Ruthenium-Catalyzed Tandem Olefin Migration/Aldol and Mannich-Type Reactions in Water and Protic Solvents

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Cross-coupling between 3-buten-2-ol (**2**) and aldehyde in the presence of a catalytic amount of $[RuCl_2(PPh_3)_3]$ has been developed, through a tandem olefin migration/aldol reaction in a water/toluene mixture. The presence of $In(OAc)_3$ promoted the aldol reaction with α-vinylbenzyl alcohol (**4**) and aldehyde, while treatment of 3-buten-2-ol (**2**) with imines generated Mannich-type reaction products; *syn* isomers were formed as the major diastereomers for the aldol products **3a**–**3g** and **5a**–**5e** and the Mannich products **7a**–**7g**.

Introduction

The aldol and Mannich-type reactions are among the most important C−C bond-forming reactions in organic synthesis. Under classical aldol reaction conditions, however, dimerization, polymerization, and self-condensation also occur.[1] The classical Mannich reaction also has limitations.[2] An important modification of the classical aldol and Mannich reactions is the Lewis acid catalyzed condensation of enol silyl ethers with carbonyl compounds (Mukaiyama aldol reaction)[3] and imines.[4] More recently, Trost has reported the highly efficient formation of aldol-type products through vanadium-catalyzed coupling between propargyl alcohols and aldehydes.[5] Recent developments have also included hydrometalation/aldol[6] and α-C−H activation/aldol reactions of carbonyl compounds.[7] Motherwell developed the Rh- and Ni-catalyzed isomerization of allylic lithium alkoxides to lithium enolates that then undergo further aldol reactions,[8] while Grée recently reported the $[Fe(CO)_5]$-catalyzed isomerization, under photolytic conditions, of allyl alcohol to its enol, which then reacted with aldehydes to give aldol products (together with other by-products).[9a] These workers also found that $[RhCl(PPh_3)_3]$/BuLi combinations are effective catalysts for the coupling of allyl alcohols with aldehydes. However, no reaction was observed without the lithium co-reagent.[9b]

There has recently been growing interest in the development of organic reactions in aqueous media.[10] For aqueous aldol-type condensations, Chan has developed tin- and zinc-mediated cross-couplings between halo ketones and aldehydes,[11] while Lubineau,[12] Kobayashi,[13] Loh,[14] and others[15] have developed aqueous Mukaiyama-type reactions. In addition, aqueous Mannich-type reactions through the use of silyl enol ethers or silyl ketene acetals have been carried out by Kobayashi[16a] and Akiyama.[16b]

Previously, during our studies of the development of air- and water-tolerant catalysis, we reported that the functional groups of homoallyl alcohols and allyl alcohols underwent reshuffling in air and water in the presence of a catalytic amount of $[RuCl_2(PPh_3)_3]$ (Figure 1, path a). A side product of the isomerization is the formation of a ketone (Figure 1, path b).[17] The formation of this product was explained in terms of a competing process involving the cleavage of the allylic C−H bond (rather than the C−O bond) to form a ruthenium−enol complex, which was then hydrolyzed to give the ketone.[18] We postulated that, in the presence of an aldehyde, such a ruthenium−enol complex might be captured,[19] and our initial work reported the successful capture of the intermediate by aldehydes to afford aldol-type products in water.[20] Subsequently, we found that the $[RuCl_2(PPh_3)_3]$-catalyzed tandem olefin migration/aldol reaction in water can be significantly improved with the aid of the water-tolerant Lewis acid $In(OAc)_3$. In addition, cross-couplings of imines with allyl alcohols efficiently generated Mannich-type reaction products under similar conditions in methanol. Here we wish to describe the results of these studies.

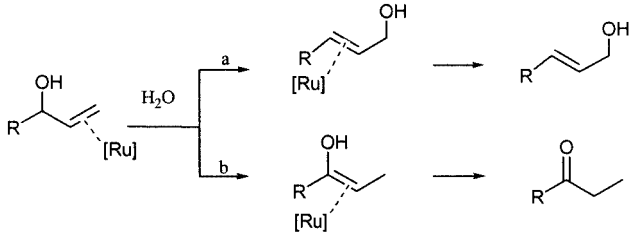

Figure 1. Ruthenium-catalyzed olefin migration in water

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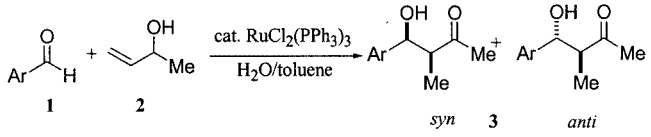
At the beginning of our study, benzaldehyde (**1a**) was stirred in water at 110 °C (oil bath) for 5 h with 3-buten-2-ol (**2**) and a catalytic amount of $[RuCl_2PPh_3)_3]$ (3 mol%), but none of the desired product was obtained (Scheme 1). The benzaldehyde (**1a**) was found to have been partially oxidized into benzoic acid. No reaction was observed when the solvent was changed to toluene, THF, DMSO, $CHCl_3$, or CH_2Cl_2 at their reflux temperatures. When the reaction was performed in a 1:4 (v/v) mixture of water and toluene, no reaction occurred at 70 °C. However, when the reaction temperature was increased to 110 °C, the desired aldol product **3a** was obtained (in a *syn*/*anti* ratio of 70:30) in 50% isolated yield (Entry 1 in Table 1). A change of the solvent ration to 4:1 (water/toluene) further increased the yield (76%) and also produced a slight increase in the *syn*/*anti* ratio (73:27) of the aldol product **3a** (Entry 2 in Table 1). The use of a water/ethanol (4:1) mixture decreased both the yield (40%) and the diastereoselectivity (*syn*/*anti* = 60:40, Entry 3 in Table 1). Subsequently, a variety of aromatic aldehydes **1b**−**1g** were examined under the same reaction conditions. In most cases, the desired aldol products **3a**−**3g** were obtained in good yields (Entries 4−10 in Table 1). When 3-fluorobenzaldehyde (**1b**) was used, the use of water alone as the solvent provided the desired product **3b** in 76% isolated yield (Entry 4 in Table 1). The use of aliphatic aldehydes provided complicated mixtures, and efforts to improve the reactions with such aldehydes are currently underway.



Scheme 1

The above method having been established, aldol reactions between α-vinylbenzyl alcohol (**4**) and aromatic aldehydes were examined (Scheme 2 and Table 2). Under the same conditions, however, treatment of benzaldehyde (**1a**) with **4** gave the product **5a** only in low yield (10%, Entry 1 in Table 2). Most of the α-vinylbenzyl alcohol (**4**) was converted into propiophenone, the result of olefin migration by path b as described in Figure 1. We speculated that, to decrease the production of propiophenone and increase the yield of aldol product, a Lewis acid was needed to activate the aldehyde. Through screening, $In(OAc)_3$ was found to be an excellent co-catalyst.[21,22c] With the $[RuCl_2(PPh_3)_3]$ (3 mol%) + $In(OAc)_3$ (8 mol%)] catalyst system, the yield of aldol product **5a** was dramatically increased from 10 to 80% (Entries 1 vs. 2 in Table 2). However, no reaction occurred between propiophenone and benzaldehyde under the same conditions, which ruled out a mechanism involving a ketone formation/aldol reaction. When aldehydes **1c**, **1e**, **1g**, and **1h** were used, the reactions gave the desired aldol-type products **5b**−**5e** in moderate to high yields (51−82%, Entries 2−6 in Table 2).

Our success with the aldol-type reaction prompted us to explore a related coupling between allyl alcohols and imines to generate Mannich-type reaction products (Scheme 3, Table 3), which had not been reported in the literature. In our experiments, imines **6a**−**6g** were generated in situ from aldehydes and *p*-anisidine, and the reactions between imines **6a**−**6g** and 3-buten-2-ol (**2**) were carried out at 110 °C (oil bath temperature) with $[RuCl_2(PPh_3)_3]$ as a catalyst. The results in Table 3 show that, when water was chosen as reaction solvent, a complicated mixture of products including imine adduct **7** and aldol product **3** was obtained. In H_2O/toluene (1:4), the reaction between **6a** and 3-buten-2-ol (**2**) proceeded smoothly to generate the desired imine adduct **7a** in moderate yield (47%, *syn*/*anti* = 76:24), together with the aldol product **3a** (27% yield; *syn*/*anti* = 59:41, Entry 1 in Table 3). When the ratio of H_2O/toluene was changed from 1:4 to 4:1, only the aldol product **3a** was obtained (Entry 3 in Table 3). It was speculated that, in the H_2O/toluene system, competition exists between imine **6a** being hydrolyzed to aldehyde **1a** and its coupling with the enol intermediate, due to the poor electrophilicity of imine. Increasing the ratio of H_2O/toluene did not favor the Mannich-type reaction. In H_2O/toluene (1:4), the presence of Lewis acids such as $Sc(OTf)_3$, $Zn(OTf)_3$, $ZnBr_2$, or $ZnCl_2$

Table 1. $[RuCl_2(PPh_3)_3]$-catalyzed aldol-type reactions between allyl alcohols **2** and aldehydes **1** in aqueous media; reaction conditions: $[RuCl_2(PPh_3)_3]$ (3 mol%), 110 °C (oil bath temperature), 5 h

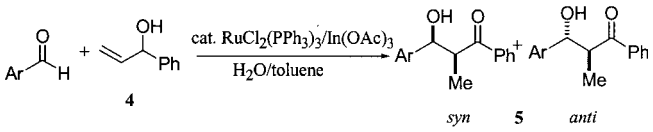
Entry	Substrate **1**, Ar	Solvent	Product **3**, Ar	Yield (%)[a]	*syn*/*anti*[b]
1	**1a**, Ph	H_2O/toluene (1:4)	**3a**, Ph	50	70:30
2	**1a**, Ph	H_2O/toluene (4:1)	**3a**, Ph	76	73:37
3	**1a**, Ph	H_2O/EtOH (4:1)	**3a**, Ph	40	60:40
4[c]	**1b**, *m*-FC_6H_4	H_2O	**3b**, *m*-FC_6H_4	72	66:34
5[c]	**1c**, *p*-ClC_6H_4	H_2O	**3c**, *p*-ClC_6H_4	35	60:40
6	**1c**, *p*-ClC_6H_4	H_2O/toluene (4:1)	**3c**, *p*-ClC_6H_4	70	74:26
7	**1d**, *p*-$MeOC_6H_4$	H_2O/toluene (4:1)	**3d**, *p*-$MeOC_6H_4$	68	51:49
8	**1e**, *p*-BrC_6H_4	H_2O/toluene (4:1)	**3e**, *p*-BrC_6H_4	73	79:21
9	**1f**, *p*-PhC_6H_4	H_2O/toluene (4:1)	**3f**, *p*-PhC_6H_4	27	67:33
10	**1g**, 2-naphthyl	H_2O/toluene (4:1)	**3g**, 2-naphthyl	44	63:37

[a] Isolated yields were reported. [b] *syn*/*anti* ratios were determined by the ^1H NMR spectra of the product mixtures (by comparison of doublet peaks from −CHOH of the isomers). [c] Reaction time was 5.5 h.

Table 2. $[RuCl_2(PPh_3)_3]$/$[In(OAc)_3]$-catalyzed aldol-type reactions between allyl alcohols **4** and aldehydes **1** in aqueous media; reaction conditions: solvent H_2O/toluene (4:1), 110 °C (oil bath temperature), 7 h

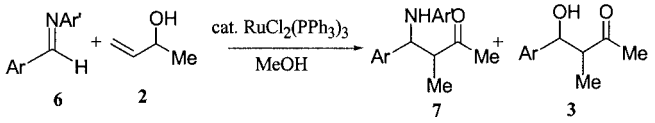
Entry	Substrate **1**, Ar	Catalyst	Product **5**, Ar	Yield (%)[a]	*syn*/*anti*[b]
1	**1a**, Ph	$RuCl_2(PPh_3)_3$(3 mol%)	**5a**, Ph	10	60:40
2	**1a**, Ph	$RuCl_2(PPh_3)_3$ (3 mol%) + $In(OAc)_3$ (8 mol%)	**5a**, Ph	80	68:32
3	**1c**, *p*-ClC_6H_4	$RuCl_2(PPh_3)_3$ (3 mol%) + $In(OAc)_3$ (8 mol%)	**5b**, *p*-ClC_6H_4	79	63:37
4	**1e**, *p*-BrC_6H_4	$RuCl_2(PPh_3)_3$ (3 mol%) + $In(OAc)_3$ (8 mol%)	**5c**, *p*-BrC_6H_4	82	61:39
5	**1g**, 2-naphthyl	$RuCl_2(PPh_3)_3$ (3 mol%) + $In(OAc)_3$ (8 mol%)	**5d**, 2-naphthyl	51	60:40
6	**1h**, *p*-MeC_6H_4	$RuCl_2(PPh_3)_3$ (3 mol%) + $In(OAc)_3$ (8 mol%)	**5e**, *p*-MeC_6H_4	54	63:37

[a] Isolated yields reported. [b] *syn*/*anti* ratios were determined by the ^1H NMR spectra of the product mixtures.



Scheme 2

as co-catalysts did not increase the reactivity of the imine, both **7a** and **3a** being generated in yields similar to those in Entry 1. No reaction was observed when the reaction was carried out in DMF or toluene, the imines being recovered completely. When methanol was used as the solvent, a clean reaction between **6a** and 3-buten-2-ol (**2**) occurred to provide only the Mannich-type product **7a** (54% yield), and no aldol-type product **3a** was observed (Entry 4 in Table 3). Interestingly, either in H_2O/toluene or in methanol, an increase in the catalyst loading from 4 to 8 mol% reduced the yields of both **7a** and **3a** (Entries 1 vs. 2 and 4 vs. 5 in Table 3). This suggests that increasing the catalyst $[RuCl_2(PPh_3)_3]$ loading favored the ketone formation (by path b in Figure 1) over the Mannich-type reaction. Subsequently, a variety of imines **6b**−**6g** generated from aromatic aldehydes were examined under the same reaction conditions (Entries 6−15 in Table 3). In methanol, imines reacted effectively to generate the desired Mannich-type products **7b**−**7g** (yields 44−70%). In H_2O/toluene (1:4), both the Mannich-type products **7a**−**e** (35−45% yield) and the aldol-type products **3b**−**3e** (23−35%) were obtained. The use of imines generated from aliphatic aldehydes gave complicated mixtures of products both in methanol and H_2O/toluene.



Scheme 3

A tentative mechanism for the product formation is depicted in Figure 2. The ruthenium complex isomerizes the allyl alcohol **2** or **4** to an enol that is coordinated with the

Table 3. $[RuCl_2(PPh_3)_3]$-catalyzed Mannich-type reaction between imines **6** and allyl alcohol **2** in aqueous or protic media; reaction conditions: $[RuCl_2(PPh_3)_3]$ (4 mol%), 110 °C (oil bath temperature), 10 h; imines were generated in situ from aldehydes and *p*-anisidine

Entry	Substrate **6**, R	Solvent[a]	Product R	Product Yield (%)[c]	*syn*/*anti* [b] **7** (**3**)
1	**6a**, Ph	H_2O/toluene (1:4)	Ph	**7a**, 47 (**3a**, 27)	76:24 (59:41)
2[d]	**6a**, Ph	H_2O/toluene (1:4)	Ph	**7a**, 20 (**3a**, 20)	70:30 (59:41)
3	**6a**, Ph	H_2O/toluene (4:1)	Ph	(**3a**, 43)	(64:36)
4	**6a**, Ph	MeOH	Ph	**7a**, 54	58:42
5[d]	**6a**, Ph	MeOH	Ph	**7a**, 45	56:44
6	**6b**, *m*-FC_6H_4	MeOH	*m*-FC_6H_4	**7b**, 70	63:37
7	**6b**, *m*-FC_6H_4	H_2O/toluene (1:4)	*m*-FC_6H_4	**7b**, 45 (**3b**, 30)	60:40 (65:35)
8	**6c**, *p*-ClC_6H_4	MeOH	*p*-ClC_6H_4	**7c**, 68	59:41
9	**6c**, *p*-ClC_6H_4	H_2O/toluene (1:4)	*p*-ClC_6H_4	**7c**, 38 (**3c**, 34)	55:45 (55:45)
10	**6d**, *p*-BrC_6H_4	MeOH	*p*-BrC_6H_4	**7d**, 61	63:37
11	**6d**, *p*-BrC_6H_4	H_2O/toluene (1:4)	*p*-BrC_6H_4	**7d**, 35 (**3e**, 35)	60:40 (55:45)
12	**6e**, *p*-$MeOC_6H_4$	MeOH	*p*-$MeOC_6H_4$	**7e**, 60	57:43
13	**6e**, *p*-$MeOC_6H_4$	H_2O/toluene (1:4)	*p*-$MeOC_6H_4$	**7e**, 40 (**3d**, 23)	55:45 (60:40)
14	**6f**, *o*-MeC_6H_4	MeOH	*o*-MeC_6H_4	**7f**, 44	50:50
15	**6g**, 2-naphthyl	MeOH	2-naphthyl	**7g**, 60	57:43

[a] H_2O/toluene ratio in v/v. [b] *syn*/*anti* ratios were determined by the ^1H NMR spectra of the product mixtures (by comparison of doublet peaks from −CHN− of the isomers). [c] Isolated yield. [d] 8 mol% of the catalyst was used.

ruthenium catalyst, and in situ coupling between the ruthenium−enol complex with the aldehyde or imine generates the aldol or Mannich-type product. The formation of primarily the *syn* isomer (Tables 1−3) is consistent with previous studies on aldol- or Mannich-type reactions with silyl enol ether.[16,22]

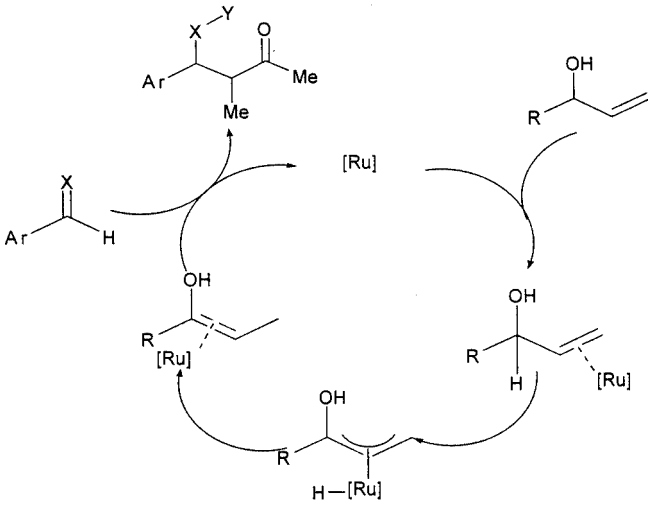


Figure 2. Tentative mechanism for the ruthenium-catalyzed Aldol-type or Mannich-type reactions (R = Me or Ph; X = O or *p*-$MeOC_6H_4N$; Y = H)

In conclusion, ruthenium-catalyzed tandem olefin migration/aldol and Mannich-type reactions in aqueous media or in methanol have been developed. The scope (such as asymmetric synthesis), mechanisms, and synthetic applications of these novel reactions are under investigation.

Experimental Section

General: Commercially available chemicals were used directly as received. Flash chromatography employed E. Merck silica gel (Kieselgel 60, 230−400 mesh) purchased from Scientific Adsorbents. High-resolution mass spectrometry was performed at the Institute of Chemistry, the Chinese Academy of Sciences.

General Procedure for Tandem Olefin Migration/Aldol-Type Reaction in Aqueous Media: A mixture of the aldehyde (0.5 mmol), allyl alcohol (1.25 mmol), and $[RuCl_2(PPh_3)_3]$ (0.015 mmol, 3 mol%) in H_2O/toluene (4 mL/1 mL) was stirred in air at 110 °C (oil bath temperature) for 5 h. The reaction mixture was then allowed to cool to room temperature, diluted with diethyl ether, washed with brine, and dried with anhydrous Na_2SO_4. The mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: hexane/EtOAc) to afford the aldol-type products **3a**,[23] **3b**, **3c**,[24] **3d**, **3e**,[24] **3f**, **3g**, **5a**,[25] **5b**,[26] **5c**,[25] **5d**,[27] and **5e**.[28]

General Procedure for Tandem Olefin Migration/Mannich-Type Reaction in Methanol: A mixture of the aldehyde (0.5 mmol) and *p*-anisidine (0.55 mmol) in methanol (5 mL) was heated at gentle reflux (under air). After 2 h, allyl alcohol (1.25 mmol) and $[RuCl_2(PPh_3)_3]$ (0.02 mmol, 4 mmol%) were added, and the mixture was stirred in air for 10 h. The reaction mixture was then allowed to cool to room temperature, diluted with diethyl ether, washed with brine, and dried with anhydrous Na_2SO_4. The mixture was then concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: hexane/EtOAc) to afford the Mannich-type products **7a**−**7g**.

Characterization of the New Compounds

4-(3-Fluorophenyl)-4-hydroxy−3-methylbutan-2-one (3b) (*syn*/*anti* = 66:34). 3b, *syn*: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.24−7.31 (m, 1 H), 7.03−7.08 (m, 2 H), 6.90−6.96 (m, 1 H), 5.12 (d, *J* = 3.6 Hz, 1 H), 3.20 (br. s, 1 H), 2.79 (dq, *J* = 3.6, 8.0 Hz, 1 H), 2.17 (s, 3 H), 1.04 (d, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 213.9, 164.3, 161.9, 144.6(2), 130.2(2), 121.6(2), 114.5, 114.3, 113.3, 113.1, 72.2(2), 53.0, 29.5, 10.0 ppm. IR (film): $\tilde{\nu}$ = 3436, 2937, 1708, 1591, 1449, 1359, 1245, 1179, 1133, 1028 cm^{-1}. **3b, *anti*:** ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.26−7.33 (m, 1 H), 7.02−7.09 (m, 2 H), 6.94−7.00 (m, 1 H), 4.73 (dd, *J* = 3.6, 8.0 Hz, 1 H), 2.97 (d, *J* = 3.6 Hz, 1 H), 2.83−2.92 (m, 1 H), 2.20 (s, 3 H), 0.95 (d, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 213.5, 164.4, 161.9, 144.8(2), 130.3, 130.2, 122.5(2), 115.2, 115.0, 113.8, 113.6, 76.0, 53.6, 30.3, 14.3 ppm. IR (film): $\tilde{\nu}$ = 3426, 2924, 1708, 1591, 1451, 1359, 1246, 1170, 1023 cm^{-1}. HRMS: *m*/*z* calcd. for $C_{11}H_{13}FO_2$: 219.0792 [M + Na], 197.0972 [M + H]; found 219.0793 [M + Na], 197.0970 [M + H].

4-Hydroxy-4-(4-methoxyphenyl)-3-methylbutan-2-one (3d) (*syn*/*anti* = 51:49). 3d, *syn*: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.19−7.24 (m, 2 H), 6.83−6.87 (m, 2 H), 4.99 (d, *J* = 4.0 Hz, 1 H), 3.77 (s, 3 H), 2.91 (br. s, 1 H), 2.79 (dq, *J* = 4.0, 8.0 Hz, 1 H), 2.10 (s, 3 H), 1.08 (d, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 213.9, 159.1, 134.1, 127.3, 113.9, 73.1, 55.5, 53.5, 29.8, 10.7 ppm. IR (film): $\tilde{\nu}$ = 3435, 2936, 1707, 1611, 1513, 1357, 1248, 1176, 1031 cm^{-1}. **3d, *anti*:** ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.19−7.25 (m, 2 H), 6.83−6.88 (m, 2 H), 4.67 (d, *J* = 8.4 Hz, 1 H), 3.78 (s, 3 H), 2.83−2.91 (m, 1 H), 2.75 (br. s, 1 H), 2.20 (s, 3 H), 0.88 (d, *J* = 8.4 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): δ = 213.8, 159.5, 134.3, 128.1, 114.1, 76.3, 55.5, 54.0, 30.2, 14.3 ppm. IR (film): $\tilde{\nu}$ = 3428, 2934, 1706, 1611, 1513, 1249, 1176, 1032 cm^{-1}. HRMS: *m*/*z* calcd. for $C_{12}H_{16}O_3$: 208.1094, 231.0992 [M + Na]; found 208.1095, 231.0991 [M + Na].

4-Hydroxy-3-methyl-4-(4-phenylphenyl)butan-2-one (3f) (*syn*/*anti* = 67:33). 3f, *syn*: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.54−7.59 (m, 4 H), 7.30−7.45 (m, 5 H), 5.15 (d, *J* = 3.6 Hz, 1 H), 3.08 (br. s, 1 H), 2.86 (dq, *J* = 3.6, 8.0 Hz, 1 H), 2.17 (s, 3 H), 1.11 (d, 3 H, 7.2 Hz) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 214.0, 141.0, 140.4, 129.0, 127.5, 127.3, 127.2, 126.6, 72.9, 53.3, 29.6, 10.4 ppm. IR (film): $\tilde{\nu}$ = 3439, 2926, 1703, 1486, 1358, 1178, 1008 cm^{-1}. **3f, *anti*:** ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.55−7.59 (m, 4 H), 7.31−7.45 (m, 5 H), 4.78 (d, *J* = 8.0 Hz, 1 H), 2.91−3.00 (m, 1 H), 2.85 (br. s, 1 H), 2.85 (br. s, 1 H), 2.23 (s, 3 H), 0.97 (d, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): δ = 213.7, 141.1(2), 141.0, 129.0, 127.6, 127.5, 127.3(2), 76.5, 53.8, 30.3, 14.4 ppm. IR (film): $\tilde{\nu}$ = 3426, 2926, 1708, 1485, 1357, 1241, 1170, 1008 cm^{-1}. HRMS: *m*/*z* calcd. for $C_{17}H_{18}O_2$: 254.1301; found 254.1308.

4-Hydroxy-3-methyl-4-(2-naphthyl)butan-2-one (3g) (*syn*/*anti* = 63:37). 3g, *syn*: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.79−7.84 (m, 4 H), 7.42−7.50 (m, 2 H), 7.35−7.39 (m, 1 H), 5.26 (d, *J* = 3.6 Hz, 1 H), 3.25 (br. s, 1 H), 2.92 (dq, *J* = 3.6, 8.0 Hz, 1 H), 2.16 (s, 3 H), 1.09 (d, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 214.0, 139.3, 133.4, 133.0, 128.2, 127.9, 126.4, 126.1, 125.0, 124.1, 73.2, 53.2, 29.6, 10.3 ppm. IR (film): $\tilde{\nu}$ = 3429, 2980, 1709, 1413, 1358, 1177, 1022 cm^{-1}. **3g, *anti*:** ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.79−7.85 (m, 3 H), 7.73−7.76 (m, 1 H), 7.44−7.50 (m, 3 H), 4.90 (d, *J* = 8.0 Hz, 1 H), 2.98−3.07 (m, 1 H), 2.95 (br. s, 1

H), 2.22 (s, 3 H), 0.94 (d, J = 7.2 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): δ = 213.7, 139.5, 133.4, 133.3, 128.7, 128.2, 127.9, 126.5, 126.3, 126.1, 124.4, 53.7, 30.4, 14.4 ppm. IR (film): ṽ = 3415, 2929, 1707, 1358, 1239, 1172, 1021 cm^{-1}. HRMS: *m*/*z* calcd. for $C_{15}H_{16}O_2$: 228.1145, 251.1042 [M + Na]; found 228.1144, 251.1039 [M + Na].

4-(4-Methoxyphenylamino)-3-methyl-4-phenylbutan-2-one (7a) (*syn*/*anti* = 56:44). 7a, *syn*: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.18−7.32 (m, 5 H), 6.62−6.67 (m, 2 H), 6.41−6.48 (m, 2 H), 4.65 (d, J = 5.2 Hz, 1 H), 3.66 (s, 3 H), 2.95−3.07 (m, 1 H), 2.09 (s, 3 H), 1.06 (d, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 211.0, 152.3, 141.6, 141.5, 128.8, 127.5, 127.2, 115.1, 114.9, 55.9, 53.2, 29.6, 15.5, 11.3 ppm. IR (film): ṽ = 3390, 2933, 1707, 1512, 1453, 1243, 1178, 1037 cm^{-1}. **7a, *anti*:** ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.17−7.33 (m, 5 H), 6.61−6.66 (m, 2 H), 6.40−6.47 (m, 2 H), 4.38 (d, J = 8.0 Hz, 1 H), 3.65 (s, 3 H), 2.87−2.95 (m, 1 H), 2.01 (s, 3 H), 1.07 (d, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 212.8, 152.3, 141.4, 141.3, 128.9, 127.8, 127.3, 115.0, 114.9, 59.8, 55.9, 54.0, 29.2, 15.3 ppm. IR (film): ṽ = 3390.0, 2931.4, 1707.2, 1623.9, 1506.8, 1453.4, 1288.6, 1246.3, 1191.1, 1034.1 cm^{-1}. HRMS: *m*/*z* calcd. for $C_{18}H_{21}NO_2$: 284.1645 [M + H]; found 284.1647.

4-(3-Fluorophenyl)-4-(4-methoxyphenylamino)-3-methylbutan-2-one (7b) (*syn*/*anti* = 63:37). 7b, *syn*: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.25−7.30 (m, 1 H), 6.99−7.10 (m, 2 H), 6.87−6.94 (m, 1 H), 6.63−6.69 (m, 2 H), 6.38−6.46 (m, 2 H), 4.64 (d, J = 5.2 Hz, 1 H), 3.67 (s, 3 H), 2.93−3.01 (m, 1 H), 2.11 (s, 3 H), 1.06 (d, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 210.6, 164.6, 162.1, 152.5, 144.6, 140.9, 130.4, 130.3, 122.8, 122.7, 115.0, 114.9, 114.6, 114.4, 114.2, 113.9, 59.4, 55.9, 53.0, 29.6, 11.0 ppm. IR (film): ṽ = 3387, 2932, 1708, 1590, 1513, 1446, 1241, 1038 cm^{-1}. **7b, *anti*:** ^{1}H NMR ($CDCl_3$, 400 MHz: δ = 7.22−7.29 (m, 1 H), 7.03−7.07 (m, 1 H), 6.95−7.00 (m, 1 H), 6.87−6.93 (m, 1 H), 6.63−6.68 (m, 2 H), 6.42−6.47 (m, 2 H), 4.38 (d, J = 7.6 Hz, 1 H), 3.66 (s, 3 H), 2.86−2.94 (m, 1 H), 2.02 (s, 3 H), 1.09 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 212.2, 164.6, 152.4, 144.7, 140.8, 130.4 (2), 122.8 (2), 115.0 (2), 114.7, 114.5, 114.0, 113.8, 61.3, 55.9, 53.6, 29.4, 15.3 ppm. IR (film): ṽ = 3360, 2931, 1707, 1590, 1513, 1449, 1241, 1037 cm^{-1}. HRMS: *m*/*z* calcd. for $C_{18}H_{20}FNO_2$: 301.1472; found 301.1472.

4-(4-Chlorophenyl)-4-(4-methoxyphenylamino)-3-methylbutan-2-one (7c) (*syn*/*anti* = 59:41). 7c, *syn*: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.12−7.23 (m, 5 H), 6.56−6.63 (m, 2 H), 6.32−6.40 (m, 2 H), 4.56 (d, J = 5.6 Hz, 1 H), 3.61 (s, 3 H), 2.85−2.93 (m, 1 H), 2.04 (s, 3 H), 1.00 (d, 3 H, J = 7.2) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 209.5, 151.3, 139.7, 139.1, 131.8, 127.8, 127.2, 113.8, 113.7, 58.0, 54.6, 52.4, 28.1, 14.1 ppm. IR (film): ṽ = 3396, 2932, 1709, 1622, 1510, 1245, 1178, 1091, 1035 cm^{-1}. **7c, *anti*:** ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.13−7.24 (m, 5 H), 6.55−6.62 (m, 2 H), 6.31−6.40 (m, 2 H), 4.32 (d, J = 7.6 Hz, 1 H), 3.61 (s, 3 H), 2.84−2.94 (m, 1 H), 2.00 (s, 3 H), 1.03 (d, J = 7.2 Hz, 3 H ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 211.0, 151.2, 139.6, 138.8, 132.0, 127.8, 127.3, 113.8, 113.7, 59.8, 51.8, 28.4, 9.9 ppm. IR (film): ṽ = 3423, 2931, 1709, 1621, 1507, 1253, 1093, 1032 cm^{-1}. HRMS: *m*/*z* calcd. for $C_{18}H_{20}ClNO_2$: 317.1177; found 317.1178.

4-(4-Bromophenyl)-4-(4-methoxyphenylamino)3-methylbutan-2-one (7d) (*syn*/*anti* = 63:37). 7d, *syn*: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.32−7.39 (m, 2 H), 7.10−7.15 (m, 2 H), 6.58−6.64 (m, 2 H), 6.39−6.47 (m, 2 H), 4.60 (d, J = 5.6 Hz, 1 H), 3.66 (s, 3 H), 2.90−2.99 (m, 1 H), 2.10 (s, 3 H), 1.05 (d, 3 H, J = 7.2Hz) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 212.3, 152.5, 140.9, 140.6, 132.0, 129.0, 121.4, 115.5, 115.0, 59.3, 55.8, 53.6, 29.7, 11 ppm. IR (film): ṽ = 3393, 2932, 1707, 1512, 1358, 1243, 1177, 1036, 1009 cm^{-1}. **7d, *anti*:** ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.33−7.39 (m, 2 H), 7.09−7.14 (m, 2 H), 6.57−6.64 (m, 2 H), 6.38−6.48 (m, 2 H), 4.30 (d, J = 7.6 Hz, 1 H), 3.61 (s, 3 H), 2.85−3.00 (m, 1 H), 2.01 (s, 3 H), 1.03 (d, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 210.7, 152.4, 140.9, 140.8, 132.0, 129.1, 121.6, 115.0, 114.9, 61.2, 55.9, 53.3, 29.4, 15.3. IR (film): ṽ = 3364, 2931, 1705, 1512, 1357, 1239, 1176, 1036, 1009 cm^{-1}. HRMS: *m*/*z* calcd. for $C_{18}H_{20}BrNO_2$: 362.0750 [M + H]; found 362.0749.

4-(4-Methoxyphenyl)-4-(4-methoxyphenylamino)-3-methylbutan-2-one (7e) (*syn*/*anti* = 57:43). 7e, *syn*: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.17−7.21 (m, 2 H), 6.80−6.84 (m, 2 H), 6.62−6.67 (m, 2 H), 6.41−6.46 (m, 2 H), 4.58 (d, J = 5.6 Hz, 1 H), 3.76 (s, 3 H), 3.66 (s, 3 H), 2.90−3.00 (m, 1 H), 2.06 (s, 3 H), 1.06 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 211.3, 158.9, 152.3, 141.3, 133.3, 128.1, 115.0, 114.9, 114.2, 59.4, 55.4, 53.5, 29.9, 29.7, 11.4 ppm. IR (film): ṽ = 3383, 2929, 1707, 1607, 1511, 1247, 1177, 1031 cm^{-1}. **7e, *anti*:** 1H NMR ($CDCl_3$, 400 MHz): δ = 7.09−7.15 (m, 2 H), 6.74−6.79 (m, 2 H), 6.56−6.62 (m, 2 H), 6.38−6.43 (m, 2 H), 4.28 (d, J = 8.0 Hz, 1 H), 3.70 (s, 3 H), 3.61 (s, 3 H), 2.77−2.86 (m, 1 H), 1.97 (s, 3 H), 1.05 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 212.8, 159.0, 152.3, 141.1, 133.5, 128.1, 115.1, 114.9, 114.2, 61.1, 55.9, 54.2, 29.9, 29.1, 15.3 ppm. IR (film): ṽ = 3433, 2923, 1709, 1622, 1511, 1364, 1251, 1029 cm^{-1}. HRMS: *m*/*z* calcd. for $C_{19}H_{23}NO_3$: 313.1672; found 313.1671.

4-[(4-Methoxyphenyl)amino]-3-methyl-4-(2-methylphenyl)butan-2-one (7f) (*syn*/*anti* = 51:49). 7f, *syn*: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.28−7.32 (m, 1 H), 7.08−7.18 (m, 3 H), 6.61−6.66 (m, 2 H), 6.34−6.38 (m, 2 H), 4.88 (d, J = 4.4 Hz, 1 H), 3.65 (s, 3 H), 2.92−3.01 (m, 1 H), 2.47 (s, 3 H), 2.17 (s, 3 H), 1.04 (d, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 210.7, 152.4, 141.4, 139.1, 134.6, 131.2, 127.3, 126.8, 126.5, 114.9, 114.8, 55.9, 55.7, 50.7, 29.4, 19.4, 10.4. IR (film): ṽ = 3396, 2930, 1708, 1512, 1463, 1357, 1243, 1179, 1037 cm^{-1}. **7f, *anti*:** 1H NMR ($CDCl_3$, 400 MHz): δ = 7.18−7.23 (m, 1 H), 7.07−7.15 (m, 3 H), 6.61−6.66 (m, 2 H), 6.37−6.43 (m, 2 H), 4.63 (d, J = 7.2 Hz, 1 H), 3.65 (s, 3 H), 2.93−3.01 (m, 1 H), 2.43 (s, 3 H), 1.97 (s, 3 H), 1.10 (d, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 213.1, 152.3, 141.3, 139.1, 135.4, 130.9, 127.3, 126.8, 125.9, 115.2, 114.9, 57.9, 55.9, 52.5, 30.3, 29.9, 19.7, 15.1 ppm. IR (film): ṽ = 3405, 2926, 1708, 1620, 1506, 1461, 1244, 1035 cm^{-1}. HRMS: *m*/*z* calcd. for $C_{19}H_{23}NO_2$: calcd. 297.1723; found 297.1722.

4-(4-Methoxyphenylamino)-3-methyl-4-(2-naphthyl)butan-2-one (7g) (*syn*/*anti* = 57:43). 7g, *syn*: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.74−7.82 (m, 4 H), 7.41−7.47 (m, 3 H), 6.60−6.66 (m, 2 H), 6.44−6.49 (m, 2 H), 4.82 (d, J = 5.2 Hz, 1 H), 3.64 (s, 3 H), 3.05−3.14 (m, 1 H), 2.12 (s, 3 H), 1.09 (d, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 211.0, 152.4, 141.3, 139.0, 133.6, 133.0, 128.7, 128.1, 127.9, 126.4, 126.1, 126.0, 125.0, 115.1, 114.9, 60.0, 55.9, 53.2, 29.6, 11.1 ppm. IR (film): ṽ = 3396, 2932, 1709, 1511, 1359, 1243, 1178, 1036 cm^{-1}. **7g, *anti*:** ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.71−7.81 (m, 4 H), 7.38−7.47 (m, 3 H), 6.59−6.65 (m, 2 H), 6.47−6.52 (m, 2 H), 4.54 (d, J = 7.6 Hz, 1 H), 3.63 (s, 3 H), 2.98−3.06 (m, 1 H), 2.03 (s, 3 H), 1.10 (d, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 212.6, 152.4, 141.1, 139.1, 128.9, 128.1, 127.9, 126.4, 126.3, 126.1, 124.7, 115.2, 114.9, 62.0, 55.9, 53.8, 29.3, 15.4 ppm. IR (film): ṽ = 2390, 2935, 2832, 1697, 1613, 1504, 1453, 1350, 1228, 1170, 1029 cm^{-1}. HRMS: *m*/*z* calcd. for $C_{22}H_{23}NO_2$: 334.1801 [M + H]; found 334.1799.

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[1] M. B. Smith, J. March, *Advanced Organic Chemistry: Reactions, Mechanisms and Structure*, 4th ed., Wiley-Interscience, New York, **1992**.
[2] R. Bloch, *Chem. Rev.* **1998**, *98*, 1407 and references cited therein.
[3] [3a] T. Mukaiyama, *Org. React.* **1982**, *28*, 203. [3b] For the mechanism of the Mukaiyama aldol reaction see: T. K. Hollis, B. Bosnich, *J. Am. Chem. Soc.* **1995**, *117*, 4570; S. E. Denmark, W. Lee, *J. Org. Chem.* **1994**, *59*, 707.
[4] [4a] S. Kobayashi, H. Ishitani, *Chem. Rev.* **1999**, *99*, 1069 and references cited therein. [4b] K. Ishihara, M. Miyata, K. Hattori, T. Tada, H. Yamamoto, *J. Am. Chem. Soc.* **1994**, *116*, 10520. [4c] S. J. Danishefsky, S. Chackalamannil, P. Harrision, M. Silvestri, P. Cole, *J. Am. Chem. Soc.* **1985**, *107*, 2474. [4d] P. G. Cozzi, B. Di Simone, A. Umani-Ronichi, *Tetrahedron Lett.* **1996**, *37*, 1691. [4e] G. Cainelli, M. Contento, A. Drusiani, M. Panunzio, L. Plessi, *Chem. Commun.* **1985**, 240.
[5] B. M. Trost, S. Oi, *J. Am. Chem. Soc.* **2001**, *123*, 1230.
[6] [6a] S. Sato, I. Matsuda, M. Shibata, *J. Organomet. Chem.* **1989**, *377*, 347. [6b] I. Matsuda, M. Shibata, S. Sato, *J. Organomet. Chem.* **1988**, *340*, C5; for use of Rh enolate intermediates in aldol reactions, see: [6c] G. A. Slough, R. G. Bergman, C. H. Heathcock, *J. Am. Chem. Soc.* **1989**, *111*, 938. [6d] M. T. Reetz, A. E. Vougioukas, *Tetrahedron Lett.* **1987**, *28*, 793. [6e] S. Sato, I. Matsuda, Y. Izumi, *Tetrahedron Lett.* **1986**, *27*, 5517.
[7] For examples, see: [7a] B. M. Trost, E. R. Silcoff, H. Ito, *Org. Lett.* **2001**, *3*, 2497. [7b] S. Murahashi, H. Takaya, *Acc. Chem. Res.* **2000**, *33*, 225. [7c] Y. R. Lin, X. T. Zhou, L. X. Dai, J. Sun, *J. Org. Chem.* **1997**, *62*, 1799. [7d] S. I. Murahashi, T. Naota, H. Taki, M. Mizuno, H. Takaya, S. Komiya, Y. Mizuho, N. Oyasato, M. Hiraoka, M. Hirano, A. Fukuoka, *J. Am. Chem. Soc.* **1995**, *117*, 12436. [7e] M. Picquet, C. Bruneau, P. M. Dixneuf, *Tetrahedron* **1999**, *55*, 3937. [7f] E. Gómez-Bengoa, J. M. Cuerva, C. Mateo, A. M. Echavarren, *J. Am. Chem. Soc.* **1996**, *118*, 8553.
[8] L. J. Gazzard, W. B. Motherwell, D. A. Sandham, *J. Chem. Soc., Perkin Trans. 1* **1999**, 979.
[9] [9a] C. Crévisy, M. Wietrich, V. LeBoulaire, R. Umea, R. Grée, *Tetrahedron Lett.* **2001**, *42*, 395. [9b] R. Uma, M. Davies, C. Crévisy, R. Grée, *Tetrahedron Lett.* **2001**, *42*, 3069.
[10] [10a] C. J. Li, T. H. Chan, *Organic Reactions in Aqueous Media* John Wiley & Sons, New York, **1997**. [10b] *Organic Synthesis in Water* (Ed.: P. A. Grieco), Blackie Academic & Professional, Glasgow, **1998**.
[11] T. H. Chan, C. J. Li, Z. Y. Wei, *Chem. Commun.* **1990**, 505.
[12] A. Lubineau, *J. Org. Chem.* **1986**, *51*, 2142.
[13] S. Kobayashi, I. Hachiya, *J. Org. Chem.* **1994**, *59*, 3590.
[14] T. P. Loh, J. Pei, G. Q. Cao, *Chem. Commun.* **1996**, 1819.
[15] H. Y. Tian, Y. J. Chen, D. Wang, C. C. Zeng, C. J. Li, *Tetrahedron Lett.* **2000**, *41*, 2529.
[16] [16a] S. Kobayashi, K. Manabe, *Acc. Chem. Res.* **2002**, *35*, 209 and references cited therein. [16b] T. Akiyama, J. Takaya, H. Kagoshima, *Tetrahedron Lett.* **2001**, *42*, 4025.
[17] [17a] C. J. Li, D. Wang, D. L. Chen, *J. Am. Chem. Soc.* **1995**, *117*, 12867. [17b] D. Wang, D. L. Chen, J. X. Haberman, C. J. Li, *Tetrahedron* **1998**, *54*, 5129. [17c] D. Wang, C. J. Li, *Synth. Commun.* **1998**, *28*, 507.
[18] For other examples of Ru enolates, see: [18a] J. F. Hartwig, R. G. Bergman, R. A. Anderson, *Organometallics* **1991**, *10*, 3326. [18b] B. T. Rasley, M. Rapta, R. J. Kulawiec, *Organometallics* **1996**, *15*, 2852. [18c] S. Chang, Y. Na, E. Choi, S. Kim, *Org. Lett.* **2001**, *3*, 2089. For a review on ruthenium-catalyzed nonmetathesis reactions, see: [18d] B. M. Trost, F. D. Toste, A. B. Pinkerton, *Chem. Rev.* **2001**, *101*, 2067.
[19] Ru−enol intermediates have previously been captured by aldehydes in a Michael addition reaction: [19a] B. M. Trost, A. B. Pinkerton, *J. Am. Chem. Soc.* **2000**, *122*, 8081. For capturing of Pd and Pt enolates by aldehydes, see [19b] O. Fujimura, *J. Am. Chem. Soc.* **1998**, *120*, 10032. [19c] M. Sodeoka, K. Ohrai, M. Shibasaki, *J. Org. Chem.* **1995**, *60*, 2648.
[20] M. Wang, C. J. Li, *Tetrahedron Lett.* **2002**, *43*, 3589.
[21] Lewis acids $Sc(OTf)_3$, $Cu(OTf)_2$, CuBr, $Zn(OTf)_2$, $ZnBr_2$, and $InCl_3$ were found to be ineffective in the aldol reaction between allyl alcohol **4** and aldehyde **1**.
[22] For examples of aldol and Mannich reactions, see also: [22a] S. Kobayashi, T. Busujima, S. Nagayama, *Chem. Eur. J.* **2000**, *6*, 3491; for aldol reactions in aqueous media, see: [22b] S. Kobayashi, S. Nagayama, T. Busujima, *Tetrahedron* **1999**, *55*, 8739; for Mannich reactions in aqueous media, see: [22c] T.-P. Loh, S. B. K. W. Liung, K. L. Tan, L.-L. Wei, *Tetrahedron* **2000**, *56*, 3227.
[23] H. Yatagai, Y. Yamamoto, K. Maruyama, *J. Am. Chem. Soc.* **1980**, *102*, 4548.
[24] Y. Huang, C. Chen, Y. Shen, *J. Chem. Soc., Perkin Trans. 1* **1988**, 2855.
[25] S. E. Denmark, K.-T. Wong, R. A. Stavenger, *J. Am. Chem. Soc.* **1997**, *119*, 2333.
[26] S. Nagayama, S. Kobayashi, *J. Am. Chem. Soc.* **2000**, *122*, 11531.
[27] A. J. Fry, M. Susla, M. Weltz, *J. Org. Chem.* **1987**, *52*, 2496.
[28] T. Mukaiyama, N. Iwasawa, R. W. Stevens, T. Haga, *Tetrahedron* **1984**, *40*, 1381.

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