ORGANIC LETTERS

2005
Vol. 7, No. 10
2071−2073

Rhodium-Catalyzed Addition of Arylzinc Reagents to Aryl Alkynyl Ketones: Synthesis of β,β-Disubstituted Indanones

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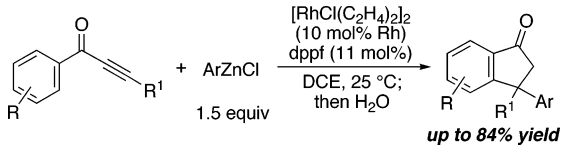
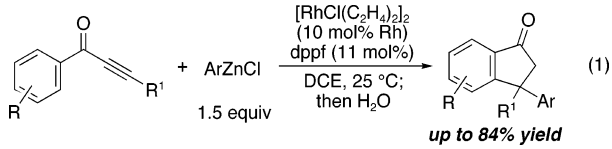
Received March 30, 2005

ABSTRACT



A rhodium-catalyzed addition of arylzinc reagents to aryl alkynyl ketones for the synthesis of highly substituted indanones has been developed. The key to success has proved to be a proper choice of the reaction system, which involves the employment of dppf as a ligand and 1,2-dichloroethane as a solvent.

Transition-metal-catalyzed multiple-bond-forming reactions are powerful methods for the efficient construction of structurally complex molecules, and rhodium-catalyzed processes involving a 1,4-rhodium migration from an alkenyl or alkyl carbon to an aryl carbon are becoming useful ways of achieving such transformations in a single operation.[1,2] In this context, Iwasawa[1d] and our group[1e] reported a rhodium-catalyzed isomerization of α-arylpropargyl alcohols to β-monosubstituted indanones and proposed the intermediacy of an aryl alkynyl ketone species, which undergoes a hydrorhodation followed by a 1,4-rhodium migration. This reaction cascade prompted us to focus on the development of a rhodium-catalyzed addition of organometallic reagents to aryl alkynyl ketones for the synthesis of β,β-disubstituted indanones.[3] Here we describe our significant progress toward this goal: specifically, a Rh/dppf complex can effectively catalyze the addition of arylzinc reagents to aryl alkynyl ketones, furnishing highly substituted indanones in good yield (eq 1).



(1)

Although phenylrhodation is known to occur to an internal alkyne, generating an alkenylrhodium species,[1b,c,4] one can

(1) (a) Oguma, K.; Miura, M.; Satoh, T.; Nomura, M. *J. Am. Chem. Soc.* **2000**, *122*, 10464. (b) Hayashi, T.; Inoue, K.; Taniguchi, N.; Ogasawara, M. *J. Am. Chem. Soc.* **2001**, *123*, 9918. (c) Miura, T.; Sasaki, T.; Nakazawa, H.; Murakami, M. *J. Am. Chem. Soc.* **2005**, *127*, 1390. (d) Yamabe, H.; Mizuno, A.; Kusama, H.; Iwasawa, N. *J. Am. Chem. Soc.* **2005**, *127*, 3248. (e) Shintani, R.; Okamoto, K.; Hayashi, T. *J. Am. Chem. Soc.* **2005**, *127*, 2872.

(2) For recent examples of palladium-catalyzed transformations involving a 1,4-palladium migration, see: (a) Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2002**, *124*, 14326. (b) Campo, M. A.; Huang, Q.; Yao, T.; Tian, Q.; Larock, R. C. *J. Am. Chem. Soc.* **2003**, *125*, 11506. (c) Huang, Q.; Campo, M. A.; Yao, T.; Tian, Q.; Larock, R. C. *J. Org. Chem.* **2004**, *69*, 8251. (d) Zhao, J.; Larock, R. C. *Org. Lett.* **2005**, *7*, 701.

(3) For recent examples of synthetic methods for β,β-disubstituted indanones, see: (a) Rendy, R.; Zhang, Y.; McElrea, A.; Gomez, A.; Klumpp, D. A. *J. Org. Chem.* **2004**, *69*, 2340. (b) Prakash, G. K. S.; Yan, P.; Török, B.; Olah, G. A. *Catal. Lett.* **2003**, *87*, 109. (c) Fillion, E.; Fishlock, D. *Org. Lett.* **2003**, *5*, 4653. (d) Fillion, E.; Fishlock, D.; Wilsily, A.; Goll, J. M. *J. Org. Chem.* **2005**, *70*, 1316. (e) Lee, S. I.; Son, S. U.; Choi, M. R.; Chung, Y. K.; Lee, S.-G. *Tetrahedron Lett.* **2003**, *44*, 4705.

(4) (a) Shintani, R.; Okamoto, K.; Otomaru, Y.; Ueyama, K.; Hayashi, T. *J. Am. Chem. Soc.* **2005**, *127*, 54. (b) Miura, T.; Shimada, M.; Murakami, M. *J. Am. Chem. Soc.* **2005**, *127*, 1094.

10.1021/ol0506819 CCC: $30.25
Published on Web 04/09/2005

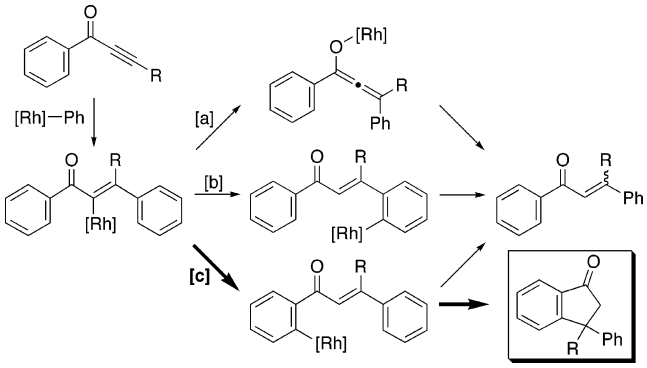


Figure 1. Possible pathways (desired and undesired) for the formation of β,β-disubstituted indanones by phenylrhodation of aryl alkynyl ketones.

imagine several pathways it could take when an aryl alkynyl ketone is used as the alkyne component (Figure 1). One possibility is the formation of a rhodium enolate (or an oxa-π-allylrhodium) through path a,[5] whose fate would be an undesired α,β-enone product. Alternatively, the alkenylrhodium species could undergo a 1,4-rhodium migration via path b,[1b,c] which would also end up with the α,β-enone product. The third and only desirable possibility is the formation of the other arylrhodium species by a 1,4-shift through path c.[1d,e] This intermediate could cyclize by an intramolecular 1,4-addition to form the targeted indanone, although it could also be led to the uncyclized α,β-enone product.

Despite the above-mentioned potential difficulties in achieving the desired transformation, we have successfully found a set of conditions that uniquely provide the indanones in high yield (Table 1). Thus, substrate **1a** preferentially gives the corresponding indanone **2a** by the use of PhZnCl in the presence of a catalytic amount of Rh/dppf (dppf = 1,1′-bis-(diphenylphosphino)ferrocene)[6] in 1,2-dichloroethane at 25 °C (80% isolated yield; entry 1).[7] The choices of solvent and ligand are critical for the realization of this selective formation of indanone **2a**. For example, in other solvents such as THF or toluene, the yield of **2a** becomes much lower (6−8% yield) and a significant amount of undesired enone **3a** is formed (entries 2 and 3).[8] The use of bisphosphine ligands other than dppf produces only a negligible amount of indanone **2a**, and the major product is undesired enone **3a** (entries 4 and 5). PPh_3 is somewhat effective for generating indanone **2a**, but it has much lower efficiency (31% yield; entry 6) than dppf. The use of diene ligands

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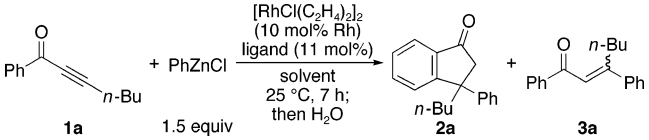
(6) Gan, K.-S.; Hor, T. S. A. In *Ferrocenes*; Togni, A., Hayashi, T., Eds.; VCH: Weinheim, 1995; Chapter 1.

(7) For an example of the use of arylzinc reagents in the rhodium-catalyzed conjugate addition reactions, see: Shintani, R.; Tokunaga, N.; Doi, H.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, *126*, 6240.

(8) 1,2-Dichloroethane is uniquely effective compared to other chlorinated solvents as well (e.g., dichloromethane or chloroform).

Table 1. Rhodium-Catalyzed Synthesis of β,β-Disubstituted Indanones: Impact of Reaction Parameters



1a **2a** **3a**

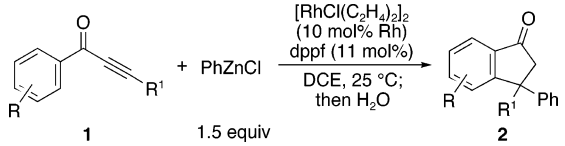
entry	ligand	solvent	yield of **2a** (%)[a]	yield of **3a** (%)[a]
1	dppf	DCE	81 (80)[b]	6
2	dppf	THF	8	24
3	dppf	toluene	6	51
4	dppp	DCE	<2	50
5	dppb	DCE	<2	59
6	2 PPh_3	DCE	31	51
7	cod	DCE	<2	70

[a] Determined by ^{1}H NMR against an internal standard ($MeNO_2$). [b] Isolated yield in parentheses.

such as cod instead of phosphine ligands preferentially produces enone **3a** as well (entry 7).

Under these optimized conditions with Rh/dppf in 1,2-dichloroethane, the scope of aryl alkynyl ketones is shown in Table 2. Thus, several substrates bearing an alkyl group on the alkyne undergo this addition/cyclization process to furnish the desired β,β-disubstituted indanones in good yield (75−84% yield; entries 1−3),[9] and various substitution patterns can be tolerated on the aromatic portion of the substrate as well to afford the desired products in relatively high yield (63−77% yield; entries 4−7). With regard to the nucleophilic component, the scope of substituents on the aryl group is fairly broad, furnishing the corresponding indanones in high yield (72−81% yield; Table 3, entries 2−5), although the yield becomes somewhat modest when the relatively bulky *o*-tolyl group is used (53% yield; entry 6).

Table 2. Rhodium-Catalyzed Synthesis of β,β-Disubstituted Indanones: Scope of the Aryl Alkynyl Ketone



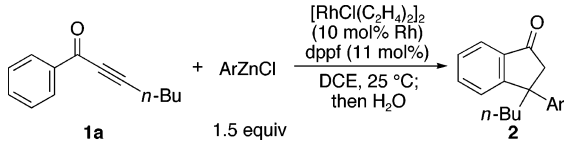
1 **2**

entry	substrate			yield (%)[a]
1	R = H	R^1 = *n*-Bu	(**1a**)	80
2	R = H	R^1 = *n*-Hex	(**1b**)	84
3	R = H	R^1 = *i*-Bu	(**1c**)	75
4	R = 4-Me	R^1 = *n*-Bu	(**1d**)	74
5	R = 4-MeO	R^1 = *n*-Bu	(**1e**)	63
6	R = 4-F	R^1 = *n*-Bu	(**1f**)	68
7	R = 2-Me	R^1 = *n*-Bu	(**1g**)	77

[a] Isolated yield.

By analogy with the mechanism of the rhodium-catalyzed isomerization of α-arylpropargyl alcohols to indanones,[1d,e]

Table 3. Rhodium-Catalyzed Synthesis of β,β-Disubstituted Indanones: Scope of the Arylzinc Reagent



entry	Ar	product	yield (%)[a]
1	Ph	**2a**	80
2	4-MeOC$_6$H$_4$	**2h**	81
3	4-FC$_6$H$_4$	**2i**	72
4	3,5-Me$_2$C$_6$H$_4$	**2j**	74
5	2-naphthyl	**2k**	77
6	2-MeC$_6$H$_4$	**2l**	53

[a] Isolated yield.

coupled with the mechanistic studies on the rhodium-catalyzed 1,4-addition of organometallic reagents to α,β-enones in aprotic media,[10] a proposed reaction pathway of the present transformation is illustrated in Figure 2. Thus, insertion of an alkyne into the aryl−rhodium bond generates alkenylrhodium intermediate **A**, which undergoes a 1,4-hydrogen shift to produce arylrhodium species **B**. Intramolecular 1,4-addition of **B** leads to oxa-π-allylrhodium **C**, and transmetalation of an aryl group from zinc to **C** releases the product as a zinc enolate along with an arylrhodium species for the next cycle. Consistent with this mechanism, the employment of deuterated substrate **4** led to a quantitative migration of deuterium from the ortho-position to the α-position (eq 2). Furthermore, to utilize the formation of a zinc enolate, we decided to functionalize it by the addition of electrophiles. For example, the addition of allyl bromide provides α-allylated indanone **6** in 60% yield, generating three carbon−carbon bonds, a new ring, and adjacent tertiary

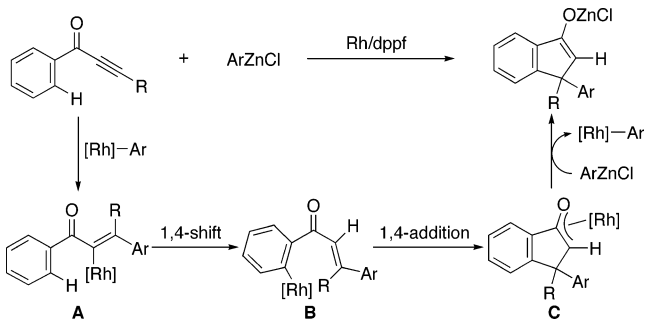
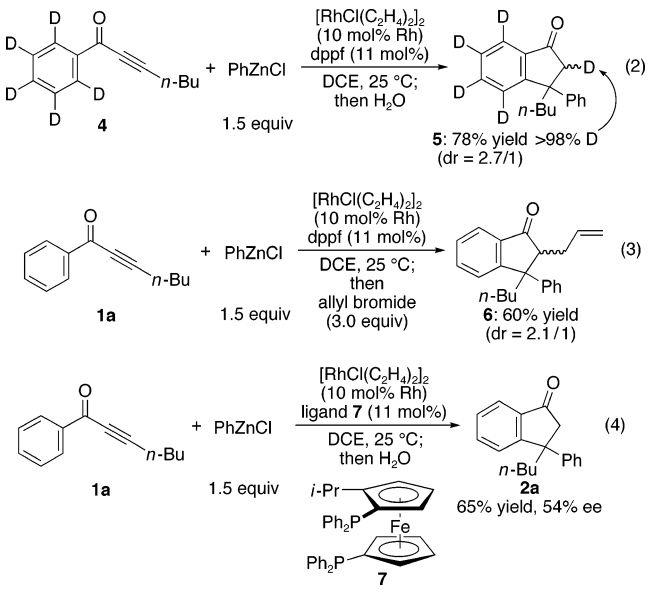


Figure 2. Proposed catalytic cycle of the rhodium-catalyzed addition of arylzinc reagents to aryl alkynyl ketones.

and quaternary stereocenters in a single addition/cyclization−alkylation sequence (eq 3). In addition, a preliminary result shows that the use of planar-chiral ferrocene-based bisphosphine ligand **7**[11] leads to the formation of indanone **2a** in 54% ee (eq 4).



In summary, we have developed a rhodium-catalyzed addition of arylzinc reagents to aryl alkynyl ketones for the synthesis of highly substituted indanones. The key to success has proved to be a proper choice of the reaction system, which involves the employment of dppf as a ligand and 1,2-dichloroethane as a solvent. Future studies will focus on the development of an effective asymmetric variant of this process.

Acknowledgment. Support has been provided in part by a Grant-in-Aid for Scientific Research, the Ministry of Education, Culture, Sports, Science and Technology, Japan (21 COE on Kyoto University Alliance for Chemistry).

Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0506819

(9) Aryl groups, as well as sterically demanding alkyl or silyl groups, are not very good substituents on the alkyne under the same conditions, leading to <40% of the desired indanones.

(10) (a) Yoshida, K.; Ogasawara, M.; Hayashi, T. *J. Org. Chem.* **2003**, *68*, 1901. (b) Hayashi, T.; Tokunaga, N.; Yoshida, K.; Han, J. W. *J. Am. Chem. Soc.* **2002**, *124*, 12102.

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