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Sequential Aldol Condensation-Transition Metal-Catalyzed Addition Reactions of Aldehydes, Methyl Ketones, and Arylboronic Acids

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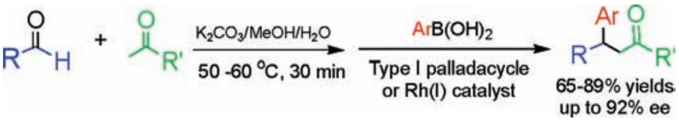
ABSTRACT



Sequential aldol condensation of aldehydes with methyl ketones followed by transition metal-catalyzed addition reactions of arylboronic acids to form *β*-substituted ketones is described. By using the 1,1′-spirobiindane-7,7′-diol (SPINOL)-based phosphite, an asymmetric version of this type of sequential reaction, with up to 92% ee, was also realized. Our study provided an efficient method to access *β*-substituted ketones and might lead to the development of other sequential/tandem reactions with transition metal-catalyzed addition reactions as the key step.

Transition metal-catalyzed addition reactions of arylboronic acids with carbonyl-containing compounds and derivatives have recently emerged as useful transformations for organic synthesis in part due to the nature of low toxicity and air/moisture stability of arylboronic acids.[1,2] One of the most noteworthy achievements in this field might be transition metal-catalyzed addition reactions of arylboronic acids with α,*β*-unsaturated ketones, which yield synthetically useful *β*-substituted ketones as the products.[2,3] While good to high enantioselectivities have been achieved for this type of addition reaction, the prepurifed α,*β*-unsaturated ketones were used. Although α,*β*-unsaturated ketones can be "readily" obtained from the aldol condensation of aldehydes and/or ketones, the use of prepurified α,*β*-unsaturated ketones apparently posed some limits: they require an extra purification/separation step from aldehydes/ketones and are less available than aldehydes/ketones. During our study on transition metal-catalyzed addition reactions of arylboronic acids with carbonyl-containing compounds,[4–7] we became interested in combining the formation of α,*β*-unsaturated ketones, the aldol condensation, with the addition reactions in a tandem or sequential fashion.[8] We reasoned that achieving such tandem/sequential reactions will minimize the effort for the preparation of α,*β*-unsaturated ketones because prepurification for such α,*β*-unsaturated ketones is eliminated and may also expand the α,*β*-unsaturated ketone substrate scope. Herein, we report our results on such new sequential reactions, including an asymmetric Rh(I)-catalyzed sequential reaction.

We began our study by mixing benzaldehyde, acetone and *p*-tolylboronic acid together with palladacycle **1**[1,9–11] or [Rh(COD)Cl]$_2$ as the catalyst. We found with toluene or THF-MeOH as the solvent, the desired reaction product (**A**) was the minor product and the major product was the 1,2-addition product (**B**) (Table 1). We speculated that this reaction outcome was likely due to the fact that transition metal-catalyzed addition of *p*-tolylboronic acid with benzaldehyde occurred faster than the aldol condensation of benzaldehyde with acetone under the reaction condition.

To overcome the fast 1,2-addition reaction issue, we decided to carry out the reaction of aldehydes, methyl ketones and arylboronic acids in a sequential fashion: the arylboronic acids, and the catalyst were introduced into the

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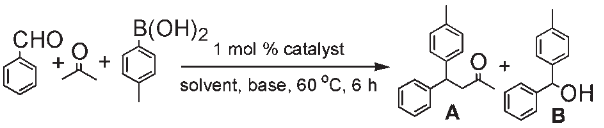
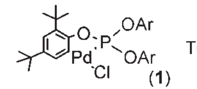
[1] For recent reviews: (a) Glorius, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 3364–3366. (b) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829–2844. (c) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169–196 and references cited therein.

[2] (a) Miyaura, N. *Synlett* **2009**, 2039–2050. (b) Gutnov, A. *Eur. J. Org. Chem.* **2008**, 4547–4554.

10.1021/ol200457q

Table 1. Tandem Aldol Condensation-Transition Metal-Catalyzed Reaction of Benzaldehyde, Acetone, and *p*-Tolylboronic Acid [a]

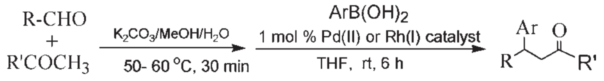


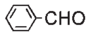
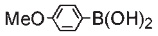
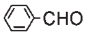
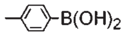
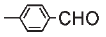
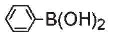
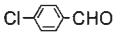
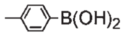
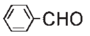
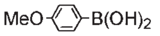
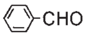
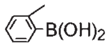
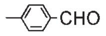
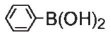
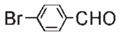
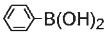
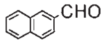
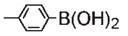
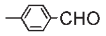
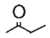
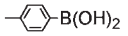
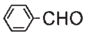
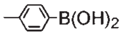
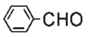
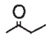
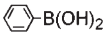
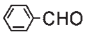
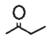
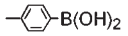
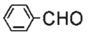
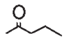
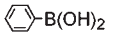
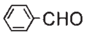
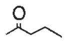
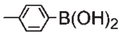
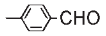
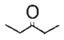
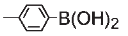
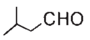
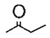
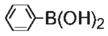
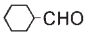
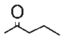
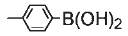
entry	catalyst	solvent	base	conv (%) [b]	A/B [b]
1	 (1) (Ar = 2,4-di-*t*-BuC$_6$H$_3$)	Toluene	K_3PO_4	99	1:99
2	1	Toluene	K_3PO_4	63 [c]	12:88
3	[Rh(COD)Cl]$_2$	Toluene	K_3PO_4	30	1:99
4	1	THF-MeOH	K_2CO_3	24 [d]	1:99 [e]
5	[Rh(COD)Cl]$_2$	THF-MeOH	K_2CO_3	87 [d]	1:99 [f]

[a] Reaction condition: benzaldehyde (0.25 mmol), acetone (0.3 mL), *p*-tolylboronic acid (2.0 equiv), toluene (0.7 mL) or THF/MeOH (1.0 mL/0.1 mL), base (3.0 equiv), 60 °C. [b] Based on GC-MS analysis. [c] H_2O (2.0 equiv) was added to the reaction system. [d] H_2O (22 equiv) was added to the reaction system. [e] Phenyl *p*-tolyl ketone (14%) was observed. [f] Phenyl *p*-tolyl ketone (9%) was observed.

reaction system after the completion of the aldol condensation. We found with K_2CO_3 as the base and THF/MeOH as the solvent, the sequential reactions of acetone, aldehydes and arylboronic acids occurred smoothly at room temperature (Table 2, entries 1−3). Different aldehydes and arylboronic acids were tested for the sequential reaction, and good yields were observed (Table 2, entries 1−9). We also tested 2-butanone, 2-pentanone, acetophenone and 3-penta-

Table 2. Sequential Aldol Condensation-Transition Metal-Catalyzed Addition Reactions of Aldehydes, Methyl Ketones, and Arylboronic Acids[a]



entry	catalyst	RCHO	R'COCH$_3$	Ar'B(OH)$_2$	yield(%) [b]
1	1				84
2	[Rh(COD)Cl]$_2$				81 [c]
3	1				87
4	1				88
5	[Rh(COD)Cl]$_2$				82
6	[Rh(COD)Cl]$_2$				85
7	[Rh(COD)Cl]$_2$				89
8	[Rh(COD)Cl]$_2$				86
9	[Rh(COD)Cl]$_2$				84
10	1				86
11	1				74
12	[Rh(COD)Cl]$_2$				86
13	[Rh(COD)Cl]$_2$				85
14	[Rh(COD)Cl]$_2$				81
15	[Rh(COD)Cl]$_2$				84
16	1				0 [d]
17	1				65
18	[Rh(COD)Cl]$_2$				82

[a] Reaction condition: aldehyde (0.25 mmol,1.0 equiv), acetone (0.1 mL), H_2O (0.1 mL) and K_2CO_3 (1.0 equiv), 50 °C for 30 min, then **1** or [Rh(COD)Cl]$_2$ (1 mol %), THF (1 mL) and arylboronic acids (0.5 mmol, 2.0 equiv) were added into the mixture at rt for another 6 h. [b] Isolated yield. [c] Reaction was carried out in 2.5 mmol scale. [d] 1-Phenyl-2-methyl-1-penten-3-one (16%) was observed.

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(3) For examples since 2009: (a) Jeletic, M. S.; Ghiviriga, I.; Abboud, K.; Veige, A. S. *Dalton Transactions* **2010**, *39*, 6392–6394. (b) Lang, F.; Li, D.; Chen, J.; Chen, J.; Li, L.; Cun, L.; Zhu, J.; Deng, J.; Liao, J. *Adv. Synth. Catal.* **2010**, *352*, 843–846. (c) Hu, X.; Cao, Z.; Liu, Z.; Wang, Y.; Du, H. *Adv. Synth. Catal.* **2010**, *352*, 651–655. (d) Drinkel, E.; Briceno, A.; Dorta, R.; Dorta, R. *Organometallics* **2010**, *29*, 2503–2514. (e) Nishimura, T.; Yasuhara, Y.; Sawano, T.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 7872–7873. (f) Lin, S.; Lu, X. *Org. Lett.* **2009**, *12*, 2536–2539. (g) Chen, Q.-A.; Dong, X.; Chen, M.-W.; Wang, D.-S.; Zhou Y.-G.; Li, Y.-X. *Org. Lett.* **2009**, *12*, 1928–1931. (h) Xu, Q.; Zhang, R.; Zhang, T.; Shi, M. *J. Org. Chem.* **2010**, *75*, 3935–3937. (i) Chen, J.; Chen, J.–M.; Lang, F.; Zhang, X.-Y.; Cun, L.-F.; Zhu, J.; Deng, J.-G.; Liao, J. *J. Am. Chem. Soc.* **2010**, *132*, 4552–4553. (j) Hahn, B. T.; Tewes, F.; Froehlich, R.; Glorius, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 1143–1146. (k) Gendrineau, T.; Genet, J.-P.; Darses, S. *Org. Lett.* **2009**, *12*, 308–310. (l) Brown, M. K.; Corey, E. J. *Org. Lett.* **2009**, *12*, 172–175. (m) Chen, Q.; Kuriyama, M.; Hao, X.; Soeta, T.; Yamamoto, Y.; Yamada, K.-i.; Tomioka, K. *Chem. Pharm. Bull.* **2009**, *57*, 1024–1027. (n) Hu, X.; Zhuang, M.; Cao, Z.; Du, H. *Org. Lett.* **2009**, *11*, 4744–4747. (o) Minuth, T.; Boysen, M. K. *Org. Lett.* **2009**, *11*, 4212–4215. (p) Yuan, W.-C.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *Tetrahedron* **2009**, *65*, 4130–4141. (q) Wallace, G. A.; Gordon, T. D.; Hayes, M. E.; Konopacki, D. B.; Fix-Stenzel, S. R.; Zhang, X.; Grongsaard, P.; Cusack, K. P.; Schaffter, L. M.; Henry, R. F.; Stoffel, R. H. *J. Org. Chem.* **2009**, *74*, 4886–4889. (r) Kim, S. B.; Cai, C.; Faust, M. D.; Trenkle, W. C.; Sweigart, D. A. *Organometallics* **2009**, *28*, 2625–2628. (s) Buergi, J. J.; Mariz, R.; Gatti, M.; Drinkel, E.; Luan, X.; Blumentritt, S.; Linden, A.; Dorta, R. *Angew. Chem., Int. Ed.* **2009**, *48*, 2768–2771. (t) Korenaga, T.; Osaki, K.; Maenishi, R.; Sakai, T. *Org. Lett.* **2009**, *11*, 2325–2328. (u) Yamamoto, T.; Iizuka, M.; Takenaka, H.; Ohta, T.; Ito, Y. *J. Organomet. Chem.* **2009**, *694*, 1325–1332. (v) Iuliano, A.; Facchetti, S.; Funaioli, T. *Chem. Commun.* **2009**, 457–459. (w) Facchetti, S.; Cavallini, I.; Funaioli, T.; Marchetti, F.; Iuliano, A. *Organometallics* **2009**, *28*, 4150–4158. (x) Jana, R.; Tunge, J. A. *Org. Lett.* **2009**, *11*, 971–974.

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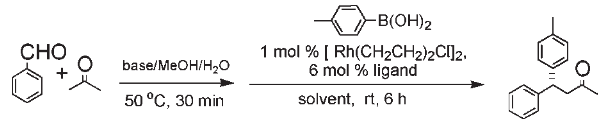
(8) For examples of intramolecular tandem reactions initialized by Rh(I)-catalyzed addition reactions of arylboronic acids with α,β-unsaturated ketones or esters: (a) Navarro, C.; Csaky, A. G. *Synthesis* **2009**, 860–863. (b) Youn, S. W.; Song, J.-H.; Jung, D.-I. *J. Org. Chem.* **2008**, *73*, 5658–5661. (c) Navarro, C.; Csakye, A. G. *Org. Lett.* **2008**, *10*, 217–219. (d) Bocknack, B. M.; Wang, L.-C.; Krische, M. J. *Proc. Nat. Acad. Sci.* **2004**, *101*, 5421–5424. (e) Cauble, D. F.; Gipson, J. D.; Krische, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 1110–1111. (f) Nishikata, T.; Kobayashi, Y.; Kobayshi, K.; Yamamoto, Y.; Miyaura, N. *Synlett* **2007**, 3055–3057.

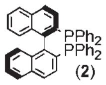
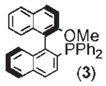
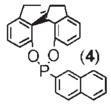
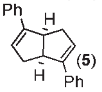
(9) Recent reviews of metalacycles: (a) Dupont, J.; Consorti, C. S.; Spencer, J. *Chem. Rev.* **2005**, *105*, 2527–2572. (b) Beletskaya, I. P.; Cheprakov, A. V. *J. Organomet. Chem.* **2004**, *689*, 4055–4082. (c) Bedford, R. B. *Chem. Commun.* **2003**, 1787–1796. (d) Newkome, G. R.; Puckett, W. E.; Gupta, V. K.; Kiefer, G. E. *Chem. Rev.* **1986**, *86*, 451–489.

none for the reaction. We found that 2-butanone, 2-pentanone and acetophenone were suitable ketones (Table 2, entries 10–15). On the other hand, we also found that 3-pentanone was inefficient for the sequential reaction (Table 2, entry 16), likely because the aldol condensation between benzaldehyde and 3-pentanone occurred too slowly. We also found aliphatic aldehydes, which can also undergo aldol reactions with themselves, were suitable starting materials for the new sequential reaction (Table 2, entries 17, 18).

We next turned our attention to the asymmetric version of this sequential β-aryl ketone formation process. We selected Rh(I) complexes for our study because Rh(I)/chiral ligand-catalyzed 1,4-addition reactions of arylboronic acids with α,β-unsaturated ketones have been established.[1,3] We examined four optically active ligands, **2**,[12] **3**,[13] 1,1′-spirobiindane-7,7′-diol (SPINOL)-based phosphite **4**[14] and **5**,[15] that were available to us and our results are listed in Table 3. We found while Rh(I)/ligand **3** and Rh(I)/ligand **5** were poor catalysts for the sequential aldol condensation-addition reaction (Table 3, entries 2, 4), Rh(I)/(*R*)-BINAP **2** and Rh(I)/ligand **4** exhibited good catalytic activities and enantioselectivities (Table 3, entries 1, 3). Other factors that could influence the enantioselectivity of the reaction were then examined. We found that with **4** as the ligand, K_2CO_3 as the base and THF as the solvent, the enantioselectivity could be improved to 89% (Table 3, entries 6- 11). Decreasing the reaction temperature from room temperature to 0 °C further improved the enantioselectivity to 92% (Table 3, entry 12).

Table 3. Asymmetric Sequential Aldol Condensation-Rh(I)/Ligand-Catalyzed Addition Reaction of Benzaldehyde, Acetone, and *p*-Tolylboronic Acid [a]

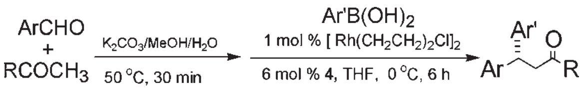


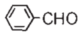
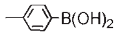
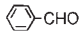
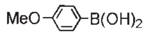
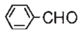
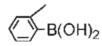
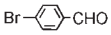
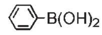
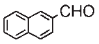
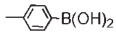
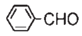
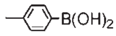
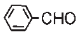
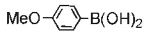
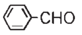
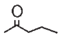
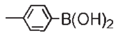
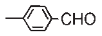
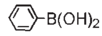
entry	ligand	base	temp	solvent	yield (%) [b]	ee (%) [c]
1	 (**2**)	KOH	100 °C	Toluene	82	81
2	 (**3**)	KOH	rt	Toluene	10	—
3	 (**4**)	KOH	rt	Toluene	81	79
4	 (**5**)	KOH	rt	Toluene	30	—
5	**2**	K_2CO_3	rt	THF	80	80
6	**4**	K_2CO_3	rt	THF	83	89
7	**4**	K_2CO_3	rt	THF	81 [d]	88
8	**4**	K_2CO_3	rt	Toluene	78	81
9	**4**	K_3PO_4	rt	Toluene	70	53
10	**4**	Cs_2CO_3	rt	Toluene	81	75
11	**4**	K_2CO_3	rt	1,4-dioxane	76	83
12	**4**	K_2CO_3	0 °C	THF	84	92

[a] Reaction condition: benzaldehyde (0.25 mmol,1.0 eqiuv), *p*-tolylboronic acid (2.0 equiv), solvent (1 mL), acetone (0.2 mL), H_2O (0.1 mL), base (1.0 equiv). [b] Isolated yield. [c] Determined by HPLC (Chiralcel OD Column). [d] **4** (4 mol %) was used.

Several aldehydes, methyl ketones and arylboronic acids were examined for the asymmetric sequential aldol condensation-Rh(I)/**4**-catalyzed addition reaction. Optically active β-arylated ketones were obtained in good yields and good enantioselectivity (Table 4, entries 1–8). Because this sequential reaction involved α,β-unsaturated ketones, generated from the aldol condensation of aldehydes and methyl ketones, and arylboronic acids, we reasoned that optically active β-arylated ketones with opposite chiral configurations could be obtained with the same Rh(I)/**4** catalyst by simply reversing the aryl groups on aldehydes and arylboronic acids. We found indeed that (*R*)-4-phenyl-4-*p*-tolylbutan-2-one, generated from benzaldehyde, acetone and *p*-tolylboronic acid, and (*S*)-4-phenyl-4-*p*-tolylbutan-2-one, generated from *p*-tolualdehyde, acetone and phenylboronic acid, were obtained in excellent enantioselectivity with the same Rh(I)/**4** catalyst (Table 4, entries 1, 9).

Table 4. Asymmetric Sequential Aldol Condensation-Rh(I)-Catalyzed Addition Reactions of Aldehydes, Methyl Ketones, and Arylboronic Acids [a]



entry	ArCHO	RCOCH3	Ar'B(OH)2	yield (%) [b]	ee (%) [c]
1				84	92 (*R*) [d]
2				80	87 (*R*) [d]
3				87	82
4				87	83
5				85	86
6				81	87
7				80	82
8				83	86
9				86	91 (*S*)

[a] Reaction condition: aldehyde (0.25 mmol,1.0 equiv), arylboronic acid (2.0 equiv), MeOH (0.1 mL), ketone (0.2 mL), H_2O(0.1 mL), K_2CO_3 (3.0 equiv), 0 °C. [b] Isolated yield. [c] Determined by HPLC analysis (Chiral OD Column) [d] Established by comparison of the HPLC data with reported ones.

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(10) Most Type I palladacycles are known to exist as bridged dimers and to dissociate into monomeric forms during reactions. Type I palladacycles in this paper were drawn in monomeric forms.

(11) For other examples: (a) Suzuma, Y.; Hayashi, S.; Yamamoto, T.; Oe, Y.; Ohta, T.; Ito, Y. *Tetrahedron: Asymmetry* **2009**, *20*, 2751–2758. (b) Yu, A.; Cheng, B.; Wu, Y.; Li, J.; Wei, K. *Tetrahedron Lett.* **2008**, *49*, 5405–5407. (c) Bedford, R. B.; Betham, M.; Charmant, J. P. H.; Haddow, M. F. A.; Orpen, G.; Pilarski, L. T.; Coles, S. J.; Hursthouse, M. B. *Organometallics* **2007**, *26*, 6346–6353. (d) Gibson, S.; Foster, D. F.; Eastham, G. R.; Tooze, R. P.; Cole-Hamilton, D. J. *Chem. Commun.* **2001**, 779–780.

In summary, we demonstrated that the aldol condensation of aldehydes with methyl ketones followed by transition metal-catalyzed addition reactions with arylboronic acids could occur efficiently in a sequential fashion, affording various β-arylated ketones. By using an optically active 1,1′-spirobiindane-7,7′-diol (SPINOL)-based phosphite as the ligand, a Rh(I)-catalyzed asymmetric version of such a sequential reaction has been realized and up to 92% ee was achieved. Our study provided an efficient method to access β-substituted ketones from readily available aldehydes with methyl ketones, and might lead to the development of other new sequential/tandem reactions with transition metal-catalyzed addition reactions as part of the reaction sequence.

Acknowledgment. We gratefully thank the NSF (CHE-0719311) and NIH (1R15 GM094709) for funding. Partial support from PSC–CUNY Research Award Programs is also acknowledged. We thank the Frontier Scientific for its generous gifts of arylboronic acids.

Supporting Information Available. General procedures and product characterization for sequential aldol condesation-transition metal-catalyzed addition reactions of aldehydes, methyl ketones and arylboronic acids. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) (a) Duan, H.-F.; Xie, J.-H.; Shi, W.-J.; Zhang, Q.; Zhou, Q.-L. *Org. Lett.* **2006**, *8*, 1479–1481. (b) Duan, H. F.; Xie, J.-H.; Qiao, X.-C.; Wang, L.-X.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2008**, *47*, 4351–4353.

(15) Wang, Z.-Q.; Feng, C.-G.; Xu, M.-H.; Lin, G.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 5336–5337.