppm and the



Scheme 2. Prior cyclization and control experiments.

C=O stretching vibration of the carbonyl was $\Delta 6\ cm^{-1}$ from that previously reported in the IR spectrum. Therefore, we confirmed our structural assignment by extensive 2D NMR.[19]



(2)

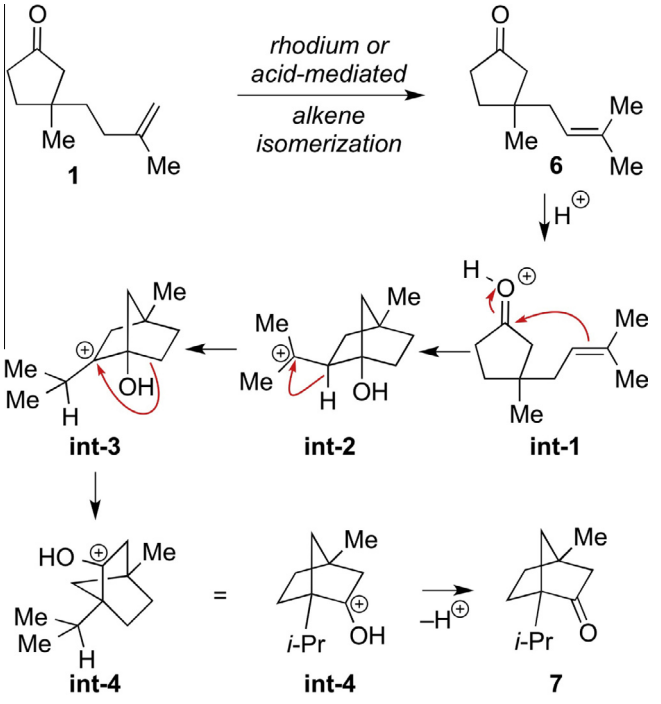
The process by which norcamphor **7** formed was potentially interesting. Jun and co-workers have previously concluded that the norcamphor ring system appears to be a suitable resting point for isomeric cycloalkanones engaged in rhodium-mediated C–C bond activation.[13] This implied that **7** might result from a rhodium-catalyzed cyclization and skeletal rearrangement. At this point, however, the role of rhodium in our reaction and the mechanistic pathway for the formation of **7** from **1** was unclear.

We ran control experiments to determine the role of the rhodium, in particular to determine if metal mediated C–C bond activation was involved in the rearrangement. Addition of 25 mol % of 2-amino-3-picoline (**8**) or 3-methyl-5-(pyrrolidin-1-yl)pyridin-2-amine (**9**)[20] to the reaction of **1** with $Rh(cod)_2OTf$ only prevented the cyclization, with no **7** detected in the ^1H NMR of the crude product mixtures. If C–C bond activation were involved, we might expect 2-amino-3-methyl pyridines to promote the formation of **7**.[13]

These results led us to further question the role of rhodium in the cyclization of **1** to produce **7**. We noted that Agosta and Wolff observed the formation of **7** upon treatment of 2-hydroxy-4-isopentyl-4-methylcyclopentanone (**10**) with polyphosphoric acid (Scheme 2).[18] They proposed that alkene isomer **6** formed as an intermediate in this conversion, but they did not isolate or otherwise report detecting **6** in their experiments. Based on Agosta and Wolff's hypothesis, we decided to test if Brønsted acid was responsible for the conversion of **1** to **7**, potentially via **6**. Lack of product detection upon quench of any Brønsted acid impurities would explain the lack of product **7** in reaction mixtures containing 2-aminopyridines. Indeed, we observed the formation of **6** in low yield (<5%), but we did not observe **7** when **1** was allowed to react with 5 mol % $Rh(cod)_2OTf$ and 60 mol % 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) in *m*-xylene at 140 °C for 24 hours.[21] The remainder of the mass balance was unconsumed cyclopentanone **1**. These results implicate the importance of strong Brønsted acid in the conversion of **6** to **7**.[22] The above experiments also indicate that strong Brønsted acid is not required for the conversion of **1** to **6**. The alkene isomerization of **1** to **6** might be a rhodium-mediated processes.

We then tested if Brønsted acid alone could effect the conversion of **1** to **7** or possibly **6**. We conducted two experiments in which we allowed **1** to react with 25 mol % triflic acid (TfOH) or *p*-tosic acid (TsOH) in *m*-xylene at 140 °C for 24 hours. For the reaction with TsOH, analysis of the ^1H NMR of the crude product mixture revealed the presence of both **6** (54% yield) and **7** (14% yield).[21] For the reaction with TfOH, analysis of the ^1H NMR of the crude product mixture revealed only the presence of **7** (70% yield).[21] These experiments indicate that either rhodium or Brønsted acid can mediate the isomerization of **1** to **6** that likely precedes the formation of **7** and that norcamphor formation is particularly effective with TfOH.

An implication of our work is that some samples of $Rh(cod)_2OTf$ may be contaminated with Brønsted acid, likely triflic acid. Alternatively, triflic acid might be generated in situ from the metal triflate.[23–27] We feel our work confirms Agosta and Wolff's long-standing hypothesis that alkene **6** is the key intermediate in the acid-promoted formation of the norcamphor **7**. Our unified



Scheme 3. Hypothesis for acid-mediated formation of **7**.

mechanistic proposal is shown in Scheme 3. After isomerization of **1** to **6**, protonation of the ketone of **6** would generate oxocarbenium ion **int-1**. Attack of the tethered alkene would generate the 2.2.1 bridged ring system and the tertiary cation in **int-2**. A hydride shift would then lead to the formation of the norbornyl cation in **int-3**. At this point, a norbornyl cation rearrangement to **int-4** followed by deprotonation would generate norcamphor **7**. We cannot rule out an alternative carbonyl-ene reaction of **6** (not shown) for initial C–C bond formation and formation of the tertiary alcohol. Regardless, after cyclization, a hydride shift and norbornyl cation rearrangement can account for the formation of norcamphor **7**.

In closing, we have identified an unexpected cyclization pathway during an attempted alkene carboacylation reaction. Our results implicate the presence of Brønsted acid impurities in $Rh(cod)_2OTf$ in the cyclization of alkene-bearing cyclopentanones to the norcamphor ring system. These findings highlight the importance of control experiments in the emerging area of metal catalyzed alkene carboacylation and catalysis via C–C bond activation. Our identification of alkene **6** is also in accordance with Agosta and Wolff's longstanding hypothesis that this intermediate is responsible for the acid-mediated cyclization of unsaturated cyclopentanones to the norcamphor ring system. We hope that these finding will inform future work in the area of C–C bond activation, particularly the potentially deleterious role of Brønsted acid impurities.

Acknowledgments

We thank the National Science Foundation (CHE-1151547) for funding. NMR spectra were recorded on an instrument purchased with support from the National Institute of Health (S10 OD011952).

Supplementary data

Supplementary data (experimental procedures for the preparation of **1** and **7**, and details for the assignment of **7**. In addition,

copies of spectral data for **1** and **7**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.07.086.

References

1. Xu, T.; Dermenci, A.; Dong, G. C–C Bond Activation. In *Topics in Current Chemistry*; Dong, G., Ed.; ; Springer: Berlin, Germany, 2014; vol. 346, pp 233–257.
2. Dreis, A. M.; Douglas, C. J. *J. Am. Chem. Soc.* **2009**, *131*, 412–413.
3. Wentzel, M. T.; Reddy, V. J.; Hyster, T. K.; Douglas, C. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 6121–6123.
4. Rathbun, C. M.; Johnson, J. B. *J. Am. Chem. Soc.* **2011**, *133*, 2031–2033.
5. Lutz, J. P.; Rathbun, C. M.; Stevenson, S. M.; Powell, B. M.; Boman, T. S.; Baxter, C. E.; Zona, J. M.; Johnson, J. B. *J. Am. Chem. Soc.* **2012**, *134*, 715–722.
6. Suggs, J. W.; Jun, C.-H. *J. Am. Chem. Soc.* **1984**, *106*, 3054–3056.
7. Suggs, J. W.; Jun, C.-H. *J. Chem. Soc., Chem. Commun.* **1985**, 92–93.
8. Ko, H. M.; Dong, G. *Nat. Chem.* **2014**, *6*, 739–744.
9. Xu, T.; Ko, H. M.; Savage, N. A.; Dong, G. *J. Am. Chem. Soc.* **2012**, *134*, 20005–20008.
10. Xu, T.; Dong, G. *Angew. Chem., Int. Ed.* **2012**, *51*, 7567–7571.
11. Murakami, M.; Itahashi, T.; Ito, Y. *J. Am. Chem. Soc.* **2002**, *124*, 13976–13977.
12. Murakami, M.; Ashida, S. *Chem. Commun.* **2006**, 4599–4601.
13. Jun, C.-H.; Lee, H.; Lim, S.-G. *J. Am. Chem. Soc.* **2001**, *123*, 751–752.
14. Wolff, S.; Schreiber, W. L.; Smith, A. B., III; Agosta, W. C. *J. Am. Chem. Soc.* **1972**, *94*, 7797–7806.
15. Bagnell, L.; Bliese, M.; Cablewski, T.; Strauss, C. R.; Tsanaktsidis, J. *Aust. J. Chem.* **1997**, *50*, 921–925.
16. 4-Bromo-2-methyl-1-butene was prepared in two steps from the corresponding alcohol via the mesylate according to Zgani, I.; Menut, C.; Seman, M.; Gallois, V.; Laffont, V.; Liautard, J.; Liautard, J.-P.; Criton, M.; Montero, J.-L. *J. Med. Chem.* **2004**, *47*, 4600–4612.
17. The reaction conditions for organocopper addition to 3-methyl-2-cyclopentanone were adapted from the following: Guay, B.; Deslongchamps, P. *J. Org. Chem.* **2003**, *68*, 6140–6148.
18. Agosta, W. C.; Wolff, S. *J. Org. Chem.* **1976**, *41*, 2605–2607.
19. **7** was characterized by ^{1}H NMR, ^{13}C NMR, IR, MS, DEPT, COSY, HSQC, and HMBC. See the Supporting information for tabulated data, peak assignment, and copies of the spectra.
20. Beletskiy, E. V.; Sudheer, C.; Douglas, C. J. *J. Org. Chem.* **2012**, *77*, 5884–5893.
21. Yield determined by ^{1}H NMR using dibromomethane as an internal standard. See Supporting information.
22. For an example of using DTBMP to implicate Brønsted acids in reactions thought to be Lewis acid catalyzed, see: Wabnitz, T. C.; Yu, J.-Q.; Spencer, J. B. *Chem. Eur. J.* **2004**, *10*, 484–493.
23. Numerous alkene addition reactions previously thought to be catalyzed by precious metal triflate salts are likely to be catalyzed by triflic acid. For leading references see Refs. 22,24–26.
24. Dang, T. T.; Boeck, F.; Hintermann, L. *J. Org. Chem.* **2011**, *76*, 9353–9361.
25. Rosenfeld, D. C.; Shekhar, S.; Takemiya, A.; Utsunomiya, M.; Hartwig, J. F. *Org. Lett.* **2006**, *8*, 4179–4182.
26. Kang, Y.-B.; Gade, L. H. *J. Am. Chem. Soc.* **2011**, *133*, 3658–3667.
27. A reviewer suggested the possibility of contamination of $Rh(cod)_2OTf$ with AgOTf, which might function as a Lewis acid catalyst for norcamphor formation from **1**. Indeed, when we performed a control experiment in which **1** is heated at 140 °C with AgOTf (5 mol %) in *m*-xylene for 24 h, we observed that **7** was produced in 65% yield. In a second experiment in which AgOTf (5 mol %) and DTBMP (60 mol %) were allowed to react with **1** under the same conditions, however, no **7** was detected in the crude product mixture (^{1}H NMR). We note that AgOTf can be a source of triflic acid, see Ref. [24].