The Cram Rule Revisited Once More — Revision of the Felkin−Anh Model

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The reaction mechanism of the LiH addition to α-chiral ketones and acylsilanes was calculated at the ab initio MP2/6-311+G**//RHF/6-31G* level. The selectivities predicted on the basis of the computed transition states and reaction barriers compare well with the experimental data. For compounds possessing very large groups, anti-Cram selectivity was found; silicon-containing compounds should show the same types of selectivity as their carbon analogs. The calculations suggest that a revision of the Felkin–Anh model is necessary and a proposal for such a revision is given.

Introduction

The synthesis of molecules with predefined stereochemistry is a cornerstone of modern organic chemistry. Fifty years ago, Cram and co-workers conceived the widely known and applied stereochemical rules that bear his name.[1−3] The Cram rules allow us to predict the stereochemical outcome of nucleophilic additions to aldehydes and ketones possessing a stereogenic center in the position α to the carbonyl group. With respect to the reactions that proceed in an open-chained fashion — i.e. not via transient chelate structures — several models have been developed to account for the origin of the observed selectivities.[4−13] Among those, the Felkin−Anh model[9] with Heathcock's refinements[10−12] is presently the most widely accepted rationale. This model explains the π-facial selectivities of the addition reactions by comparison of the two diastereomeric transition structures **A** and **B** (Figure 1). Due to a lower repulsive interaction of the incoming nucleophile with the small- (S), rather than the medium-sized group (M), the reaction *via* intermediate **A** is regarded as favored. The two relevant conformations [with the large group (L) positioned *anti* to the attacking nucleophile] and the trajectories of the nucleophilic attacks were surmised, successively, from spectroscopic,[14,15] X-ray crystallographic,[16] and computational[12,17] investigations.

With regard to the definition of "large", both steric and electronic effects of the groups S, M, and L have to be considered.[4,11] Lodge and Heathcock suggested that for compounds possessing substituents with competing electronic and steric properties, four major transition structures have to be taken into account,[11] comprising two conformers for each diastereotopic approach of the nucleophile (not shown here).

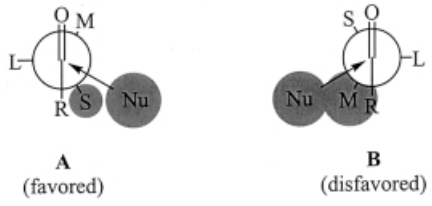

Figure 1. Transition structures for the nucleophilic addition to α-chiral ketones as suggested by the Felkin−Anh model

The Cram rule holds for a wide variety of chiral carbonyl compounds. In the course of our investigations of chiral silicon auxiliaries, however, we found that it does not apply to the addition of organometallic reagents to acylsilanes **1** (Scheme 1). For instance, the major product of the treatment of **1** (R = Me) with PhLi, performed in THF under nonchelating conditions, was the anti-Cram compound **2′** rather than the Cram product **2**.[18] Thus, the question arose as to whether the Si atom, as the holder of the chiral information, or another feature of the substrates is responsible for the unexpected stereoselectivity observed with the silicon-containing compounds. To address this question, we performed a series of ab initio calculations. The energetically most favorable transition state structures for the two diastereotopic attacks of LiH to the model ketones **3a−c** and **4b,c** were characterized computationally, and the resulting relative energies were used to predict the stereoselectivities.

Our computations largely followed the lines of Wu and Houk,[13] with the difference that our calculations were fully

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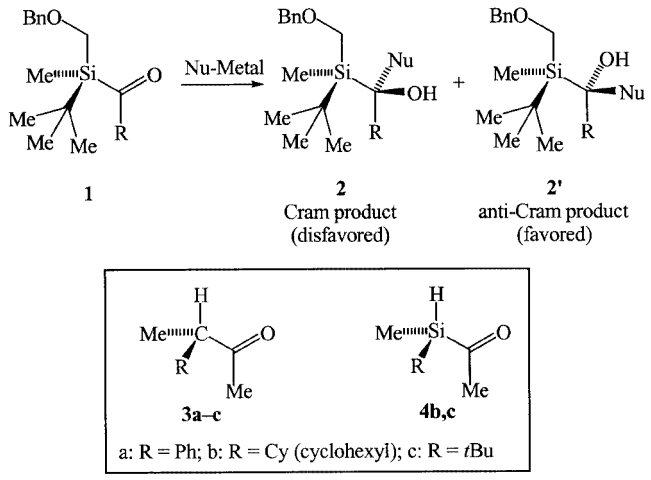


Scheme 1

performed ab initio rather than with a combination of ab initio and MM2 force-field techniques.

Computational Details

All computations were performed with the Gaussian 94 package.[19] Standard methods and standard basis sets were used throughout.[20] The transition state structure for the addition of LiH to acetone, fully optimized at the RHF/6-31G* level, served as the basic skeleton to construct the starting structures for the subsequent calculations. For this purpose, two of the three Me H atoms were replaced by a Me group and the respective second substituent, affording all possible permutations. The corresponding acylsilanes were derived by replacing the α-C atoms with Si atoms. Additional starting structures were generated by allowing for conceivable conformational changes in the substituents.

The calculations were initiated by partial optimization of the whole set of starting conformations at the RHF/3-21G level with frozen C−O−Li−H subunits. From the structures obtained for each compound, the energetically most favorable representatives (within 15 kJ/mol) for both diastereotopic attacks of LiH were then subjected to full transition state optimizations, without any constraints, at the RHF/6-31G* level. Of these, the most favorable structures for the two diastereotopic attacks were selected for each model reaction and were characterized as transition states by calculation of their harmonic vibrational frequencies. Finally, the single point energies of these verified transition structures were determined at the RHF/6-311+G** and MP2/6-311+G** levels. The theoretical stereoselectivities derived from these data (according to a Boltzmann distribution at 293 K) are compiled in Table 1 together with the respective structures and — as far as known — the experimental selectivities and the selectivities calculated by Wu and Houk.[13] A referee pointed out that the use of just the lowest transition states for the two sites of attack, rather than of all possible ones, already constitutes a substantial approximation for the resulting selectivities. We feel, however, that this error — due to the exponential decay of the contributions from higher-lying structures in the Boltzmann factor — will be much smaller than other possible shortcomings of our theoretical model. We have verified that the inclusion of energetically close transition states does not affect our qualitative statements in any case. For instance, for compound **4b**, the most critical case with five transition state structures lying within 3.09 kJ/mol (MP2/6-311+G** + ZPE level), the selectivities calculated from only the energetically lowest transition structures for the two sites of attack (54:46) differ just slightly from those obtained with consideration of all five relevant structures (68:32). As a reference, the energies for all six types of transition states of all compounds **3a**−**c** and **4b**,**c**, calculated at several levels, are summarized in the Supporting Information. For the optimized transition structures displayed in Table 1, the cartesian coordinates are also given in the Supporting Information.

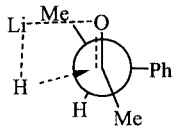
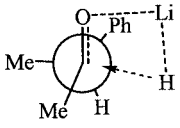
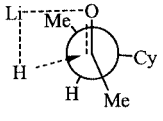
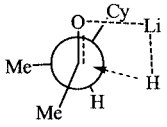
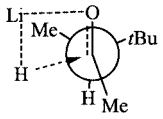
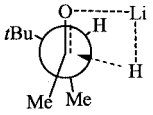
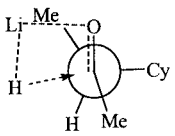
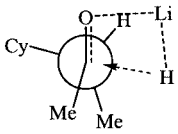
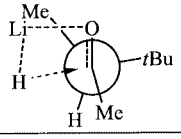
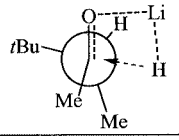
We have used the above ab initio-based methodology, rather than one including more modern flavors of density functional theory, for compatibility with previous theoretical work in this area.[21−27] Moreover, the supposed superiority of DFT over HF geometries does not necessarily mean the latter will furnish inferior results in correlation-energy calculations. For a related problem, for the π-facial selectivity of cyclohexanone reductions, computations at the B3LYP/6-31+G* + ZPE level have been reported with $LiAlH_4$ as the nucleophile.[28] For comparison, we have also calculated the respective transition states and relative energies with LiH as the nucleophile at the B3LYP/6-31+G* + ZPE as well as at the MP2/6-311+G**//RHF/6-31G* level. The preference of the axial versus the equatorial transition states by 5.7 kJ/mol for the $LiAlH_4$ reduction calculated at the B3LYP/6-31+G* + ZPE level is well reproduced with LiH as the reagent, computed at the same level (7.3 kJ/mol) and using our MP2/6-311+G**//6-31G* + ZPE combination (5.9 kJ/mol). Thus, neither DFT calculations instead of the methodology employed here nor the use of $LiAlH_4$ in place of LiH as the model nucleophile is likely to change our qualitative conclusions.

Results and Discussion

Reactions with Ketones

Our results for the reactions of ketones **3a** and **3b** are in line with the Cram rule and agree well with the results of Wu and Houk,[13] which were obtained with less sophisticated methods. For the reduction of **3c**, however, anti-Cram attack would be anticipated on the basis of our calculations, and in fact, preferred anti-Cram attack was found for the reduction of **3c** with $LiAlH_4$ (see below). Interestingly, despite the consistency of computational and "wet-chemical" experiments, the well-accepted Felkin−Anh model is not reproduced in any of the three cases. The actual, calculated transition structures relevant for the transformations of **3a**,**b** — the respective two conformations with the H atoms

Table 1. Theoretical stereoselectivities with the respective structures, experimental selectivities and selectivities calculated by Wu and Houk[13]

No.	Favored Transition States[a] for Cram Product	anti-Cram Product	Calc. Selectivities and Rel. Energies[b] RHF/6-311 +G**	MP2/6-311 +G**	MP2/6-311 +G**+ ZPE	Selectivities of Other Sources Wu and Houk [13]	Experimental (with $LiAlH_4$)
	with Carbon						
3a			77:23 (+2.90)	81:19 (+3.54)	75:25 (+2.64)	74:26	60:40
3b			82:18 (+3.63)	89:11 (+5.10)	89:11 (+4.99)	62:38	69:31
3c			26:74 (–2.58)	27:73 (–2.38)	20:80 (–3.42)	—	40:60
	with Silicon						
4b			60:40 (+0.95)	57:43 (+0.70)	54:46[c] (+0.36)	—	—[d]
4c			34:66 (–1.64)	28:72 (–2.32)	28:72 (–2.35)	—	—[d]

[a] The drawings reflect the correct geometries (dihedral angles, trajectories of the nucleophilic attacks, and atom positions); cy = cyclohexyl. [b] Selectivities (Cram/anti-Cram) calcd. for reactions performed at 293 K; energies of "anti-Cram attack" rel. to "Cram attack" in $kJ \cdot mol^{-1}$; no scaling factors have been applied to ZPEs. [c] The selectivity calculated with consideration of five energetically rather close transition structures is 68:32, corroborating qualitatively the result derived from the energetically lowest transition structures only. [d] Experimental selectivities are not available because the respective ketones have not been synthesized.

located in the "outside" positions — diverge markedly from the transition structures proposed by Felkin and Anh. On the other hand, the modes of interaction must differ for the reduction of **3c**, where the calculated transition states correspond to those proposed by the Felkin–Anh model but the selectivities are opposite! In fact, our results suggest that the repulsive interaction of the incoming nucleophile with the "inside" rather than the "outside" groups is dominant and thus decisive for the selectivity. This is true not only for the transformation of **3c** but also for the transformations with **3a** and **3b**. Hence our results — and the results of Wu and Houk — suggest that the Felkin–Anh model does not reflect the correct reaction modes and has to be modified.

Wu and Houk have nicely demonstrated in their conformational analysis of the transition states for the NaH addition to propionaldehyde that the "inside" position of the Me group, structure **5**, is favored as compared to the "outside" or the "anti" positions, structures **5′** and **5′′** (Figure 2). This finding was explained by the destabilization of the transition structures **5′** and **5′′** with respect to structure **5**. Destabilization of the "outside" location of the Me group is proposed to cause unfavorable steric interactions; destabilization of the "anti" position of the Me group would be due to the unfavorable electronic interaction of the better donating Me group (as compared to H) within the electron-rich transition state. Extrapolating these results and explanations for groups other than Me would suggest that the "outside" conformations should be successively destabilized with increasing bulk of the new substituent, while the stability of the "anti" conformation would only be marginally affected. For the "inside" structures, no such direct extrapolation is possible. Wu and Houk have shown, however, that removal of the Na^+ from the transition states **5**, **5′** and **5′′** causes a considerable decrease in the relative energy of **5**. This can be interpreted in terms of an unfavorable steric interaction of the "inside" Me group with the Na atom. Thus, exchange of the Me group with a larger substituent should gradually destabilize the "inside" transition structures as well.

Thus, α,α-disubstituted chiral ketones should prefer transition structures where the M and L groups are posi-

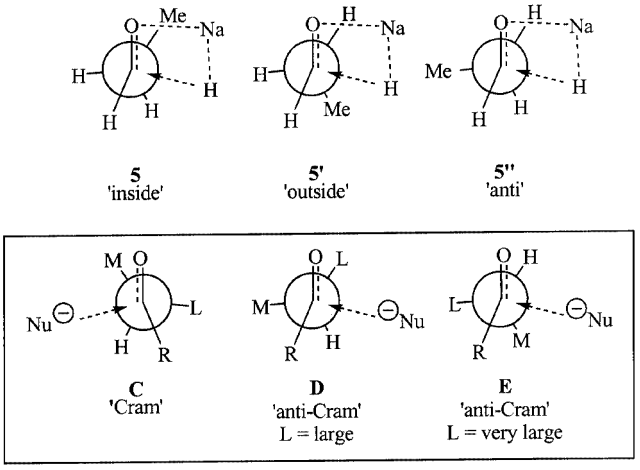


Figure 2. Conformational analysis of the transition state for the NaH addition to propanal by Wu and Houk[13] (top) and relevant transition structures for the addition of LiH to α-chiral ketones (bottom) as calculated by us at the ab initio MP2/6-311+G**//RHF/6-31G* level

tioned "inside" and "anti" (i.e., structures **C** and **D**), thus avoiding unfavorable steric interactions of these groups as would be expected if they were positioned "outside". In fact, exactly these types of transition states were calculated to be relevant for the reductions of compounds **3a** and **3b**, although not for compound **3c**. For the latter compound, in addition to a transition structure of type **C**, a transition structure of type **E** rather than **D** becomes important. Apparently, for compounds with very large groups L, like the *t*Bu group, destabilization of conformation **D** is caused by the repulsive interaction of the large group with the Li−H moiety. This repulsion is strong enough to favor structure **E** with the principally unfavorable location of the M group in the "outside" position. Thus, transition states **C** and **E**, rather than **C** and **D** become important for **3c**.

For the prediction of the type of stereoselectivity (Cram or anti-Cram direction) in terms of a general model, not only the knowledge of the relevant transition structures but also the estimates of their relative energies is important. Such an estimate appears easy for transition states of type **C/D**. These transition states are very similar in structure for the region of the nucleophilic attack, differing primarily in the size of the groups positioned "inside". Thus, the repulsive interactions between the incoming nucleophile and the groups located "inside" should be decisive. These interactions would be expected to be larger for **D** (interaction with L) than for **C** (interaction with M). In fact, structures **C** were calculated as favorable over structures **D**, consistent with the observed Cram selectivity. The situation is more complex for reactions involving the two competing transition structures of type **C** and **E**. In such cases, the incoming nucleophile "senses" the same two groups for both diastereotopic attacks, namely an H atom and the M group, located at exchanged positions. In contrast to the assumption underlying the Felkin−Anh model, it appears from our calculations that the repulsive interaction of the nucleophile with the "inside" rather than the "outside" group is dominant and thus leads to preferred reaction via transition state structure **E** (affording predominantly the anti-Cram product).

The revised Cram rules for the "open-chain-controlled" nucleophilic addition to α-chiral ketones thus read: (1) in the relevant conformations, neither the M nor the L groups are located "outside", or, if a very large group is present, the L groups are located "anti" in the two relevant transition states; (2) in the preferred transition structure the interaction of the incoming nucleophile with the "inside" group is minimized.

Reactions with Acylsilanes

The interpretation of the data related to the acylsilanes is hampered by the lack of experimental data for the reduction of the model compounds. The computed transition states and reaction barriers for the addition of LiH to acylsilanes **4b** and **4c** suggest qualitatively the same stereochemical results as observed for the respective ketones (see the Table 1). The cyclohexyl-substituted compound **4b** should be reduced predominantly to the Cram product, while the *t*Bu-substituted material **4c** would be expected to lead predominantly to the "anti-Cram" alcohol. The estimated selectivities, however, are less pronounced and the relevant transition states — at least for the cyclohexyl-substituted compound **4b** — differ for the silicon compounds from those computed for the normal ketones. The former result is not too astonishing. As a matter of fact, it was expected a priori that the intramolecular steric interactions related to the relevant conformational changes would decrease due to the Si−C bond being longer than the C−C bond. Thus, the transition state energies related to the structures of type **C**, **D**, and **E** should get closer to each other and affect the Boltzmann distribution. More striking, however, is the fact that for the two compounds **4b** and **4c** the two relevant transition structures are of the same type (**C** and **E**, the Felkin−Anh conformations, Figure 3), but with reversed relative energies, suggesting opposite stereoselectivities for the two compounds. The result would be largely in agreement with the observed "anti-Cram" selectivity found for the Grignard reaction with acylsilane **1**.[18]

The reason for the preference of structures **E** over structures **D** for the silicon compounds is not clear. It seems that the steric interactions of the "outside" groups with R is reduced relative to the interactions of the "inside" groups with the metal cation. This reduces the destabilizing effect of a group located in the "outside" position relative to that of a group located "inside" and would allow the placement of a reasonably sized M group, like the Me group, "outside". The different discrimination between the two transition structures **C** and **E** for the two compounds is possibly due to the particular conformations assumed in the respective transition states. In the transition state structure **C** of the *t*Bu-substituted compound **4c**, the dihedral angle between the ketone Me group and the L group is increased by approximately 8° relative to that of the related transition state of **4b**. This drives the "inside" Me group closer to the

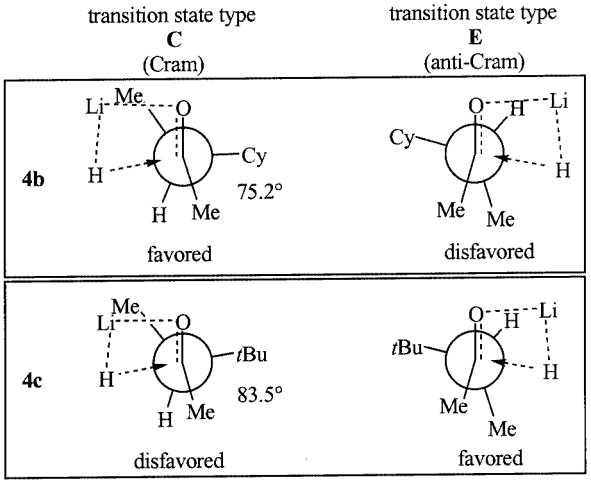
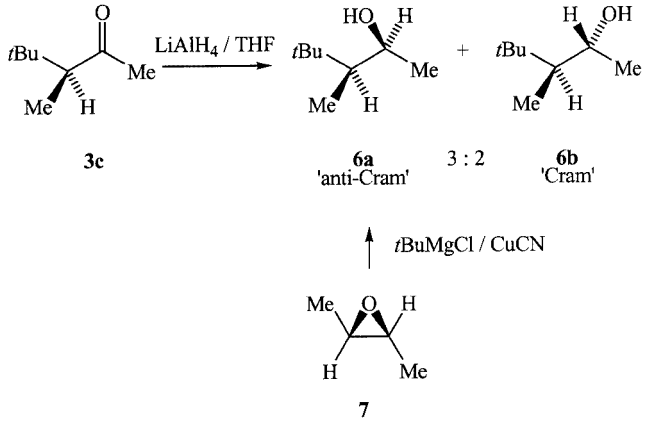


Figure 3. Relevant transition states calculated for the addition of LiH to the α-chiral acylsilanes **4b** and **4c**

Li−H moiety for **4c** than for **4b**, destabilizing structure **C** to a greater extent for **4c** than for **4b**. Thus, transition state **C** is still favored, if only marginally, for the reduction of compound **4b**, but not for the reaction of **4c**.

Reduction of 3c and Proof of Stereoselectivity

Since according to our calculations, ketone **3c** was predicted to be reduced with anti-Cram selectivity, the respective selectivity was tested experimentally. Compound **3c**,[29−33] as well as its reduction,[29,34,35] had already been described. However, the type of selectivity has not been determined yet. To this end, **3c** was reduced with $LiAlH_4$ in THF, reproducing the 3:2 selectivity found earlier for the formation of the two diastereomeric alcohols **6a,b**.[35] The stereospecific synthesis of **6a** by opening of oxirane **7** with *t*BuMgCl in presence of CuCN proved the relative configurations of the products as depicted in Scheme 2, thereby corroborating the predicted selectivity.



Scheme 2

We are aware that LiH is probably not a perfect model for the reducing agents typically used, such as $LiAlH_4$. We have neglected the effects of aggregation and solvation, which could well fine-tune the selectivities under scrutiny. We are confident, however, that the geometrical preferences in the relevant transition structures are intrinsic to the substrates, and that the qualitative conclusions from the model calculations are also valid for the real systems. The good accord of computed and, subsequently, determined selectivities is testimony to the predictive power of these models and, thus, of the proposed modifications to the Felkin−Anh model.

Conclusion

According to our calculations, the Felkin−Anh model does not correctly represent the modes of reaction on the course of nucleophilic attack to α-chiral carbonyl compounds. For typical reactions, the two transition states with the M and L groups arranged "inside" and "anti" are the key structures, and discrimination is due to the repulsive interactions of the incoming nucleophiles with the "inside" groups. For compounds with very large groups L, the relevant transition structures are those with this L group placed "anti" (Felkin−Anh conformations). For the discrimination, the interaction of the incoming nucleophile with the "inside" rather than the "outside" group is relevant. This leads to anti-Cram selectivity for such compounds. Acylsilanes should show the same selectivities as the related ketones. The selectivities, however, are expected to be lower and the relevant transition structures might differ from those of the carba analogs.

Experimental Section

General Remarks: Manipulations were carried out under Ar in oven-dried glassware. For reactions, Et_2O and THF were freshly distilled from Na with benzophenone ketyl as indicator. All organic solvents were distilled prior to use. Extracts were washed with sat. aq. NH_4Cl soln. and brine and were dried over $MgSO_4$. Solutions for workup procedures were prepared in deionized H_2O. Chromatography: Merck silica gel 60 (40−63 μm). ^1H NMR spectra on a Bruker AM-300 in $CDCl_3$ at 300 MHz; δ in ppm relative to $CHCl_3$ (δ = 7.26 ppm), *J* in Hz. ^{13}C NMR spectra in $CDCl_3$ at 75.5 MHz; δ in ppm relative to $CDCl_3$ (δ = 77.0 ppm); multiplicities from DEPT-135 and DEPT-90 experiments.

(2*R,3*R**)-3,4,4-Trimethylpentan-2-ol (6a) and (2*S**,3*R**)-3,4,4-Trimethylpentan-2-ol (6b):** $LiAlH_4$ (0.03 g, 0.9 mmol) was added at −78 °C to a solution of 3,4,4-trimethylpentan-2-one[33] (**3c**, 0.40 g, 3.2 mmol) in THF (10 mL). The mixture was stirred for 1 h at −78 °C, quenched with sat. aq. NH_4Cl soln. (2 mL), warmed to 23 °C, and extracted with Et_2O. The solvent was evaporated to leave the crude alcohols as a mixture of (2*R**,3*R**)-3,4,4-trimethylpentan-2-ol (**6a**) and (2*S**,3*R**)-3,4,4-trimethylpentan-2-ol (**6b**) in a ratio of 3:2 (0.30 g, 2.3 mmol, 72%). Separation to deliver the pure isomers as colorless oils was performed by chromatography (hexane/Et_2O 10:1).

A solution of *tert*-butylmagnesium chloride in Et_2O (2M, 10 mL, 20.0 mmol) was added at −78 °C to a suspension of CuCN (0.70 g, 7.8 mmol) in Et_2O (10 mL). The mixture was stirred at −78 °C for 30 min, *trans*-2,3-dimethyloxirane (**7**, 0.5 mL, 5.6 mmol) was ad-

ded, the solution was warmed to 0 °C, and stirred for 3 h. It was quenched with dil. aq. NH_4Cl (10 mL), warmed to 23 °C, and extracted with Et_2O. The solvent was evaporated to leave **6a** (0.23 g, 1.77 mmol, 31%) as a colorless oil.

6a: ^{1}H NMR: δ = 4.20 (dq, *J* = 6.5, 1.2, *H*COH), 2.22 (s, HO), 1.23−1.14 [m, *H*CMe(*t*Bu)], 1.17 (d, *J* = 6.5, *Me*CHOH), 0.93 (s, Me_3C), 0.87 [d, *J* = 7.2, *Me*CH(*t*Bu)] ppm. ^{13}C NMR: δ = 67.2 (d, CHOH), 48.2 [d, *C*HMe(*t*Bu)], 33.2 (s, *C*Me$_3$), 28.2 (q, Me_3C), 23.8 (q, *Me*CHOH), 6.9 [q, *Me*CH(*t*Bu)]. M.p. of 3,5-dinitrobenzoate (hexane): 92.6−93.2 °C; no corresponding literature value.

6b: ^{1}H NMR: δ = 4.03 (dq, *J* = 6.3, 3.7, *H*COH), 2.22 (s, HO), 1.46 [dq, *J* = 7.1, 3.6, *H*CMe(*t*Bu)], 1.12 (d, *J* = 6.3, *Me*CHOH), 0.91 (s, Me_3C), 0.85 [d, *J* = 7.2, *Me*CH(*t*Bu)] ppm. ^{13}C NMR: δ = 68.4 (d, CHOH), 49.7 [d, *C*HMe(*t*Bu)], 33.5 (s, *C*Me$_3$), 28.4 (q, Me_3C), 19.8 (q, *Me*CHOH), 8.9 [q, *Me*CH(*t*Bu)]. M.p. of 3,5-dinitrobenzoate (hexane): 74.6−75.0 °C {ref.: 72.0−72.5 °C (petroleum ether),[34] 75.9−76.5 °C (petroleum ether)[35]}.

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