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# 1-(*N,N*-Diisopropylcarbamoyloxy)-1-tosyl-1-alkenes—$a^2d^1$ Synthons via Tandem Umpolung

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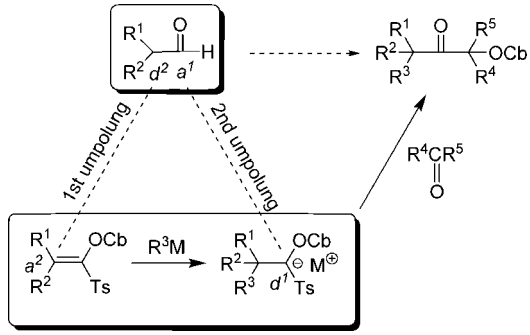
*Received February 16, 2009*




1-(*N,N*-Diisopropylcarbamoyloxy)-1-tosyl-alkenes have been developed as an $a^2d^1$ synthon via tandem umpolung. Upon addition of Grignard reagents and further quench by carbonyl compounds, this synthon produces α,α′-branched-α′-oxygenated ketones. Strategically, this widely applicable method installs respectively a carbanion unit and a carbonyl unit formally onto the α-carbon and the carbonyl center of an aldehyde in one-pot.



## 1. Introduction

A major body of synthetic organic chemistry employs carbonyl compounds with their inherent reactivity as $a^1$ and $d^2$ synthon (for example when the α-position of a carbonyl compound is capable of deprotonation) to construct complex structures.[1] However, several problems have long been recognized: some complex structures can not be readily achieved by applying the $a^1$ synthon directly; synthesis utilizing the $d^2$ synthon is frequently affected by side reactions such as self-condensation. The umpolung of an $a^1$ synthon to a $d^1$ synthon by the early stoichiometric dithiane chemistry[2] and the recent catalytic NHC chemistry[3] can be considered as breakthrough for solving the first problem. Analogously, an umpolung of the $d^2$ synthon to an $a^2$ synthon on carbonyl structures might be a potential solution for the second problem. To the best of our knowledge, this strategy has not been clearly proposed.[4]

Herein, we would like to present our discovery of a readily prepared 1-(*N,N*-diisopropylcarbamoyloxy)-1-tosyl-1-alkene structure (**1**, OR = *N,N*-diisopropylcarbamoyloxy (OCb), $SO_2R^1$ = tosyl), which serves as an $a^2d^1$ synthon[5] via a tandem umpolung. By this, we wish to extend the solution for the above-mentioned first problem, and in particular, to address the second problem

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(1) Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; WILEY-VCH: New York, 1995.

(2) (a) Seebach, D. *Angew. Chem., Int. Ed.* **1979**, *18*, 239–258. (b) Gröbel, B. T.; Seebach, D. *Synthesis* **1977**, 357–402. (c) *Umpoled Synthons. A Survey of Sources and Uses in Synthesis*; Hase, T. A., Ed.; John Wiley & Sons: New York, 1987. For some recent applications of dithiane chemistry in organic synthesis, see: (d) Chen, Y.-L.; Leguijt, R.; Redlich, H. *J. Carbohydr. Chem.* **2007**, *26*, 279–303. (e) Chen, Y.-L.; Leguijt, R.; Redlich, H.; Fröhlich, R. *Synthesis* **2006**, 4212–4218. (f) Chen, Y.-L.; Leguijt, R.; Redlich, H. *Synthesis* **2006**, 2242–2250. (g) Chen, Y.-L.; Redlich, H.; Bergander, K.; Fröhlich, R. *Org. Biomol. Chem.* **2007**, *5*, 3330–3339.

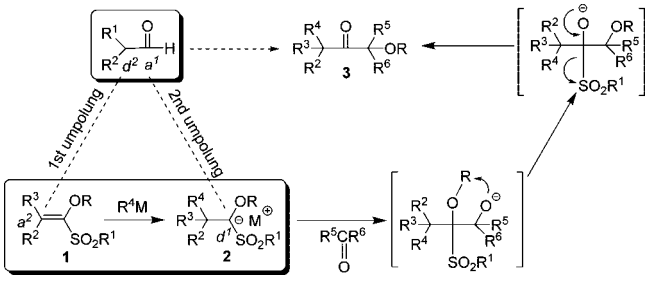
(3) (a) Marion, N.; Díez-González, S.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2988–3000. (b) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606–5655.

(4) Some formal substitutions of α-halogenated esters by carbanion sources were reported: a formal substitution of α-halogenated esters by addition and rearrangement of Grignard reagent: (a) Hussey, A. S.; Herr, R. R. *J. Org. Chem.* **1959**, *24*, 843–845. Using organocadmium reagents for substitution of α-bromoesters: (b) Jones, P. R.; Young, J. R. *J. Org. Chem.* **1968**, *33*, 1675–1676. (c) Amano, T.; Yoshikawa, K.; Sano, T.; Ohuchi, Y.; Shiono, M.; Ishiguro, M.; Fujita, Y. *Synth. Commun.* **1986**, *16*, 499–507. Using boron reagents for substitution of α-bromoesters: (d) Cai, J.; Nemoto, H.; Singaram, B.; Yamamoto, Y. *Tetrahedron Lett.* **1996**, *37*, 3383–3386. Co catalyzed coupling reactions between Grignard reagents and α-bromoesters: (e) Ohmiya, H.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2006**, *128*, 1886–1889. Fe catalyzed coupling reactions between Grignard reagents and α-bromoesters: (f) Fürstner, A.; Martin, R.; Krause, H.; Seidel, G.; Goddard, R.; Lehmann, C. W. *J. Am. Chem. Soc.* **2008**, *130*, 8773–8787.



10.1021/jo900347s CCC: $40.75 
Published on Web 05/04/2009

**SCHEME 1. Proposed One-Pot Tandem Umpolung Leads to an $a^2d^1$ Synthon**




from the aspect of umpolung. As illustrated in Scheme 1, the C-1 position on structure **1** is regarded as a masked carbonyl group. When the structure **1** is subjected into transition metal catalyzed addition reactions, carbanion $R^4$ could be transferred to the $a^2$ position, which results in a tandem umpolung and generates a $d^1$ synthon **2**. Structure **2** can be further coupled with another carbonyl center, revealing the masked carbonyl center (structure **3**) after migration of the carbamoyl group and elimination of the sulfonyl group based on the early findings in our group.[6] Strategically, 1-(*N,N*-diisopropylcarbamoyloxy)-1-tosyl-1-alkene **1** serves as an $a^2d^1$ synthon via a tandem umpolung, which, in a highly economic[7] fashion (four steps in one pot), formally installs a carbanion unit and a carbonyl unit respectively onto the α-carbon and the carbonyl center of an aldehyde (Scheme 1).

## 2. Results and Disscussion

We explored this strategy in two steps: (1) the first addition, in which intermediate **2** is quenched by hydrolysis and (2) the *in situ* second addition/migration/elimination, which completes the tandem umpolung and reveals the masked carbonyl structure, leading to structure **3** in one pot.

**2.1. Establish the Conditions for the First Addition.** The first addition in Scheme 1 describes the addition of an organometallic reagent to 1-oxygenated-1-sulfonyl alkenes, which is strategically new and demanding. It is common to perform transition metal catalyzed nonanionic addition reactions (such as hydrogenation[8] or aryl transfer[9]) to inactivated C=C double bond or C=C double bond with geminal electron-donating substituent and electron-withdrawing substituent (the contradictorily operating substituents lead to practically less activated alkenes). On the contrary, after surveying the liturature, we noticed that, although it could be very important for organic synthesis, catalytic anionic addition reactions on C=C bond with geminal electron-donating substituent (OR group) and electron-withdrawing substituent (sulfonyl group) are rare.[10] We believe that to achieve the success on the catalytic anionic addition to such substrates, a good electronic balance among the OR group, the sulfonyl group and the $R^4M$ reagent is essential. In the course of our research, we have discovered that copper-catalyzed addition of Grignard reagents onto tosylated enol carbamate derivatives (**1**, R = Cb, $R_1$ = *p*-tolyl) is a general and high yielding method for the desired first addition.

To establish a general method, we have synthesized a series of compounds of structure **1** by varying the sulfone group, and tested addition of different $R^4M$ reagents with several transition metal catalysts. The OR substitution on structure **1** was chosen as OCb[11] for the reason that they are stable toward various organometallic reagents, enable good chelation with metal cations which may facilitate the desired addition, and are readily removed.

During the further investigation of the first addition in Scheme 1, we have found: (1) The desired addition is promoted by various Cu(I) or Cu(II) salts with organolithium and Grignard reagents. Ni(II) leads to a direct substitution of the sulfonyl group.[12] (2) The readily available Grignard reagents as the $R^4M$ reagent gave the best result. They are mild enough to avoid significant double-bond migration when an allylic proton is present on the $R^2$ or $R^3$ group, and are compatible with many functional groups. Organolithium reagents can be used for the addition reaction,[13] but their strong basicity induces frequently the double bond migration in the presence of the allylic proton, and tolerates fewer functional groups. Meanwhile, the very mild and readily prepared organozinc compounds were too unreactive for the conjugate addition.[14] (3) Substituent $R^1$ on structure **1** is preferably *p*-Tol. When 2-pyridyl or *n*-$C_4F_9$ was used, the first addition intermediate **2**, independent from the metal applied, is prone to remove the sulfonyl group *in situ*. (4) Additives such as TMSCl, $BF_3 \cdot Et_2O$ or HMPA failed to accelarate the addition as they usually do in the Michael type addition.[15] Therefore, the primary focus is on copper-catalyzed Grignard additions of 1-(*N,N*-diisopropylcarbamoyloxy)-1-tosyl-alkenes.

As demonstrated in Scheme 2, enol carbamates **4a**−**c** were used to prepare the sulfones **5a**−**d** as the $a^2d^1$ synthon. Compound **4a** was readily prepared by elimination of HCl from 2-chloroethyl carbamate.[6e] Compound **4b** was prepared by double bond migration of allylic alcohol carbamate with high



(5) Intentions of using ketene dithioacetals as $a^2d^1$ synthons were described: (a) Mikolajczyk, M.; Grzejszczak, S.; Zatorski, A.; Mlotkowska, B.; Gross, H.; Costisella, B. *Tetrahedron* **1978**, *34*, 3081–3088. (b) Thuillier, A. *Phosphorus Sulfur* **1985**, *23*, 253–276.

(6) (a) Reggelin, M.; Tebben, P.; Hoppe, D. *Tetrahedron Lett.* **1989**, *30*, 2915–2918. (b) Tebben, P.; Reggelin, M.; Hoppe, D. *Tetrahedron Lett.* **1989**, *30*, 2919–2922. (c) Hoppe, D.; Tebben, P.; Reggelin, M.; Bolte, M. *Synthesis* **1997**, 183–190. (d) Zimmermann, M.; Wibbeling, B.; Hoppe, D. *Synthesis* **2004**, 765–774. (e) Siemer, M.; Fröhlich, R.; Hoppe, D. *Synthesis* **2008**, 2264–2270.

(7) A recent example demonstrating the efficiency of one-pot reaction for synthesis of (−)-oseltamivir: Ishikawa, H.; Suzuki, T.; Hayashi, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 1304–1307.

(8) See for example: Brown, J. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds; Springer: Berlin, 1999; Vol. 1, Chapter 5.1

(9) See for example: (a) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829–2844. (b) Navarre, L.; Darses, S.; Genet, J.-P. *Eur. J. Org. Chem.* **2004**, 69–73.

(10) Some conjugate addition of stoichiometrical lithium organocuprate to α-oxygenated-α,β-unsatured carbonyl compounds are known: (a) Brehm, M.; Göckel, V. H; Jarglis, P.; Lichtenthaler, F. W. *Tetrahedron: Asymmetry* **2008**, *19*, 358–373. (b) Verdaguer, X.; Vázquez, J.; Fuster, G.; Bernardes-Génisson, V.; Greene, A. E.; Moyano, A.; Pericás, M. A.; Riera, A. *J. Org. Chem.* **1998**, *63*, 7037–7052. (c) Denmark, S. E.; Dappen, M. S.; Sear, N. L.; Jacobs, R. T. *J. Am. Chem. Soc.* **1990**, *112*, 3466–3474. (d) Luengo, J. I.; Koreeda, M. *J. Org. Chem.* **1989**, *54*, 5415–5417. Several copper-catalyzed conjugate addition reactions to α-oxygenated-α,β-unsatured carbonyl compounds are known for certain substrates: (e) Cativiela, C.; Diaz-de-Villegas, M. D.; Galvez, J. A. *Can. J. Chem.* **1992**, *70*, 2325–2328. (f) Lander, P. A.; Hegedus, L. S. *J. Am. Chem. Soc.* **1994**, *116*, 8126–8132. (g) Cardillo, G.; Gentilucci, L.; Tolomelli, A.; Tomasini, C. *Tetrahedron* **1999**, *55*, 6231–6242.

(11) According to unpublished results in our group, substituent R on structure **1** can be either Cb or 2,2,4,4-tetramethyl-1,3-oxazolidin-3-carbonyl (Cby). Generally Cb leads to slightly higher yield for the addition reaction leading to structure **2**.

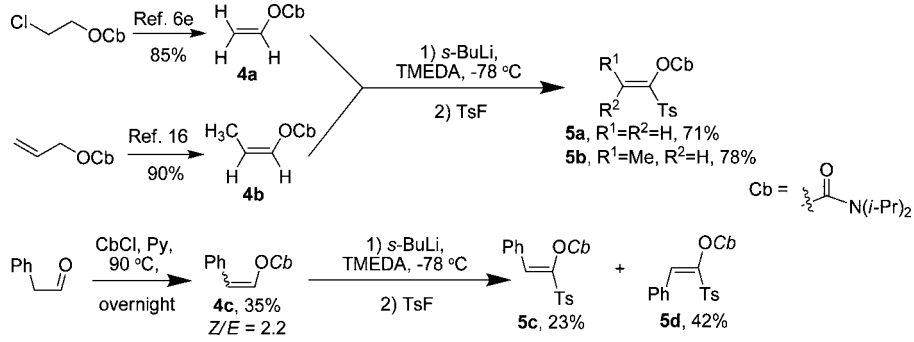
(12) Ni or Pd catalyzed substitution and reduction of α,β-unsaturated sulfone: (a) Fabre, J.-L.; Julia, M. *Tetrahedron Lett.* **1983**, *24*, 4311–4314. Ni catalyzed substitution of α,β-unsaturated sulfone was reported: (b) Fabre, J. L.; Julia, M.; Verpeaux, J.-N. *Bull. Soc. Chim. Fr* **1985**, *5*, 762–771.

(13) Unpublished results in this group.

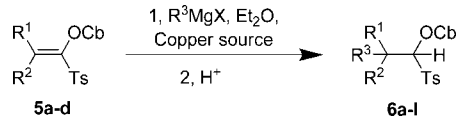
(14) For review, see: Alexakis, A.; Bäckvall, J. E; Krause, N.; Pàmies, O.; Diéguez, M. *Chem. Rev* **2008**, *108*, 2796–2823.

(15) Lipschutz, B. H. In *Organometallics in Synthesis - A Manual*, 2nd ed.; Schlosser, M., Ed.; John Wiley & Sons Inc: New York, 2002; pp 666−815.

**SCHEME 2. Syntheses of the Sulfone Substrates 5a−d**




**SCHEME 3. General Procedure for the First Addition**




*Z*-selectivity.[16] Compound **4c** was produced as an *E/Z* mixture via condensation between phenylacetaldehyde and CbCl. The starting materials **5a−d** for the first addition were readily prepared by lithiation with *s*-BuLi and condensation with TsF from compounds **4a−c**.[17] In the conversion from compound **4b** to **5b**, no significant *E/Z* change was observed; while condensation of the *E/Z*-**4c** with TsF yielded double bond isomers **5c** and **5d** which are readily separated by silica gel chromatography. In all the cases, it is essential to add the lithiated enol carbamates into TsF solution to avoid the conjugate addition of the lithiated enol carbamates onto the tosylated products. In general, the wide availability of compounds **4a−c** as well as the reliable lithiation-condensation methods contribute to a broadly applicable strategy.

Virtually all common Grignard reagents gave moderate to excellent yields for the copper-catalyzed first addition to substrates **5a-d** (Scheme 3 and Table 1). The results with alkyl, alkenyl, allylic, and aryl Grignad reagents are demonstrated in Table 1. Less reactive Grignard reagents such as vinylmagnesium bromide (Table 1, entries 1 and 8) or less reactive sulfone substrates such as **5b** (Table 1, entries 5 and 7) required higher temperature or prolonged reaction times. Allylmagnesium bromide (Table 1, entries 2, 6 and 12) demonstrated high reactivity and completed the reaction at low temperature or in short reaction times. Also, the *E/Z* configuration of the sulfone substrates has little effect on the yield (Table 1, entries 10−15). Diethyl ether was found a widely applicable solvent for this reaction. Generally, the reaction temperature needs to be below −20 °C to avoid decomposition of intermediate **2**. The diastereoselectivity of this reaction is sensitive to the reaction conditions and is of interest for further investigation.[18]

During investigation of the first addition, several major side products were also identified. For less reactive sulfone substrates such as **5b**, the OCb group is prone to reductive cleavage when an α-proton in the Grignard reagent is present (Scheme 4, the first reaction). With highly reactive Grignard reagents, or prolonged reaction time at higher temperature, further substitutions of the Ts[12] and the OCb[19] group were observed (Scheme 4, next two reactions).

The above examples have demonstrated a general and efficient method for the copper-catalyzed addition of Grignard reagents to 1-(*N,N*-diisopropylcarbamoyloxy)-1-tosyl-1-alkenes (**5a−d**). As a new method for catalytic anionic addition to less activated alkenes, it allows one to perform deprotecting manipulations on the products **6a−l** as well as an *in situ* second addition/migration/elimination sequence to complete the tandem umpolung.

**2.2. Synthetic Application of the First Addition Products.** Products of the first addition can serve as useful synthetic intermediates. The OCb and the Ts substitution allow many potential functional group conversions. We briefly demonstrate here that the OCb protection and the sulfonyl group on compounds **6j−l** can be removed reductively in one pot to efficiently offer α-branched alcohols **11a−c** (Scheme 5). Compared to common preparations of those α-branched alcohols by hydrolysis of alkenes or ring-opening of epoxides, this method circumvents the regioselectivity problem.

**2.3. Establish the Conditions for the Second Addition/Migration/Elimination.** Armed with the knowledge from the first addition, one can proceed to the second addition/migration/elimination to complete the tandem umpolung by quenching the magnesiated intermediate **2** with aldehydes or ketones.

After a few initial experiments, it was found that the magnesiated sulfone intermediate **2** reacts with chloroformates, aldehydes and simple ketones, but does not react with MeI, TMSCl, and hindered ketones.[13] This indicates a relatively hard nature[20] of the metalated sulfone and its sensitivity toward steric hindrance.

Further investigation indicated the magnesiated sulfone intermediate **2** to be a mild base which suffers no significant α-deprotonation of carbonyl compounds, compared to its lithiated analogous. This advantage enables many carbonyl compounds to be applied in the new method, but several problems were recognized: (1) Upon quenching with aldehydes or ketones, magnesiated intermediate **2** is less reactive than its lithiated analogues. Longer reaction time and higher temperature for improving the yield caused further decomposition of unreacted intermediate **2**. (2) The dsired elimination of the Ts substituent may not be complete due to many reasons such as conformations, additives and temperature. (3) As the most critical factor for tandem reaction, the reaction condition for the second addition/migration/elimination must be compatible

(16) Hoppe, D.; Hanko, R.; Brönneke, A.; Lichtenberg, F.; van Huelsen, E. *Chem. Ber.* **1985**, *118*, 2822–2851.

(17) For the lithiation of the enol carbamates **4a**, **b** and **c**, see: (a) Sengupta, S.; Snieckus, V. *J. Org. Chem.* **1990**, *55*, 5680–5683. (b) Peschke, B. Dissertation, University of Kiel, 1991. (c) Kocienski, P.; Dixon, N. J. *Synlett* **1989**, 52–54. (d) Kocienski, P.; Barbar, C. *Pure Appl. Chem.* **1990**, *62*, 1933–1942.

(18) For discussion of lithiated sulfones and their H/D exchange experiments, see: Boche, G. *Angew. Chem., Int. Ed.* **1989**, *28*, 277–297.

(19) For Ni catalyzed substitution of enol carbamate by Grignard reagent: see ref 17c.

(20) *Chemical Hardness - Applications From Molecules to Solids*; Pearson, R. G., Ed.; Wiley-VCH: Weinheim, 1997.

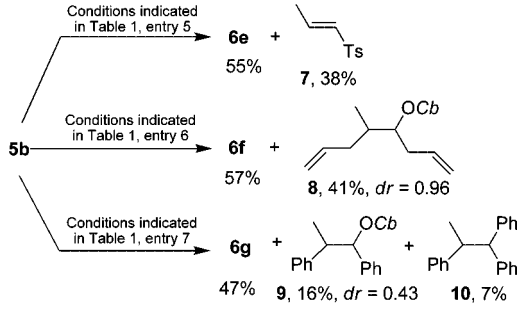
**TABLE 1. Examples for the First Addition**[a]

| entry | starting material/product | $R^1/R^2$ | Grignard reagent (equiv. to carbamate) | $T$ (°C)/reaction time | yield (%)/$dr$[d] |
|---|---|---|---|---|---|
| 1[b] | **5a/6a** | H/H | Vinyl-MgBr (1.4) | −20 to −25/8 h | 87/− |
| 2[b] | **5a/6b** | H/H | Allyl-MgBr (1.4) | −78/15 min | 89/− |
| 3[b] | **5a/6c** | H/H | *i*-PrMgBr (1.4) | −25 to −30/2 h | 79/− |
| 4[b] | **5a/6d** | H/H | *p*-Methoxyphenyl-MgBr (1.4) | −25 to −30/2 h | 93/− |
| 5[c] | **5b/6e** | Me/H | *n*-BuMgBr (2) | −30 to −35/16 h | 55/0.83 |
| 6[c] | **5b/6f** | Me/H | Allyl-MgBr (2) | −25 to −30/1 h | 57/0.85 |
| 7[b] | **5b/6g** | Me/H | PhMgBr (3) | −30 to −35/16 h | 47/0.82 |
| 8[b] | **5b/6h** | Me/H | Vinyl-MgBr (2) | −20 to −25/8 h | 71/n.a. |
| 9[b] | **5b/6i** | Me/H | 1-Methylvinyl-MgBr (2) | −30 to −35/8 h | 88/0.40 |
| 10[b] | **5c/6j** | Ph/H | *p*-Methoxyphenyl-MgBr (3) | −30 to −35/16 h | 70/0.50 |
| 11[b] | **5c/6k** | Ph/H | 1-Methylvinyl-MgBr (2) | −40 to −45/16 h | 84/0.42 |
| 12[b] | **5c/6L** | Ph/H | Allyl-MgBr (1.2) | −40 to −45/0.5 h | 95/1.0 |
| 13[b] | **5d/6j** | H/Ph | *p*-Methoxyphenyl-MgBr (3) | −30 to −35/16 h | 78/0.50 |
| 14[b] | **5d/6k** | H/Ph | 1-Methylvinyl-MgBr (2) | −40 to −45/16 h | 92/2.5 |
| 15[b] | **5d/6l** | H/Ph | Allyl-MgBr (1.2) | −40 to −45/0.5 h | 84/0.95 |

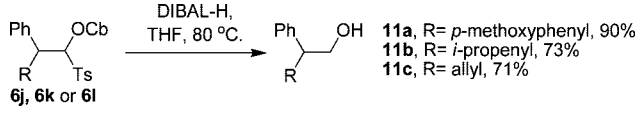
[a] General procedure: copper source was reacted with Grignard reagent at the indicated reaction temperature, and then a solution of the sulfone **5a−d** in toluene was added. The mixture was stirred at the indicated temperature for the specified time, and was quenched by addition of saturated aqueous $NH_4Cl$ solution. [b] Using 15% equiv. $Cu(OTf)_2$ as copper source. [c] Using 15% equiv. $CuBr\cdot Me_2S$ as copper source. [d] *dr* was measured by GC. Stereochemistry of the diastereomeric products **6a−l** was not determined.



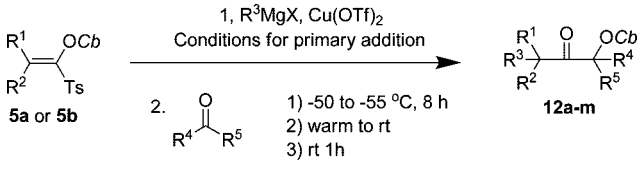
**SCHEME 4. Side Reactions of the First Addition**




**SCHEME 5. Preparation of α-Branched Alcohols from the First Addition Products**




**SCHEME 6. General Procedure for Utilizing the $a^2d^1$ Synthon by the Second Addition/Migration/Elimination**




with the condition of the first addition. Therefore, the reaction requires a careful selection of temperatures, reaction time, and additives.

We found that a procedure of 8 h at −50 to −55 °C for the second addition, warming to rt slowly, and then 1 h at rt for completing the migration and elimination, is optimal. Also, additives are necessary: tetraisopropoxytitanium (TIPT) generally leads to higher yields, while LiBr significantly decreases the α-deprotonation of the carbonyl compounds. Following those conditions, different carbonyl compounds, including aliphatic aldehydes, aryl aldehydes and acetone can be applied to the second addition/migration/elimination sequence to give moderate to excellent yields.

As demonstrated in Scheme 6 and Table 2, benzaldehyde and substituted benzaldehydes gave excellent yields of the desired second addition/migration/elimination (Table 2, entries 1−3), while sterically hindered pivaldehyde gave moderate yields (Table 2, entry 7). Using (*S*)-2-(*t*-butyldimethylsilyloxy)propanal[21] and 2,3-*O*-isopropylidene-D-glyceraldehyde[22] as the quenching reagents gave readily separated enantio-enriched diastereoisomers **12 h-k** (Table 2, entries 8 and 9). Entry 10 demonstrated the mild magnesiated sulfone **2** (compared to its lithiated analogues) and the mild second addition/migration/elimination condition can be used to produce β,γ-unsaturated ketones, which are highly susceptible to double bond migration. More interestingly, entry 11 showed that acetone, with its low reactivity and six acidic protons, can be used as the quenching reagent. With the aid of LiBr at the specified temperature and reaction time, intermediate **2** was able to give a moderate yield of the desired product **12m**. Further deprotection and functional group manipulations on analogues of **12a-m** can be achieved using the methods developed in our group.[6c]

As indicated by the above experiments, a general and efficient procedure has been developed for the second addition/migration/elimination to complete the desired tandem umpolung on the $a^2d^1$ synthon. Combined with certain additives, the mild magnesiated sulfone **2** allows various aldehydes and acetone to be applied in this procedure to generate α, α′-branched-α′-oxygenated ketones as useful building blocks in moderate to excellent yields.

## 3. Conclusions

In summary, a series of readily prepared 1-(*N,N*-diisopropylcarbamoyloxy)-1-tosyl-1-alkenes was developed as substrates for copper-catalyzed addition by Grignard reagents. The resulting magnesiated sulfones from this first addition can be hydrolyzed and produce useful synthetic intermediates. More importantly, the magnesiated sulfone intermediates can be directly quenched by carbonyl compounds to yield α-branched-α′-oxygenated ketones. Most types of Grignard reagents as well as most typical aldehydes can be applied to this tandem reaction and give moderate to good yields. From the retrosynthetic point of view, 1-(*N,N*-diisopropylcarbamoyloxy)-1-tosyl-1-alkenes, upon the first Grignard reagent addition and second carbonyl

(21) Marshall, J. A.; Yanik, M. M.; Adams, N. D.; Ellis, K. C.; Chobanian, H. R. *Org. Synth.* **2005**, *81*, 157–170.
(22) Schmid, C. R.; Bryant, J. D. *Org. Synth.* **1995**, *72*, 6–13.

**TABLE 2. Examples for Utilizing the $a^2d^1$ Synthon by the Second Addition/Migration/Elimination with Different Carbonyl Compounds As the Quenching Reagents[a]**

| Entry | Starting material /Product | $R^1/R^2$ | $R^3$ | $R^4$ | $R^5$ | Overall Yield(%)/ Yield based on the first addition (%) |
|---|---|---|---|---|---|---|
| 1[b] | **5a/12a** | H/H | *i*-Pr | Ph | H | 78/99 |
| 2[b] | **5a/12b** | H/H | *i*-Pr | *p*-Methoxyphenyl | H | 76/96 |
| 3[b] | **5a/12c** | H/H | *i*-Pr | *p*-Trifluoromethylphenyl | H | 80/quant. |
| 4[b] | **5a/12d** | H/H | *i*-Pr | 2-Pyridyl | H | 61/77 |
| 5[b] | **5a/12e** | H/H | *i*-Pr | 2-Naphthyl | H | 73/92 |
| 6[b] | **5a/12f** | H/H | *i*-Pr | *i*-Pr | H | 68/86 |
| 7[b] | **5a/12g** | H/H | *i*-Pr | *t*-Bu | H | 49/62 |
| 8[b] | **5a/12h,i**[d] | H/H | *i*-Pr |  | H | 69/87 *dr* =1.3 |
| 9[c] | **5a/12j,k**[d] | H/H | *i*-Pr |  | H | 41/52 *dr* = 3.9 |
| 10[b] | **5b/12l** | Me/H | 1-methyl-vinyl | Ph | H | 81/92 *dr* = 1.7 |
| 11[c] | **5b/12m** | Me/H | 1-methyl-vinyl | Me | Me | 59/67 |

[a] General procedure: following the general procedure illustrated in Scheme 3 and Scheme 6, upon the end of the first addition, the reaction mixture was not quenched, but cooled to −50 to −55 °C, and to which additive and the carbonyl compound were added. After being stirred for 8 h, the mixture was warmed to rt and then quenched by addition of saturated aqueous $NH_4Cl$ solution. [b] With TIPT as an additive. [c] With LiBr as an additive. [d] Stereochemistry of the products was not determined.



compounds addition/migration/elimination, serve as a new $a^2d^1$ synthon via an unprecedented tandem umpolung and installs respectively a carbanion unit and a carbonyl unit formally onto the α-carbon and the carbonyl center of an aldehyde.

## 4. Experimental Section

**General Procedure for the Preparation of Substrates 5a−d.** *s*-BuLi (40 mL, 1.22 M in n-hexane, 48.8 mmol, 1.2 equiv) was added dropwise to a solution of TMEDA (7.3 mL, 5.6 g, 48.8 mmol, 1.2 equiv) in 150 mL of diethyl ether at −78 °C. To the above solution, carbamate substrate (**4a−c**, neat, 40.5 mmol, 1 equiv) was added dropwise. The resulting light-yellow mixture was then stirred at −78 °C for 4 h and transferred by a cannular in a dropwise manner into a solution of TsF (9.0 g, 51.7 mmol, 1.3 equiv) in 100 mL of diethyl ether at −78 °C. After the transfer being finished, stirring of the resulting mixture was continued for another hour at −78 °C. The reaction was quenched by addition of 2 N aq. HCl and the water phase was extracted several times by diethyl ether. Combined organic layers were washed with 2 N HCl, sat. aq. $NaHCO_3$ and brine in turn and evaporated to dryness. The residue was purified by MPLC to yield sulfone **5a−d**.

**(*E*)-1-Tosylprop-1-enyl *N*,*N*-Diisopropylcarbamate (5b).** From compound **4b**[oc] (7.5 g, 40.5 mmol), product **5b** (10.7 g, 31.5 mmol, 78%) was produced as a light-yellow oil. Compound **5b** was readily crystallized from diethyl ether to produce a white crystalline solid. $R_f$ 0.35 (ethyl acetate: cyclohexane, 1/2); mp 100−101 °C (diethyl ether); $t_R$ 20.1 min (HP-5); NMR data were resolved with the aid of $^1H-^1H$ COSY, $^1H-^{13}C$ HMQC, and $^1H-^{13}C$ HMBC methods; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 7.78 (d, $J$ = 8.2 Hz, 2H, Ts), 7.29 (m, 2H, Ts), 6.84 (q, $J$ = 7.1 Hz, 1H, CH═), 4.03−3.96 (m, 1H, Cb), 3.71−3.65 (m, 1H, Cb), 2.41 (s, 3H, Ts), 1.72 (d, $J$ = 7.2 Hz, 3H, ═CH−C$\underline{H}_3$), 1.21 (d, $J$ = 6.8 Hz, 6H, Cb), 1.09 (d, $J$ = 6.8 Hz, 6H, Cb); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 149.4 (C═O), 145.8 (Ts), 144.6 (Ts(OCb)C═), 135.1 (Ts), 129.5 (2 C, Ts), 128.9 (2 C, Ts), 126.3 (CH═), 47.0 (Cb), 46.7 (Cb), 21.6 (Ts), 21.1 (2 C, Cb), 21.0 (2 C, Cb), 11.9 (═CH−$\underline{C}H_3$); FTIR ($CHCl_3$ cast film microscope) $\nu$ 3065 (m), 2972 (s), 2935 (m), 2878 (m), 1732 (s), 1666 (m), 1597 (m), 1437 (s), 1319 (s), 1280 (s), 1127 (s), 670 (s); HRMS (ESI+) calcd for $C_{17}H_{25}NO_4SNa^+$ 362.1397, found 362.1408; Anal. Calcd for $C_{17}H_{25}NO_4S$ (339.45) C 60.15, H 7.42, N 4.14, found C 60.10, H 7.34, N 4.08.

**General Procedure for the Copper-Catalyzed Addition of Grignard Reagents to Sulfone Substrates 5a−d.** Copper source (15 mol%, taken directly from the commercially available materials, dried under vacuum *in situ* at rt) and diethyl ether (5 mL, dried over sodium) was added into a predried Schlenk tube, and cooled to the described reaction temperature. Grignard reagent (in diethyl ether or THF, normally as a 0.5−3 M solution) was added dropwise to the above mixture. The suspension was stirred at this temperature for 10 min followed by addition of the substrate (normally as a 0.2−0.3 M solution in toluene). The resulting mixture was then stirred for the described time at the described temperature. For quenching the reaction, a solution of formic acid in MeOH was added at the reaction temperature followed by addition of sat. aq. $NH_4Cl$. The organic phase was then separated and the water phase was washed several times with diethyl ether. Combined organic layers were passed through a silica gel pad and evaporated to dryness. The residue was purified by MPLC (with a standard program: *n*-pentane: diethyl ether = 30:1 to 20:1 to 10:1 to 5:1 to 2:1 to 1:1) to yield the products **6a−l**.

**3-Methyl-1-tosylbutyl *N*,*N*-Diisopropylcarbamate (6c).** From compound **5a** (200 mg, 0.62 mmol), compound **6c** (179 mg, 0.48 mmol, 79%) was produced as a colorless oil. $R_f$ 0.46 (ethyl acetate: cyclohexane, 1/2); $t_R$ 20.3 min (HP-5); NMR data were resolved with the aid of $^1H-^1H$ COSY, $^1H-^{13}C$ HMQC, and $^1H-^{13}C$ HMBC

methods; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.72 (d, $J$ = 8.3 Hz, 2H, Ts), 7.24 (d, $J$ = 7.9 Hz, 2H, Ts), 5.89 (dd, $J$ = 3.8 Hz, 9.7 Hz, 1H, CH-Ts), 3.94−3.88 (m, 1H, Cb), 3.51−3.44 (m, 1H, Cb), 2.35 (s, 3H, Ts), 1.96−1.84 (m, 2H, $CH_2$), 1.71−1.60 (m, 1H, CH), 1.08 (d, $J$ = 6.9 Hz, 3H, Cb), 1.06 (d, $J$ = 6.9 Hz, 3H, Cb), 1.01 (d, $J$ = 6.8 Hz, 3H, Cb), 0.91 (d, $J$ = 6.7 Hz, 3H, $CH_3$), 0.87 (d, $J$ = 6.8 Hz, 3H, Cb), 0.87 (d, $J$ = 6.7 Hz, 3H, $CH_3$); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 151.6 (C=O), 145.0 (Ts), 133.5 (Ts), 129.6 (2 C, Ts), 129.5 (2 C, Ts), 84.5 (Ts), 46.3 (Cb), 46.1 (Cb), 34.9 ($CH_2$), 24.7 (CH), 23.1 ($CH_3$), 21.6 (Ts), 21.5 ($CH_3$), 21.3 (Cb), 20.9 (Cb), 20.1 (Cb), 19.9 (Cb); FTIR ($CHCl_3$ cast film microscope) $\nu$ 2965 (s), 2937 (m), 2898 (m), 2874 (m), 1711 (s), 1598 (m), 1433 (s), 1323 (s), 1283 (s), 1154 (s), 1138 (s), 1078 (s), 1042 (s), 660 (s), 580 (s); HRMS (ESI+) calcd for $C_{19}H_{31}NO_4SNa^+$ 392.1866, found 392.1870; Anal. Calcd for $C_{19}H_{31}NO_4S$ (369.52) C 61.76, H 8.46, N 3.79, found C 61.44, H 8.48, N 3.63.

**2,3-Dimethyl-1-tosylbut-3-enyl *N*,*N*-Diisopropylcarbamate (6i).** From compound **5b** (200 mg, 0.59 mmol), compound **6i** (198 mg, 0.52 mmol, 88%) was obtained as a colorless oil. Major isomer: minor isomer = 1: 0.4; $R_f$ 0.50 (ethyl acetate: cyclohexane, 1/2); $t_R$ 20.8 min (minor diastereomer), 20.9 min (major diastereomer) (HP-5); NMR data were recorded from compound **6i** as a diastereomeric mixture and resolved below separately, with the aid of $^1$H−$^1$H COSY, $^1$H−$^{13}$C HMQC, and $^1$H−$^{13}$C HMBC methods; NMR of major isomer: $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.72−7.69 (m, 2H, Ts), 7.23−7.20 (m, 2H, Ts), 5.73 (d, $J$ = 9.7 Hz, 1H, Ts(OCb)C<u>H</u>), 4.75 (s, 1H, $CH_2$=), 4.70 (s, 1H, $CH_2$=), 4.04−3.96 (m, 1H, Cb), 3.25−3.18 (m, 1H, Cb), 3.09−3.03 (m, 1H, Me(isopropenyl)C<u>H</u>), 2.32 (s, 3H, Ts), 1.58 (s, 3H, =C−C<u>H</u>$_3$), 1.33 (d, $J$ = 6.9 Hz, 3H, $CH_3$), 1.00 (d, $J$ = 6.6 Hz, 3H, Cb), 0.94 (d, $J$ = 6.8 Hz, 6H, Cb), 0.76 (d, $J$ = 6.8 Hz, 3H, Cb); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 150.7 (C=O), 144.8 (Me−<u>C</u>=), 144.7 (Ts), 134.5 (Ts), 129.54 (Ts), 129.49 (Ts), 129.33 (Ts), 129.31 (Ts), 113.5 ($CH_2$=), 86.7 (Ts(OCb)<u>C</u>H), 46.7 (Cb), 45.2 (Cb), 41.2 (Me(isopropenyl)<u>C</u>H), 21.5 (Ts), 20.4 (Cb), 20.2 (Cb), 20.0 (Cb), 19.8 (Cb), 18.4 (=C−<u>C</u>H$_3$), 16.5 ($CH_3$); NMR of minor isomer: $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.72−7.69 (m, 2H, Ts), 7.23−7.20 (m, 2H, Ts), 5.85 (d, $J$ = 4.1 Hz, 1H, Ts(OCb)C<u>H</u>), 4.78 (s, 1H, $CH_2$=), 4.77 (s, 1H, $CH_2$=), 4.04−3.96 (m, 1H, Cb), 3.44−3.38 (m, 1H, Cb), 3.16−3.11 (m, 1H, Me(isopropenyl)C<u>H</u>), 2.33 (s, 3H, Ts), 1.68 (s, 3H, =C−C<u>H</u>$_3$), 1.24 (d, $J$ = 7.0 Hz, 3H, $CH_3$), 1.09 (*pseudo*-t, $J$ = 6.5 Hz, 6H, Cb), 1.01 (d, $J$ = 6.3 Hz, 3H, Cb), 0.85 (d, $J$ = 6.8 Hz, 3H, Cb); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 151.3 (C=O), 145.1 (Me−<u>C</u>=), 144.9 (Ts), 134.5 (Ts), 129.54 (Ts), 129.49 (Ts), 129.33 (Ts), 129.31 (Ts), 113.0 ($CH_2$=), 86.1 (Ts(OCb)<u>C</u>H), 46.6 (Cb), 45.9 (Cb), 39.2 (Me(isopropenyl)<u>C</u>H), 21.6 (Ts), 20.72 (Cb), 20.65 (Cb), 20.2 (=C−<u>C</u>H$_3$),20.0 (Cb), 19.9 (Cb), 14.4 ($CH_3$); FTIR ($CHCl_3$ cast film microscope) $\nu$ 3074 (m), 2971 (s), 2939 (m), 2879 (m), 1715 (s), 1598 (m), 1433 (s), 1330 (s), 1149 (s), 1067 (s), 1042 (s), 657 (s); HRMS (ESI+) calcd for $C_{20}H_{31}NO_4SNa^+$ 404.1866, found 404.1861; Anal. Calcd for $C_{20}H_{31}NO_4S$ (381.53) C 62.96, H 8.19, N 3.67; found C 62.81, H 8.19, N 3.54.

**3-Methyl-2-phenyl-1-tosylbut-3-enyl *N*,*N*-Diisopropylcarbamate (6k).** From compound **5c** (150 mg, 0.37 mmol), compound **6k** (136 mg, 0.31 mmol, 84%) was obtained as a colorless oil. Major isomer: minor isomer = 2.4: 1; $R_f$ 0.41 (ethyl acetate: cyclohexane, 1/2); $t_R$ 24.0 min (major isomer), 24.2 min (minor isomer) (HP-5); NMR data were recorded from compound **6k** as a diastereomeric mixture and resolved below separately, with the aid of $^1$H−$^1$H COSY, $^1$H−$^{13}$C HMQC, and $^1$H−$^{13}$C HMBC methods; NMR of major isomer: $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.73 (d, $J$ = 8.3 Hz, 2H, Ts), 7.22 (d, $J$ = 7.8 Hz, 2H, Ts), 7.19−7.13 (m, 5H, Ph), 6.43 (d, $J$ = 10.3 Hz, 1H, Ts(OCb)C<u>H</u>), 5.18 (s, 1H, $CH_2$=), 4.89 (s, 1H, $CH_2$=), 4.24 (d, $J$ = 10.3 Hz, 1H, Ph(isopropenyl)C<u>H</u>), 3.65−3.60 (m, 1H, Cb), 3.18−3.15 (m, 1H, Cb), 2.33 (s, 3H, Ts), 1.71 (s, 3H, $CH_3$), 0.89 (d, $J$ = 6.8 Hz, 3H, Cb), 0.75 (d, $J$ = 6.8 Hz, 3H, Cb), 0.69 (d, $J$ = 6.8, 3H, Cb), 0.54 (d, $J$ = 6.8 Hz, 3H, Cb); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 149.8 (C=O), 143.8 (Ts−), 141.6 (Me−<u>C</u>=), 137.6 (Ph), 133.4 (Ts), 128.7 (2 C, Ts), 128.2 (2 C, Ts), 127.4 (Ph), 127.3 (Ph), 127.2 (Ph), 126.4 (Ph), 125.9 (Ph), 113.6 ($CH_2$=), 83.6 (Ts(OCb)<u>C</u>H), 51.5 (Ph(isopropenyl)<u>C</u>H), 45.4 (Cb), 44.4 (Cb), 20.6 (Ts), 19.3 (Cb), 19.2 ($CH_3$), 19.0 (Cb), 18.9 (Cb), 18.8 (Cb); NMR of minor isomer: $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.46 (d, $J$ = 8.3 Hz, 2 H, Ts), 7.08 (d, $J$ = 8.1 Hz, 2 H, Ts), 7.19−7.13 (m, 5 H, Ph), 6.39 (d, $J$ = 10.7 Hz, 1 H, Ts(OCb)C<u>H</u>), 4.91(s, 1 H, $CH_2$=), 4.75 (s, 1 H, $CH_2$=), 4.12 (d, $J$ = 10.7 Hz, 1 H, Ph(isopropenyl)C<u>H</u>), 4.03−3.93 (m, 1 H, Cb), 3.58−3.51 (m, 1 H, Cb), 2.29 (s, 3 H, Ts), 1.57 (s, 3 H, $CH_3$), 0.95 (d, $J$ = 6.8 Hz, 3 H, Cb), 1.10−1.06 (m, 9 H, Cb−$CH_3$); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 150.8 (C=O), 143.3 (Ts), 142.7 (Me−<u>C</u>=), 136.0 (Ph), 133.9 (Ts), 128.3 (2 C, Ts), 128.0 (2 C, Ts), 127.4 (Ph), 127.3 (Ph), 127.2 (Ph), 126.4 (Ph), 125.9 (Ph), 111.7 ($CH_2$=), 85.2 (Ts(OCb)<u>C</u>H), 51.5 (Ph(isopropenyl)<u>C</u>H), 45.5 (Cb), 45.1 (Cb), 20.5 (Ts), 20.1 (Cb), 19.9 ($CH_3$), 19.8 (Cb), 19.2 (Cb), 19.1 (Cb); FTIR ($CHCl_3$ cast film microscope) $\nu$ 3073 (m), 3030 (m), 2970 (s), 2933 (m), 2878 (m), 1740 (s), 1716 (s), 1649 (m), 1598 (m), 1434 (s), 1371 (s), 1324 (s), 1155 (s), 1097 (m), 1062 (m), 1041 (m), 895 (m), 755 (s), 703 (m), 667 (m); HRMS (ESI+) calcd for $C_{25}H_{33}NO_4SNa^+$ 466.2023, found 466.2017; Anal. Calcd for $C_{25}H_{33}NO_4S$ (443.60) C 67.69, H 7.50, N 3.16, found C 67.47, H 7.62, N 3.11.

**General Procedure for One-Pot Reduction of Compounds 6j−l.** DIBAL-H (6 mL, 1 M in hexane, 20 equiv.) was added dropwise into a solution of starting material **6j**, **6k** or **6l** (0.30 mmol) in THF (4 mL) at rt. The mixture was then heated at 80 °C in a sealed Schlenk tube for 8 h (with interval release of internal pressure). Afterward sat. aq. potassium sodium tartrate (Rochelle salt) was added and the mixture was vigorously stirred for 0.5 h. The organic phase was separated and the water phase was extracted by diethyl ether several times. Combined organic phases were evaporated (bath temperature and pressure should be regulated to avoid loss of product) and the residue was purified by MPLC (with a standard program: *n*-pentane: diethyl ether = 10:1 to 5:1 to 2:1 to 1:1 to 1:2) to yield the products **11a**−**c**.

**2-(4-Methoxyphenyl)-2-phenylethanol (11a).** From compound **6j** (153 mg, 0.30 mmol), compound **11a** (61 mg, 0.27 mmol, 90%) was produced as a colorless oil. $R_f$ 0.29 (ethyl acetate: cyclohexane, 1/2); $t_R$ 17.3 min (HP-5); NMR data were resolved with the aid of $^1$H−$^1$H COSY, $^1$H−$^{13}$C HMQC, and $^1$H−$^{13}$C HMBC methods; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.21−7.09 (m, 5H, Ph), 7.06−7.04 (m, 2H, Ph), 6.77−6.72 (m, 2H, Ph), 4.04−3.95 (m, 3H, CH, $CH_2$), 3.64 (s, 3H, MeO), 1.75 (s, 1H, OH); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 158.4 (<u>Ph</u>−OMe), 141.9 (Ph), 133.6 (Ph), 129.3 (2 C, Ph), 128.7 (2 C, Ph), 128.3 (2 C, Ph), 126.7 (Ph), 114.1 (2 C, Ph), 66.2 (C-OH) 55.3 (MeO), 52.8 (<u>C</u>-Ph); FTIR ($CHCl_3$ cast film microscope) $\nu$ 3378 (brs), 3060 (m), 3028 (m), 3001 (m), 2953 (m), 2934 (m), 1611 (m), 1512 (s), 1249 (s), 829 (m); HRMS (ESI+) calcd for $C_{15}H_{16}O_2Na^+$ 251.1048, found 251.1050. Above analyses match the reported data.[23]

**General Procedure for the Tandem Umpolung Including the Second Addition/Rearrangement/Elimination.** Following the standard condition for the first addition (normally with 0.5−0.9 mmol carbamate starting material), and before quenching the reaction with protic compounds, the mixture was cooled to −70 °C and tetraisopropoxytitanium (TIPT, neat, 1 equiv. to the Grignard reagent) or LiBr (as beads, 1 equiv. to the Grignard reagent) was added. After 30 min, the aldehyde component (neat, 1.5 equiv to the Grignard reagent) was added dropwise and the resulting mixture was stirred at −50 to −55 °C for 8 h before it was gradually warmed to rt. The mixture was then stirred for another hour at rt and quenched by a solution of formic acid in MeOH (1 M, 1 equiv to the Grignard reagent). The quenched mixture was passed through a silica gel pad which was later washed several times by diethyl ether. Combined organic layers were evaporated and the residue

(23) Taylor, S. K.; Clark, D. L.; Heinz, K. L.; Schramm, S. B.; Westermann, C. D.; Barnell, K. K. *J. Org. Chem.* **1983**, *48*, 592–596.

was purified by MPLC (*n* -pentane: diethyl ether = 30:1 to 20:1 to 10:1 to 5:1 to 1:1) to yield the products **12a**−**m**.

**4-Methyl-2-oxo-1-phenylpentyl *N*,*N*-Diisopropylcarbamate (12a).** From compound **5a** (163 mg, 0.50 mmol), compound **12a** (124 mg, 0.39 mmol, 78%) was obtained as a colorless oil. $R_f$ 0.51 (ethyl acetate: cyclohexane, 1/2); $t_R$ 17.2 min (HP-5); NMR data were resolved with the aid of $^1$H−$^1$H COSY, $^1$H−$^{13}$C HMQC, and $^1$H−$^{13}$C HMBC methods; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.37−7.22 (m, 5H, Ph), 5.86 (s, 1H, C$\underline{H}$−Ph), 4.06−3.90 (brs, 1H, Cb), 3.88−3.70 (brs, 1H, Cb), 2.33−2.28 (m, 1H, $CH_2$), 2.15−2.09 (m, 1H, $CH_2$), 2.07−2.00 (m, 1H, CH), 1.29−1.13 (m, 12H, Cb), 0.77 (d, $J$ = 6.6 Hz, 3H, $CH_3$), 0.65 (d, $J$ = 6.5 Hz, 3H, $CH_3$); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 204.8 (C═O), 154.6 (C═O), 134.0 (Ph), 128.9 (Ph), 128.8 (2 C, Ph), 128.2 (2 C, Ph), 81.3 (CH-O), 47.4 ($CH_2$), 46.6 (Cb), 45.7 (Cb), 23.8 (CH), 22.5 ($CH_3$), 22.2 ($CH_3$), 21.5 (Cb), 21.3 (Cb), 20.52 (Cb), 20.47 (Cb); FTIR ($CHCl_3$ cast film microscope) $\nu$ 3033 (m), 2961 (s), 2935 (m), 2873 (m), 1731 (s), 1691 (s), 1437 (s), 1368 (s), 1299 (s), 1216 (m), 1135 (m), 1046 (s), 701 (s), 633 (s); HRMS (ESI+) calcd for $C_{19}H_{29}NO_3Na^+$ 342.2040, found 342.2030; Anal. Calcd for $C_{19}H_{29}NO_3$ (319.44) C 71.44, H 9.15, N 4.38, found C 71.40, H 9.38, N 4.25.

**(2*S*,3*R*)-2-(*tert*-Butyldimethylsilyloxy)-6-methyl-4-oxoheptan-3-yl *N*,*N*-Diisopropylcarbamate and (2*S*,3*S*)-2-(*tert*-Butyldimethylsilyloxy)-6-methyl-4-oxoheptan-3-yl *N*,*N*-Diisopropylcarbamate (12 h, i).** From compound **5a** (300 mg, 0.92 mmol), TLC faster moving component (148 mg, 0.36 mmol, 39%) was produced as a colorless oil. $R_f$ 0.65 (ethyl acetate: cyclohexane, 1/2); $t_R$ 17.2 min (HP-5); NMR data were resolved with the aid of $^1$H−$^1$H COSY, $^1$H−$^{13}$C HMQC, and $^1$H−$^{13}$C HMBC methods; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 4.79 (d, $J$ = 4.3 Hz, 1H, CH-O), 4.15−4.09 (m, 1H, CH-O), 3.93−3.83 (m, 2H, Cb), 2.34 (ddd, $J$ = 6.7 Hz, 17.8 Hz, 24.0 Hz, 2H, $CH_2$), 2.14−2.04 (m, 1H, CH), 1.26−1.16 (m, 12H, Cb), 1.14 (d, $J$ = 6.3 Hz, 3H, $CH_3$), 0.85 (d, $J$ = 4.6 Hz, 3H, CH(C$\underline{H}_3$)$_2$), 0.83 (d, $J$ = 4.6 Hz, 3H, CH(C$\underline{H}_3$)$_2$), 0.80 (s, 9H, *t*-Bu), 0.00 (s, 3H, Si−$CH_3$), −0.01 (s, 3H, Si−$CH_3$); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 207.9 (C═O), 154.6 (C═O), 82.5 (CH−O), 68.7 (CH-O), 49.7 ($CH_2$), 46.4 (Cb), 45.9 (Cb), 25.7 (3 C, *t*-Bu), 23.2 (CH), 22.7 (CH($\underline{C}H_3$)$_2$), 22.6 (CH($\underline{C}H_3$)$_2$), 21.4−20.4 (4 C, Cb), 20.0 ($CH_3$), 17.9 (*t*-Bu), −4.6 (Si−$CH_3$), −5.0 (Si−$CH_3$); FTIR ($CHCl_3$ cast film microscope) $\nu$ 2958 (s), 2932 (s), 2859 (m), 1730 (s), 1696 (s), 1468 (s), 1435 (s), 1369 (s), 1319 (s), 1289 (s), 1255 (s), 1217 (s), 1145 (s), 1072 (s), 1046 (s), 1005 (s), 832 (s), 776 (s), 668 (s); $[\alpha]_D$ +12.4 (*c* 1, $CHCl_3$); HRMS (ESI+) calcd for $C_{21}H_{43}NO_4SiNa^+$ 424.2854, found 424.2852; Anal. Calcd for $C_{21}H_{43}NO_4Si$ (401.66) C 62.80, H 10.79, N 3.49, found C 62.71, H 11.04, N 3.43.

From compound **5a** (300 mg, 0.92 mmol), TLC slower moving component (118 mg, 0.28 mmol, 30%) was produced as a colorless oil. $R_f$ 0.62 (ethyl acetate: cyclohexane, 1/2); $t_R$ 17.3 min (HP-5); NMR data were resolved with the aid of $^1$H−$^1$H COSY, $^1$H−$^{13}$C HMQC, and $^1$H−$^{13}$C HMBC methods; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 4.89 (d, $J$ = 2.7 Hz, 1H, CH-O), 4.27 (qd, $J$ = 2.7 Hz, 6.4 Hz, 1H, CH-O), 4.15−4.02 (m, 1H, Cb), 3.81−3.67 (m, 1H, Cb), 2.41−2.29 (m, 2H, $CH_2$), 2.12−2.02 (m, 1H, CH), 1.30−1.14 (m, 12H, Cb), 1.12 (d, $J$ = 6.4 Hz, 3H, $CH_3$), 0.85 (d, $J$ = 1.8 Hz, 3H, CH(C$\underline{H}_3$)$_2$), 0.84 (d, $J$ = 1.7 Hz, 3H, CH(C$\underline{H}_3$)$_2$), 0.80 (s, 9H, *t*-Bu), 0.00 (s, 3H, Si-$CH_3$), −0.04 (s, 3H, Si−$CH_3$);$^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 208.0 (C═O), 155.1 (C═O), 82.2 (CH-O), 68.8 (CH−O), 49.5 ($CH_2$), 46.9 (Cb), 45.5 (Cb), 25.7 (3 C, *t*-Bu), 23.3 (CH), 22.8 (CH($\underline{C}H_3$)$_2$), 22.6 (CH($\underline{C}H_3$)$_2$), 21.7 (Cb), 21.6 (Cb), 20.5 (Cb), 20.4 (Cb), 20.1 ($CH_3$), 17.9 (*t*-Bu), −4.4 (Si−$CH_3$), −5.1 (Si-$CH_3$); FTIR ($CHCl_3$ cast film microscope) $\nu$ 2958 (s), 2932 (s), 2859 (m), 1721 (s), 1694 (s), 1468 (s), 1439 (s), 1368 (s), 1321 (s), 1288 (s), 1256 (s), 1216 (s), 1146 (s), 1094 (s), 1064 (s), 953 (s), 837 (s), 776 (s), 632 (s); $[\alpha]_D$ −18.4 (*c* 1, $CHCl_3$); HRMS (ESI+) calcd for $C_{21}H_{43}NO_4SiNa^+$ 424.2854, found 424.2848; Anal. Calcd for $C_{21}H_{43}NO_4Si$ (401.66) C 62.80, H 10.79, N 3.49, found C 62.52, H 10.69, N 3.39.

**3,4-Dimethyl-2-oxo-1-phenylpent-4-enyl *N*,*N*-Diisopropylcarbamate 12l.** From compound **5b** (250 mg, 0.74 mmol), compound **12l** (198 mg, 0.60 mmol, 81%) was obtained as a colorless oil. Major isomer: minor isomer = 1: 0.58; $R_f$ 0.48 (ethyl acetate/cyclohexane, 1/2); $t_R$ 17.4 min (minor diastereomer), 17.5 min (major diastereomer) (HP-5); NMR data were recorded from compound **12l** as a diastereomeric mixture and resolved below separately, with the aid of $^1$H−$^1$H COSY, $^1$H−$^{13}$C HMQC, and $^1$H−$^{13}$C HMBC methods; NMR of major isomer: $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.38−7.26 (m, 5H, Ph), 6.03 (s, 1H, Ph(OCb)CH), 4.67 (s, 2H, $CH_2$═), 4.10−3.88 (brs, 1H, Cb), 3.85−3.63 (brs, 1H, Cb), 3.42 (q, $J$ = 7.0 Hz, 1H, Me(isopropenyl)C$\underline{H}$), 1.19 (s, 3H, ═C−C$\underline{H}_3$), 1.28−1.09 (m, 12H, Cb), 1.16 (d, $J$ = 7.0 Hz, 3H, $CH_3$); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 205.9 (C═O), 154.6 (C═O), 143.2 (Me−$\underline{C}$═), 133.8 (Ph), 128.93 (Ph), 128.90 (Ph), 128.86 (Ph), 128.7 (Ph), 128.6 (Ph), 114.0 ($CH_2$═), 80.0 (Ph(OCb)$\underline{C}$H), 51.1 (CH), 46.7 (Cb), 45.7 (Cb), 21.3 (2 C, Cb), 20.4 (2 C, Cb), 19.9 (═C−$\underline{C}H_3$), 15.6 ($CH_3$); NMR of minor isomer: $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.38−7.26 (m, 5H, Ph), 6.22 (s, 1H, Ph(OCb)CH), 4.90 (s, 1H, $CH_2$═), 4.81 (s, 1H, $CH_2$═), 4.10−3.88 (brs, 1H, Cb), 3.85−3.63 (br, 1H, Cb), 3.17 (q, $J$ = 6.8 Hz, 1H, Me(isopropenyl)C$\underline{H}$), 1.65 (s, 3H, ═C−C$\underline{H}_3$), 1.28−1.09 (m, 12H, Cb), 0.95 (d, $J$ = 6.8 Hz, 3H, $CH_3$); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 205.3 (C═O), 154.4 (C═O), 144.4 (Me−$\underline{C}$═), 134.6 (Ph), 128.93 (Ph), 128.90 (Ph), 128.86 (Ph), 128.7 (Ph), 128.6 (Ph), 114.7 ($CH_2$═), 79.4 (Ph(OCb)$\underline{C}$H), 50.3 (CH), 46.7 (Cb), 45.7 (Cb), 21.3 (2 C, Cb), 20.4 (2 C, Cb), 19.4 (═C−$\underline{C}H_3$), 14.6 ($CH_3$); FTIR ($CHCl_3$ cast film microscope) $\nu$ 3066 (m), 3034 (m), 2973 (s), 2936 (s), 2876 (m), 1731 (s), 1695 (s), 1437 (s), 1370 (s), 1294 (s), 1135 (s), 700 (s); HRMS (ESI+) calcd for $C_{20}H_{29}NO_3Na^+$ 354.2040, found 354.2043; Anal. Calcd for $C_{20}H_{29}NO_3$ (331.45) C72.47, H 8.82, N 4.23, found: C 72.37, H 8.95, N 4.08.

**Acknowledgment.** Generous support by the Fonds der Chemischen Industrie and the Deutsche Forschungsgemeinschaft is gratefully acknowledged.

**Note Added after ASAP Publication.** There was an error in the abstract and TOC graphic in the version published ASAP May 4, 2009; the corrected version was published May 8, 2009 then additional typographical errors were corrected on May 13, 2009.

**Supporting Information Available:** Detailed experimental procedures, characterization data, and NMR spectra for all obtained compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO900347S