Geminal Disubstitution

DOI: 10.1002/anie.201003823

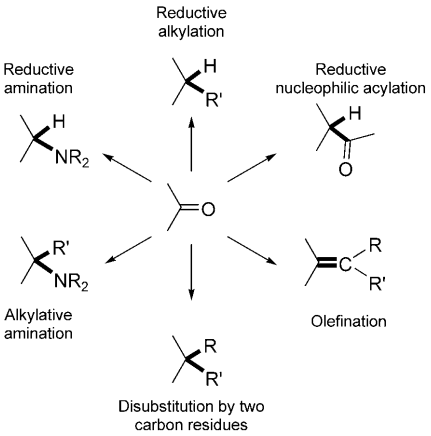
Generation of Secondary, Tertiary, and Quaternary Centers by Geminal Disubstitution of Carbonyl Oxygens

*Dieter Seebach**

amides · organometallic reagents · quaternary carbon centers · tertiary alkylamines · thioamides

Dedicated to Albert Eschenmoser on the occasion of his 85th birthday

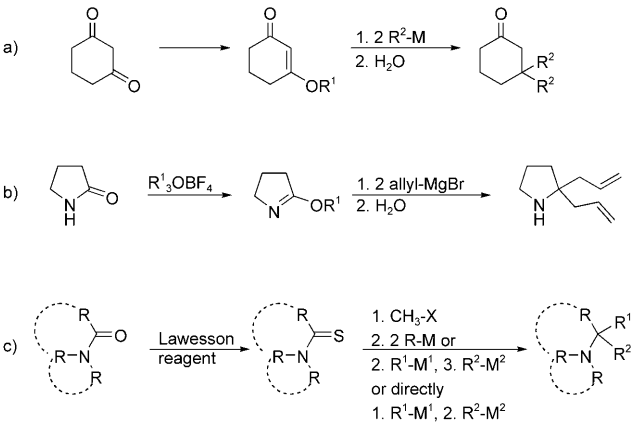
***M**ethods for replacing the carbonyl oxygen by two new substituents (C=O→CR^{1}R^2) are discussed in this Minireview, whereby R may be H, NR$_2$, alkyl, allyl, benzyl, vinyl, alkynyl, aryl, heteroaryl, or acyl groups. The most frequently used starting materials for geminal disubstitution with the formation of two C–C bonds (R^1,R^2 ≠H, NR$_2$) are amides and thioamides, which react with organometallic nucleophiles R–M (M = Li, MgX, CeX$_2$, TiX$_3$, ZrX$_3$) to give tertiary sec- and tert-alkylamines. Quaternary centers can be built directly from ketones by treatment with Me$_3$Al, MeTiCl$_3$, or Me$_2$TiCl$_2$ (R^{1}R^{2}C=O→R^{1}R^{2}CMe$_2$). The scope and limitations of the various methods and mechanistic models are briefly discussed. The remarkable variety and diversity of structures thus accessible are demonstrated by numerous examples.*



Scheme 1. Transformations in which the carbonyl oxygen atom is replaced by two new substituents. The representation is taken from publications from 1982 (Scheme 1 in Ref. [5]) and 1983 (Scheme 12 in Ref. [6]), as well as from a dissertation from 1986 (Scheme 5 in Ref. [7]).

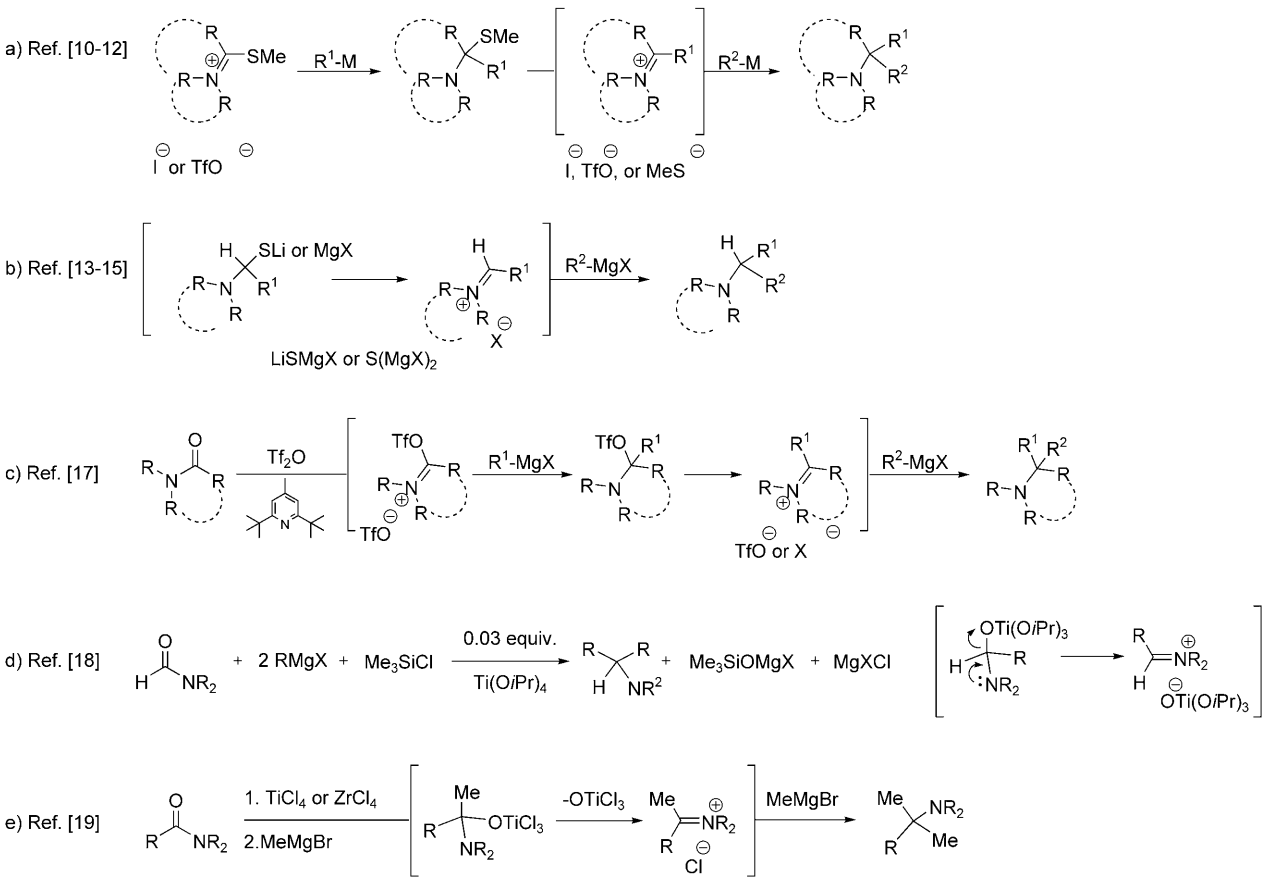
The carbonyl group plays *the* central role in synthetic organic chemistry.[1–3] Of special interest is a group of transformations, in which the carbonyl oxygen is replaced by two new substituents in a *single* preparative procedure consisting of more than one reaction step. Examples are the carbonyl-to-methylene reduction, the reductive amination, alkylation, acylation, and carboxylation, the alkylative or carbo-amination, and the geminal disubstitution by two carbon residues (alkyl, alkenyl, alkynyl, aryl); the carbonyl olefination may also be included (Scheme 1).[4]

One of the transformations shown in Scheme 1 has been the subject of a number of papers published in recent years: the replacement of the carbonyl oxygen by two carbon substituents (C=O→CR^{1}R^2). Depending on the nature of the carbonyl compound employed (aldehyde, ketone, ester, amide), secondary, tertiary, and quaternary centers are formed.[8] In most cases the starting materials are converted



Scheme 2. Geminal disubstitution of carbonyl oxygens via isolated derivatives. a) β-Alkoxyenones and b) imidate esters[9] react by addition/elimination/addition. c) Thioamide groups are activated in situ by S-methylation and then treated with organometallic reagents;[10–12] this is possible either by direct addition of 2 equiv of a metal derivative or by stepwise addition of two different polar organometallic reagents,[13–15] M = Li, MgX, or CeCl$_2$. For examples see Scheme 3.

[*] Prof. Dr. D. Seebach
Laboratorium für Organische Chemie, Departement für Chemie und Angewandte Biowissenschaften, ETH-Zürich
Hönggerberg HCI H331, Wolfgang-Pauli-Strasse 10
8093 Zürich (Schweiz)
Fax: (+41) 44-632-1144
E-mail: seebach@org.chem.ethz.ch
Homepage: http://infosee.ethz.ch/seebach/seebach.html



Scheme 3. Procedures for the geminal disubstitution of amide carbonyl oxygens with formation of tertiary *sec*- and *tert*-alkylamines and proposed reactive intermediates.[10–15,17–19] The thioamide precursors for reactions (a) and (b) are prepared from amides and lactams, respectively, with the Lawesson reagent. For examples see Table 1.

to activated derivatives that are isolated and reacted in one or more than one step with organometallic reagents (Scheme 2).

Preferred intermediates are thioamides for the preparation of tertiary amines with a *sec* or *tert* substituent on nitrogen; these products are important targets for various purposes.[16] The procedure involves methylation on sulfur (with MeI or MeOTf) to form methylthioiminium salts and in situ addition of an organolithium compound to give an—isolable[10,11]— N,S-acetal or ketal, which is usually directly treated with a Grignard reagent, leading to the product of geminal disubstitution (Scheme 2c, Scheme 3a). For the introduction of two identical substituents in situ treatment of the methylthioimminium salts with excess RMgX or $RCeCl_2$[12] is recommended.

Thioformamides may also be converted to tertiary *sec*-alkylamines by treatment with an organolithium or -magnesium reagent, without prior S-methylation.[13–15] This is remarkable for two reasons: The thioformyl (CH=S)[20] as well as the formyl (CH=O)[21,22] hydrogen is acidic and is deprotonated by LDA ($\rightarrow R_2N$-CX-Li),[23] while RLi and RMgX obviously add to the C=X group. In this case LiSMgX or $S(MgX)_2$, quite unusual leaving groups, must be eliminated from the tetrahedral intermediates (see Scheme 3b).[24]

To avoid the use of the Lawesson reagent and the formation of nasty-smelling by-products (MeSH, H_2S) it would be desirable to replace amide oxygens directly by two R groups. To this end, stronger activating reagents or more oxophilic metal derivatives are required than those used when thioamides serve as the starting material.[17–19] The former procedure has been realized recently:[17] amides or lactams are triflated on oxygen (trifluoromethanesulfonic acid anhydride/2,6-di(*tert*-butyl)-4-methylpyridine (DTBMP)) and

Dieter Seebach was born in Karlsruhe in 1937 and studied chemistry at the local Technische Hochschule (now KIT), where he received a PhD degree in 1964 with a thesis on small-ring compounds and peroxides (supervisor. R. Criegee). After a two-year stay at Harvard University as a Postdoctoral Fellow (with E. J. Corey) and Lecturer he returned to Karlsruhe for a Habilitation (1969) on S- and Se-stabilized carbanion and carbene derivatives. In 1971 he became Full Professor at the Justus-Liebig University Giessen and in 1977 he moved to ETH Zürich. He held longer-term guest professorships at the University of Wisconsin (Madison), Caltech (Pasadena), and Harvard University. Since 2003 Seebach has been Professor Emeritus at ETH, where he leads a group of postdoctoral co-workers in research mainly on β-peptides and the mechanism of organocatalysis.

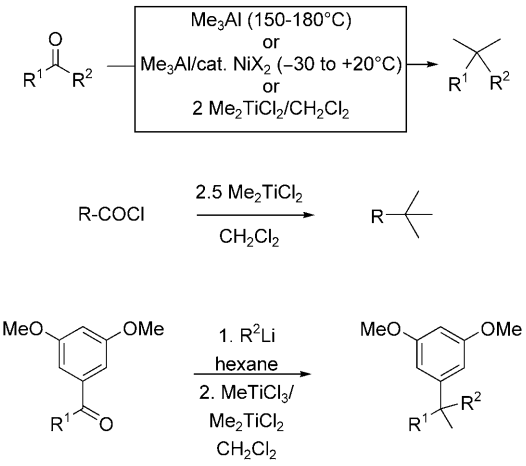
treated in situ with Grignard reagents; two different Mg compounds, added stepwise, cleanly lead to the transfer of two different R groups (see Scheme 3c); the method is expensive: 50 g $(CF_3SO_2)_2O$ cost roughly € 300 and 25 g DTBMP cost about € 410.[25a]

More economical is the use of Si, Ti, and Zr derivatives. These metals have strong affinities for oxygen (cf. bond energies Me_3Si–OMe 122, $(iPrO)_3Ti$–O*i*Pr 115, $(iPrO)_3Zr$–O*i*Pr 132 kcal mol^{-1})[25b] and are literally able to "suck" oxygen out of organic compounds, as evidenced by numerous applications.[26–31] One method, which is restricted to formamides, for preparing *sec*-alkyl amines is outlined in Scheme 3d. It involves reaction of the formamide with 2 equiv Grignard reagent and 1 equiv Me_3SiCl in the presence of 3 mol% $Ti(OiPr)_4$ and, surprisingly, employment of a 1:1 mixture of MeMgCl and ArlMgBr cleanly leads to the "mixed" products R_2N-CHMeArl![18] Tertiary *tert*-alkyl amines $R^1{}_2N$-CMe_2R^2 are formed from various amides, MeMgBr, and $TiCl_4$ (1:3:1); this reaction is limited to methylation[19,32] (vide infra; geminal dimethylations with MeTi derivatives were published almost 20 years earlier[30,31]).

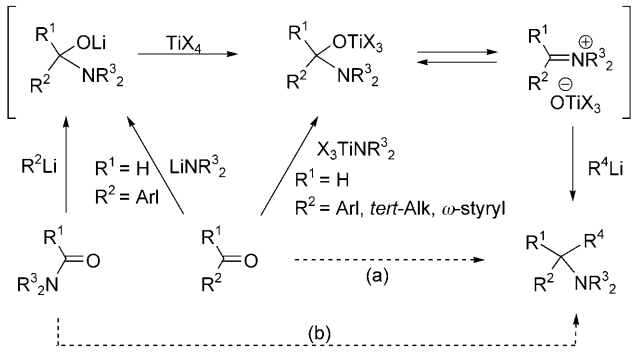
A more generally applicable method is outlined in Scheme 4: after addition of an organolithium compound to an amide carbonyl group[34] the tetrahedral intermediate is transmetalated to a titanium α-aminoalkoxide, a precursor of an iminium salt, to which a second Li compound is added (see the examples collected in Table 2, and a typical procedure described in reference [35]). Due to the fact that amides (as well as thioamides) and carbamates can also be metalated adjacent to nitrogen ($\rightarrow R^1$-CX-$NR^2(CHLiR^3)$)[36–39] or *ortho*-metalated on N-aryl groups,[40] the moderate to good yields of this process are remarkable. The method was described in 1986 in an ETH dissertation[7] but never published (motto: "*He who comes late misses the boat*").

All the geminal disubstitutions discussed so far are carried out with amides or thioamides. They most likely occur through the quite stable imminium ion intermediates (R_2C=NR_2^+, see Schemes 3 and 4) and produce tertiary *sec*- and *tert*-alkylamines.[41] Quaternary centers can be generated by reaction of ketones or acid chlorides with trimethylaluminum[42] or methyltitanium chlorides[43] (Scheme 5), methods that were published 36 and 29 years ago, respectively. By first adding an organolithium reagent and then Me_xTiCl_{4-x} to an aromatic ketone, an alkyl and a methyl group can be introduced.[44] None of the more recent papers on geminal dialkylation refer to this old work (motto: "*Premature discoveries are ignored*"). A disadvantage of these, at first sight so simple transformations is the necessity of working with solutions of pyrophoric Me_3Al and Me_2Zn (cf. *t*BuLi!). Thus, the reagent Me_2TiCl_2 is generated in CH_2Cl_2 by combining $TiCl_4$ with Me_2Zn.[43b] Although the reactions supposedly[30,31,42–44] take place through intermediate tertiary carbocations no Wagner–Meerwein rearrangements, cyclopropane ring openings, or transannular reactions have been reported (see the examples in Table 3).

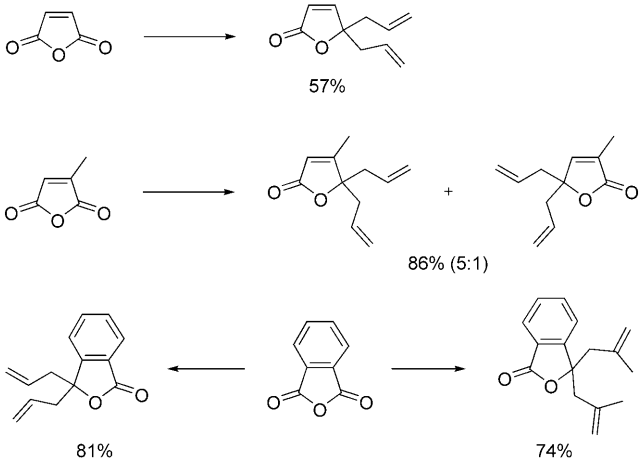
Another geminal disubstitution, not involving iminium ion intermediates, is observed when maleic or phthalic anhydride is treated with allylic halides and indium powder (Scheme 6);[45] with 3-substituted allylic bromides (Me-CH=CH-CH_2Br, Me_2C=CH-CH_2Br) only a simple carbonyl addi-



Scheme 5. Di- and trimethylations and alkylative methylation of ketones and acid chlorides with Me_3Al[42] and Me-Ti reagents. For reviews on the Ti reagents see Refs. [30,31]; for examples see Table 3.

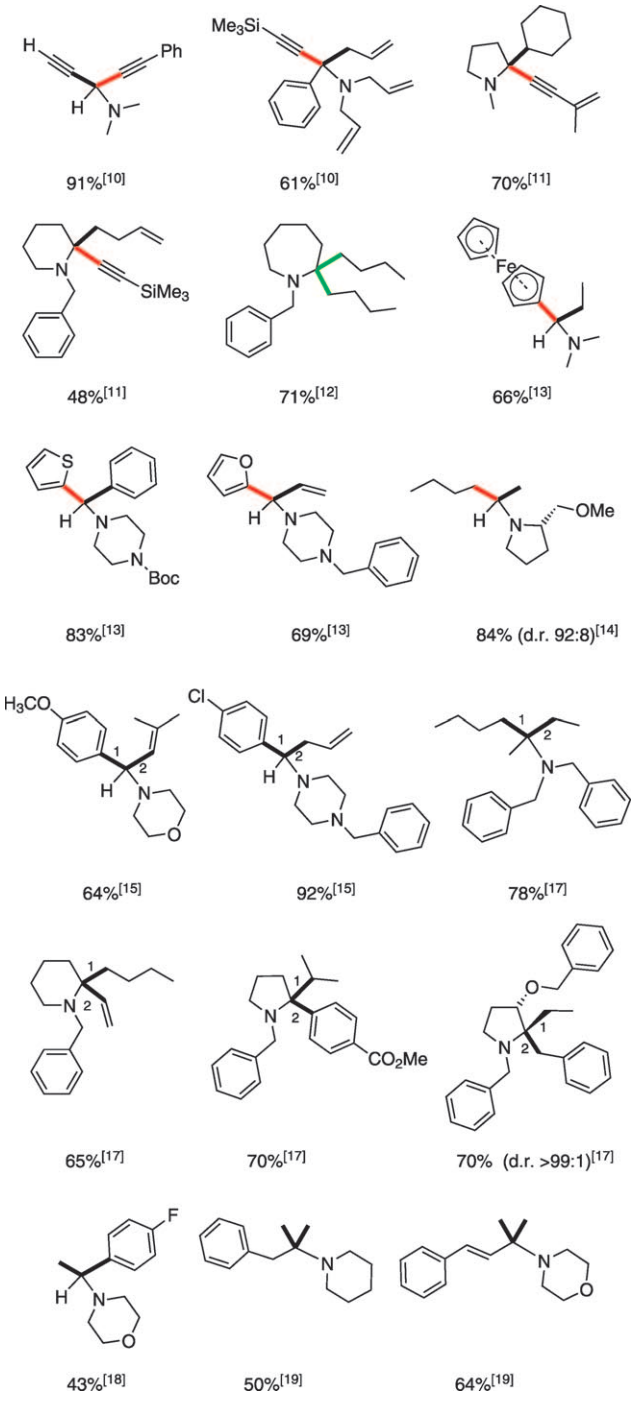


Scheme 4. a) Alkylative amination of aromatic (or other non-enolizable) aldehydes[5–7,27–31,33] and b) geminal disubstitution of amide oxygens[7] via α-amino–Li and –Ti alkoxides; when R^4Li is a Li enolate, Mannich bases are formed.[33b] For examples see Table 2.



Scheme 6. Geminal diallylation[45] of maleic and phthalic anhydrides with In powder and allylic halides (ratio 1:2:3 equiv) in DMF at room temperature (1 h). Metathesis of the products should lead to cyclopentane derivatives.

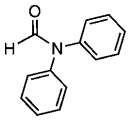
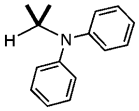
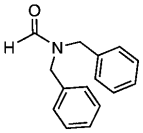
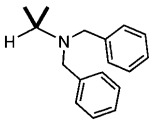
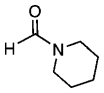
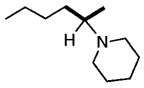
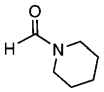
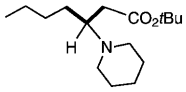
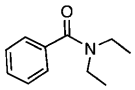
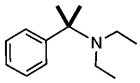
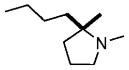
Table 1: Structural formulae of amines prepared from amides.[a]



[a] The corresponding methods (Scheme 3) are described in the references. The bonds in bold were created by geminal disubstitution. In the red/black combinations the red-colored bond indicates the primary introduction of a substituent with RLi, while the black-colored bond was generated with RMgX. In the black/black combinations the bonds were formed with two different Grignard reagents; the numbers 1 and 2 indicate the order of bond formation. The green-colored bonds resulted from reaction with $RCeCl_2$.

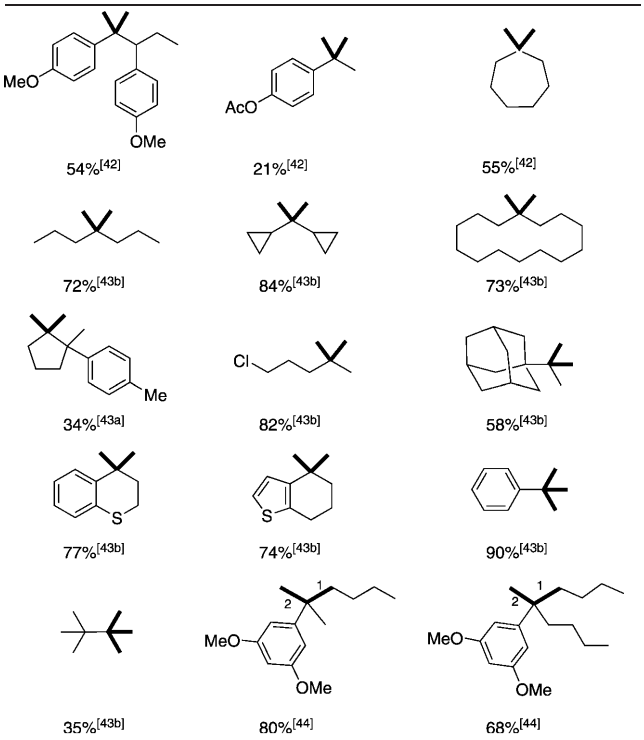
tion with formation of a hydroxy lactone takes place. Details about the mechanism of this reaction are unknown (see Ref. [8a]).

Table 2: Geminal disubstitution of amide carbonyl oxygen atoms (Scheme 4b) by sequential addition of R^2Li (1 equiv), $TiCl_4$ (1 equiv), and R^4Li (2 equiv) to a toluene solution of the amide (R^1-CO-NR^3_2 in Scheme 4).[a]

Amide	R^2Li	R^4Li	Product	Yield [%]
	MeLi	MeLi		70
	MeLi	MeLi		20
	BuLi	MeLi		74
	BuLi			67
	MeLi	MeLi		70
	MeLi	MeLi		39
	BuLi	MeLi		42

[a] For typical procedures see Ref. [7] and footnote [35].

Table 3: Geminal dimethylation and alkylation/methylation of ketones and trimethylation of acid chlorides by the methods outlined in Scheme 5.[a]



[a] For general reviews on organotitanium chemistry see Refs. [6], [27], [28], [30], [31]. The C–C bonds created in the process are in bold; the numbers 1 and 2 indicate the order of their formation.

The multitude and variety of compounds with secondary, tertiary, and quaternary carbon centers available by means of geminal disubstitution of carbonyl oxygens by two carbon residues, are evident from the representative examples collected in Tables 1, 2, and 3 and in Scheme 6. Other methods for the, also enantioselective, generation of tertiary and quaternary centers ("a formidable challenge"[46]) have been summarized in a monograph published in 2005,[47] in review articles,[48] and in a most recent *Synlett Cluster*.[46,49–51]

The help of A. K. Beck and Dr. A. Lukaszuk in producing the manuscript is gratefully acknowledged.

Received: June 23, 2010
Published online: December 9, 2010

[1] See the discussion in: R. E. Ireland, *Organic Synthesis*, Prentice Hall, Englewood Cliffs, **1969**, p. 4. Included are, of course, the carbonyl analogues with C=N and C=S groups.

[2] In browsing through the recent three books by K. C. Nicolaou et al., it becomes evident that this is still true today: K. C. Nicolaou, E. J. Sorensen, *Classics in Total Synthesis*, VCH, Weinheim, **1996**; K. C. Nicolaou, S. A. Snyder, *Classics in Total Synthesis II*, Wiley-VCH, Weinheim, **2003**; K. C. Nicolaou, T. Montagon, *Molecules that Changed the World*, Wiley-VCH, Weinheim, **2008**.

[3] Thus, the currently probably "hottest" area of synthetic organic chemistry, organocatalysis with *sec*-amino derivatives, is simply the chemistry of carbonyl compounds, with enamines and iminium ions as reactive intermediates. For recent reviews on organocatalysis with discussions of the historical background see: C. F. Barbas III, *Angew. Chem.* **2008**, *120*, 44; *Angew. Chem. Int. Ed.* **2008**, *47*, 42; D. W. C. MacMillan, *Nature* **2008**, *455*, 304; B. List, *Angew. Chem.* **2010**, *122*, 1774; *Angew. Chem. Int. Ed.* **2010**, *49*, 1730.

[4] There are review articles, book chapters, and monographs about most of these transformations. For some older references see Section 7 in Ref. [6]. Many classical name reactions are involved (Leuckart-Wallach, Wolff–Kishner, Knoevenagel, Mannich, Strecker, Michael, Henry, Wittig, Horner–Emmons–Wadsworth, etc.).; books on name reactions: H. Krauch, W. Kunz, *Reaktionen der organischen Chemie*, Hüthig, Heidelberg, **1997**; A. Hassner, C. Stumer, *Organic Syntheses Based on Name Reactions*, Pergamon, Amsterdam, **2002**; L. Kürti, B. Czakó, *Strategic Applications of Named Reactions in Organic Synthesis. Background and Detailed Mechanisms*, Elsevier, Amsterdam, **2005**. Examples of these transformations, with references, can be readily retrieved by a reaction search in the data banks *Scifinder*, *Beilstein*, and *Houben-Weyl* ("Science of Synthesis").

[5] D. Seebach, M. Schiess, *Helv. Chim. Acta* **1982**, *65*, 2598.

[6] B. Weidmann, D. Seebach, *Angew. Chem.* **1983**, *95*, 12; *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 31.

[7] M. Schiess, Diss. ETH Nr. 7935, ETH Zürich, **1986**.

[8] a) The reaction of esters with excess Grignard reagents, with formation of tertiary alcohols R^1-C**O**-OR^2 + 2 R^3MgX→ $R^1(R^3)_2$C-**O**H + R^2OH, *does not* involve replacement of the carbonyl oxygen atom; b) Classical series of transformations (alluded to in Ref. [4]) include: 1) The nucleophilic addition to a carbonyl group, followed by nucleophilic substitution (R^1_2C=O→R^1_2C R^2(OH)→$R^1_2CR^2R^3$; a recent example: M. Niggemann, M. J. Meel, *Angew. Chem.* **2010**, *122*, 3767; *Angew. Chem. Int. Ed.* **2010**, *49*, 3684. 2) The aldol or nitroaldol condensation or olefination with stabilized ylids or phosphonates, followed by conjugate addition: R^1_2C=O→ R^1_2C=CH-EWG→$R^1_2R^2$C-CH_2-EWG; example: B. List, C. Castello, *Synlett* **2001**, 1687.

[9] M. F. Semmelhack, B. P. Chong, R. D. Stauffer, T. D. Rogerson, A. Chong, L. D. Jones, *J. Am. Chem. Soc.* **1975**, *97*, 2507.

[10] T. Murai, Y. Mutoh, Y. Ohta, M. Murakami, *J. Am. Chem. Soc.* **2004**, *126*, 5968.

[11] T. Murai, R. Toshio, Y. Mutoh, *Tetrahedron* **2006**, *62*, 6312.

[12] A. Agosti, S. Britto, P. Renaud, *Org. Lett.* **2008**, *10*, 1417.

[13] T. Murai, F. Asai, *J. Am. Chem. Soc.* **2007**, *129*, 780.

[14] T. Murai, F. Asai, *J. Org. Chem.* **2008**, *73*, 9518.

[15] T. Murai, K. Ui, Narengerile, *J. Org. Chem.* **2009**, *74*, 5703.

[16] For instance as bulky, non-nucleophilic bases, for protection from enzymatic oxidation, as intermediates in synthesis (cf. azaspirocycles), for accelerated cyclizations and stabilization of rings (*Thorpe—Ingold* effect).

[17] K.-J. Xiao, J.-M. Luo, K.-Y. Ye, Y. Wang, P.-Q. Huang, *Angew. Chem.* **2010**, *122*, 3101; *Angew. Chem. Int. Ed.* **2010**, *49*, 3037.

[18] O. Tomashenko, V. Sokolov, A. Tomashevskiy, H. A. Buchholz, U. Welz-Biermann, V. Chaplinski, A. de Meijere, *Eur. J. Org. Chem.* **2008**, 5107.

[19] S. M. Denton, A. Wood, *Synlett* **1999**, 55.

[20] Thus, in the course of our work on the umpolung of amine and imine reactivity in the early 1970s we used lithiated thioformamides for reactions with electrophiles, with subsequent desulfurization: R_2N-CHS→R_2N-CS-Li→R_2N-CS-R^{El}→ R_2N-CH_2-R^{El}; D. Enders, D. Seebach, *Angew. Chem.* **1973**, *85*, 1104; *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 1014; D. Seebach, D. Enders, *Angew. Chem.* **1975**, *87*, 1; *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 15; D. Seebach, W. Lubosch, D. Enders, *Chem. Ber.* **1976**, *109*, 1309.

[21] B. Bánhidai, U. Schöllkopf, *Angew. Chem.* **1973**, *85*, 861; *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 836.

[22] R. R. Fraser, P. R. Hubert, *Can. J. Chem.* **1974**, *52*, 185.

[23] The rate of deprotonation ("kinetic acidity") of DMF is so fast that upon addition of LDA to a mixture of Me_2NCHO and an aldehyde or ketone (cf. cyclohexanone), in THF/Et_2O/−75 °C, adducts of the type Me_2N-CO-CR^1R^2(OH) are isolated (45–85 %).[21]

[24] The H_2S derivatives LiSMgX and S$(MgX)_2$ were trapped with PhCOCl or *o*-Ph$(COCl)_2$.[13,15]

[25] a) Aldrich Prizes, as of June 10, 2010; b) Y.-R. Luo, *Comprehensive Handbook of Chemical Bond Energies*, CRC, Boca Raton, **2007**; Table 4 on p. 37 in Ref. [31].

[26] See olefinations by the McMurry, Tebbe, and Peterson reactions, enamines by the Weingarten method, and our alkylative amination.[5,7] For literature on organotitanium and –zirconium chemistry see the reviews[6,27–30] and a monograph.[31]

[27] D. Seebach, B. Weidmann, L. Widler in *Modern Synthetic Methods 1983* (Ed.: R. Scheffold), Salle + Sauerländer, Wiley, Aarau, **1983**, p. 217.

[28] D. Seebach, A. K. Beck, M. Schiess, L. Widler, A. Wonnacott, *Pure Appl. Chem.* **1983**, *55*, 1807.

[29] C. Betschart, D. Seebach, *Chimia* **1989**, *43*, 39.

[30] M. T. Reetz, *Top. Curr. Chem.* **1982**, *106*, 1.

[31] M. T. Reetz, *Organotitanium Reagents in Organic Synthesis*, Springer, Berlin, **1986**.

[32] Due to β-H abstraction in R-CH_2-CH_2-TiX_3, cf. the Kulinkovich reaction which is formally also a geminal disubstitution: RCO_2Me + EtMgBr + Ti(O*i*Pr)$_4$→$(CH_2)_2$C(OH)R; O. G. Kulinkovich, S. V. Sviridov, D. A. Vasilevski, *Synthesis* **1990**, 234; E. J. Corey, S. A. Rao, M. C. Noe, *J. Am. Chem. Soc.* **1994**, *116*, 9345; A. de Meijere, S. I. Kozhushkov, J. K. Gawronski, A. I. Savchenko, *J. Organomet. Chem.* **2004**, *689*, 2033.

[33] For the addition of $LiNR_2$ to non-enolizable aldehydes see: a) D. L. Comins, J. D. Brown, *Tetrahedron Lett.* **1981**, *22*, 4213; D. L. Comins, J. D. Brown, N. B. Mantlo, *Tetrahedron Lett.* **1982**, *23*, 3979; D. L. Comins, J. D. Brown, *J. Org. Chem.* **1984**, *49*,

1078; b) D. Seebach, C. Betschart, M. Schiess, *Helv. Chim. Acta* **1984**, *67*, 1593; D. Seebach, M. Schiess, W. B. Schweizer, *Chimia* **1985**, *39*, 272; c) D. Seebach, T. Weber, *Tetrahedron Lett.* **1983**, *24*, 3315; D. Seebach, T. Weber, *Helv. Chim. Acta* **1984**, *67*, 1650; P. E. O'Bannon, W. P. Dailey, *J. Am. Chem. Soc.* **1989**, *111*, 9244.

[34] H. W. Gschwend, H. R. Rodriguez, *Org. React.* **1979**, *26*, 1.

[35] Typical procedure for the conversion of *N*-formylpiperidine to *N*-(2-hexyl)-piperidine with BuLi/MeLi:[7] BuLi (10 mmol, in hexane) was added to a solution of *N*-formylpiperidine (1.13 g, 10 mmol in 70 mL toluene), which was cooled to −73 °C; a suspension formed. The reaction temperature was kept at −73 °C for 3.5 h and then raised shortly to −47 °C. The reaction mixture was cooled to −75 °C, and $TiCl_4$ (1.1 mL, 10 mmol) was then added by syringe; after 3 h the reaction mixture was allowed to warm to +20 °C within 30 min. The reaction mixture was cooled again to −76 °C before MeLi (20 mmol, in Et_2O) was added and the temperature was slowly raised to RT overnight. Owing to the formation of suspensions vigorous stirring is necessary during all steps of the procedure. The reaction mixture was diluted with Et_2O and poured into an Erlenmeyer flask containing aq. 2 N KOH and stirred; the resulting white suspension was filtered through celite. The aqueous phase was extracted with Et_2O (3×), and the amine was extracted from the combined organic phases with 1 N HCl. From the acidic aqueous phase the amine was liberated by addition of 2 N KOH (to pH 9–10) and extraction with Et_2O. After drying ($MgSO_4$) the solvent was removed and the residue subjected to Kugelrohr distillation (ca. 180 °C/12 Torr), providing hexylpiperidine (1.25 g, 74 %) as colorless liquid. M.p. (picrate): 107.5–108.5 °C (EtOH). ^{1}H NMR (Varian 90 MHz, $CDCl_3$): $\delta = 0.7$–1.76 (m, 18 H), 2.3–2.66 ppm (m, 5 H, CH_2, NCH); MS (Hitachi–Perkin—Elmer RMU-6M): 169 (M^+, 2.1), 154 (11), 113 (8), 112 (100), 84 (4); elemental analysis (%) calcd for $C_{17}H_{26}O_7N_4$ (picrate): C 51.25, H 6.58, N 14.06; found.: C51.37, H 6.53, N 13.38.

[36] P. Beak, R. Farney, *J. Am. Chem. Soc.* **1973**, *95*, 4771; P. Beak, A. Basu, D. J. Gallagher, Y. S. Park, S. Thayumanavan, *Acc. Chem. Res.* **1996**, *29*, 552.

[37] D. Seebach, W. Lubosch, *Angew. Chem.* **1976**, *88*, 339; *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 313; R. Schlecker, D. Seebach, *Helv. Chim. Acta* **1977**, *60*, 1459; R. Schlecker, D. Seebach, W. Lubosch, *Helv. Chim. Acta* **1978**, *61*, 512; D. Seebach, T. Hassel, *Angew. Chem.* **1978**, *90*, 296; *Angew. Chem. Int. Ed. Engl.Angew. Chem. Int. Ed.* **1978**, *17*, 274; T. Hassel, D. Seebach *Helv. Chim. Acta* **1978**, *61*, 2237; W. Lubosch, D. Seebach, *Helv. Chim. Acta* **1980**, *63*, 102; J.-J. Lohmann, D. Seebach, M. A. Syfrig, M. Yoshifuji, *Angew. Chem.* **1981**, *93*, 125; *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 128; D. Seebach, M. A. Syfrig, *Angew. Chem.* **1984**, *96*, 235; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 248; D. Seebach, J. Hansen, P. Seiler, J. M. Gromek, *J. Organomet. Chem.* **1985**, *285*, 1; D. Seebach, I. M. P. Huber, *Chimia* **1985**, *39*, 233; D. Seebach, I. M. P. Huber, M. A. Syfrig, *Helv. Chim. Acta* **1987**, *70*, 1357; E. Pfammatter, D. Seebach, *Liebigs Ann. Chem.* **1991**, 1323; D. Seebach, E. Pfammatter, V. Gramlich, T. Bremi, F. Kühnle, S. Portmann, I. Tironi, *Liebigs Ann. Chem.* **1992**, 1145.

[38] D. Hoppe, *Angew. Chem.* **1984**, *96*, 930; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 932; D. Hoppe, T. Hense, *Angew. Chem.* **1997**, *109*, 2376; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2282; V. Bagutski, R. M. French, V. K. Aggarwal, *Angew. Chem.* **2010**, *122*, 5268; *Angew. Chem. Int. Ed.* **2010**, *49*, 5142.

[39] In a paper that has just appeared, lithiation of *N*-thiopivaloylazetidine on the four-membered ring is described: D. M. Hodgson, J. Kloesges, *Angew. Chem.* **2010**, *122*, 2962; *Angew. Chem. Int. Ed.* **2010**, *49*, 2900.

[40] V. Snieckus, *Chem. Rev.* **1990**, *90*, 879; M. C. Whisler, S. MacNeil, V. Snieckus, P. Beak, *Angew. Chem.* **2004**, *116*, 2256; *Angew. Chem. Int. Ed.* **2004**, *43*, 2206.

[41] From a recent communication it may be concluded that the primary adducts of Weinreb reactions form *N*-methoxyiminium ions, under the influence of Lewis acids: $R^1R^2C(OM)NMe(OMe) \rightarrow R^1R^2C{=}N^+Me(OMe) \rightarrow R^1R^2R^3C\text{-}NMe(OMe)$; K. Shirokane, Y. Kurosaki, T. Sato, N. Chida, *Angew. Chem.* **2010**, *122*, 6513; *Angew. Chem. Int. Ed.* **2010**, *49*, 6369.

[42] A. Meisters, T. Mole, *Aust. J. Chem.* **1974**, *27*, 1655; E. A. Jeffery, A. Meisters, T. Mole, *Aust. J. Chem.* **1974**, *27*, 2569.

[43] a) M. T. Reetz, J. Westermann, R. Steinbach, *J. Chem. Soc. Chem. Commun.* **1981**, 237; b) M. T. Reetz, J. Westermann, S.-H. Kyung, *Chem. Ber.* **1985**, *118*, 1050.

[44] M. T. Reetz, J. Westermann, *J. Org. Chem.* **1983**, *48*, 254.

[45] S. Araki, N. Katsumura, H. Ito, Y. Butsugan, *Tetrahedron Lett.* **1989**, *30*, 1581.

[46] L. E. Overman, *Synlett* **2010**, 1692.

[47] J. Christoffers, A. Baro, *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*, Wiley-VCH, Weinheim, **2005**.

[48] J. Christoffers, A. Baro, *Adv. Synth. Catal.* **2005**, *347*, 1473; B. M. Trost, C. H. Jiang, *Synthesis* **2006**, 369; O. Riant, J. Hannedouche, *Org. Biomol. Chem.* **2007**, *5*, 873; M. Shibasaki, M. Kanai, *Chem. Rev.* **2008**, *108*, 2853; M. M. Hussain, P. J. Walsh, *Acc. Chem. Res.* **2008**, *41*, 883; M. Bella, T. Gasperi, *Synthesis* **2009**, 1583.

[49] D. Müller, C. Hawner, M. Tissot, L. Palais, A. Alexakis, *Synlett* **2010**, 1694; T. Seiser, G. Cathomen, N. Cramer, *Synlett* **2010**, 1699; F. Pesciaioli, X. Tian, G. Bencivenni, G. Bartoli, P. Melchiorre, *Synlett* **2010**, 1704; J. C. Hsieh, S. Ebata, Y. Nakao, T. Hiyama, *Synlett* **2010**, 1709; N. T. McDougal, S. C. Virgil, B. M. Stoltz, *Synlett* **2010**, 1712; Z. Gu, A. T. Herrmann, C. E. Stivala, A. Zakarian, *Synlett* **2010**, 1717; S. E. Denmark, T. W. Wilson, *Synlett* **2010**, 1723.

[50] The degree of fascination for this subject is evident from the fact that the logic of language was disregarded in the title "Stereoselective *Synthesis* of Quaternary Carbons",[46,49] rather than, for instance, "Enantioselective Construction of Quaternary Stereocenters" (J. Christoffers, A. Mann, *Angew. Chem.* **2001**, *113*, 4725; *Angew. Chem. Int. Ed.* **2001**, *40*, 4591).

[51] A spectacular coupling of two tertiary centers with diastereoselective formation of a hexasubstituted ethane moiety has just been disclosed (reaction of 2-chloro-2-methylcyclohexanone tosylhydrazone with a tertiary Grignard reagent under Cu-catalysis): J. M. Hatcher, D. M. Coltart, *J. Am. Chem. Soc.* **2010**, *132*, 4546.

