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Synthesis of β-Hydroxy and β-Amino Ketones from Allylic Alcohols Catalyzed by $Ru(\eta^5\text{-}C_5Ph_5)(CO)_2Cl$

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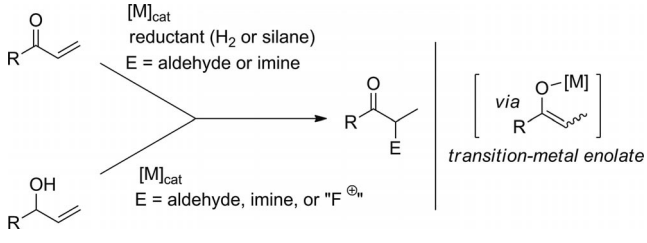
An efficient method for the synthesis of β-hydroxy and β-amino ketones from allylic alcohols catalyzed by $Ru(\eta^5\text{-}C_5Ph_5)(CO)_2Cl$ is described. The influence of the stereoelectronic properties of the catalyst on the reaction outcome has been studied. Optimization of the reaction conditions suppressed the formation of undesired side products such as saturated ketones, benzyl alcohols, and α,β-unsaturated ketones. Several aromatic and aliphatic allylic alcohols have been reacted with a large variety of aldehydes or imines to produce β-hydroxy ketones or β-amino ketones, respectively, in yields up to 99 %. Based on experimental data, a mechanism via ruthenium alkoxides and ruthenium aldoxides is proposed. In addition, a *C*-bound ruthenium enolate has been characterized.

Introduction

Metal enolates are very important intermediates in synthetic organic transformations in which C–C or C–heteroatom bonds are formed.[1] Enolates of transition metals have emerged as synthetically appealing alternative intermediates to enolates of main group elements. Methods to prepare transition metal enolates[2] include the reduction of enones by hydrogen or silane mediated by rhodium and other transition metals.[3] These intermediates can also be prepared from allylic alcohols in a process whereby an internal redox reaction is catalyzed by the metal complex.[4] Both methods have been used in the formation of C–C bonds in the presence of aldehydes or imines (Scheme 1).[3,5,6] We have recently reported the iridium-catalyzed conversion of allylic alcohols to α-fluoro ketones, which was achieved with an electrophilic fluorinating reagent.[7]



Scheme 1. Synthesis of α-substituted ketones from enones or allylic alcohols catalyzed by transition metal complexes.

The transition-metal-catalyzed coupling of allylic alcohols with aldehydes or imines has been hampered by its moderate efficiency, which is due to the formation of variable amounts of unsubstituted ketones by isomerization of the allylic alcohols (i.e. reaction with the electrophile, aldehyde or imine, did not occur; E = H in Scheme 1).[4] In 2006, an important breakthrough was achieved when Grée and co-workers reported the use of nickel hydride complexes in the coupling of allylic alcohols with aldehydes to obtain aldols in high yields.[5m] The same group have recently reported the use of *N*-sulfonylimines and *N*-*tert*-butanesulfinimines as electrophiles with Fe and Ni complexes, respectively.[5m,5o] In the latter case, the tandem isomerization/Mannich reaction was used as the key step in the enantioselective synthesis of *ent*-nikkomycin and *ent*-funebrine.[5o] Our own contributions, namely, the transition-metal-catalyzed coupling of allylic alcohols with aldehydes or imines, include the use of ruthenium[6a] and rhodium[6b] catalyst systems $[Ru(\eta^5\text{-}C_5Ph_5)(CO)_2Cl$ (**1a**) and $[Rh(COD)Cl]_2/PPh_3$ (COD = cyclooctadiene), respectively. Complex **1a** afforded aldol products in high yields under mild reaction conditions. The rhodium system, on the other hand, not only catalyzed the coupling of allylic alcohols with aromatic aldehydes or imines efficiently, but also that of homoallylic and bishomoallylic alcohols. One limitation of both of these catalytic systems is their incompatibility with aliphatic aldehydes as electrophiles, which afforded aldol products through self-condensation reactions without participation of the allylic alcohols.

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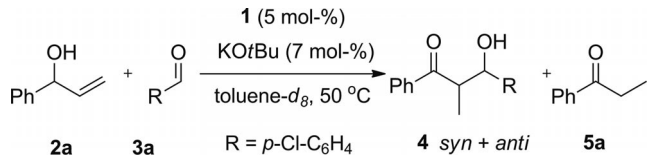
Herein, we report our studies on the scope of the tandem isomerization/C–C bond formation catalyzed by **1a**. The reaction has been extended to the use of aliphatic aldehydes, α,β-unsaturated aldehydes and imines as electrophiles. We also report further mechanistic investigations.

Results and Discussion

Synthesis of β-Hydroxy Ketones (Aldols) – Scope and Limitations

In our previous communication,[6a] we reported the activity of a variety of ruthenium chloride complexes (**1a**–**1d**, Figure 1) in the reaction between α-vinylbenzyl alcohol (**2a**) and *p*-chlorobenzaldehyde (**3a**, Scheme 2). Activation of the ruthenium chlorides was achieved by reaction with KO*t*Bu, which displaces the chloride ligand to form ruthenium *tert*-butoxide intermediates.[8] Whereas commercially available ruthenium chloride complexes $Ru(PPh_3)_3Cl_2$ (**1b**) and $Ru(\eta^5\text{-Cp})(PPh_3)_2Cl$ (**1c**, Figure 1) afforded the desired aldol **4** in low yields (27–31%) along with large amounts of ketone byproduct **5a** (Table 1, Entries 1–2), complexes **1a** and **1d**, which have bulky pentasubstituted cyclopentadienyl ligands, gave good results (Table 1, Entries 3–4). The best results were achieved with **1a**, which bears five phenyl groups on the cyclopentadienyl ring (Entry 3). Further optimization of the reaction conditions revealed that at a lower temperature, **1a** afforded quantitative yields of **4** (Table 1, Entry 5). In order to examine the possibility of a catalytic system that works in a wider temperature range, we have synthesized a new catalyst (**1e**, Figure 1), which is similar to **1a** and has an α-naphthyl substituent on the cyclopentadienyl ring. Unfortunately, **1e** afforded large amounts of **5a** (Table 1, Entry 6). Other catalyst modifications, such as the introduction of a MeO or NH*i*Pr group on the cyclopentadienyl ligand (**1f**[9] and **1g**,[10] Figure 1) did not afford better results (Table 1, Entries 7 and 8). Substitution of the Cl ligand in **1a** by Br or I (Figure 1, **1h**[11] and **1i**,[12] respectively) gave comparable results to those obtained with **1a** (Table 1, Entries 9–10 vs. 5).



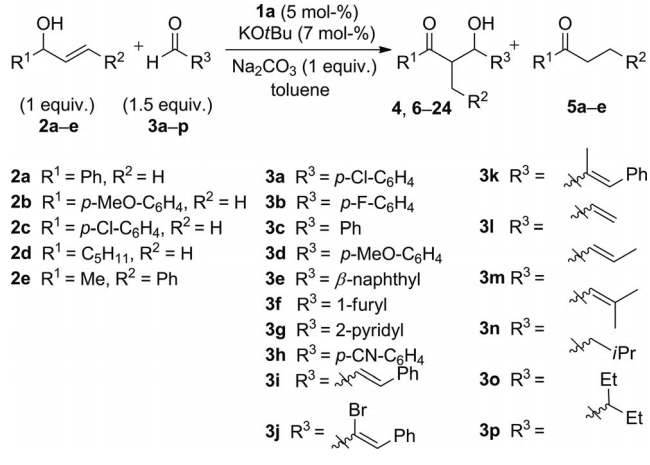
Scheme 2. Coupling of **2a** with **3a** catalyzed by **1a**–**i**.

Table 1. Catalyst screening.

Entry	Catalyst	Conversion [%][a]	*t*	**4**/**5a**[a]	*syn*/*anti*[a]
1	**1b**	73	16 h	43:57	71:29
2	**1c**	85	16 h	32:68	84:16
3	**1a**	> 99	13 min	85:15	65:35
4	**1d**	> 99	1.5 h	96:4	62:38
5[b]	**1a**	> 99	6 h	99:1	84:16
6	**1e**	> 99	40 min	63:37	62:38
7[b,c]	**1f**	13	18 h	50:50	–
8[b]	**1g**	57	18 h	91:9	75:25
9[b]	**1h**	94	18 h	87:13	78:22
10[b]	**1i**	70	18 h	97:3	77:23

[a] Measured by ^{1}H NMR spectroscopic analysis of the crude reaction mixtures. [b] 20 °C. [c] Together with **5a**, several decomposition products were formed.

Under the optimized reaction conditions (Table 1, Entry 5), a variety of allylic alcohols **2a**–**e** were reacted with a number of aromatic and aliphatic aldehydes (**3a**–**p**) to afford aldols **4** and **6**–**24** in excellent yields (Scheme 3, Table 2), and in most cases, under mild reaction conditions. In general, the reaction of aromatic allylic alcohols (**2a**–**c**) with aromatic aldehydes (**3a**–**f**) proceeded smoothly regardless their electronic properties (Table 2, Entries 1–6 and 9–10). The presence of certain potentially coordinating groups, such as 4-methoxy or 1-furyl, did not affect the reaction rates (Table 2, Entries 4 and 6). On the other hand, reactions



Scheme 3. Synthesis of **4** and **6**–**24** from **2a**–**e** and **3a**–**p**.

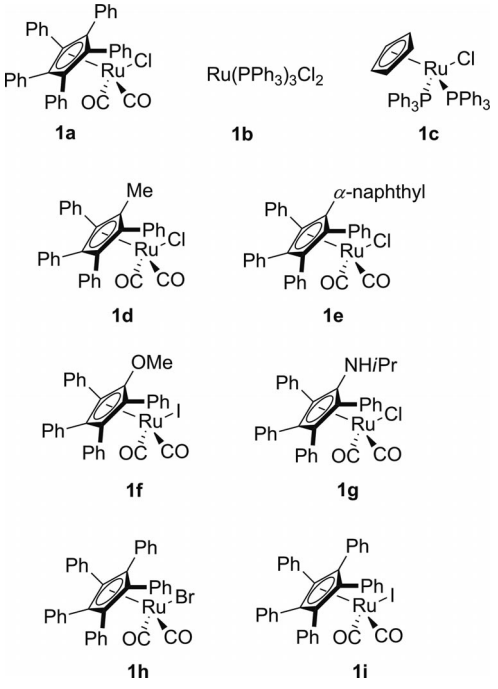
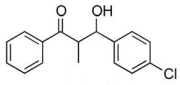
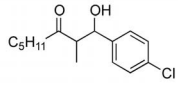
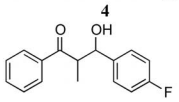
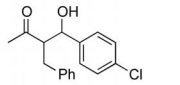
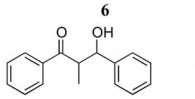
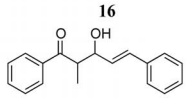
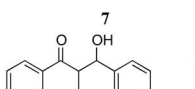
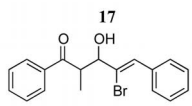
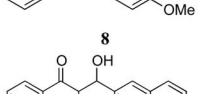
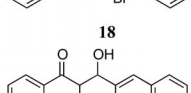
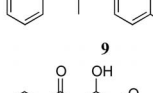
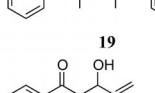
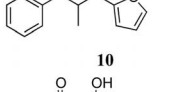
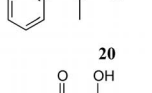
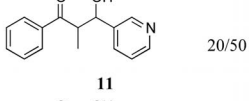
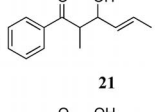
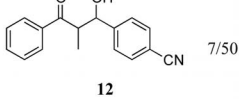
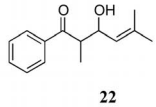


Figure 1. Ruthenium catalysts **1a**–**1i**.

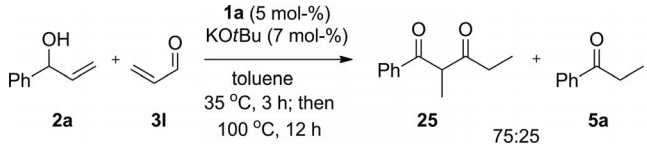
Table 2. Coupling of allylic alcohols with aldehydes catalyzed by **1a**.[a]

Entry	2 / 3	Aldol	*t* [h]/ *T* [°C]	Aldol/**5** [%] [b]	*syn*/ *anti* [%] [b]	Entry	2 / 3	Aldol	*t* [h]/ *T* [°C]	Aldol/**5** [%] [b]	*syn*/ *anti* [%] [b]
1	**2a / 3a**	**4** 	3.5/25	>99(88)/1	77/23	11	**2d / 3a**	**15** 	18/65	>99(59)/1	60/40
2	**2a / 3b**	**6** 	3.5/25	>99(78)/1	83/17	12 [c]	**2e / 3a**	**16** 	5/35	>99(79)/1	40/60
3	**2a / 3c**	**7** 	2.5/35	99(84)/1	69/31	13	**2a / 3i**	**17** 	12/35	92(75)/8	54/46
4	**2a / 3d**	**8** 	1/35	95(93) /5	60/40	14	**2a / 3j**	**18** 	1/35	97(79)/3	87/13
5	**2a / 3e**	**9** 	5/25	99(97)/1	82/18	15	**2a / 3k**	**19** 	13/35	78(48)/22	50/50
6	**2a / 3f**	**10** 	7/25	>99(78)/1	70/30	16	**2a / 3l**	**20** 	3/35	96(72)/4	56/44
7	**2a / 3g**	**11** 	20/50	>99(91)/1	83/17	17	**2a / 3m**	**21** 	3/35	97(86)/3	48/52
8	**2a / 3h**	**12** 	7/50	>99(80)/1	82/18	18	**2a / 3n**	**22** 	4.5/35	96(77)/4	73/27
9	**2b / 3a**	**13** 	4/25	>99(79)/1	79/21	19 [d]	**2a / 3o**	**23** 	3/35	96(92)/4	92/8
10	**2c / 3a**	**14**	2/35	>99(75)/1	75/25	20 [d]	**2a / 3p**	**24**	2.5/35	91(76)/9	89/11

[a] Reactions conditions: KO*t*Bu [56 μL, 0.5 M in tetrahydrofuran (THF), 7 mol-%] was added to a mixture of **1a** (13 mg, 0.020 mmol, 5 mol-%) and Na_2CO_3 (42 mg, 0.4 mmol) in degassed toluene (1 mL) under a nitrogen atmosphere. The mixture was stirred for 3 min before a solution of **2** (0.4 mmol) and **3** (0.6 mmol) in degassed toluene (1 mL) was added by syringe. [b] Determined by ^{1}H NMR spectroscopy of the crude mixture. In parenthesis, isolated yield of aldols. [c] At room temperature, **16** was obtained in 75% yield, *syn*/*anti* 80:20 after 24 h. [d] MS 4 Å were added instead of Na_2CO_3.

with aromatic aldehydes that contain cyano and pyridyl moieties were slower and had to be performed at higher temperatures (Table 2, Entries 7 and 8). Aliphatic alcohols **2d** and **2e** (Table 2, Entries 11–12) could also be used in the coupling. In general, **2a**–**d**, which have no substituents on the terminal carbon atom of the double bond, reacted much faster than those that bear substituents (i.e. **2e**). Catalyst **1a** could also be used with α,β-unsaturated aldehydes. The resulting aldol products contain an allylic alcohol functionality that could potentially react further (Table 2, Entries 13–18). These compounds, however, were formed exclusively, and no further isomerization/aldolization was observed under the reaction conditions applied.[13] However, when the reaction temperature was maintained for 3 h at 35 °C and then raised to 100 °C for an additional 12 h, aldol **20**, formed from alcohol **2a** and aldehyde **3l**, was transformed into a mixture of 1,3-diketone **25** and **5a** (Scheme 4). Hence, this methodology offers an alternative to currently existing procedures[14] to synthesize 1,3-dicarbonyl building blocks.[15] The reaction conditions had to be modified in order to successfully couple aliphatic aldehydes, which have hardly ever been used before in similar reac-

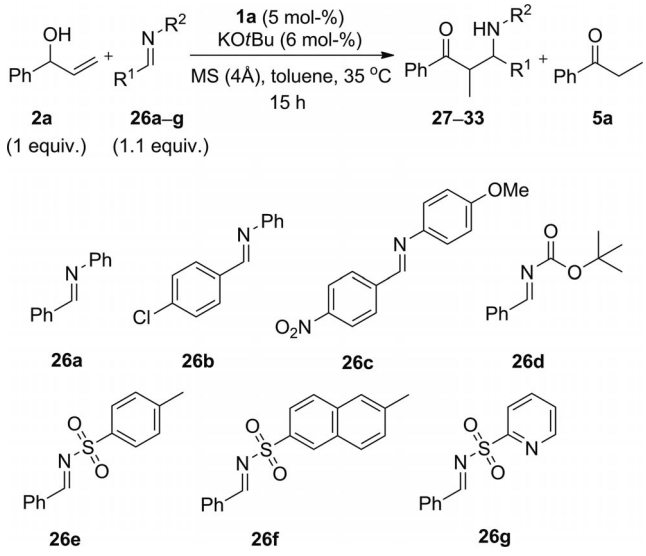
tions.[5m] To avoid self-condensation of the highly reactive aliphatic aldehydes under the reaction conditions, Na_2CO_3, which was used before as a drying agent, was substituted by molecular sieves (MS) 4 Å. Both aliphatic aldehydes used (Table 2, Entries 19–20) afforded the corresponding aldols in high yields with very high *syn*/*anti* ratios (up to 92:8). This ratio is among the highest observed in this transformation. On the other hand, neither primary nor highly substituted allylic alcohols (e.g. 3-buten-1-ol, geraniol, 2-methyl-3-buten-2-ol) gave any coupling product. In all successful reactions, the new C–C bond was formed exclusively at the carbon atom that originated from the double bond in the starting allylic alcohol.



Scheme 4. Tandem isomerization/aldol/isomerization reaction to form 1,3-diketones.

Synthesis of β-Amino Ketones – Scope and Limitations

We next investigated the use of imines as electrophiles (Scheme 5). The products obtained, β-amino ketones, are important intermediates in the synthesis of a variety of nitrogen-containing drugs and natural products.[16,17] Our preliminary experiments that used **1a** under identical reaction conditions as those used with aromatic aldehydes (vide supra) afforded β-amino ketones in low yields. Small amounts of the imine substrates were hydrolyzed to the corresponding aldehydes, which participated in the coupling reaction to yield β-hydroxy ketones. However, when we used the reaction conditions employed with aliphatic aldehydes instead (i.e. replacement of Na_2CO_3 by MS 4 Å, Table 2, Entries 19 and 20), imine hydrolysis was minimized. We evaluated the reactivity of a variety of imines (Scheme 5, Table 3) under the optimized conditions. *N*-aryl aldimines[5g,18] **26a**–**c** did not give the desired products (Table 3, Entries 1–3), instead **2a** was quantitatively isomerized into **5a**. *N*-Boc-protected imine **26d** (Table 3, Entry 4)[19] afforded side products as a result of a nucleophilic attack of the hydroxy group in **2a** to the Boc moiety. *N*-Sulfonylaldimine **26e**, on the other hand, gave good results (Table 3, Entry 5) and produced β-amino ketone **31** in 90% yield.[5n,6b,20] To study the influence of the *N*-sulfonyl imine structure on the reaction outcome, particularly on the diastereoselectivity, in addition to *N*-tosyl imine **26e**, we tested two other *N*-sulfonyl imines: 6-methylnaphthyl- and 2-pyridylsulfonylimines (**26f** and **26g**, respectively). Increasing the steric bulk of the imines, however, did not lead to an improvement in the *syn*/*anti* ratio: **26f** gave very similar results to those obtained with **26e** (Table 3, Entry 6 vs. 5), and the presence of an additional chelating group on the imine **26g**[21] suppressed the coupling reaction completely (Table 3, Entry 7).



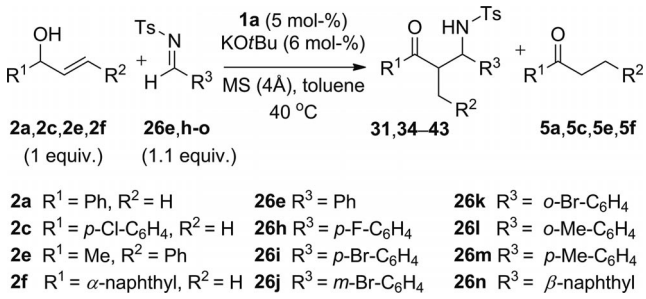
Scheme 5. Synthesis of β-amino ketones from **2a**. Scope of the imines.

Table 3. Scope of the imines in the coupling with **2a** catalyzed by **1a**.

Entry	Imine	β-Amino ketone	β-Amino ketone/**5**[a]	*syn*/*anti*[a]
1	**26a**	**27**	0:100	–
2	**26b**	**28**	0:100	–
3	**26c**	**29**	0:100	–
4	**26d**	**30**	20:80[b]	n.d.[c]
5	**26e**	**31**	90:10	71:29
6	**26f**	**32**	92:8	73:27
7	**26g**	**33**	0:100	–

[a] Determined by ^{1}H NMR spectroscopy. [b] Formation of side products. [c] N.d. = not determined.

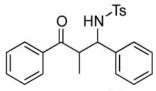
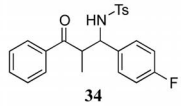
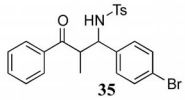
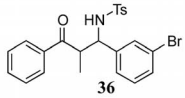
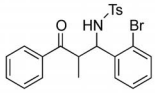
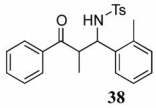
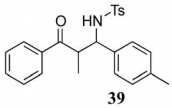
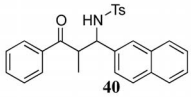
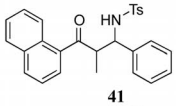
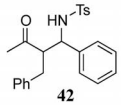
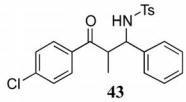
The best reaction conditions (35 °C, toluene, MS 4 Å, *N*-tosyl imines, Table 3 Entries 5–6) were used to prepare a number of β-amino ketones (**31**, **34**–**43**, Scheme 6, Table 4). Several aromatic imines that contained electron-donating and -withdrawing substituents in *ortho*, *meta*, and *para* positions could be used (Table 4). The same alcohols that worked well in aldol-type reactions could be coupled with imines with equally good results (Table 4). The diastereo-



Scheme 6. Synthesis of β-amino ketones from allylic alcohols.

selectivity was, however, poor with *syn*/*anti* ratios of up to 3:1. Only when **2f**, which contains a large α-naphthyl substituent, was used was a very good diastereomeric ratio (*dr* = 86:14) obtained (Table 4, Entry 9).

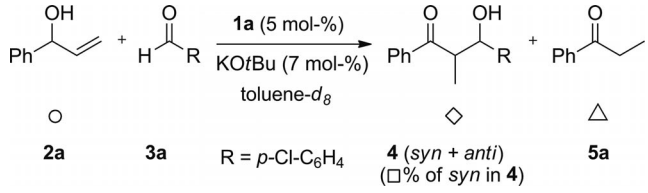
Table 4. Scope of the Mannich-type reaction catalyzed by **1a**.[a]

Entry	2 / 26	Amino ketone	*t* [h]	Amino ketone /**5**[%] [b]	*syn*/*anti* [%][b]	Amino ketone [%][c]
1	**2a** / **26e**	 **31**	15	90/10	71/ 29	90 (80)
2	**2a** / **26h**	 **34**	15	95/5	62/ 38	89 (78)
3[d]	**2a** / **26i**	 **35**	30	94/6	73/ 27	94 (78)
4	**2a** / **26j**	 **36**	14	94/6	63/ 37	94 (83)
5[d]	**2a** / **26k**	 **37**	30	95/5	56/ 44	95 (75)
6	**2a** / **26l**	 **38**	11	77/23	66/ 34	77 (70)
7	**2a** / **26m**	 **39**	11	81/19	53/ 47	81 (70)
8	**2a** / **26n**	 **40**	15	89/11	61/ 39	89 (76)
9	**2f** / **26e**	 **41**	15	88/12	86/ 14	81 (68)
10	**2e** / **26e**	 **42**	12	93/7	49/ 51	93 (79)
11	**2c** / **26e**	 **43**	15	94/6	60/ 40	94 (80)

[a] Reaction conditions: KO*t*Bu (48 μL, 0.5 M in THF, 6 mol-%) was added to a mixture of **1a** (13 mg, 0.020 mmol, 5 mol-%) and MS 4 Å (20 mg) in degassed toluene (1 mL) under a nitrogen atmosphere. The mixture was stirred for 3 min before a solution of **2** (0.4 mmol) and **26** (0.44 mmol) in degassed toluene (1 mL) was added by syringe. The mixture was stirred at 40 °C for the time indicated. [b] Determined by ^{1}H NMR spectroscopy. [c] Isolated yield in parenthesis. [d] Reaction in THF.

Mechanistic Investigations

To understand the reaction outcome observed at different temperatures (vide supra, Table 1), we followed the coupling between **2a** and **3a** catalyzed by **1a** by ^{1}H NMR spectroscopy in [D_8]toluene (Scheme 7 and Figure 2a–c). At 50 °C, 80% of **4** was produced after only 12 min (Figure 2, a) and the formation of **5a** was observed after 2 min. Interestingly, after reaching a maximum yield of 80% (at 12 min), the amount of **4** decreased. Simultaneously, the yield of **5a** increased at a similar rate as that of the decomposition of **4**, which indicates that **5a** can be formed not only by Ru-catalyzed isomerization of the allylic alcohol **2a**[4] but also from **4** by retroaldolization (Scheme 8 and Supporting Information, page S10). It was also observed that the *syn*/*anti* ratio of **4** was ca. 80:20 at the beginning of the reaction and decreased as the coupling proceeded.



Scheme 7. Reaction of **2a** and **3a** in [D_8]toluene catalyzed by **1a** at different temperatures.

Similar kinetic data were obtained when the same experiment was performed at 35 °C (Figure 2b), the difference being that **4** was formed in 99% yield within 30 min. In this case, **5a** was formed in minute amounts, even after prolonged reaction times (<3% within 90 min). Furthermore, **5a** seems to form exclusively by retroaldolization as it started to build up only after **2a** had been consumed. The *syn*/*anti* ratio was 81:19 for the first 10 min, after which epimerization occurred until a thermodynamic mixture was obtained (ca. 55:45 *syn*/*anti*). In the last experiment, performed at room temperature (Figure 2c), **4** was exclusively formed, although at a lower reaction rate, and retroaldolization was suppressed, even with extended reaction times (12 h). The rate of epimerization was significantly reduced (the *syn*/*anti* ratio decreased from 94:6 to 84:16 after 6 h). Interestingly, at 20 °C (Figure 2c) the plot of product formation as a function of time produces a sigmoidal curve. Such behavior is in agreement with recent studies on this catalytic system that showed that **1a** undergoes activation through CO dissociation, which may be slower at 20 °C.[22]

From these plots, we conclude that the excellent results obtained at 20 and 35 °C in the coupling of **2a** with **3a** catalyzed by **1a** (Figure 2b–c) can be ascribed to a diminished degradation of **4** (Table 1, Entry 5 vs. 3). This decomposition occurred at 50 °C by retroaldolization to produce **5a** from **4** (Scheme 8). Furthermore, the formation of **5a** by allylic alcohol isomerization was suppressed at mild reaction conditions (25–35 °C).

Similarly, we followed the reaction of **2a** with **26h** by ^{1}H NMR spectroscopy (Scheme 9, Figure 3). In comparison to the aldol reaction, which was finished within 30 min at 35 °C, the Mannich-type process was much slower and re-

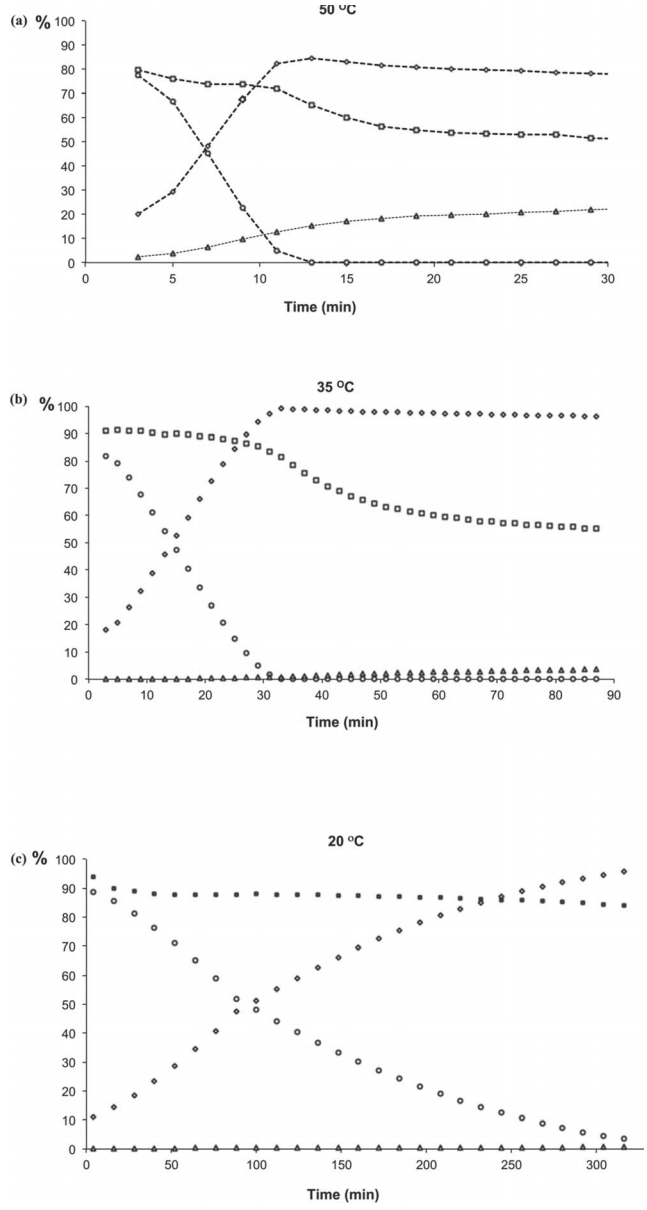
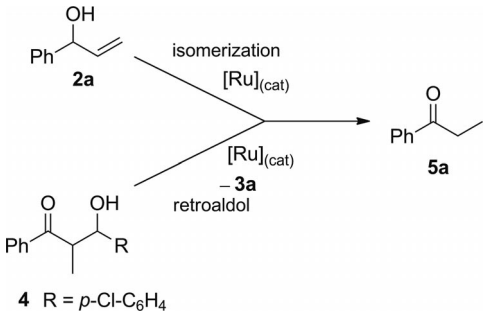
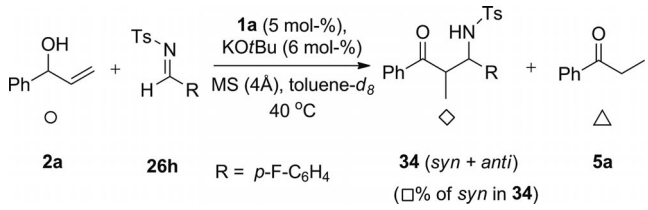


Figure 2. Reaction of **2a** and **3a** in [D_8]toluene catalyzed by **1a** at 50 °C (a), 35 °C (b) and 20 °C (c). Time = 4 min corresponds to the first ^{1}H NMR spectrum recorded. [○: **2a**; ◇: **4** (*syn* + *anti*); □:% of *syn* in **4**; Δ: **5a**].



Scheme 8. Ketone **5a** can be produced by **2a** isomerization or by retroaldolization from **4**.

quired 3 h at 40 °C to reach full conversion. Formation of β-amino ketone **34** was found to be irreversible, and decomposition to **5a** (analogous to retroaldolization) was not observed. Ketone **5a** was thus formed exclusively by isomerization of **2a** and was detected in small quantities after short reaction times. The *syn*/*anti* ratio was low to moderate, but gratifyingly, the epimerization proceeded at a very slow rate (i.e. the diastereoisomeric ratio decreased only from 70:30 to 65:35 over 6 h at 40 °C).



Scheme 9. Reaction of **2a** and **26h** in [D_8]toluene catalyzed by **1a** at 40 °C.

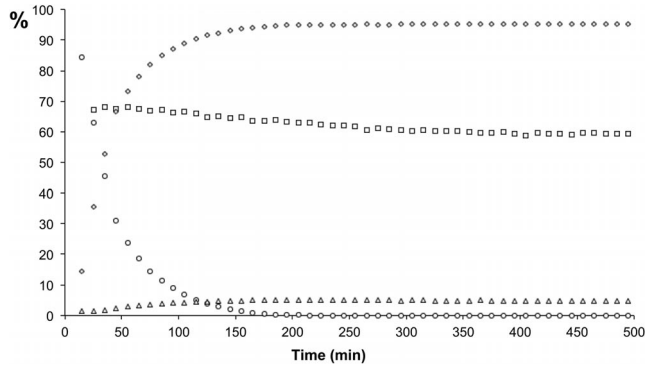
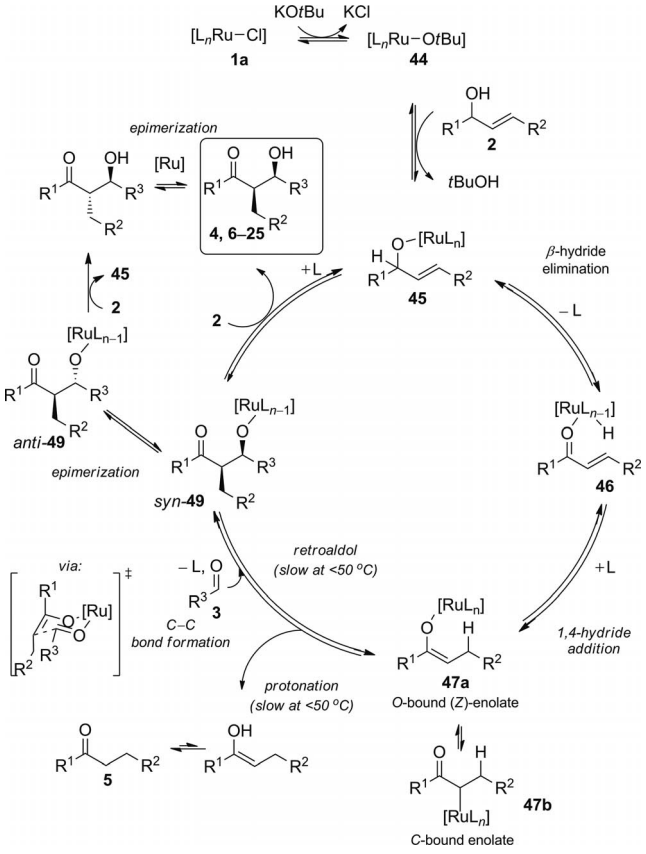


Figure 3. Cross-coupling of **2a** and **26h** in [D_8]toluene catalyzed by **1a** at 40 °C. Time = 4 min corresponds to the first ^{1}H NMR spectrum recorded. [○: **2a**; ◇: **34** (*syn* + *anti*); □:% of *syn* in **34**; Δ: **5a**].

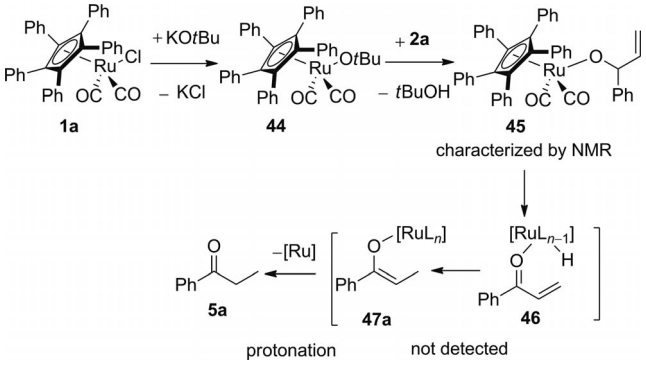
From the results obtained and the additional experiments described below, we propose a mechanism via ruthenium alkoxides,[23,24] which is depicted in Scheme 10.

The activation of **1a** by KO*t*Bu forms an alkoxide complex [Ru–O*t*Bu] (**44**). Bäckvall and co-workers have studied the formation of this intermediate both experimentally and computationally.[22,24] The reaction of **44** with **2** produced a new alkoxide complex **45**. We studied the mechanism of these initial steps by NMR spectroscopy (Scheme 11). Thus, the reaction of KO*t*Bu (1.2 equiv.) with **1a** in [D_8]toluene afforded **44**,[24] which was smoothly transformed into **45** upon addition of **2a** (1 equiv., see Supporting Information).[5a] Based on the previous mechanistic investigations by Bäckvall and co-workers, ruthenium alkoxides (such as **45**) undergo CO dissociation to generate the coordination site required for the following step in the catalytic cycle (i.e. β-hydride elimination).[22] Oxidation of the allylic alcohol would produce a ruthenium hydride **46** and an enone intermediate. Transfer of the hydride to the olefin of the enone would form an *O*-bound ruthenium enolate **47a**.



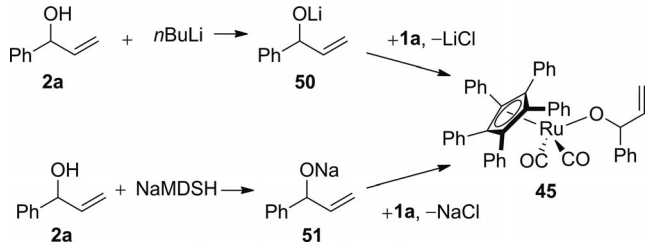
Scheme 10. Plausible catalytic cycle.

We have been unable to identify these last two intermediates (**46** and **47a**). Instead, **5a** was formed under these experimental conditions.



Scheme 11. Stoichiometric mechanistic investigations.

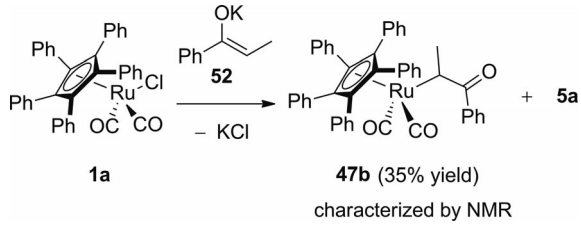
In an attempt to characterize ruthenium enolate intermediates, we designed a similar experiment to that shown in Scheme 11, in which the presence of electrophiles, including alcohols such as *t*BuOH, was minimized. [Ru–Cl] **1a** was transformed directly into allylic alkoxide complex **45** by reaction with a lithium or sodium allylic alkoxide salt (**50** or **51**) generated from **2a** and strong bases [*n*BuLi or sodium hexamethyldisilazide (NaHMDS), respectively, Scheme 12]. Although the same alkoxide complex **45** was obtained using either base, the transmetallation of the Li alkoxide to the Ru center was much slower than that of the Na alkoxide (for ^{1}H NMR spectra, see Supporting Information). Unfortunately, **45** did not evolve into ruthenium enolate intermediates (i.e. **47a**), instead, **45** and **5a** were the only two species detected in these NMR experiments (Scheme 12).



Scheme 12. Formation of **45** from lithium or sodium allylic alkoxides.

When we used **45** (5 mol-%), generated in any of the above ways (Scheme 12), as the catalyst in the isomerization of **2a**, **5a** was formed in quantitative yield. This experiment supports a mechanism through allylic alkoxide intermediates **45**.

In another attempt to form an *O*-bound ruthenium enolate species **47a**,[25] we reacted **1a** with preformed potassium enolate **52** (Scheme 13). Interestingly, a *C*-bound ruthenium enolate **47b** was formed instead in about 35% yield. The remaining sodium enolate **52** was converted into **5a**. Attempts to isolate **47b** were unsuccessful due to decomposition. Therefore, the structure of **47b** was proposed based on ^{1}H and ^{13}C NMR spectroscopy (Figure 4) of the reaction mixture obtained in this experiment. The structure of **47b** agrees well with the data obtained from 2D heteronuclear single quantum coherence (HSQC) experiments (see Supporting Information). In the ^{1}H NMR spectrum of **47b** the CH_3 group [Ru–CH–(COPh)CH_3] gives a doublet at 1.69 ppm with a coupling constant of 6.5 Hz, and the proton α to the carbonyl group [Ru–C*H*–(COPh)CH_3] appears as a quartet at 3.91 ppm (J = 6.5 Hz, Figure 4). In the ^{13}C NMR spectrum, the CH_3 group resonates at 22.3 ppm, and the *C*H group directly bound to ruthenium [Ru–*C*H–(COPh)CH_3] at 27.1 ppm. The latter chemical shift is similar to that obtained for other *C*-bound ruthenium enolates (e.g. 23.6 ppm)[25c] and clearly differs from that of *O*-bound ruthenium enolates (e.g. 76 ppm).[25b] Furthermore, the ketone carbonyl group appears at 203.8 ppm. In reported *O*-bound enolates, such carbon atoms, now part of the double bond in the enolate form, appear at 169 ppm.[25b] A comparison of these chemical shifts with those reported[25] for *O*- and *C*-bound ruthenium enolates is shown in the



Scheme 13. Stoichiometric mechanistic investigations.

Supporting Information. Complex **47b** did not decompose or isomerize to **47a** when analyzed by NMR spectroscopy at temperatures from –50 to +50 °C. In addition, **47b** catalyzed neither the isomerization of **2a** nor the tandem isomerization/aldolization, which indicates that **47b** is not a catalytically active species. A plausible explanation is that the catalytically active species requires the dissociation of one of the CO ligands,[22] which may be difficult from **47b**. Complex **47b** may have been formed from the corresponding *O*-bound ruthenium enolate, a process well described and studied for related enolate complexes.[25]

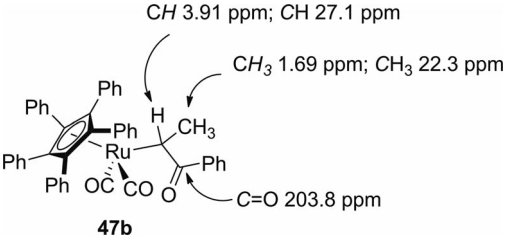
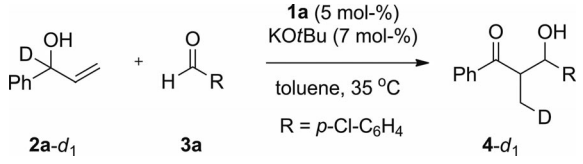


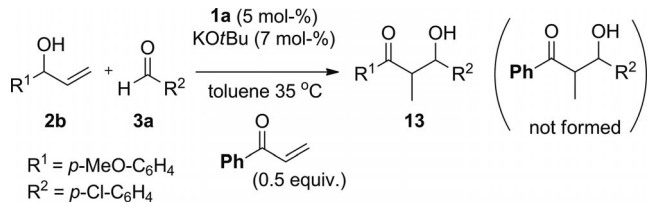
Figure 4. *C*-Bound ruthenium enolate **47b**.

To obtain insights into the elusive 1,4-addition step, additional experiments with deuterated substrates were carried out. The coupling between deuterated allylic alcohol [D_1]-**2a** and **3a** afforded monodeuterated [D_1]-**4**, with the deuterium label incorporated at the methyl group (Scheme 14). This deuterium distribution agrees with the proposed mechanism shown in Scheme 10.

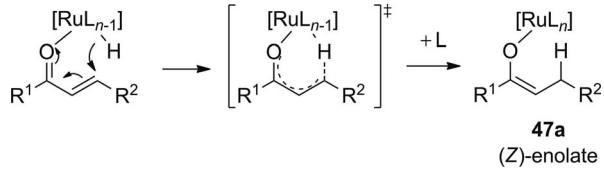


Scheme 14. Coupling of a deuterium-labeled allylic alcohol.

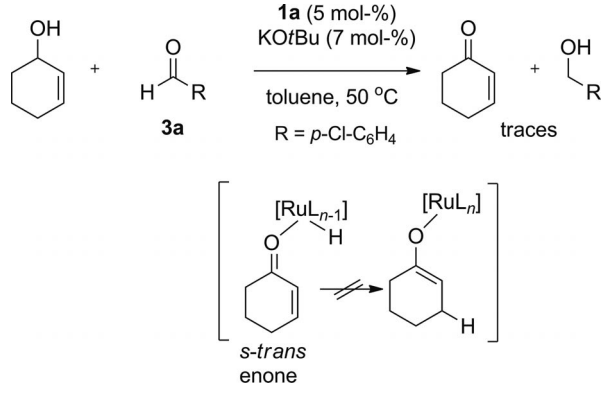
To verify whether the enone intermediate stays coordinated to the ruthenium center as in Ru hydride **46**, we performed a crossover experiment (Scheme 15), namely, the Ru-catalyzed reaction of **2b** and **3a** in the presence of phenyl vinyl ketone. Aldol **13** was formed as the sole product, which indicates that the enone produced within the coordination sphere of the metal is reduced before it can diffuse into the reaction mixture. Further support for the coordination of the α,β-unsaturated ketone to the Ru hydride comes from the fact that the aldehydes **3** used as electrophiles are not reduced to the corresponding alcohols during the reaction. Thus, we propose that the 1,4-hydride addition occurs intramolecularly via an *s-cis* conformation of the enone intermediate (Scheme 16). This process would result in a stereospecific (*Z*)-enolate formation. The support for this hypothesis is that, in a separate experiment, 2-cyclohexen-1-ol failed to isomerize to cyclohexanone or to yield any aldol in the presence of **3a** (Scheme 17). Only traces of 2-cyclohexenone and *p*-chlorobenzyl alcohol were detected. Thus, for this particular allylic alcohol, β-hydride elimination occurred, and the following 1,4-hydride addition step did not take place, which suggests that an *s-cis* conformation of the unsaturated ketone, impossible for 2-cyclohexenone, is required. From the *s-cis* conformation of **46**, 1,4-hydride addition would yield (*Z*)-enolate **47a**.



Scheme 15. Crossover experiment.



Scheme 16. Enone reduction step.



Scheme 17. Unsuccessful coupling of 2-cyclohexen-1-ol with **3a**.

The next step in the reaction mechanism is the C–C bond formation. Preferential formation of the *syn*-aldol from (*Z*)-enolate **47a** and **3** can be explained by a Zimmerman–Traxler six-membered transition state.[26] We propose that under the applied reaction conditions, the C–C bond is formed from a ruthenium intermediate in which both aldehyde and enolate are bound to the metal center, rather than from a free enol without participation of the ruthenium.[5m] This is supported by several arguments. First, it is highly unlikely that the free enol would react exclusively with the aldehyde and would not, at least partially, tautomerize to the corresponding ketone **5a** (Scheme 8). Secondly, we observed that the retroaldol reaction occurs only in the presence of the ruthenium catalyst. When **4** is subjected to the reaction conditions in the absence of **1a**, KO*t*Bu, or **44**, decomposition of **4** does not occur. Thus, the retroaldol process (C–C bond breaking) is catalyzed by the Ru complex, which was confirmed by the reaction of **4** with **44** (Supporting Information, pages S10 and S13). According to the microscopic reversibility principle,[27] the C–C bond formation should be also mediated by the ruthenium complex. Finally, it is reasonable to assume that the *anti*-aldol is mainly pro-

duced by Ru-catalyzed epimerization of the *syn*-aldol (vide supra, Figure 2 shows how the *syn*/*anti* ratio diminishes as the reaction proceeds). It is known that **1a** catalyzes a fast racemization of *sec*-alcohols, which proceeds by consecutive β-hydride elimination and 1,2-hydride addition.[24] Epimerization of aldolate *syn*-**49** would occur before protonation by ligand exchange with allylic alcohol. This process would produce aldolate *anti*-**49**, which would lead to the formation of *anti*-aldol. Indeed, when *syn*-**49** was prepared from *syn*-**4**, epimerization into *anti*-**49** occurred within minutes (characterization of *syn*- and *anti*-**49** and their equilibration is shown in the Supporting Information).

Conclusions

We have expanded the scope of the reaction of allylic alcohols with aldehydes catalyzed by **1a**. Both aromatic and aliphatic aldehydes afforded β-hydroxy ketones in excellent yields. This tandem isomerization/C–C bond formation process has been extended to the use of imines as electrophiles as well, which resulted in the formation of β-amino ketones from allylic alcohols. The higher efficiency of the reaction in terms of yields at milder reaction conditions is explained by the suppression of a retroaldolization reaction. Investigations of the tandem isomerization/aldol coupling supported a mechanism through ruthenium allylic alkoxide intermediates, which undergo β-hydride elimination to produce ruthenium hydride species and the corresponding enones. Consecutive 1,4-hydride addition to the enones in an (*S*)-*cis* conformation produces ruthenium (*Z*)-enolates. A Zimmerman–Traxler transition state in the following C–C bond formation step would form a ruthenium *syn*-aldolate, which agrees with the high diastereoselectivity obtained at short reaction times (*syn*/*anti* = 94:6). A *C*-bound ruthenium enolate has been prepared and characterized by NMR and was found to be catalytically inactive.

Experimental Section

General: All reactions were carried out under dry argon atmosphere in flame-dried glassware. Reagents were of analytical grade, obtained from commercial suppliers, and used without further purification. Compounds **26a**–**o**,[28] **1f**,[9] **1g**,[10] **1h**,[11] **1i**,[12] **2a**,[29] **2b**,[30] **2c**,[31] **2e**,[32] **2f**,[31] [L_nRu–O*t*Bu] **44**,[6a] and **45**[6a] were prepared as described previously. Anhydrous THF and toluene were obtained using a VAC solvent purifier system. Flash chromatography was carried out with Davisil silica gel 60 (35–70 μm). ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, with a Bruker Avance spectrometer. Chemical shifts (δ) are reported in ppm using the residual solvent peak in $CDCl_3$ (δ_H = 7.26 and δ_C = 77.00 ppm) or [D_8]toluene (δ_H = 2.09 and δ_C = 20.40 ppm) as internal standards, and coupling constants (J) are given in Hz; quint stands for quintuplet, and app. stands for apparent. HRMS were recorded with a Bruker microTOF ESI-TOF mass spectrometer. MS 4 Å powder was dried at 400 °C overnight before use.

Ruthenium Complex 1e: Complex **1e** was prepared in three steps from 1-bromonaphthalene. *t*BuLi (21 mL, 1.7 M solution in pentane, 34.9 mmol) was added to a 250 mL 2-necked flask that contained dry THF (30 mL) at –66 °C under a nitrogen atmosphere. 1-Bromonaphthalene (3.7 mL, 26.8 mmol) was added dropwise at –66 °C. After the addition was finished, the clear yellowish solution was stirred for 1 h at –66 °C and then warmed to 0 °C. A solution of 2,3,4,5-tetraphenylcyclopentadienone (5.14 g, 13.4 mmol) in dry THF (80 mL) was added slowly to the reaction mixture at 0 °C. After stirring overnight at ambient temperature, the mixture was quenched with dilute HCl (aq.) and water and extracted with toluene. The combined organic phases were dried with Na_2CO_3, filtered, and the solvents evaporated. Purification by column chromatography (SiO_2, pentane/EtOAc, 15:1) afforded 1-(1-naphthyl)-2,3,4,5-tetraphenylcyclopentadienol (yellow solid, 6.1 g, 89%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.68 (s, 1 H), 6.8–7.2 (m, 20 H), 7.40–7.50 (m, 3 H), 7.73 (d, J = 8.20 Hz, 1 H), 7.73 (dd, J = 8.6, 1.6 Hz, 1 H), 8.12 (dd, J = 7.4, 1.2 Hz, 1 H), 8.64 (dd, J = 8.5, 1 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 89.8, 124.3, 125.3, 125.4, 125.9, 126.1, 127.0, 127.1, 127.5, 127.9, 128.7, 128.8, 129.4, 129.7, 129.8, 133.7, 133.8, 135.1, 135.2, 143.1, 148.7 ppm.

Compound **54** (1.8 g, 3.5 mmol) was dissolved in glacial acetic acid (45 mL) at 100 °C, and HCl (1.8 mL, 12 M solution in H_2O, 21.6 mmol) was added dropwise over 5 min. The color of the solution changed from yellow to light orange. The mixture was heated to reflux for 1.5 h. H_2SO_4 (0.2 mL, 18.4 M, 3.7 mmol, 1.05 equiv.) was added dropwise, and the reaction mixture was heated to reflux for an additional 1.5 h. The reaction mixture was allowed to cool to 100 °C, and zinc dust was added in two portions (485 mg, 7.4 mmol; after two hours of reflux, additional Zn was added: 250 mg, 3.6 mmol). HCl (11 M, 0.5 mL) was added, and the mixture was heated to reflux for another 2 h. The reaction was neutralized with NaOH and extracted with toluene (60 mL). Drying over $MgSO_4$ and evaporation afforded a brown viscous oil. The mixture was purified by gradient flash column chromatography (SiO_2) with pentane/EtOAc, 30:1 to 10:1 as eluent system. Tetraphenyl-(1-naphthyl)cyclopentadiene (**55**) was obtained as a mixture of isomers (800 mg, 1.6 mmol, 46.0%). ^{1}H NMR (400 MHz, $CDCl_3$; selected peaks): δ = 5.20 (s), 5.37 (s), 5.41 (s), 8.21–6.82 ppm. A suspension of **55** (1.092 g, 2.2 mmol) and $Ru_3(CO)_{12}$ (478 mg, 0.74 mmol) in a mixture of decane (8 mL) and toluene (4 mL) was heated at 160 °C in a 35 mL sealed tube for 3 d. After cooling the mixture to room temperature, $CHCl_3$ (1 mL) was added and the mixture was heated at 160 °C for 1 h. After cooling to room temperature, pentane was added and the resulting yellow powder was collected by filtration. After purification by column chromatography (SiO_2, pentane/CH_2Cl_2, 3:1), **1e** was obtained as a yellow solid (908 mg, 60%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93–6.80 (m) ppm. ^{13}CNMR (100 MHz, $CDCl_3$): δ = 101.1, 103.6, 113.8, 124.9, 125.7, 125.8, 126.3, 127.3, 127.6, 128.0, 128.4, 128.4, 128.5, 129.0, 129.4, 129.9, 131.1, 132.2, 132.3, 133.1, 133.8, 196.8 ppm.

General Procedure for the Synthesis of β-Hydroxy and β-Amino Ketones: KO*t*Bu (0.5 M in THF, 0.024 mmol, 6–7 mol-%) was added to a mixture of **1a** (13 mg, 0.020 mmol, 5 mol-%), powdered ms (4 Å) (20 mg) or Na_2CO_3 (42 mg, 0.4 mmol) in degassed toluene (1 mL) under a nitrogen atmosphere (MS 4 Å, were added instead of Na_2CO_3 in order to suppress self-aldolization of aliphatic aldehydes **3o** and **3p**, and was also used for all Mannich-type reactions to suppress hydrolysis of imines **26**). The mixture was stirred for 3 min before a solution of **2** (0.4 mmol) and **3** (0.6 mmol) or **26** (0.44 mmol) in degassed toluene (1 mL) was added by syringe. The mixture was heated at the appropriate temperature (Table 2 and Table 4). The products were isolated by column chromatography (SiO_2, pentane/AcOEt systems) usually as an inseparable mixture of *syn* and *anti* diastereomers. If necessary, further purification was

performed by preparative HPLC (RI detector, M2-Preparative column, 250 × 20 mm, 100 SIL, 5 μm).

3-Hydroxy-2-methyl-1-phenyl-3-(pyridin-2-yl)propan-1-one (11): *syn*-**11**/*anti*-**11** = 83:17 (88 mg, 91%), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.68–8.64 (m, 1 H *syn* + 1 H *anti*), 8.58–8.53 (m, 1 H *syn* + 1 H *anti*), 7.99–7.95 (m, 2 H *syn*, 2 H *anti*), 7.83–7.78 (m, 1 H *syn*, 1 H *anti*), 7.67–7.59 (m, 1 H *syn*, 1 H *anti*), 7.55–7.48 (m, 2 H *syn*, 2 H *anti*), 7.35–730 (m, 1 H *syn*, 1 H *anti*), 5.33 (*syn*) (d, *J* = 2.8 Hz, 1 H), 5.07 (*anti*) (d, *J* = 8.3 Hz, 1 H), 3.94 (*syn*) (br. s, 1 H), 3.86 (*anti*) (app. quint, *J* = 7.6 Hz, 1 H), 3.71 (*syn*) (dq, *J* = 3.0, 7.3 Hz, 1 H), 3.40 (*anti*) (br. s, 1 H), 1.22 (*syn*) (d, *J* = 7.3 Hz, 3 H), 1.16 (*anti*) (d, *J* = 7.3 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) *syn*, *anti*: δ = 205.1, 204.4, 149.1, 148.6, 148.5, 147.8, 138.1, 137.7, 136.6, 135.5, 134.5, 134.2, 133.8, 133.5, 128.9, 128.8, 128.52, 128.51, 123.6, 123.3, 74.4, 71.3, 47.9, 47.0, 15.6, 11.5 ppm. HRMS (ESI): calcd. for $C_{15}H_{15}NNaO_2$ $[M]^+$ 264.0995; found 264.0989.

3-(4-Chlorophenyl)-3-hydroxy-1-(4-methoxyphenyl)-2-methylpropan-1-one (13): *syn*-**13**/*anti*-**13** = 79:21 (96 mg, 79%), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96–7.90 (m, 2 H *syn*, 2 H *anti*), 7.38–7.29 (m, 4 H *syn*, 4 H *anti*), 6.98–6.89 (m, 2 H *syn*, 2 H *anti*), 5.20 (*syn*) (dd, *J* = 1.9, 2.7 Hz, 1 H), 4.94 (*anti*) (dd, *J* = 5.3, 7.5 Hz, 1 H), 3.99 (*syn*) (d, *J* = 1.9 Hz, 1 H), 3.88 (*syn*) (s, 3 H), 3.87 (*anti*) (s, 3 H), 3.73 (*anti*) (app. quint, *J* = 7.4 Hz, 1 H), 3.58 (*syn*) (dq, *J* = 2.7, 7.2 Hz, 1 H), 3.33 (*anti*) (d, *J* = 5.3 Hz, 1 H), 1.14 (*syn*) (d, *J* = 7.3 Hz, 3 H), 1.07 (*anti*) (d, *J* = 7.5 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) *syn*, *anti*: δ = 204.3, 203.2, 164.1, 163.0, 141.0, 140.4, 133.4, 132.9, 130.9, 130.8, 129.4, 128.6, 128.4, 128.3, 128.0, 127.5, 114.0, 113.9, 77.2, 76.1, 72.5, 55.6, 47.3, 46.3, 16.0, 11.2 ppm. HRMS (ESI): calcd. for $C_{17}H_{17}ClNaO_3$ $[M]^+$ 327.0758; found 327.0754.

1,3-Bis(4-chlorophenyl)-3-hydroxy-2-methylpropan-1-one (14): *syn*-**14**/*anti*-**14** = 75:25 (93 mg, 75%), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95–7.91 (m, 2 H *anti*), 7.91–7.86 (m, 2 H *syn*), 7.51–7.45 (m, 2 H *syn*, 2 H *anti*), 7.38–7.34 (m, 4 H *syn*, 4 H *anti*), 5.23 (*syn*) (dd, *J* = 2.1, 3.2 Hz, 1 H), 4.98 (*anti*) (dd, *J* = 4.7, 8.1 Hz, 1 H), 3.74 (*anti*) (app. quint, *J* = 7.3 Hz, 1 H), 3.61 (*syn*) (d, *J* = 2.1 Hz, 1 H), 3.61 (*syn*) (dq, *J* = 3.2, 7.2 Hz, 1 H), 2.93 (*anti*) (d, *J* = 4.7 Hz, 1 H), 1.19 (*syn*) (d, *J* = 7.2 Hz, 3 H), 1.08 (*anti*) (d, *J* = 7.3 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) *syn*, *anti*: δ = 204.2, 203.4, 140.6, 140.30, 140.26, 140.0, 135.0, 133.9, 133.8, 133.2, 133.0, 129.2, 129.1, 128.7, 128.5, 128.1, 127.8, 127.5, 76.1, 72.6, 48.0, 47.1, 15.6, 11.4 ppm. HRMS (ESI): calcd. for $C_{16}H_{14}Cl_2NaO_2$ $[M]^+$ 331.0263; found 331.0251.

(*E*)-3-Hydroxy-2-methyl-1,5-diphenylpent-4-en-1-one (17):[33] *syn*-**17**/*anti*-**17** = 54:46 (80 mg, 75%), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) *syn*: δ = 8.02–7.98 (m, 2 H), 7.66–7.59 (m, 1 H), 7.56–7.49 (m, 2 H), 7.43–7.39 (m, 2 H), 7.37–7.30 (m, 2 H), 7.29–7.24 (m, 1 H), 6.75 (dd, *J* = 1.5, 16.0 Hz, 1 H), 6.27 (dd, *J* = 5.8, 16.0 Hz, 1 H), 4.83 (a t, *J* = 3.5 Hz, 1 H), 3.67 (dq, *J* = 3.5, 7.3 Hz, 1 H), 3.34 (br. s, 1 H), 1.34 (d, *J* = 7.3 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) *syn*: δ = 205.3, 136.7, 135.9, 133.6, 131.1, 129.2, 128.8, 128.6, 128.5, 127.6, 126.5, 72.2, 45.4, 11.8 ppm. ^{1}H NMR (400 MHz, $CDCl_3$) *anti*: δ = 8.05–7.98 (m, 2 H), 7.64–7.58 (m, 1 H), 7.55–7.47 (m, 2 H), 7.43–7.37 (m, 2 H), 7.37–7.30 (m, 2 H), 7.28–7.23 (m, 1 H), 6.70 (d, *J* = 15.9 Hz, 1 H), 6.30 (dd, *J* = 7.2, 15.9 Hz, 1 H), 4.62 (m, 1 H), 3.72 (app. quint, *J* = 7.2 Hz, 1 H), 2.92 (d, *J* = 7.2 Hz, 1 H), 1.29 (d, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) *anti*: δ = 204.8, 136.7, 136.5, 133.4, 132.1, 129.7, 128.7, 128.6, 128.5, 127.8, 126.6, 75.3, 46.4, 15.4 ppm. HRMS (ESI) *syn, anti*: calcd. for $C_{18}H_{18}NaO_2$ $[M]^+$ 289.1199; found 289.1208.

(*Z*)-4-Bromo-3-hydroxy-2-methyl-1,5-diphenylpent-4-en-1-one (18): *syn*-**18**/*anti*-**18** = 87:13 (109 mg, 79%), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) *syn*: δ = 8.08–8.00 (m, 2 H), 7.68–7.48 (m, 5 H), 7.42–7.26 (m, 4 H), 4.85 (br. s, 1 H), 4.18 (dq, *J* = 3.9, 7.3 Hz, 1 H), 3.66 (br. s, 1 H), 1.32 (d, *J* = 7.3 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) *syn*: δ = 204.8, 135.7, 135.3, 133.8, 129.1, 129.0, 128.9, 128.6, 128.1, 128.0, 125.0, 76.5, 42.8, 11.2 ppm. ^{1}H NMR (400 MHz, $CDCl_3$) *anti*: δ = 8.08–8.02 (m, 2 H), 7.66–7.57 (m, 3 H), 7.56–7.49 (m, 2 H), 7.42–7.31 (m, 3 H), 7.19 (br. s, 1 H), 4.65 (t, *J* = Hz, 1 H 6.9), 4.15 (app. quint, *J* = 7.3 Hz, 1 H), 3.29 (d, *J* = Hz, 1 H 6.6), 1.28 (d, *J* = 7.3 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) *anti*: δ = 204.3, 136.7, 134.9, 133.6, 130.3, 129.2, 128.8, 128.6, 128.3, 128.2, 127.6, 80.0, 43.9, 15.7 ppm. HRMS (ESI) *syn, anti*: calcd. for $C_{18}H_{17}BrNaO_2$ $[M]^+$ 367.0304; found 367.0322.

(*E*)-3-Hydroxy-2,4-dimethyl-1,5-diphenylpent-4-en-1-one (19):[33] *syn*-**19**/*anti*-**19** = 50:50 (54 mg, 48%), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) *syn*: δ = 8.02–7.98 (m, 2 H), 7.66–7.60 (m, 1 H), 7.56–7.51 (m, 2 H), 7.37–7.20 (m, 5 H), 6.73 (br. s, 1 H), 4.63 (br. d, *J* = 2.6 Hz, 1 H), 3.79 (dq, *J* = 3.4, 7.2 Hz, 1 H), 3.46 (br. s, 1 H), 1.90 (d, *J* = 1.4 Hz, 3 H), 1.31 (d, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) *syn*: δ = 205.4, 137.7, 136.3, 136.0, 133.5, 129.0, 128.8, 128.5, 128.1, 126.39, 126.36, 75.7, 42.9, 15.4, 11.3 ppm. ^{1}H NMR (400 MHz, $CDCl_3$) *anti*: δ = 8.07–8.00 (m, 2 H), 7.65–7.58 (m, 1 H), 7.56–7.48 (m, 2 H), 7.40–7.22 (m, 5 H), 6.60 (br. s, 1 H), 4.56 (dd, *J* = 4.3, 8.4 Hz, 1 H), 3.86 (dq, *J* = 7.2, 8.4 Hz, 1 H), 2.67 (d, *J* = 4.3 Hz, 1 H), 1.97 (d, *J* = 1.3 Hz, 3 H), 1.21 (d, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) *anti*: δ = 204.9, 137.6, 137.2, 137.1, 133.3, 129.0, 128.7, 128.5, 128.4, 128.1, 126.7, 80.6, 43.9, 15.6, 13.1 ppm. HRMS (ESI) *syn, anti*: calcd. for $C_{19}H_{20}NaO_2$ $[M]^+$ 303.1356; found 303.1360.

3-Hydroxy-2-methyl-1-phenylpent-4-en-1-one (20):[34] *syn*-**20**/*anti*-**20** = 56:44 (137 mg, 72%), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05–7.99 (m, 2 H *syn*, 2 H *anti*), 7.68–7.59 (m, 1 H *syn*, 1 H *anti*), 7.58–7.49 (m, 2 H *syn*, 2 H *anti*), 5.99 (*anti*) (ddd, *J* = 6.5, 10.3, 17.3 Hz, 1 H), 5.94 (*syn*) (ddd, *J* = 5.1, 10.4, 17.2 Hz, 1 H), 5.44 (*syn*) (dt, *J* = 1.6, 17.3 Hz, 1 H), 5.40 (*anti*) (dt, *J* = 1.4, 17.3 Hz, 1 H), 5.27 (*syn*) (dt, *J* = 1.6, 10.4 Hz, 1 H), 5.26 (*anti*) (dt, *J* = 1.4 Hz, 1 H, 10.3), 4.68 (*syn*) (m, 1 H), 4.47 (*anti*) (m, 1 H), 3.66 (*anti*) (app. quint, *J* = 7.2 Hz, 1 H), 3.60 (*syn*) (dq, *J* = 3.4, 7.2 Hz, 1 H), 3.19 (*syn*) (d, *J* = 2.7 Hz, 1 H), 2.89 (*anti*) (d, *J* = 5.9 Hz, 1 H), 1.32 (*syn*) (d, *J* = 7.2 Hz, 3 H), 1.30 (*anti*) (d, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) *syn*, *anti*: δ = 205.2, 204.9, 138.5, 137.9, 136.6, 135.9, 133.5, 133.4, 128.8, 128.7, 128.5, 128.4, 116.8, 116.0, 75.4, 72.3, 45.0, 15.3, 11.6 ppm. HRMS (ESI): calcd. for $C_{12}H_{14}NaO_2$ $[M]^+$ 213.0886; found 213.0886.

(*E*)-3-Hydroxy-2-methyl-1-phenylhex-4-en-1-one (21):[35] *syn*-**21**/*anti*-**21** = 48:52 (70 mg, 86%), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03–7.94 (m, 2 H *syn*, 2 H *anti*), 7.65–7.57 (m, 1 H *syn*, 1 H *anti*), 7.54–7.46 (m, 2 H *syn*, 2 H *anti*), 5.85–5.73 (m, 1 H *syn*, 1 H *anti*), 5.61–5.52 (m, 1 H *syn*, 1 H *anti*), 4.55 (*syn*) (br. s, 1 H), 4.38 (*anti*) (m, 1 H), 3.59 (*anti*) (m, 1 H), 3.55 (*syn*) (m, 1 H), 2.99 (*syn*) (d, *J* = 2.5 Hz, 1 H), 2.68 (*anti*) (d, *J* = 5.0 Hz, 1 H), 1.76–1.71 (m, 3 H *syn*, 3 H *anti*), 1.29 (*syn*) (d, *J* = 7.3 Hz, 3 H), 1.21 (*anti*) (d, *J* = 7.3 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) *syn*, *anti*: δ = 205.3, 205.00, 136.8, 136.1, 133.4, 133.3, 131.5, 130.8, 128.9, 128.74, 128.67, 128.5, 128.4, 127.9, 75.4, 72.5, 46.3, 45.5, 17.77, 17.78, 15.4, 11.8 ppm. HRMS (ESI): calcd. for $C_{13}H_{16}NaO_2$ $[M]^+$ 227.1043; found 227.1046.

3-Hydroxy-2,5-dimethyl-1-phenylhex-4-en-1-one (22): *syn*-**22**/*anti*-**22** = 77:23 (67 mg, 77%), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00–7.91 (m, 2 H *syn*, 2 H *anti*), 7.60–7.55 (m, 1 H *syn*, 1 H

anti), 7.51–7.50 (m, 2 H *syn*, 2 H *anti*), 5.29 (*syn*) (m, 1 H), 5.26 (*anti*) (m, 1 H), 4.76 (*syn*) (dd, *J* = 4.3, 8.8 Hz, 1 H), 4.72 (*anti*) (t, *J* = 8.8 Hz, 1 H), 3.57 (*anti*) (app. quint, *J* = 7.4 Hz, 1 H), 3.55 (*syn*) (dq, *J* = 4.4, 7.1 Hz, 1 H), 2.73 (*syn*) (br. s, 1 H), 2.49 (*anti*) (br. s, 1 H), 1.79 (*anti*) (d, *J* = 1.3 Hz, 3 H), 1.76 (*anti*) (d, *J* = 1.3 Hz, 3 H), 1.72 (*syn*) (d, *J* = 1.4 Hz, 3 H), 1.71 (*syn*) (d, *J* = 1.4 Hz, 3 H), 1.33 (*syn*) (d, *J* = 7.1 Hz, 3 H), 1.17 (*anti*) (d, *J* = 7.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) *syn*, *anti*: δ = 205.13, 205.07, 137.0, 136.9, 136.4, 136.1, 133.3, 133.2, 128.74, 128.68, 128.49, 128.46, 125.5, 125.0, 70.8, 69.1, 47.1, 45.9, 26.0, 25.9, 18.6, 18.5, 15.1, 12.3 ppm. HRMS (ESI): calcd. for $C_{14}H_{18}NaO_2$ $[M]^+$ 241.1199; found 241.1197.

3-Hydroxy-2,5-dimethyl-1-phenylhexan-1-one (23): *syn*-**23**/*anti*-**23** = 92:8 (81 mg, 92%), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00–7.94 (m, 2 H *syn*, 2 H *anti*), 7.65–7.59 (m, 1 H *syn*, 1 H *anti*), 7.56–7.48 (m, 2 H *syn*, 2 H *anti*), 4.16 (*syn*) (ddd, *J* = 2.9, 3.9, 9.4 Hz, 1 H), 3.96 (*anti*) (ddd, *J* = 3.0, 5.9, 10.0 Hz, 1 H), 3.53 (*anti*) (dq, *J* = 5.9, 7.2 Hz, 1 H), 3.44 (*syn*) (dq, *J* = 2.9, 7.3 Hz, 1 H), 3.16–2.55 (br. s, 1 H *syn*, 1 H *anti*), 1.97–1.78 (m, 1 H *syn*, 1 H *anti*), 1.60 (*syn*) (ddd, *J* = 5.3, 9.4, 13.7 Hz, 1 H), 1.49 (*anti*) (ddd, *J* = 4.4, 10, 13.7 Hz, 1 H), 1.33–1.26 (*anti*) (m, 1 H), 1.29 (*anti*) (d, *J* = 7.2 Hz, 3 H), 1.28 (*syn*) (d, *J* = 7.3 Hz, 3 H), 1.19 (*syn*) (ddd, *J* = 3.9, 8.6, 13.7 Hz, 1 H), 0.97 (*syn*) (d, *J* = 3.1 Hz, 3 H), ca. 0.96 (*anti*) (d, 3 H, overlaps with 0.97 syn), 0.95 (*syn*) (d, *J* = 3.1 Hz, 3 H), 0.93 (*anti*) (d, *J* = 6.5 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) *syn*, *anti*: δ = 206.1, 206.0, 136.7, 136.0, 133.5, 133.4, 128.82, 128.77, 128.5, 128.4, 72.3, 69.2, 46.3, 45.0, 44.2, 43.5, 24.7, 24.6, 23.8, 23.5, 22.0, 21.7, 15.6, 11.2 ppm. HRMS (ESI): calcd. for $C_{14}H_{20}NaO_2$ $[M]^+$ 243.1356; found 243.1347.

4-Ethyl-3-hydroxy-2-methyl-1-phenylhexan-1-one (24): *syn*-**24**/*anti*-**24** = 89:11 (71 mg, 76%), colorless oil, only *syn* was isolated. ^{1}H NMR (400 MHz, $CDCl_3$) (*syn*): δ = 8.00–7.95 (m, 2 H), 7.65–7.59 (m, 1 H), 7.54–7.48 (m, 2 H), 3.92 (dt, *J* = 3.3, 7.3 Hz, 1 H), 3.70 (dq, *J* = 3.3, 7.1 Hz, 1 H), 2.98 (d, *J* = 3.3 Hz, 1 H), 1.76–1.62 (m, 1 H), 1.55–1.33 (m, 4 H), 1.28 (d, *J* = 7.1 Hz, 3 H), 0.94 (t, *J* = 7.3 Hz, 3 H), 0.87 (t, *J* = 7.3 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, *syn*): δ = 206.0, 136.1, 133.4, 128.8, 128.4, 72.6, 42.5, 41.9, 21.3, 20.5, 11.4, 10.7, 10.5 ppm. HRMS (ESI): calcd. for $C_{15}H_{22}NaO_2$ $[M]^+$ 257.1512; found 257.1519.

2-Methyl-1-phenylpentane-1,3-dione (25):[36] **25** could not be separated from traces of **5a** and **1a**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02–796 (m, 2 H), 7.65–7.55 (m, 1 H), 7.54–7.46 (m, 2 H), 4.53 (q, *J* = 4.5 Hz, 1 H), 2.50 (m, 2 H), 1.48 (d, *J* = 7.0 Hz, 3 H), 1.04 (t, *J* = 7.4 Hz, 3 H) ppm. HRMS (ESI): calcd. for $C_{12}H_{14}NaO_2$ $[M]^+$ 213.0886; found 213.0878.

4-Methyl-*N*-(2-methyl-3-oxo-1,3-diphenylpropyl)benzenesulfonamide (31):[37] *syn*-**31**/*anti*-**31** = 71:29 (126 mg, 80%), white powder. ^{1}H NMR (400 MHz, $CDCl_3$) *syn*: δ = 7.77–7.69 (m, 2 H), 7.57–7.49 (m, 3 H), 7.42–7.36 (m, 2 H), 7.16–7.04 (m, 7 H), 5.41 (d, *J* = 7.4 Hz, 1 H), 4.64 (t, *J* = 7.4 Hz, 1 H), 3.89 (app. quint, *J* = 7.3 Hz, 1 H), 2.33 (s, 3 H), 1.27 (d, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) *syn*: δ = 201.7, 143.1, 139.6, 135.8, 133.2, 129.3, 128.6, 128.3, 128.1, 127.4, 127.3, 127.0, 126.5, 59.6, 46.6, 21.4, 14.3 ppm. HRMS (ESI) *syn*: calcd. for $C_{23}H_{23}NNaO_3S$ $[M]^+$ 416.1291; found 416.1307. ^{1}H NMR (400 MHz, $CDCl_3$) *anti*: δ = 7.72–7.68 (m, 2 H), 7.57–7.51 (m, 3 H), 7.40–7.35 (m, 2 H), 7.14–7.03 (m, 7 H), 6.46 (d, *J* = 9.0 Hz, 1 H), 4.74 (dd, *J* = 4.7, 9.0 Hz, 1 H), 3.92 (dq, *J* = 4.7, 7.3 Hz, 1 H), 2.33 (s, 3 H), 1.30 (d, *J* = 7.3 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) *anti*: δ = 203.9, 142.7, 139.5, 138.1, 136.3, 133.5, 129.1, 128.6, 128.23, 128.20, 127.2, 126.9, 126.6, 60.7, 46.0, 21.4, 16.7 ppm. HRMS (ESI) *anti*: calcd. for $C_{23}H_{23}NNaO_3S$ $[M]^+$ 416.1291; found 416.1266.

***N*-[1-(4-Fluorophenyl)-2-methyl-3-oxo-3-phenylpropyl]-4-methylbenzenesulfonamide (34):** *syn*-**34**/*anti*-**34** = 62:38 (128 mg, 78%), white powder. ^{1}H NMR (400 MHz, $CDCl_3$) *syn*: δ = 7.75–7.68 (m, 2 H), 7.60–7.49 (m, 3 H), 7.42–7.34 (m, 2 H), 7.14–7.03 (m, 4 H), 6.81–6.71 (m, 2 H), 5.83 (d, *J* = 8.0 Hz, 1 H), 4.64 (t, *J* = 8.1 Hz, 1 H), 3.87 (app. quint, *J* = 7.1 Hz, 1 H), 2.34 (s, 3 H), 1.29 (d, *J* = 7.1 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) *syn*: δ = 201.6, 161.7 [d, $^1J(^{13}C–^{19}F)$ = 246.2 Hz], 143.3, 136.9, 135.7 [d, $^4J(^{13}C–^{19}F)$ = 3.2 Hz], 135.4, 133.4, 129.3, 128.8 [d, $^3J(^{13}C–^{19}F)$ = 8.1 Hz], 128.6, 128.1, 127.2, 115.1 [d, $^2J(^{13}C–^{19}F)$ = 21.5 Hz], 59.1, 46.7, 21.4, 14.7 ppm. HRMS (ESI) *syn*: calcd. for $C_{23}H_{22}FNNaO_3S$ $[M]^+$ 434.1197; found 434.1217. ^{1}H NMR (400 MHz, $CDCl_3$) *anti*: δ = 7.73–7.68 (m, 2 H), 7.57–7.49 (m, 3 H), 7.44–7.36 (m, 2 H), 7.14–7.08 (m, 2 H), 7.07–7.00 (m, 4 H), 6.81–6.72 (m, 2 H), 6.48 (d, *J* = 8.7 Hz, 1 H), 4.72 (dd, *J* = 4.8, 8.7 Hz, 1 H), 3.88 (dq, *J* = 4.8, 7.2 Hz, 1 H), 2.33 (s, 3 H), 1.31 (d, *J* = 7.3 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) *anti*: δ = 203.9, 162.6 [d, $^1J(^{13}C–^{19}F)$ = 248.0 Hz], 142.9, 138.0, 136.1, 135.4 [d, $^4J(^{13}C–^{19}F)$ = 3.1 Hz], 133.7, 129.2, 128.7, 128.3 [d, $^3J(^{13}C–^{19}F)$ = 8.1 Hz], 128.2, 126.9, 115.0 [d, $^2J(^{13}C–^{19}F)$ = 21.5 Hz], 60.1, 46.0, 21.4, 16.8 ppm. HRMS (ESI) *anti*: calcd. for $C_{23}H_{22}FNNaO_3S$: 434.1197; found 434.1220.

***N*-[1-(4-Bromophenyl)-2-methyl-3-oxo-3-phenylpropyl]-4-methylbenzenesulfonamide (35):** *syn*-**35**/*anti*-**35** = 73:27 (147 mg, 78%), white powder. ^{1}H NMR (400 MHz, $CDCl_3$) *syn*: δ = 7.76–7.69 (m, 2 H), 7.55–7.49 (m, 3 H), 7.43–7.37 (m, 2 H), 7.25–7.19 (m, 2 H), 7.10–7.05 (m, 2 H), 7.03–6.97 (m, 2 H), 5.65 (d, *J* = 7.5 Hz, 1 H), 4.60 (t, *J* = 7.5 Hz, 1 H), 3.85 (app. quint, *J* = 7.4 Hz, 1 H), 2.36 (s, 3 H), 1.26 (d, *J* = 7.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) *syn*: δ = 201.4, 143.4, 138.5, 136.7, 135.6, 133.5, 131.3, 129.4, 128.9, 128.7, 128.1, 127.2, 121.4, 59.1, 46.3, 21.5, 14.3 ppm. HRMS (ESI) *syn*: calcd. for $C_{23}H_{22}BrNNaO_3S$ $[M]^+$ 494.0396; found 494.0381. ^{1}H NMR (400 MHz, $CDCl_3$) *anti*: δ = 7.75–7.69 (m, 2 H), 7.58–7.50 (m, 3 H), 7.44–7.37 (m, 2 H), 7.22–7.17 (m, 2 H), 7.15–7.08 (m, 2 H), 6.97–6.91 (m, 2 H), 6.51 (d, *J* = 8.8 Hz, 1 H), 4.68 (dd, *J* = 4.6, 8.8 Hz, 1 H), 3.87 (dq, *J* = 4.9, 7.3 Hz, 1 H), 2.38 (s, 3 H), 1.33 (d, *J* = 7.3 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) *anti*: δ = 203.7, 143.1, 138.6, 137.9, 136.0, 133.8, 131.3, 129.2, 128.8, 128.5, 128.2, 126.9, 121.1, 60.2, 45.8, 21.4, 16.9 ppm. HRMS (ESI) *anti*: calcd. for $C_{23}H_{22}BrNNaO_3S$ $[M]^+$ 494.0396; found 494.0422.

***N*-[1-(3-Bromophenyl)-2-methyl-3-oxo-3-phenylpropyl]-4-methylbenzenesulfonamide (36):** *syn*-**36**/*anti*-**36** = 63:37 (156 mg, 83%), white powder. ^{1}H NMR (400 MHz, $CDCl_3$) *syn*: δ = 7.77–7.72 (m, 2 H), 7.59–7.49 (m, 3 H), 7.45–7.39 (m, 2 H), 7.27–7.22 (m, 1 H), 7.15–7.08 (m, 4 H), 7.07–7.01 (m, 1 H), 5.26 (d, *J* = 7.2 Hz, 1 H), 4.58 (t, *J* = 7.2 Hz, 1 H), 3.85 (app. quint, *J* = 7.2 Hz, 1 H), 2.36 (s, 3 H), 1.27 (d, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) *syn*: δ = 201.3, 143.5, 141.6, 136.4, 135.5, 133.5, 130.6, 130.5, 129.9, 129.4, 128.7, 128.2, 127.2, 125.5, 122.4, 58.9, 46.2, 21.5, 14.0 ppm. HRMS (ESI) *syn*: calcd. for $C_{23}H_{22}BrNNaO_3S$ $[M]^+$ 494.0396; found 494.0379. ^{1}H NMR (400 MHz, $CDCl_3$) *anti*: δ = 7.78–7.70 (m, 2 H), 7.58–7.50 (m, 3 H), 7.44–7.37 (m, 2 H), 7.21–7.14 (m, 1 H), 7.13–7.06 (m, 3 H), 7.05–7.00 (m, 1 H), 7.00–6.93 (m, 1 H), 6.49 (d, *J* = 9.0 Hz, 1 H), 4.69 (dd, *J* = 4.7, 9.0 Hz, 1 H), 3.88 (dq, *J* = 4.7, 7.2 Hz, 1 H), 2.36 (s, 3 H), 1.33 (d, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) *anti*: δ = 203.5, 143.1, 141.7, 137.8, 136.0, 133.7, 130.3, 129.9, 129.8, 129.3, 128.7, 128.2, 126.8, 125.4, 122.4, 60.2, 45.8, 21.4, 16.8 ppm. HRMS (ESI): calcd. for $C_{23}H_{22}BrNNaO_3S$ $[M]^+$ 494.0396; found 494.0383.

***N*-[1-(3-Bromophenyl)-2-methyl-3-oxo-3-phenylpropyl]-4-methylbenzenesulfonamide (37):** *syn*-**37**/*anti*-**37** = 56:44 (141 mg, 75%), white powder. ^{1}H NMR (400 MHz, $CDCl_3$) *syn*, *anti*: δ = 7.88–

6.85 (m, 13 H), 6.78 (*anti*) (d, *J* = 9.2 Hz, 1 H), 5.82 (*syn*) (br. s, 1 H), 5.06 (*anti*) (dd, *J* = 4.1, 9.2 Hz, 1 H), 4.85 (*syn*) (t, *J* = 5.6 Hz, 1 H), 4.10 (*anti*) (dq, *J* = 4.1, 7.1 Hz, 1 H), 4.05 (*syn*) (br. s, 1 H), 2.32 (*anti*) (s, 3 H), 2.27 (*syn*) (s, 3 H), 1.33 (*anti*) (d, *J* = 7.1 Hz, 3 H), 1.23 (*syn*) (br. s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) *syn*, *anti* (one carbon atom is missing due to overlap): *δ* = 204.0 (*anti*); 202.2 (*syn*), 143.1, 142.9, 138.4, 137.7, 137.5 (*syn*), 136.2, 135.4 (*syn*), 133.6, 133.5, 133.0 (*syn*), 132.6, 131.1 (*syn*), 129.24, 129.22, 129.1, 128.9 (*syn*), 128.64, 128.62, 128.5, 128.4 (*syn*), 128.2, 127.4 (*syn*), 127.3, 127.2, 126.9, 122.2 (*anti*), 121.9 (*syn*), 59.5 (*anti*), 57.6 (*syn*), 42.8 (*anti*), 42.3 (*syn*), 21.42, 21.40, 16.7 (*anti*), 11.5 (*syn*) ppm. HRMS (ESI): calcd. for $C_{23}H_{22}BrNNaO_3S$ $[M]^+$ 494.0396; found 494.0379.

4-Methyl-*N*-[2-methyl-3-oxo-3-phenyl-1-(*o*-tolyl)propyl]benzenesulfonamide (38): *syn*-**38**:*anti*-**38** = 66:34 (114 mg, 70%), white powder. ^{1}H NMR (400 MHz, $CDCl_3$) *syn*: *δ* = 7.74–7.67 (m, 2 H), 7.54–7.47 (m, 3 H), 7.40–7.33 (m, 2 H), 7.25–7.20 (m, 1 H), 7.10–7.04 (m, 2 H), 7.03–6.94 (m, 2 H), 6.93–6.87 (m, 1 H), 5.55 (d, *J* = 7.5 Hz, 1 H), 4.86 (t, *J* = 7.5 Hz, 1 H), 3.91 (dq, *J* = 7.1, 7.5 Hz, 1 H), 2.33 (s, 3 H), 2.21 (s, 3 H), 1.33 (d, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) *syn*: *δ* = 202.0, 143.0, 138.0, 137.1, 136.1, 135.3, 133.2, 130.4, 129.2, 128.5, 128.0, 127.3, 127.1, 126.5, 126.1, 55.2, 46.0, 21.4, 19.3, 14.9 ppm. HRMS (ESI) *syn*: calcd. for $C_{24}H_{25}NNaO_3S$ $[M]^+$ 430.1447; found 430.1450. ^{1}H NMR (400 MHz, $CDCl_3$) *anti*: *δ* = 7.69–7.61 (m, 2 H), 7.56–7.43 (m, 3 H), 7.41–7.32 (m, 2 H), 7.08–7.00 (m, 3 H), 6.98–6.90 (m, 2 H), 6.84–6.75 (m, 1 H), 6.39 (d, *J* = 8.5 Hz, 1 H), 4.98 (dd, *J* = 4.9, 8.5 Hz, 1 H), 3.82 (dq, *J* = 4.9, 7.3 Hz, 1 H), 2.38 (s, 3 H), 2.32 (s, 3 H), 1.29 (d, *J* = 7.3 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) *anti*: *δ* = 204.0, 142.6, 137.9, 137.5, 136.5, 134.3, 133.4, 130.3, 129.0, 128.6, 128.1, 127.0, 126.8, 126.5, 126.0, 56.6, 44.3, 21.4, 19.3, 16.7 ppm. HRMS (ESI) *anti*: calcd. for $C_{24}H_{25}NNaO_3S$ $[M]^+$ 430.1447; found 430.1436.

4-Methyl-*N*-[2-methyl-3-oxo-3-phenyl-1-(*p*-tolyl)propyl]benzenesulfonamide (39): *syn*-**39**/*anti*-**39** = 53:47 (114 mg, 70%), white powder. ^{1}H NMR (400 MHz, $CDCl_3$) *syn*: *δ* = 7.77–7.71 (m, 2 H), 7.57–7.50 (m, 3 H), 7.43–7.36 (m, 2 H), 7.11–7.05 (m, 2 H), 7.04–6.91 (m, 4 H), 5.25 (br. s, 1 H), 4.57 (t, *J* = 7.1 Hz, 1 H), 3.87 (app. quint, *J* = 7.1 Hz, 1 H), 2.34 (s, 3 H), 2.24 (s, 3 H), 1.26 (d, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) *syn*: *δ* = 201.4, 143.4, 138.5, 136.7, 135.6, 133.5, 131.3, 129.4, 128.9, 128.7, 128.1, 127.2, 121.4, 59.1, 46.3, 21.5, 21.0, 14.3 ppm. ^{1}H NMR (400 MHz, $CDCl_3$) *anti*: *δ* = 7.77–7.70 (m, 2 H), 7.57–7.49 (m, 3 H), 7.42–7.35 (m, 2 H), 7.11–7.05 (m, 2 H), 6.96–6.85 (m, 2 H), 6.38 (d, *J* = 9.0 Hz, 1 H), 4.69 (dd, *J* = 5.1, 9.0 Hz, 1 H), 3.90 (dq, *J* = 5.1, 7.3 Hz, 1 H), 2.35 (s, 3 H), 2.21 (s, 3 H), 1.27 (d, *J* = 7.3 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) *anti*: *δ* = 203.9, 142.6, 138.1, 136.8, 136.5, 136.3, 133.4, 129.1, 128.9, 128.6, 128.2, 127.0, 126.6, 60.5, 46.1, 21.4, 20.9, 16.6 ppm. HRMS (ESI) *syn*, *anti*: calcd. for $C_{24}H_{25}NNaO_3S$ $[M]^+$ 430.1447; found 430.1440.

4-Methyl-*N*-[2-methyl-1-(naphthalen-2-yl)-3-oxo-3-phenylpropyl]benzenesulfonamide (40): *syn*-**40**/*anti*-**40** = 61:39 (135 mg, 76%), white powder. ^{1}H NMR (400 MHz, $CDCl_3$) *syn*: *δ* = 7.77–7.65 (m, 3 H), 7.63–7.56 (m, 2 H), 7.53–7.26 (m, 9 H), 6.88 (d, *J* = 8.1 Hz, 2 H), 5.89 (d, *J* = 8.2 Hz, 1 H), 4.85 (t, *J* = 8.1 Hz, 1 H), 4.05 (to dq, *J* = 7.2, 8.1 Hz, 1 H), 2.13 (s, 3 H), 1.36 (d, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) *syn*: *δ* = 201.6, 143.1, 136.9, 136.5, 135.8, 133.2, 132.9, 132.5, 129.1, 128.6, 128.3, 128.1, 127.9, 127.4, 127.2, 126.8, 126.0, 125.9, 124.4, 59.9, 46.5, 21.2, 14.8 ppm. HRMS (ESI) *syn*: calcd. for $C_{27}H_{25}NNaO_3S$ $[M]^+$ 466.1447; found 466.1437. ^{1}H NMR (400 MHz, $CDCl_3$) *anti*: *δ* = 7.78–7.67 (m, 3 H), 7.61–7.54 (m, 2 H), 7.52–7.45 (m, 3 H), 7.44–7.38 (m, 3 H), 7.38–7.30 (m, 2 H), 7.20 (dd, *J* = 1.9, 8.5 Hz, 1 H), 6.87 (d, *J* = 8.1 Hz, 2 H), 6.60 (d, *J* = 9.0 Hz, 1 H), 4.90 (dd, *J* = 5.2, 9.0 Hz, 1 H), 4.03 (dq, *J* = 5.2, 7.2 Hz, 1 H), 2.11 (s, 3 H), 1.35 (d, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) *anti*: *δ* = 203.8, 142.7, 137.9, 136.4, 136.2, 133.5, 132.9, 132.5, 129.0, 128.6, 128.21, 128.17, 127.9, 127.4, 126.9, 126.2, 126.0, 125.9, 124.4, 61.0, 45.9, 21.1, 16.9 ppm. HRMS (ESI) *anti*: calcd. for $C_{27}H_{25}NNaO_3S$ $[M]^+$ 466.1447; found 466.1443.

4-Methyl-*N*-[2-methyl-3-(naphthalen-1-yl)-3-oxo-1-phenylpropyl]benzenesulfonamide (41): *syn*-**41**:*anti*-**41** = 84:16 (122 mg, 69%), white powder. ^{1}H NMR (400 MHz, $CDCl_3$) *syn*: *δ* = 8.10–8.03 (m, 1 H), 7.96–7.90 (m, 1 H), 7.86–7.81 (m, 1 H), 7.58–7.45 (m, 5 H), 7.43–7.37 (m, 1 H), 7.14–7.04 (m, 7 H), 5.27 (d, *J* = 7.9 Hz, 1 H), 4.72 (t, *J* = 7.9 Hz, 1 H), 3.84 (app. quint, *J* = 7.5 Hz, 1 H), 2.32 (s, 3 H), 1.36 (d, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) *syn*: *δ* = 205.7, 143.1, 139.4, 137.0, 135.8, 133.8, 132.6, 130.2, 129.3, 128.4, 128.3, 127.8, 127.5, 127.3, 127.2, 126.6, 126.5, 125.4, 124.1, 59.9, 50.8, 21.4, 14.6 ppm. HRMS (ESI) *syn*: calcd. for $C_{27}H_{25}NNaO_3S$ $[M]^+$ 466.1447; found 466.1460. ^{1}H NMR (400 MHz, $CDCl_3$) *anti*: *δ* = 8.24–8.17 (m, 1 H), 7.97–7.87 (m, 1 H), 7.87–7.80 (m, 1 H), 7.62–7.49 (m, 4 H), 7.37–7.25 (m, 2 H), 7.11 (s, 5 H), 7.10–7.04 (m, 2 H), 6.64 (d, *J* = 8.7 Hz, 1 H), 4.80 (dd, *J* = 4.8, 8.7 Hz, 1 H), 3.89 (adq, *J* = 4.8, 7.2 Hz, 1 H), 2.33 (s, 3 H), 1.35 (d, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) *anti*: *δ* = 208.1, 142.7, 139.7, 138.1, 135.9, 133.8, 132.8, 130.1, 129.2, 128.37, 128.36, 128.0, 127.3, 127.1, 126.9, 126.7, 126.6, 125.4, 124.1, 60.9, 50.1, 21.4, 16.4 ppm. HRMS (ESI): calcd. for $C_{27}H_{25}NNaO_3S$ $[M]^+$ 466.1447; found 466.1447.

***N*-(2-Benzyl-3-oxo-1-phenylbutyl)-4-methylbenzenesulfonamide (42):** *syn*-**42**/*anti*-**42** = 49:51 (129 mg, 79%), white powder. ^{1}H NMR (400 MHz, $CDCl_3$) *syn*, *anti*: *δ* = 7.58–7.50 (m, 4 H), 7.32–7.92 (m, 24 H), 6.37 (*anti*) (br. s, 1 H), 5.57 (*syn*) (br. s, 1 H), 4.68 (*anti*) (dd, *J* = 4.9, 9.2 Hz, 1 H), 4.49 (*syn*) (t, *J* = 8.7 Hz, 1 H), 3.28–3.15 (m, 3 H), 3.00–2.93 (m, 1 H), 2.91–2.79 (m, 2 H), 2.35 (*syn*) (s, 3 H), 2.33 (*anti*) (s, 3 H), 1.59 (*anti*) (s, 3 H), 1.41 (*syn*) (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) *syn*, *anti*: *δ* = 213.2, 210.4, 143.3, 142.8, 139.1, 138.7, 138.6, 138.1, 138.0, 137.1, 129.4, 129.2, 128.9, 128.83, 128.75, 128.6, 128.5, 128.4, 127.7, 127.3, 127.2, 126.93, 126.91, 126.8, 126.5, 126.3, 60.6, 59.43, 59.40, 58.9, 36.8, 35.8, 33.1, 32.7, 21.30, 21.29 ppm. HRMS (ESI): calcd. for $C_{24}H_{25}NNaO_3S$ $[M]^+$ 430.1447; found 430.1468.

***N*-[3-(4-Chlorophenyl)-2-methyl-3-oxo-1-phenylpropyl]-4-methylbenzenesulfonamide (43):** *syn*-**43**:*anti*-**43** = 60:40 (136 mg, 80%), white powder. ^{1}H NMR (400 MHz, $CDCl_3$) *syn*: *δ* = 7.69–7.64 (m, 2 H), 7.55–7.49 (m, 2 H), 7.39–7.34 (m, 2 H), 7.17–7.04 (m, 7 H), 5.22 (d, *J* = 7.7 Hz, 1 H), 4.61 (t, *J* = 7.5 Hz, 1 H), 3.82 (app. quint, *J* = 7.2 Hz, 1 H), 2.35 (s, 3 H), 1.26 (d, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) *syn*: *δ* = 200.4, 143.2, 139.8, 139.3, 136.7, 134.1, 129.5, 129.3, 128.9, 128.4, 127.6, 127.3, 126.9, 59.5, 46.7, 21.4, 13.9 ppm. HRMS (ESI) *syn*: calcd. for $C_{23}H_{22}ClNNaO_3S$ $[M]^+$ 450.0898; found 450.0901. ^{1}H NMR (400 MHz, $CDCl_3$) *anti*: *δ* = 7.67–7.60 (m, 2 H), 7.56–7.50 (m, 2 H), 7.36–7.30 (m, 2 H), 7.11–7.00 (m, 7 H), 6.37 (d, *J* = 8.8 Hz, 1 H), 4.73 (dd, *J* = 5.2, 8.8 Hz, 1 H), 3.86 (dq, *J* = 5.2, 7.2 Hz, 1 H), 2.33 (s, 3 H), 1.26 (d, *J* = 7.3 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) *anti*: *δ* = 202.7, 142.8, 140.0, 139.3, 137.9, 134.6, 129.6, 129.1, 128.9, 128.3, 127.3, 126.9, 126.5, 60.6, 46.0, 21.4, 16.6 ppm. HRMS (ESI) *anti*: calcd. for $C_{23}H_{22}ClNNaO_3S$ $[M]^+$ 450.0898; found 450.0920.

Preparation of 45 from 50: *n*BuLi (15 μL, 0.15 mmol, 1 M in hexanes) was added to an NMR tube that contained [D_6]benzene (0.4 mL) and **2a** (17 μL, 0.13 mmol) under a nitrogen atmosphere. ^{1}H NMR (400 MHz, [D_6]benzene, selected peaks): *δ* = 7.47–7.34

(m, 2 H), 7.33–7.27 (m, 2 H), 7.21–7.15 (m, 1 H), 6.01 (br. s, 1 H), 5.22 (d, 1 H, J = 16.8 Hz), 5.16 (br. s, 1 H), 5.00 (d, 1 H, J = 9.2 Hz) ppm. A solution of **50** (186 μL, 0.05 mmol, 0.27 M in [D_6]benzene) was added to an NMR tube that contained **1a** (30 mg, 0.047 mmol) in [D_6]benzene (0.2 mL) under a nitrogen atmosphere. When the tube was shaken vigorously, the mixture changed color from yellow to red. Slow formation of **45**[6a] was observed by ^{1}H NMR spectroscopy.

Preparation of 45 from 51: NaHMDS (70 μL, 0.14 mmol, 2 M in THF) was added to an NMR tube that contained [D_6]benzene (0.4 mL) and **2a** (17 μL, 0.13 mmol) under a nitrogen atmosphere. Compound **51** was formed quantitatively within a few seconds. ^{1}H NMR (400 MHz, [D_6]benzene): δ = 7.70–7.64 (m, 2 H), 7.41–734 (m, 2 H), 7.23–7.17 (m, 1 H), 6.33 (ddd, 1 H, J = 6.0, 10.1, 17.2 Hz), 5.60 (d, 1 H, J = 5.6 Hz), 5.09 (dt, 1 H, J = 17.4, 1.9 Hz), 5.09 (d, 1 H, J = 10.2 Hz) ppm. A solution of **51** (185 μL, 0.05 mmol, 0.27 M in [D_6]benzene) was added to an NMR tube that contained **1a** (30 mg, 0.047 mmol) in [D_6]benzene (0.4 mL) under a nitrogen atmosphere. The tube was shaken vigorously, and the mixture of **1a** and **51** changed color from yellow to red. Quantitative formation of **45** was observed within a few seconds. The NMR spectroscopic data of **45** were identical to those reported.[6a]

Preparation of 47b from 52: A solution of **5a** in pentane (10 mL, 5 mmol, 0.5 M) was added to a solution of KHMDS (24 mL, 6 mmol, 0.25 M in toluene/pentane, 100:1). After precipitation, **52** was collected by filtration, washed with pentane, and stored in a drybox.[25b] Enolate **52** was highly sensitive to moisture and could be only characterized as a mixture of **52** and **5a** in a ratio of 80:20. ^{1}H NMR (400 MHz, [D_8]THF): δ = 7.49–7.41 (m, 2 H), 7.05–6.96 (m, 2 H), 6.93–6.85 (m, 1 H), 4.13 (q, J = 6.6 Hz, 1 H), 1.57 (d, J = 6.6 Hz, 1 H) ppm. A solution of **52** (100 μL, 0.045 mmol, 0.08 M in [D_8]THF) was added to an NMR tube that contained **1a** (20 mg, 0.03 mmol) in [D_8]THF (0.4 mL) under a nitrogen atmosphere. The tube was shaken vigorously until the color of the reaction mixture had changed from yellow to red (4 min). Analysis by ^{1}H NMR spectroscopy showed the formation of **47b** in approximately 35% yield, the remainder was **5a** and unidentified Ru complexes. ^{1}H NMR (400 MHz, [D_8]THF, selected peaks): δ = 3.91 (q, 1 H, J = 6.5 Hz), 1.58 (d, 1 H, J = 6.5 Hz) ppm. ^{13}C NMR (100 MHz, [D_8]THF, selected peaks): δ = 203.8, 202.2, 201.0, 198.7, 107.6, 27.0, 22.3 ppm. See Supporting Information for further details.

Supporting Information (see footnote on the first page of this article): Characterization data and copies of the NMR spectra for **11**, **13**–**14**, **18**–**20**, **22**–**25**, **31**, and **34**–**43**. Comparison of NMR shifts of **47b** with other *C*-bound ruthenium enolates reported in literature. NMR spectra of crude **45**, and **49**–**52**

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[1] a) T. Mukaiyama, *Pure Appl. Chem.* **1983**, *55*, 1749–1758; b) P. Arya, H. Qin, *Tetrahedron* **2000**, *56*, 917–947.
[2] T. D. Sheppard, *Synlett* **2011**, 1340–1344.
[3] For recent reviews on transition-metal-catalyzed reductive aldol and Mannich reactions, see: a) H. Nishiyama, T. Shiomi, *Top. Curr. Chem.* **2007**, *279*, 105–137; b) S. B. Han, A. Hassan, M. J. Krische, *Synthesis* **2008**, 2669–2679; c) S. Garner, S. B. Han, M. J. Krische, in: *Modern Reduction Methods* (Eds.: P. Andersson, I. Munslow), Wiley-VCH, Weinheim, Germany, **2008**, pp. 387–408.
[4] For reviews on transition-metal-catalyzed isomerization of allylic alcohols, see: a) R. C. van der Drift, E. Bouwman, E. Drent, *J. Organomet. Chem.* **2002**, *650*, 1–24; b) R. Uma, C. Crévisy, R. Grée, *Chem. Rev.* **2003**, *103*, 27–51; c) V. Cadierno, P. Crochet, J. Gimeno, *Synlett* **2008**, 1105–1124; d) L. Mantilli, C. Mazet, *Chem. Lett.* **2011**, *40*, 341–344; e) N. Ahlsten, A. Bartoszewicz, B. Martín-Matute, *Dalton Trans.* DOI:10.1039/C1DT11678A.
[5] a) S. H. Bergens, B. Bosnich, *J. Am. Chem. Soc.* **1991**, *113*, 958–967; b) L. J. Gazzard, W. B. Motherwell, D. A. Sandham, *J. Chem. Soc., Perkin Trans. 1* **1999**, 979–993; c) C. Crévisy, M. Wietrich, V. Le Boulaire, R. Uma, R. Grée, *Tetrahedron Lett.* **2001**, *42*, 395–398; d) R. Uma, M. Davies, C. Crévisy, R. Grée, *Tetrahedron Lett.* **2001**, *42*, 3069–3072; e) M. Wang, C.-J. Li, *Tetrahedron Lett.* **2002**, *43*, 3589–3591; f) M. Wang, X.-F. Yang, C.-J. Li, *Eur. J. Org. Chem.* **2003**, 998–1003; g) X.-F. Yang, M. Wang, R. S. Varma, C.-J. Li, *Org. Lett.* **2003**, *5*, 5657–5660; h) R. Uma, N. Gouault, C. Crévisy, R. Grée, *Tetrahedron Lett.* **2003**, *44*, 6187–6190; i) X.-F. Yang, M. Wang, R. S. Varma, C.-J. Li, *J. Mol. Catal. A* **2004**, *214*, 147–154; j) D. Cuperly, C. Crévisy, R. Grée, *Synlett* **2004**, 93–96; k) V. Branchadell, C. Crévisy, R. Grée, *Chem. Eur. J.* **2004**, *10*, 5795–5803; l) S.-I. Kiyooka, M. Ueno, E. Ishiii, *Tetrahedron Lett.* **2005**, *46*, 4639–4642; m) D. Cuperly, J. Petrignet, C. Crévisy, R. Grée, *Chem. Eur. J.* **2006**, *12*, 3261–3274; n) H. T. Cao, T. Roisnel, R. Grée, *Lett. Org. Chem.* **2009**, *6*, 507–510; o) H. T. Cao, T. Roisnel, A. Valleix, R. Grée, *Eur. J. Org. Chem.* **2011**, 3430–3436.
[6] a) A. Bartoszewicz, M. Livendahl, B. Martín-Matute, *Chem. Eur. J.* **2008**, *14*, 10547–10550; b) N. Ahlsten, B. Martín-Matute, *Adv. Synth. Catal.* **2009**, *351*, 2657–2666.
[7] a) N. Ahlsten, B. Martín-Matute, *Chem. Commun.* **2011**, *47*, 8331–8333; b) N. Ahlsten, A. Bartoszewicz, S. Agrawal, B. Martín-Matute, *Synthesis* **2011**, 2600–2608.
[8] a) B. Martín-Matute, K. Bogár, M. Edin, F. B. Kaynak, J.-E. Bäckvall, *Chem. Eur. J.* **2005**, *11*, 5832–5842; b) M. Ito, S. Kitahara, T. Ikariya, *J. Am. Chem. Soc.* **2005**, *127*, 6172–6173; c) P. Crochet, M. A. Fernández-Zúmel, J. Gimeno, M. Scheele, *Organometallics* **2006**, *25*, 4846–4849; d) P. N. Liu, K. D. Ju, C. P. Lau, *Adv. Synth. Catal.* **2011**, *353*, 275–280.
[9] B. Schneider, I. Goldberg, D. Reshef, Z. Stein, Y. Shvo, *J. Organomet. Chem.* **1999**, *588*, 92–98.
[10] J. H. Choi, Y. H. Kim, S. H. Nam, S. T. Shin, M. J. Kim, J. Park, *Angew. Chem.* **2002**, *114*, 2479; *Angew. Chem. Int. Ed.* **2002**, *41*, 2373–2376.
[11] N. G. Connelly, I. Manners, *J. Chem. Soc., Dalton Trans.* **1989**, 283–288.
[12] G. O. Nelson, C. E. Sumner, *Organometallics* **1986**, *5*, 1983–1986.
[13] A. Mizuno, H. Kusama, N. Iwasawa, *Chem. Eur. J.* **2010**, *16*, 8248–8250.
[14] For recent methods of the preparation of 1,3-dicarbonyl compounds, see: a) C. Wiles, P. Watts, S. J. Haswell, E. Pombo-Villar, *Tetrahedron Lett.* **2002**, *43*, 2945–2948; b) K.-H. Park, L. J. Cox, *Tetrahedron Lett.* **2003**, *44*, 1067–1069; c) K. Miura, M. Tojino, N. Fujisawa, A. Hosomi, I. Ryu, *Angew. Chem.* **2004**, *116*, 2477; *Angew. Chem. Int. Ed.* **2004**, *43*, 2423–2425; d) V. Fargeas, M. Baalouch, E. Metay, J. Baffreau, D. Ménard, P. Gosselin, J.-P. Bergé, C. Barthmeuf, J. Lebreton, *Tetrahedron* **2004**, *60*, 10359–10364; e) Z. Shen, B. L. Lu, Y. Zhang, *Tetrahedron Lett.* **2005**, *46*, 8785–8788; f) S. Kamijo, G. B. Dudley, *Org. Lett.* **2006**, *8*, 175–177; g) Z. Ikeda, T. Hirayama, S. Matsubara, *Angew. Chem.* **2006**, *118*, 8380; *Angew. Chem. Int. Ed.* **2006**, *45*, 8200–8203; h) T. Fukuyama, T. Dai, S. Minamino, S. Omura, I. Ryu, *Angew. Chem.* **2007**, *119*, 5655; *Angew. Chem. Int. Ed.* **2007**, *46*, 5559–5561; i) K. Sato, S. Yamazoe, R. Yama-

moto, S. Ohata, A. Tarui, M. Omote, I. Kumadaki, A. Ando, *Org. Lett.* **2008**, *10*, 2405–2408.
[15] a) A. V. Kel'in, *Curr. Org. Chem.* **2003**, *7*, 1691–1711; b) A. V. Kel'in, A. Maioli, *Curr. Org. Chem.* **2003**, *7*, 1855–1886.
[16] a) E. F. Kleinmann, in: *Comprehensive Organic Synthesis* (Eds.: B. M. Trost, I. Fleming), Pergamon Press, New York, **1991**, vol. 2, chapter 4.1.–4.3; b) M. Arend, B. Westermann, N. Risch, *Angew. Chem.* **1998**, *110*, 1096; *Angew. Chem. Int. Ed.* **1998**, *37*, 1044–1070.
[17] a) H. Bohme, M. Haake, *Advances in Organic Chemistry*, (Eds.: E. C. Taylor), John Wiley & Sons, New York, **1976**; pp. 107–223; b) R. Muller, H. Goesmann, H. Waldmann, *Angew. Chem.* **1999**, *111*, 166; *Angew. Chem. Int. Ed.* **1999**, *38*, 184–187; c) W. Notz, F. Tanaka, S.-I. Watanabe, N. S. Chowdari, J. M. Turner, R. Thayumanavan, C. F. Barbas, *J. Org. Chem.* **2003**, *68*, 9624–9634, and references cited therein;d) A. Ting, M. Suginome, L. Uehlin, M. Murakami, *J. Am. Chem. Soc.* **2004**, *126*, 13196–13197; e) M. M. B. Marques, *Angew. Chem.* **2006**, *118*, 356; *Angew. Chem. Int. Ed.* **2006**, *45*, 348–352; f) S. E. Schaus, *Eur. J. Org. Chem.* **2007**, *35*, 5797–5815.
[18] For recent examples on the use of *N*-aryl aldimines in reductive Mannich reactions, see: a) J. A. Townes, M. A. Evans, J. Queffelec, S. J. Taylor, J. A. Morken, *Org. Lett.* **2002**, *4*, 2537–2540; b) H. Nishiyama, J. Ishikawa, T. Shiomi, *Tetrahedron Lett.* **2007**, *48*, 7841–7844.
[19] For recent examples on transition-metal-catalyzed Mannich reactions with Boc-protected imines, see: a) Q.-Y. Zhao, M. Shi, *Tetrahedron* **2011**, *67*, 3724–3732; b) Y. K. Kang, D. Y. Kim, *Tetrahedron Lett.* **2011**, *52*, 2356–2358; c) N. E. Shepherd, H. Tanabe, Y. Xu, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2010**, *132*, 3666–3667; d) E. J. Kim, Y. K. Kang, D. Y. Kim, *Bull. Korean Chem. Soc.* **2009**, *30*, 1437–1438.
[20] For recent examples on the use of *N*-tosyl imines in reductive Mannich reactions, see: a) O. Prieto, H. W. Lam, *Org. Biomol. Chem.* **2008**, *6*, 55–57; b) T. Muraoka, S.-I. Kamiya, I. Matsuda, K. Itoh, *Chem. Commun.* **2002**, 1284–1285; c) S. A. Garner, M. J. Krische, *J. Org. Chem.* **2007**, *72*, 5843–5846.
[21] For some recent examples on the use of heteroarylsulfonyl imines in organometallic catalysis, see: a) J. Esquivias, R. Gómez Arrayás, J. C. Carretero, *J. Am. Chem. Soc.* **2007**, *129*, 1480–1481; b) H. Morimoto, G. Lu, N. Aoyama, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2007**, *129*, 9588–9589; c) S. Nakamura, H. Nakashima, H. Sugimoto, H. Sano, M. Hattori, N. Shibata, T. Toru, *Chem. Eur. J.* **2008**, *14*, 2145–2152; d) S. Nakamura, H. Nakashima, A. Yamamura, N. Shibata, T. Toru, *Adv. Synth. Catal.* **2008**, *350*, 1209–1212.
[22] a) J. B. Åberg, J. Nyhlén, B. Martín-Matute, T. Privalov, J.-E. Bäckvall, *J. Am. Chem. Soc.* **2009**, *131*, 9500–9501; b) J. Nyhlén, T. Privalov, J.-E. Bäckvall, *Chem. Eur. J.* **2009**, *15*, 5220–5229; c) C. Warner, O. Verho, J.-E. Bäckvall, *J. Am. Chem. Soc.* **2011**, *133*, 2820–2823.
[23] For ruthenium alkoxide complexes, see: a) S. D. Loren, B. K. Campion, R. H. Heyn, T. D. Tilley, B. E. Bursten, K. W. Luth, *J. Am. Chem. Soc.* **1989**, *111*, 4712–4718; b) C. J. A. Daley, S. H. Bergens, *J. Am. Chem. Soc.* **2002**, *124*, 3680–3691.
[24] a) B. Martín-Matute, M. Edin, K. Bogár, J.-E. Bäckvall, *Angew. Chem.* **2004**, *116*, 6697; *Angew. Chem. Int. Ed.* **2004**, *43*, 6535–6539; b) B. Martín-Matute, M. Edin, K. Bogár, F. B. Kaynak, J.-E. Bäckvall, *J. Am. Chem. Soc.* **2005**, *127*, 8817–8825.
[25] a) J. F. Hartwig, R. A. Andersen, R. G. Bergman, *J. Am. Chem. Soc.* **1990**, *112*, 5670–5671; b) J. F. Hartwig, R. G. Bergman, R. A. Anderson, *Organometallics* **1991**, *10*, 3326–3244; c) B. T. Tasley, M. Rapta, R. J. Kulawiec, *Organometallics* **1996**, *15*, 2852–2854.
[26] H. E. Zimmerman, M. D. Traxler, *J. Am. Chem. Soc.* **1957**, *79*, 1920–1923.
[27] R. C. Tolman, *Proc. Natl. Acad. Sci. USA* **1925**, *11*, 436–439.
[28] K. Y. Lee, C. G. Lee, J. N. Kim, *Tetrahedron Lett.* **2003**, *44*, 1231–1234.
[29] L. J. Gazzard, W. B. Motherwell, D. A. Sandham, *J. Chem. Soc., Perkin Trans. 1* **1999**, 979–993.
[30] G. Smitha, C. Sanjeeva Reddy, *Synth. Commun.* **2006**, *36*, 1795–1800.
[31] A. Bouziane, M. Helou, B. Carboni, F. Carreaux, B. Demerseman, C. Bruneau, J. L. Renaud, *Chem. Eur. J.* **2008**, *14*, 5630–5637.
[32] P. M. O'Neill, E. Verissimo, S. A. Ward, J. Davies, E. E. Korshin, N. Araujo, M. D. Pugh, M. L. S. Cristiano, P. A. Stocksa, M. D. Bachic, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2991–2995.
[33] S. E. Denmark, R. A. Stavenger, K.-T. Wong, X. Su, *J. Am. Chem. Soc.* **1999**, *121*, 4982–4991.
[34] S. Kobayashi, I. Hachiya, *J. Org. Chem.* **1994**, *59*, 3590–3596.
[35] S. Kobayashi, N. Koichi, *J. Org. Chem.* **1993**, *58*, 2647–2649.
[36] T. Fukuyama, T. Dai, S. Minamino, S. Omura, I. Ryu, *Angew. Chem.* **2007**, *119*, 5655; *Angew. Chem. Int. Ed.* **2007**, *46*, 5559–5561.
[37] K. Miura, K. Tamaki, T. Nakagawa, A. Hosomi, *Angew. Chem.* **2000**, *112*, 2034; *Angew. Chem. Int. Ed.* **2000**, *39*, 1958–1958.

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