Tetrahedron Letters 55 (2014) 6399–6402

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Rhodium-catalyzed tandem aldol condensation–Robinson annulation between aldehydes and acetone: synthesis of 3-methylcyclohexenones

Fen Wang [a], Yuchen Liu [a,b], Zisong Qi [a], Wei Dai [b], Xingwei Li [a,*]

[a] Dalian Institute of Chemical Physics, Chinese Academy of Science, Dalian 116023, China
[b] School of Chemistry and Biological Sciences, Zhejiang Normal University, Jinhua 321004, China

ARTICLE INFO

Article history:
Received 7 July 2014
Revised 12 September 2014
Accepted 19 September 2014
Available online 28 September 2014

Keywords:
Rhodium catalysis
3-Methylcyclohexenones
Phenol
Robinson annulation

ABSTRACT

A simple catalytic, redox-neutral access to 3-methylcyclohexenones has been developed via rhodium catalysis in the presence of an amine additive and Ag_2CO_3. This process utilized simple aldehydes and acetone as substrates and tolerates a variety of functional groups. Disubstituted phenols were isolated in moderate yields when $Cu(OAc)_2$ was employed as an oxidant.

Transition metal catalysis has witnessed significant contributions to the construction of C–C bonds leading to molecular complexity.[1] This strategy is especially useful in synthetic chemistry when simple starting materials were utilized and the product was accessed in a tandem process. This is facilitated by transition metals owing to their diversified roles in sequentially mediating intrinsically different steps.[2]

Cyclohexenones are known to exhibit important biological activities as antitumor agents, food additive, and pheromones.[3] In particular, 3-methylcyclohexenones have been widely found as a key structural motif in natural products and in pharmaceuticals.[4] Conventionally, 3-methylcyclohexenones were prepared by Hagemann condensation and Knoevenagel condensation under rather harsh conditions.[5] Alternatively, Martinez and coworkers developed a reductive synthesis of 3-methylcyclohexenones via cyclization of heavily functionalized dihydropyrines.[6] Organocatalysis has been employed as an important method in the synthesis of 3-methylcyclohexenones, as has been reported by List[7] and Wu and Lin.[8] However, previously reported systems suffered from utilization of either less readily accessible starting materials or limited substrate scope. For example, while Wu and Lin have demonstrated the important organocatalytic synthesis of such products starting from an aldehyde and acetone under mild conditions,[8] the aldehyde seems limited to electron-poor ones since lower yields were obtained for those bearing electron-donating groups. Metal-mediated/catalyzed synthesis of 3-methylcyclohexenones has been reported, but only in a few examples. Gagosz reported a two-step synthesis of 3-methylcyclohexenones via Au-catalyzed cyclization of alkene-functionalized propargyl acetate followed by base treatment.[9] Lanthanide complexes are known as viable catalysts for the synthesis of 3-methylcyclohexenones starting from enones and ketones.[10] Despite the progress, it is necessary to develop new methods for the efficient synthesis of 3-methylcyclohexenones, preferentially starting from simple substrates.

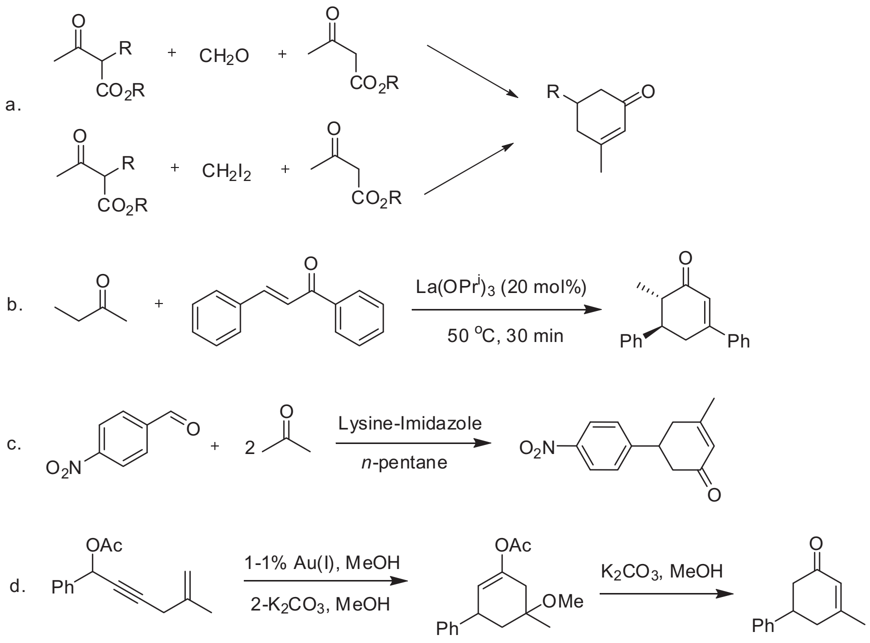
During our studies of Rh(III)-catalyzed C–H activation/coupling reactions, we found that in many cases Rh(III) complexes exhibited quite unique properties as a Lewis acid.[11] As a continuation of our interest in Rh(III) catalysis, we aim to extend coupling reactions to systems other than C–H activation.[12] We now report rhodium-catalyzed synthesis of 3-methylcyclohexenones via aldol reaction-Robinson annulation between aldehydes and acetone (Scheme 1).

We initiated our studies with the screening of the conditions for the rhodium-catalyzed coupling of benzaldehyde with acetone (solvent) in the presence of a primary amine with Ag_2CO_3 being an oxidant (100 °C). Our initial objective was to convert the aldehyde functionality to an imine, a better directing group which may allow ortho C–H activation and functionalization. To our surprise, although a reaction occurred, NMR analyses of the isolated product revealed no C–H bond activation. Instead, two equivalents of acetone were incorporated and the product (**2a**) was identified

---

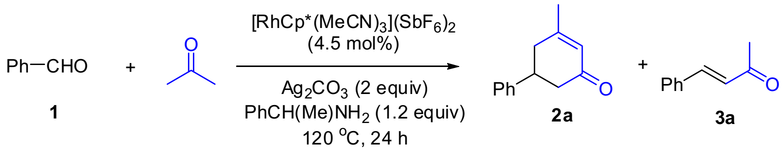
[*] Corresponding author. Tel./fax: +86 411 8437 9737.
E-mail address: xwli@dicp.ac.cn (X. Li).

http://dx.doi.org/10.1016/j.tetlet.2014.09.093



Scheme 1. Access to 3-methylcyclohexenones.

Table 1
Optimization studies[a,b]



Entry	Change from standard conditions	Yield (%)	
		2a	**3a**
1	None	76	5
2	No Rh(III) catalyst was used	nd	74
3	80 °C	<5	71
4	100 °C	65	10
5	No Ag_2CO_3 was used	nd	69
6	$PhCH(Me)NH_2$ (0.2 equiv)	10	40
7	14 h	40	42

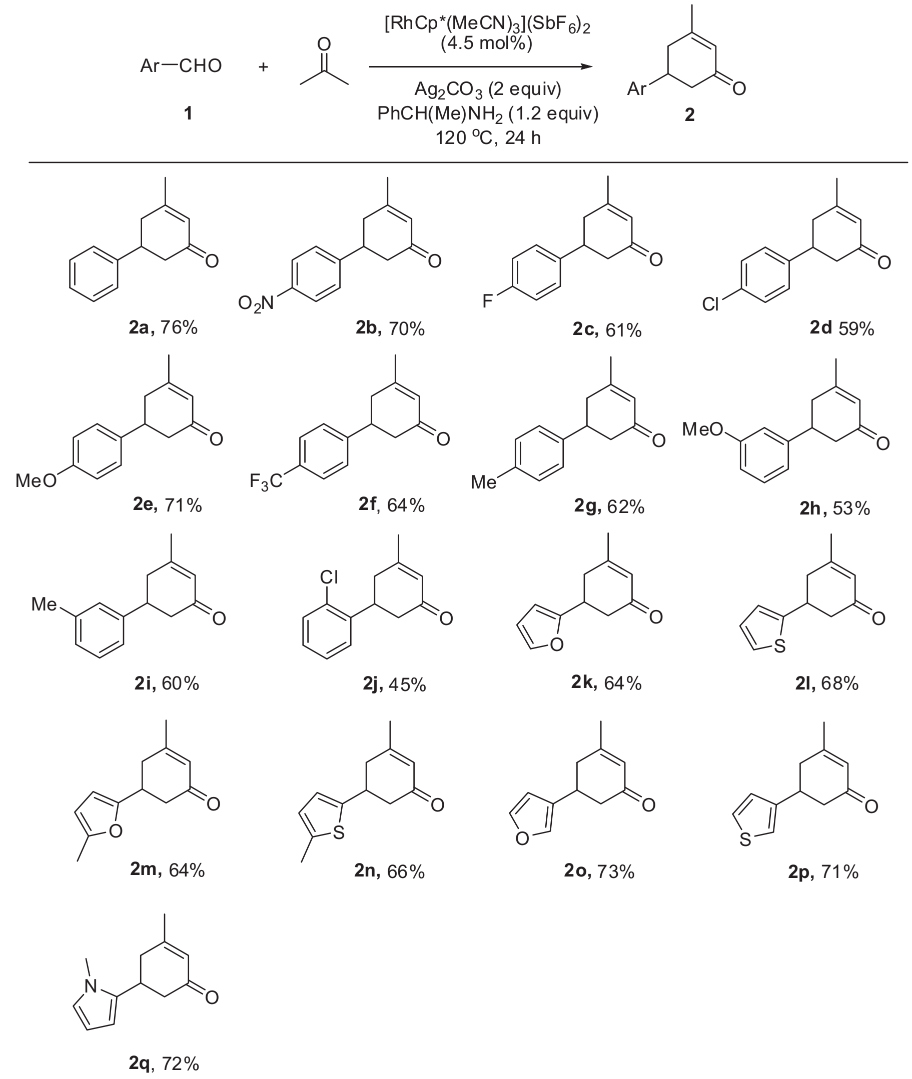
[a] Standard conditions: benzaldehyde (0.3 mmol), $[RhCp^*(MeCN)_3](SbF_6)_2$ (4.5 mol %), α-methylbenzylamine (0.36 mmol), Ag_2CO_3 (0.6 mmol), acetone (3 mL), 120 °C, 24 h.

[b] Isolated yield after column chromatography.

as a disubstituted cyclohexenone on the basis of NMR spectroscopy and mass spectrometry (Table 1). Screening studies indicated that Ag_2CO_3 is necessary because when it was omitted, the aldol condensation product (**3a**) was obtained as the major one (Table 1, entry 5). Thus the Ag_2CO_3 is probably best described as a base additive. The rhodium catalyst also proved necessary because in the absence of the catalyst, **3a** was also detected as the major product (entry 2). Although $PhCH(Me)NH_2$ is not incorporated, it is necessary in a stoichiometric amount because lowering its amount to 20 mol % only afforded **2a** in 10% yield (entry 6). The reaction temperature has some effects; increasing the temperature to 120 °C gave rise to a slightly increased yield, but lowering the temperature to 80 °C afforded the aldol condensation side product **3a** as the major one (entries 1, 3 and 4). In contrast, when the rhodium catalyst was replaced by other Lewis acid such as $In(OTf)_3$ and $Zn(OTf)_2$, no desired reaction occurred. Thus the optimal conditions consist of the following parameters (entry 1): benzaldehyde, Ag_2CO_3 (2 equiv), $PhCH(Me)NH_2$ (1.2 equiv), $RhCp^*(MeCN)_3](SbF_6)_2$ (4.5 mol %), and acetone (solvent) at 120 °C for 24 h.[13]

With the establishment of the optimized conditions, we next explored the scope and limitation of this transformation (Table 2). A variety of benzaldehydes bearing electron-donating (**2e**, **2g**, **2h**, and **2i**), -withdrawing (**2b** and **2f**), and halogen (entry **2c**, **2d**, and **2j**) groups at the *meta* and *para* positions underwent smooth coupling with acetone in consistently good yields (45–76%). The presence of halogen substituent should readily allow further functionalization of the coupled products. In contrast, *ortho* substituents have significant influence on the reactivity. *o*-Tolualdehyde reacted with poor efficiency and selectivity, and no analytically pure product could be isolated. In contrast, *o*-chlorobenzaldehyde coupled to give the desired enone **2j** in 45% isolated yield. The reaction seems limited to acetone and switching to 3-pentanone only gave rise to poor conversion, indicative of the limitation of this system. Besides using protio acetone, acetone-d_6 is also applicable and

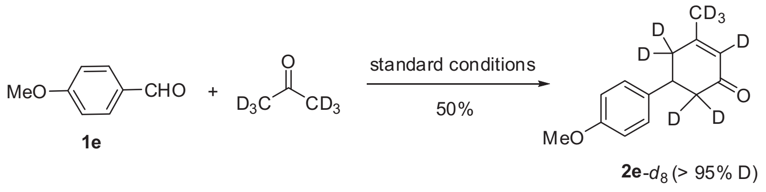
Table 2
Substrate scope[a,b]



[a] Reaction conditions: aldehyde (0.3 mmol), [RhCp*(MeCN)$_3$](SbF$_6$)$_2$ (4.5 mol %), α-methylbenzylamine (0.36 mmol), Ag$_2$CO$_3$ (0.6 mmol), acetone (3 mL), 120 °C, 24 h.

[b] Isolated yield after column chromatography.

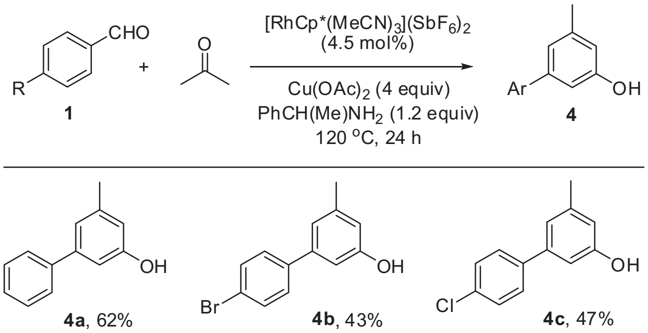
the product **2e**-d_8 was isolated in a slightly lower yield (Eq. 1). Significantly, the aldehyde is not limited to benzaldehydes, and heteroaryl aldehydes such as 2- and 3-furaldehydes and 2- and 3-thenaldehydes are well tolerated under the standard conditions, with the yield of the products comparable to those for benzaldehydes.



(1)

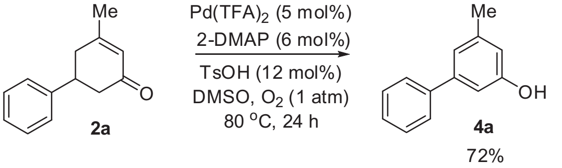
We felt that under suitable conditions, the cyclohexenone product could be oxidized to a phenol, a highly useful building block in synthesis. In fact, Stahl,[14] Li,[15] Deng,[16] and Yoshikai[17] have independently studied the oxidation of cyclohexanones or their imines to the corresponding phenols or anilines. In particular, Stahl applied palladium catalysis to the aerobic oxidation of cyclohexanones to phenols under operationally simple conditions,[14] with cyclohexenone being an intermediate. Therefore, we reasoned that these conditions could be viable for the oxidative derivatization of our cyclohexenone product. Indeed, under Stahl's conditions,[14a] enone **2a** was smoothly oxidized to phenol **4a** in 72% yield (Eq. 2).

Table 3
Oxidative synthesis of phenols[a,b]



[a] Reaction conditions: aldehyde (0.3 mmol), $[RhCp^*(MeCN)_3](SbF_6)_2$ (4.5 mol %), α-methylbenzylamine (0.36 mmol), anhydrous $Cu(OAc)_2$ (1.2 mmol), acetone (3 mL), 120 °C, 24 h.

[b] Isolated yield after column chromatography.



(2)

Although the oxidative derivatization of **2a** provides an efficient synthetic method to access disubstituted phenols, it would be more step-economic to directly access such phenols via a single step process. To achieve this goal, we replaced the Ag_2CO_3 additive with $Cu(OAc)_2$ (4 equiv) because it is widely used in oxidative coupling reactions.[12a,18] Under otherwise the same conditions, the coupling of benzaldehydes with acetone did afford the desired phenol as the major product (Table 3) although the reaction suffered from limited selectivity and the yields of the phenols were moderate (43–62%). To gain insight into this oxidation process, enone **2a** was allowed to react with $Cu(OAc)_2$ in the absence of any rhodium catalyst. However, essentially no desired phenol was detected, indicating that the rhodium catalyst played an important role in the oxidative aromatization of cyclohexanone.

Several experiments have been performed to probe the mechanism. Subjection of the aldol condensation product **3a** to the reaction conditions led to formation of product **2a** in 72% yield. Therefore enone **3a** is a likely intermediate leading to the formation of the final product. KIE experiments have been performed to explore the cleavage of the C–H bond in acetone. The reaction of **3a** and an equimolar mixture of acetone and acetone-d_6 gave a mixture of **2a** and its isotopomers. ^1H NMR analysis of this product mixture gave KIE = 0.92, and this small value indicates that the cleavage of the C–H bonds is probably not involved in the rate-limiting step.

A proposed mechanism involves a non-metal-catalyzed aldol reaction of aldehyde and acetone. Subsequent Robinson annulation was catalyzed by rhodium, which acts as a Lewis acid that activates enone **3a**. In this process, acetone is likely activated to an enamine via condensation with $PhCH(Me)NH_2$. The role of Ag_2CO_3 is unclear at this time, but it may also facilitate the activation of the enone intermediate.

In summary, we have developed a catalytic method to access 3-methylcyclohexenones via the condensation between acetone and simple aldehydes. This process was collaboratively catalyzed by a Rh(III) complex and an amine. A broad scope of aldehyde substrate has been defined. Importantly, the condensation products can be readily converted to a disubstituted phenol under palladium-catalyzed aerobic oxidation or in a one-pot fashion with $Cu(OAc)_2$ as an oxidant under rhodium catalysis. This method may find applications in the synthesis of related complex structures.

Acknowledgments

This work was supported by the Dalian Institute of Chemical Physics, Chinese Academy of Sciences and the National Natural Science Foundation of China (Grant No. 21272231).

Supplementary data

Supplementary data (representative synthetic procedure, analytical data of products, and NMR spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.09.093.

References and notes

1. Trost, B. M. M.; Crawley, L. *Chem. Rev.* **2003**, *103*, 2921.
2. (a) Eilbracht, P.; Bärfacker, L.; Buss, C.; Hollmann, C.; Kitsos-Rzychon, B. E.; Kranemann, C. L.; Rische, T.; Roggenbuck, R.; Schmidt, A. *Chem. Rev.* **1999**, *99*, 3329; (b) Sheldon, R. A. *Chem. Soc. Rev.* **2012**, *41*, 1437; (c) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115; (d) Pellissier, H. *Chem. Rev.* **2012**, *113*, 442.
3. (a) Pette, D.; Staudte, H. W.; Vrbová, G. *Naturwissenschaften* **1972**, *59*, 469; (b) Plummer, E. L.; Stewart, T. E.; Byrne, K.; Pearce, G. T.; Silverstein, R. M. *J. Chem. Ecol.* **1976**, *2*, 307; (c) Mori, K. *Tetrahedron* **1989**, *45*, 3233; (d) Mori, K.; Tamada, S.; Uchida, M.; Mizumachi, N.; Tachibana, Y.; Matsui, M. *Tetrahedron* **1901**, *1978*, 34; (e) Nakayachi, T.; Yasumoto, E.; Nakano, K.; Morshed, S. M.; Hashimoto, K.; Kikuchi, H.; Nishikawa, H.; Kawase, M.; Sakagami, H. *Anticancer Res.* **2004**, *24*, 737.
4. (a) Moorhoff, C. M. *Tetrahedron* **1997**, *53*, 2241; (b) Boeckman, R. K.; del Rosario Rico Ferreira, M.; Mitchell, L.; Shao, P. *J. Am. Chem. Soc.* **2002**, *124*, 190; (c) Halland, N.; Aburel, P. S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1272.
5. (a) Pollini, G. P.; Benetti, S.; De Risi, C.; Zanirato, V. *Tetrahedron* **2010**, *66*, 2775; (b) Horning, E. C.; Field, R. E. *J. Am. Chem. Soc.* **1946**, *68*, 384; (c) Smith, W. T. D.; Eftax, D. S. P. *J. Org. Chem.* **1956**, *21*, 174.
6. Martínez, R.; Mendoza, H. M.; Angeles, E. *Syn. Commun.* **1998**, *28*, 2813.
7. (a) List, B.; Lerner, R. A.; Barbas, C. F. *Org. Lett.* **1999**, *1*, 59; (b) Zhou, J.; Wakchaure, V.; Kraft, P.; List, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 7656.
8. Xiang, Z.; Liu, Z.; Liang, Y.; Wu, Q.; Lin, X. *Chin. J. Chem.* **2013**, *31*, 997.
9. Buzas, A.; Gagosz, F. *J. Am. Chem. Soc.* **2006**, *128*, 12614.
10. Okano, T.; Satou, Y.; Tamura, M.; Kiji, J. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 1879.
11. (a) Li, X.; Yu, S.; Wang, F.; Wan, B.; Yu, X. *Angew. Chem., Int. Ed.* **2013**, *52*, 2577; (b) Wang, F.; Qi, Z.; Sun, J.; Zhang, X.; Li, X. *Org. Lett.* **2013**, *15*, 6290; (c) Yu, S.; Li, X. *Org. Lett.* **2014**, *16*, 1220; (d) Zhang, X.; Wang, F.; Yu, S.; Qi, Z.; Li, X. *Org. Lett.* **2014**, *16*, 1586; (e) Zhao, P.; Wang, F.; Han, K.; Li, X. *Org. Lett.* **2012**, *14*, 3400.
12. (a) Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev.* **2012**, *41*, 3651; (b) Colby, D. A.; Tsai, A. S.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2011**, *45*, 814.
13. *Synthesis of* ***2a***: Benzaldehyde (31.8 mg, 0.3 mmol), Ag_2CO_3 (165.5 mg, 0.6 mmol), α-methylbenzylamine (43.6 mg, 0.36 mmol), and $[RhCp^*(MeCN)_3](SbF_6)_2$ (11.2 mg, 4.5 mol %) were weighed into a 25 mL pressure tube, to which acetone (3 mL) was added. The reaction tube was sealed, and the mixture was stirred at 120 °C for 24 h. The mixture was filtered through Celite, followed by removal of volatiles under reduced pressure. Purification was performed by flash column chromatography on silica gel using EtOAc and petroleum ether.
14. (a) Izawa, Y.; Pun, D.; Stahl, S. S. *Science* **2011**, *333*, 209; (b) Pun, D.; Diao, T.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, *135*, 8213.
15. Girard, S. A.; Hu, X.; Knauber, T.; Zhou, F.; Simon, M.-O.; Deng, G.-J.; Li, C.-J. *Org. Lett.* **2012**, *14*, 5606.
16. (a) Cao, X.; Bai, Y.; Xie, Y.; Deng, G.-J. *J. Mol. Catal. A: Chem.* **2014**, *383–384*, 94; (b) Xie, Y.; Liu, S.; Liu, Y.; Wen, Y.; Deng, G.-J. *Org. Lett.* **2012**, *14*, 1692.
17. Hajra, A.; Wei, Y.; Yoshikai, N. *Org. Lett.* **2012**, *14*, 5488.
18. Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3464.