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Cyclopropylamines from *N*,*N*-Dialkylcarboxamides and Grignard Reagents in the Presence of Titanium Tetraisopropoxide or Methyltitanium Triisopropoxide**

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Dedicated to Professor Ryoji Noyori on the occasion of his birthday

Abstract: Thirty-three different *N*,*N*-dialkyl- and *N*-alkyl-*N*-phosphorylalkyl-substituted carboxamides **9**–**17** were treated with unsubstituted as well as with 2-alkyl-, 2,2-dialkyl-, and 3-alkenyl-substituted ethylmagnesium bromides **6** in the presence of stoichiometric amounts of titanium tetraisopropoxide or methyltitanium triisopropoxide to furnish substituted cyclopropylamines **20**–**25** in 20–98% yield, depending on the substituents with no (1:1) to excellent (>25:1) diastereoselectivities. Generally higher yields (up to 98%) of the cyclopropylamines **20**–**28** without loss of the diastereoselectivity were obtained with methyltitanium triisopropoxide as the titanium mediator. Under these conditions, even dioxolane-protected ketones and halogen-substituted and chiral as well as achiral alkyloxyalkyl-substituted carboxamides could be converted to the correspondingly substituted cyclopropylamines with unsubstituted as well as phenyl- and a variety of alkyl-substituted ethylmagnesium bromides in addition to numerous heteroatom-containing (e.g., halogen-, trityloxy-, tetrahydropyranyloxy-substituted) Grignard reagents (62 examples altogether). The transformation of *N*,*N*-diformylalkylamines **54** with ethylmagnesium bromide in the presence of methyltitanium triisopropoxide to *N*,*N*-dicyclopropyl-*N*-alkylamines **55** can be brought about in up to 82% yield (6 examples). An asymmetric variant of the titanium-mediated cyclopropanation of *N*,*N*-dialkylcarboxamides has been developed by applying chiral titanium mediators generated from stoichiometric amounts of titanium tetraisopropoxide and chiral diamino or diol ligands, respectively. The most efficient chiral mediators turned out to be titanium bistaddolates that provided the corresponding cyclopropylamines with enantiomeric excesses (*ee*) of up to 84%. Evaluation of several silyl-based additives revealed that the reaction can also efficiently be carried out with substoichiometric amounts (down to 25 mol%) of the titanium reagent, as long as 2-aryl- or 2-ethenyl-substituted ethylmagnesium halides are used and a concomitant slight decrease in yields is accepted. The newly developed methodology was successfully applied for the preparation of analogues with cyclopropylamine moieties of known drugs and natural products such as the nicotine metabolite (*S*)-Cotinine as well as the insecticides Dinotefuran and Imidacloprid.

Keywords: amines · enantioselectivity · organometallics · small ring systems · titanium

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[+] Crystal-structure analyses.

[**] Cyclopropyl Building Blocks for Organic Synthesis, Part 156; Part 155: A. Lygin, M. Limbach, A. Janssen, V. S. Korotkov, C. Funke, A. de Meijere, *Eur. J. Org. Chem.* **2010**, 3665–3671.

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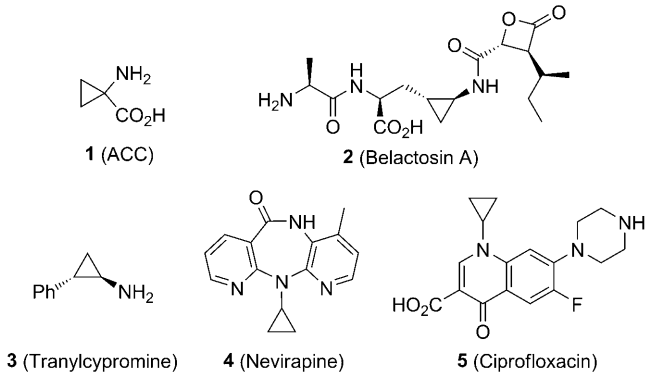
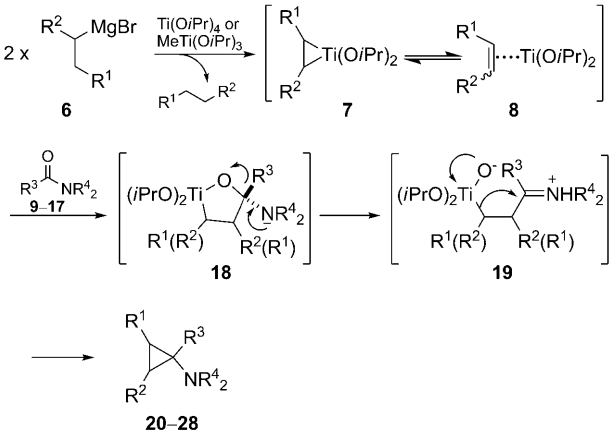
Introduction

The aminocyclopropyl moiety is a key constituent in a variety of natural and non-natural compounds that exhibit important biological activities. For example, 1-aminocyclopropanecarboxylic acid (ACC, **1**) is present in every plant on this



planet as the immediate precursor to the plant hormone ethylene, which plays a pivotal role in the induction of flowering, fruit ripening, leaf wilting, and several other plant physiological processes.[1] The *Streptomyces* sp. UCK 14 metabolite Belactosin A (**2**) and its derivatives, which contain the unusual 2-*trans*-(2-aminocyclopropyl)alanine residue, exhibit remarkable proteasome inhibitory activities.[2] The simple *trans*-2-phenylcyclopropylamine (**3**) is in use as an antidepressant (generic name Tranylcypramine).[3] The diazepinone derivative Nevirapine (**4**) is an anti-HIV drug candidate,[4] and the *N*-cyclopropylquinolone derivative Ciprofloxacin (**5**) is an important commercial antiinfectant.[5]

Until about 20 years ago, synthetic accesses to cyclopropylamines and the installation of a cyclopropyl residue on nitrogen heterocycles was rather limited.[6–8] Vilsmeier et al. pioneered and developed new accesses, in particular to interesting bicyclic cyclopropylamines from easily available 3-chloro-2-dialkylaminocycloalk-1-enes.[7] This was preceded and followed by other developments, mostly for specific target cyclopropylamines.[6,8] The advent of the titanium-catalyzed conversion of carboxylic acid esters to cyclopropanols (the Kulinkovich reaction)[9] has spurred our forays into the chemistry of organotitanium reagents and culminated in the discovery in 1996 of the novel and straightforward access to *N*,*N*-disubstituted cyclopropylamines from *N*,*N*-dialkylcarboxamides and alkylmagnesium halides in the presence of titanium tetraisopropoxide or, even better, methyltitanium triisopropoxide (Scheme 1).[10] The succeeding years have witnessed a host of modifications and applications of this extremely useful transformation.[11–14] To this end, we wish to disclose our hitherto unpublished results and experimental details in this area, which have been collected over the last decade up to the present date.



Scheme 1. Preparation of cyclopropylamines **20**–**28** from carboxamides **9**–**17** in the presence of $Ti(OiPr)_4$. For details, see Tables 1 and 2.

Results and Discussion

Reductive cyclopropanation of *N*,*N*-dialkylcarboxamides in the presence of titanium tetraisopropoxide: On the basis of our own observations and stereochemical investigations by Casey et al.,[15] the title reaction can best be described as proceeding by means of an oxatitanacyclopentane **18**, formed by insertion of the amide carbonyl group into a titanacyclopropane **7**, which can also be described as the titanium-alkene complex **8**, formed in situ from two molecules of the alkylmagnesium halide **6** and a titanium tetraalkoxide such as the most commonly used titanium tetraisopropoxide. This occurs with retention of configuration at the carbon center, which is involved in the C–C bond formation. Due to the oxophilicity of titanium and the poor nucleofugic characteristics of the dialkylamino group, this intermediate evolves into the 1,6-zwitterion **19** with a titanium oxide anion and an iminium cation terminus. Subsequent ring closure, with inversion of configuration at the carbon bound to titanium, leads to the *N*,*N*-dialkylcyclopropylamines **20**–**28** (Scheme 1).

The reaction generally proceeds in good yields (up to 92%) with *N*,*N*-dialkylcarboxamides of sterically noncongested carboxylic acids (Table 1). Thus, the reactions of formamides, acetamides, and propion- and *n*-butyramides with ethylmagnesium bromide (**6a**) in the presence of stoichiometric amounts of titanium tetraisopropoxide readily furnish the corresponding 1-alkyl-*N*,*N*-cyclopropylamines in 20–76% yield (Table 1, entries 1–10). Likewise, applications of 2-alkyl- or 2-alkenyl-substituted Grignard reagents, respectively, provide the corresponding 2-substituted as well as 1,2-disubstituted cyclopropylamines in 35–63% yield (entries 11–18), and the 2,2-dialkyl-substituted isobutylmagnesium bromide gave rise to the corresponding 1,2,2-trisubstituted cyclopropylamine (entry 19). Even 1-phosphorylethyl-substituted cyclopropylamines could be synthesized in moderate yields (39–47%) by reaction of the correspondingly substituted carboxamides with either unsubstituted or 2-alkyl-substituted ethylmagnesium bromides (entries 20–22),

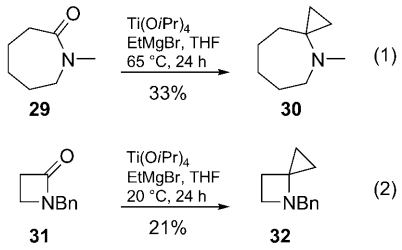
Table 1. Cyclopropylamines **20**–**25** from carboxamides **9**–**14** and unsubstituted as well as substituted EtMgBr **6** in the presence of $Ti(OiPr)_4$ (see Scheme 1).

Entry	6	R^1	R^2	Amide	R^3	$R^4{}_2$	Product	Yield [%] (d.r.)[a]
1	**a**	H	H	**9a**	H	Bn_2	**20aa**	69
2	**a**	H	H	**9b**	Me	Bn_2	**20ab**	60
3	**a**	H	H	**9c**	Et	Bn_2	**20ac**	63
4	**a**	H	H	**9d**	*n*Pr	Bn_2	**20ad**	52
5	**a**	H	H	**10a**	H	Me_2	**21aa**	73
6	**a**	H	H	**10b**	Me	Me_2	**21ab**	56
7	**a**	H	H	**11a**	H	$-(CH_2)_5-$	**22aa**	74
8	**a**	H	H	**12a**	H	$-(CH_2)_2O(CH_2)_2-$	**23aa**	74
9	**a**	H	H	**13a**	H	$(tBu)_2$	**24aa**	20
10	**a**	H	H	**14a**	H	$(iPr)_2$	**25aa**	76
11	**b**	Me	H	**9b**	Me	Bn_2	**20bb**	50[b]
12	**b**	Me	H	**9c**	Et	Bn_2	**20bc**	38[b]
13	**c**	*n*Bu	H	**9d**	*n*Pr	Bn_2	**20cd**	35[b]
14	**b**	Me	H	**9a**	H	Bn_2	**20ba**	63 (1:1)
15	**c**	*n*Bu	H	**9a**	H	Bn_2	**20ca**	52 (1:2.3)
16	**c**	*n*Bu	H	**10b**	Me	Me_2	**21cb**	37[b]
17	**d**	Et	H	**9b**	Me	Bn_2	**20db**	47[b]
18	**e**	$CH_2{=}CH-$	H	**9a**	H	Bn_2	**20ea**	42 (>25:1)
19	**f**	Me_2[c]	H	**9b**	Me	Bn_2	**20fb**	51
20	**a**	H	H	**10e**	$(MeO)PhP(O)(CH_2)_2$	Me_2	**21ae**	47
21	**b**	Me	H	**10e**	$(MeO)PhP(O)(CH_2)_2$	Me_2	**21be**	39 (8.5:1)
22	**d**	Et	H	**10e**	$(MeO)PhP(O)(CH_2)_2$	Me_2	**21de**	42 (10:1)
23	**g**	$-(CH_2)_3-$		**9a**	H	Bn_2	**20ga**	63–92[d]
24	**h**	$-(CH_2)_4-$		**9a**	H	Bn_2	**20ha**	34[d]

[a] d.r. = diastereomeric ratio. [b] Only one diastereomer was isolated, presumably with an *E* configuration. [c] 2,2-Dimethylcyclopropyl derivative. [d] Only the *exo* isomer was isolated.

and employment of cyclic Grignard reagents furnished bicyclic, that is, ring-annelated cyclopropylamines in low to very good yields of 34–92% (entries 23 and 24).

Likewise, with N-substituted lactams **29** and **31** as the amide starting materials, spirocyclopropanated nitrogen heterocycles **30** and **32** can be prepared (Scheme 2).



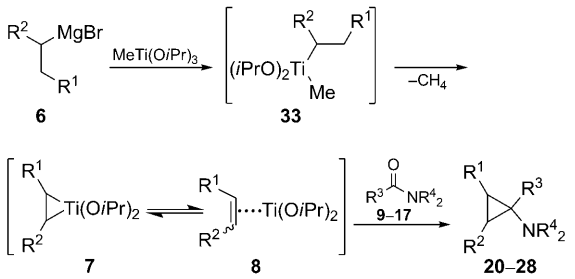
Scheme 2. Preparation of spirocyclopropane-annelated nitrogen heterocycles from N-substituted lactams.

It can be concluded that the nature of the substituents on the amide nitrogen does not impose severe limitations on the reactivity, as long as they tolerate the moderately Lewis acidic reaction media; however, a significant drop in yields is observed with a drastic increase in the steric bulk of the substituents in the substrates and reagents. Thus, on going from *N*,*N*-diisopropylformamide (**14a**) to *N*,*N*-di-*tert*-butylformamide (**13a**), the yield of the resulting corresponding *N*,*N*-dialkylcyclopropylamine drops from 76% for **25aa** to 20% for **24aa** (Table 1, entries 10 and 9). Yet the sterically most highly congested tertiary amine known to date, the *N*,*N*-di-*tert*-butylcyclopropylamine (**24aa**), can be prepared by this method. As an X-ray crystal-structure analysis of cyclopropyldiisopropylamine (**25aa**) revealed, the steric crowding in this tertiary amine does not lead to quite as much flattening of the central nitrogen (sum of C-N-C angles 340.0°)[16] as in triisopropylamine (sum of C-N-C angles 350.4°).[17]

The reactions usually proceed with moderate stereoselectivities (up to 2.5:1–3:1), thereby reflecting reduced steric interactions between the upcoming dialkylamino group and the substituent R^1 (R^2) in the transition structure between the intermediate **19** and the products **20**–**28**. In certain cases (e.g., Table 1, entry 18), however, a rather high level of diastereocontrol does occur, and this is apparently due to stabilizing polar interactions between the partially negatively charged allyl moiety and the cationic iminium terminus in the transition structure derived from **19**. Unlike the transformation of carboxylic acid esters to cyclopropanols, in which a tetraalkoxytitanium species is constantly being regenerated, the transformation of *N*,*N*-dialkylcarboxamides **9**–**17** to cyclopropylamines **20**–**28** is non-catalytic in titanium, since the oxotitanium side product most probably is oligomeric and thus can no longer participate in the reaction.

Reductive cyclopropanation of *N*,*N*-dialkylcarboxamides in the presence of methyltitanium triisopropoxide: Methyltitanium triisopropoxide has been found to be a superior titanium reagent for the reductive cyclopropanation of *N*,*N*-dialkylcarboxamides.[10b,18] Its advantage over titanium tetraisopropoxide derives from the possibility that it more rapidly reacts with the Grignard reagent to give the alkylmethyltitanium diisopropoxide **33**, which, by β-hydride transfer from the alkyl to the methyl group, selectively cleaves off methane to furnish the key reactive intermediate **7**. In comparison, the more sterically congested titanium tetraisopropoxide has to undergo two consecutive exchanges of isopropoxide with alkyl ligands from the Grignard reagent to provide the dialkyltitanium diisopropoxide as a precursor to the titanacyclopropane **7** or the titanium-alkene complex **8**, respectively. Thus, the use of methyltitanium triisopropoxide has the additional advantage that only one equivalent of a—potentially precious—alkylmagnesium halide **6** is consumed to produce the immediate precursor **7** to the cyclopropylamine

20–28, and with the use of more than one equivalent of **6**, the achievable yields of the desired products are improved (Scheme 3).



Scheme 3. Preparation of cyclopropylamines **20–28** from carboxamides **9–17** in the presence of $MeTi(OiPr)_3$. For details, see Table 2.

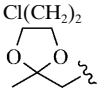
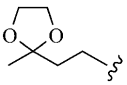
In analogy to the reductive cyclopropanation of *N*,*N*-dialkylcarboxamides **9–17** with ethylmagnesium bromide in the presence of stoichiometric amounts of titanium tetraisopropoxide, a large variety of *N*,*N*-dialkylcarboxamides and -formamides in the presence of stoichiometric amounts of methyltitanium triisopropoxide have been converted to the corresponding 1-substituted cyclopropylamines **20–28** in moderate to excellent yields (up to 96%) depending on the steric congestion evoked by the amide substituent R^3 (Scheme 3; Table 2, entries 1–16). Among the latter were even amides with benzyloxyalkyl and chloroalkyl (entries 11 and 12) as well as dioxolane moieties (entries 13 and 14), which furnished the correspondingly 1-substituted cyclopropylamines in 38–85% yield. Likewise, several 2-substituted ethylmagnesium bromides were successfully employed, thereby providing 2-alkyl- (entries 17–19 and 21–24), 2-alkenyl- (entries 20, 25, 28, 29, 32, 37, and 43), and 2-aryl-substituted (entries 26 and 27) cyclopropylamines. Phosphonate and phosphine oxide moieties are tolerated in the carboxamide and remain unaffected by the organotitanium species. Accordingly, interesting and potentially useful isosters of γ-aminocarboxylic acids as well as cyclopropyl analogues of 3-aminoalkylphosphines were prepared in 21–86% yield (entries 30–39). Carboxamides **9v** and **9w** derived from (*S*)-lactic acid were succesfully transformed with several Grignard reagents to the corresponding cyclopropylamines in 56–63% yield (entries 40–43); however, when 2-substituted Grignard reagents were used, mixtures of all four possible diastereomers were obtained, thus indicating that virtually no stereocontrol was exerted by the stereogenic center in the starting material (entries 42 and 43).

To determine whether oxygen functionalities can be incorporated into the side chain on C-2 of the cyclopropylamine, oxygen-functionalized Grignard reagents were employed in the titanium-mediated cyclopropanation reaction. Indeed, protected alcohol functionalities could be brought in by application of trityloxyalkyl-substituted alkylmagnesium halides to afford the corresponding cyclopropylamines **34a–39a**, albeit only in very low to moderate yields (2–53%). This might be a consequence of the steric congestion by the trityl group or a facile elimination of the trityloxy group from the Grignard reagent (Scheme 4; Table 3, entries 1–6). Likewise, use of tetrahydropyranyloxyalkylmagnesium halides gave the corresponding cyclopropylamines **40a–43a** (entries 7–10); however, the yields remained low to moderate (14–48%) and could not be improved significantly by application of a benzyloxy- or a *tert*-butyloxyalkyl Grignard reagent (entries 11 and 12). In contrast, a protected ketone functionality could be brought in with excellent yield (92%) by using the dioxolane-containing butylmagnesium bromide **46** to furnish cyclopropylamine **47a** (Scheme 4).

In analogy to the reductive cyclopropanation of ε-caprolactam **29** mediated by titanium tetraisopropoxide (see Scheme 2), the spirocyclopropanated azacycloheptane **30** can also be prepared using methyltitanium triisopropoxide, and in an even higher yield (47 versus 33%). An intramolecular reductive cyclopropanation of the amide carbonyl group in 6-bromo-*N*,*N*-dimethylhexaneamide (**48**) by the alkylmagnesium bromide terminus generated in situ furnished the fused bicyclic cyclopropylamine **49**, albeit in a rather low yield of 28%. Cyclobutylmagnesium bromide with *N*,*N*-dimethyl- (**9b**) and *N*,*N*-dibenzylformamide (**9a**) provided the corresponding bicyclo[2.1.0]pent-5-ylamines **50** and **51** in yields of 72 and 87%, respectively (Scheme 5). The *exo* configuration of the dimethylamino derivative **51** was unequivocally proved by an X-ray crystal-structure analysis of the hydrooxalate **50**·$(COOH)_2$ formed upon treatment of an ethereal solution of **51** with oxalic acid dihydrate.[16]

Titanium-mediated twofold reductive cyclopropanations of bisamides: In bisamides with two carboxamide functionalities, both carbonyl groups can be transformed to cyclopropyl moieties, even if they are attached to the same nitrogen atom, especially as in diformylamines **53**. Thus, several *N*-alkyl-*N*,*N*-dicyclopropylamines **54** are readily available in good yields (53–82%) by treactment of *N*-alkyldiformylamines **53** with ethylmagnesium bromide (**6a**) in the presence of methyltitanium triisopropoxide (Scheme 6; Table 4, entries 1–3, 5, and 6). *N*-Allyldiformylamine (**53d**) failed to give the corresponding *N*-allyl-*N*,*N*-dicyclopropylamine **54d** (entry 4), which may be due to a rapid ligand exchange of the allyl groups with ethylene in the titanacyclopropane intermediate of type **7**.[11g] In contrast to previous observations, according to which the conversion of a *tert*-butyl ester moiety to a cyclopropanol occurs much more slowly than that of an *N*,*N*-dibenzylformamide to a cyclopropylamine,[19] *tert*-butyl *N*,*N*-diformylglycinate **53g**, under the conditions employed in this context, furnished 1-(*N*,*N*-dicyclopropylaminomethyl)cyclopropanol (**55**) as the only isolable product in 28% yield (entry 7). The overall efficiency of this access to the peculiar tertiary amines **54** is potentiated by the straightforward preparation of diformylamines **53**, since the inexpensive formamide **52**, upon treatment with sodium methoxide in methanol, quantitatively yields sodium diformylamide with liberation of ammonia,[20,21] which undergoes

Table 2. Cyclopropylamines **20**–**28** from carboxamides **9**–**17** and unsubstituted as well as substituted EtMgBr **6** in the presence of $MeTi(OiPr)_3$ (see Scheme 3).

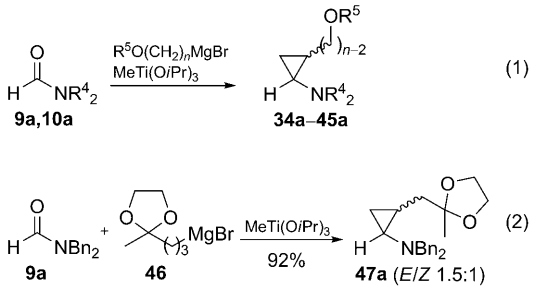
Entry	6	R^1	R^2	Amide	R^3	$R^4{}_2$	Product	Yield [%] (*E*/*Z* ratio)
1	**a**	H	H	**9a**	H	Bn_2	**20aa**	96
2	**a**	H	H	**9b**	Me	Bn_2	**20ab**	77
3	**a**	H	H	**9c**	Et	Bn_2	**20ac**	70
4	**a**	H	H	**9d**	*n*Pr	Bn_2	**20ad**	62
5	**a**	H	H	**9f**	*i*Pr	Bn_2	**20af**	44
6	**a**	H	H	**9g**	*t*Bu	Bn_2	**20ag**	25
7	**a**	H	H	**9h**	*i*Bu	Bn_2	**20ah**	56
8	**a**	H	H	**11i**	Ph	$-(CH_2)_5-$	**20ai**	73
9	**a**	H	H	**9j**	$Ph(CH_2)_2$	Bn_2	**20aj**	63
10	**a**	H	H	**9k**	Bn	Bn_2	**20ak**	47
11	**a**	H	H	**9L**	$BnO(CH_2)_2$	Bn_2	**20al**	38
12	**a**	H	H	**9m**	$Cl(CH_2)_2$	Bn_2	**20am**	49
13	**a**	H	H	**9n**		Bn_2	**20an**	53
14	**a**	H	H	**9o**		Bn_2	**20ao**	85[a]
15	**a**	H	H	**14a**	H	iPr_2	**25aa**	86
16	**a**	H	H	**15a**	H	Et_2	**26aa**	83
17	**c**	*n*Bu	H	**10b**	Me	Me_2	**21cb**	51[b]
18	**c**	*n*Bu	H	**9d**	*n*Pr	Bn_2	**20cd**	47 (10:1)
19	**b**	Me	H	**9l**	$BnO(CH_2)_2$	Bn_2	**20bl**	33 (1:3)
20	**e**	CH_2=CH−	H	**10a**	H	Me_2	**21ea**	52 (10:1)
21	**b**	Me	H	**9a**	H	Bn_2	**20ba**	89 (1.2:1)
22	**i**	*n*Pr	H	**9a**	H	Bn_2	**20ia**	85 (2.1:1)
23	**c**	*n*Bu	H	**9a**	H	Bn_2	**20ca**	87 (2.1:1)
24	**j**	CH_2*c*Pr	H	**9a**	H	Bn_2	**20ja**	85 (2.2:1)
25	**e**	CH_2=CH−	H	**9a**	H	Bn_2	**20ea**	54[c] or 98 (7.0:1)
26	**k**	Ph	H	**9a**	H	Bn_2	**20ka**	98 (2.3:1)
27	**k**	Ph	H	**11a**	H	$-(CH_2)_5-$	**22ka**	92 (1.5:1)
28	**e**	CH_2=CH−	H	**16a**	H	PhMe	**27ea**	44 (7:1)
29	**e**	CH_2=CH−	H	**9p**	CH_2NBn_2	Bn_2	**20ep**	84[c]
30	**a**	H	H	**9q**	$Ph_2P(O)(CH_2)_2$	Bn_2	**20aq**	83
31	**b**	Me	H	**10q**	$Ph_2P(O)(CH_2)_2$	Me_2	**21bq**	80 (1:3.5)
32	**e**	CH_2=CH-	H	**10q**	$Ph_2P(O)(CH_2)_2$	Me_2	**21eq**	83 (1:3)
33	**k**	Ph	H	**10q**	$Ph_2P(O)(CH_2)_2$	Me_2	**21kq**	67 (1:1.6)
34	**a**	H	H	**17r**	$Ph_2P(CH_2)_2$	Ph_2	**28ar**	21
35	**a**	H	H	**10s**	$(MeO)_2P(O)(CH_2)_2$	Me_2	**21as**	79
36	**b**	Me	H	**10s**	$(MeO)_2P(O)(CH_2)_2$	Me_2	**21bs**	81 [1:6]
37	**e**	CH_2=CH−	H	**10s**	$(MeO)_2P(O)(CH_2)_2$	Me_2	**21es**	86 (1:1.6)
38	**k**	Ph	H	**10s**	$(MeO)_2P(O)(CH_2)_2$	Me_2	**21ks**	82 (1:1.4)
39	**a**	H	H	**9t**	$(BnO)_2P(O)(CH_2)_2$	Bn_2	**20at**	62
40	**a**	H	H	**9u**		Bn_2	**20au**	63
41	**a**	H	H	**9v**		Bn_2	**20av**	56
42	**d**	Et	H	**9u**		Bn_2	**20du**	58[d]
43	**e**	CH_2=CH−	H	**9u**		Bn_2	**20eu**	61[e]

[a] Several previously published reviews[14] erroneously list an additional CH_2 group in compounds **9o** and **20ao**, respectively. [b] Only one diastereomer was isolated, presumably with an *E* configuration. [c] Two diastereomers were obtained, the ratio of which was not determined. [d] Four diastereomers were obtained, ratio 1:1.6:1.6:3.1. [e] Four diastereomers were obtained, ratio 1:1.3:2.1:3.2.

facile alkylation with various alkyl sulfates[20] and bromides (Scheme 6).[21]

Twofold cyclopropanation of the bis(*N*,*N*-dimethyl)dicarboxamide **56** derived from (*R*,*R*)-tartaric acid afforded the bis(dimethylaminocyclopropylethane derivative **58** in almost quantitative yield. Yet an attempted analogous transformation of the bis(*N*,*N*-dibenzyl)dicarboxamide **57** failed completely (Scheme 7), which must be attributed to the steric demand of the four benzyl groups suppressing formation of the required intermediate titanaoxacyclopentane derivative analogous to **18** (see Scheme 1).

Enantioselective cyclopropanation of *N*,*N*-dialkylcarboxamides in the presence of chirally modified titanium reagents: 2-Substituted ethylmagnesium halides **6** generally provide mixtures of diastereomeric 2-substituted cyclopropylamines without or with moderate at best diastereoselectivities of about 1:2 (see Table 2) in favor of the thermodynamically more stable *E* isomer. The only exception was found upon application of 3-butenylmagnesium bromide (**6e**) (homoallylmagnesium bromide) on *N*,*N*-dibenzylformamide (**9a**) to yield *N*,*N*-dibenzyl-2-ethenylcyclopropylamine (**20ea**) with an *E*/*Z* ratio of 7.0:1 (Table 2, entry 25). Since 2-substituted ethylmagnesium halides **6** in this reaction (Scheme 2) provide chiral cyclopropylamines, it was of interest to test whether or not a reasonable level of enantioselectivity could in principle be achieved by using chiral titanium alkoxide mediators instead of the established methyltitanium triisopropoxide. Such an asymmetric variant of a titanium-mediated cyclopropanation had already been described by Corey et al. for the Kulinkovich-type conversion of ethyl acetate with 2-phenylmagnesium bromide to (*Z*)-2-phenyl-1-methylcyclopropanol with an enantiomeric excess (*ee*) of up to 78% by employing a stoi-

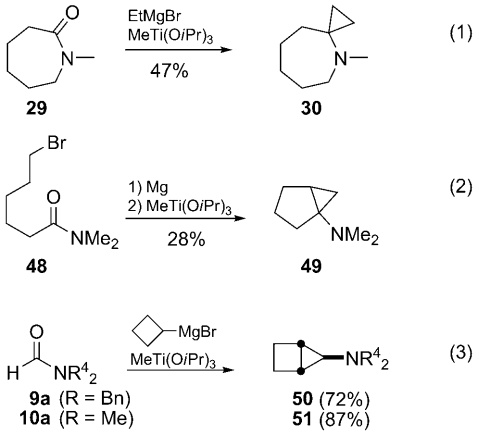


Scheme 4. Oxygen functionalities are introduced into 2-substituted cyclopropylamines with the help of oxygen-functionalized Grignard reagents. For details, see Table 3.

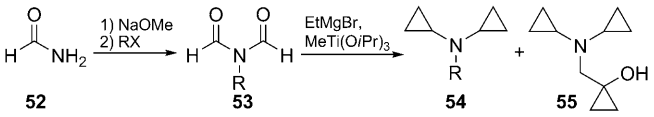
Table 3. Introducing oxygen functionalities into 2-substituted cyclopropylamines with the help of of oxygen-functionalized Grignard reagents (see Equation (1) in Scheme 4).

Entry	Amide	R^4_2	R^5	*n*	Product	Yield [%] (*E*/*Z* ratio)
1	**10a**	Me_2	Ph_3C	3	**34a**	18[a]
2	**9a**	Bn_2	Ph_3C	3	**35a**	2[a]
3	**10a**	Me_2	Ph_3C	4	**36a**	23 (1.2:1)
4	**9a**	Bn_2	Ph_3C	4	**37a**	36 (4.4:1)
5	**10a**	Me_2	Ph_3C	5	**38a**	53 (1.8:1)
6	**9a**	Bn_2	Ph_3C	5	**39a**	34 (2.7:1)
7	**10a**	Me_2	THP	4	**40a**	48 (2.5:1)[b]
8	**9a**	Bn_2	THP	4	**41a**	34 (2.1:1)[b]
9	**10a**	Me_2	THP	5	**42a**	51 (1.2:1)[b]
10	**9a**	Bn	THP	5	**43a**	14 (1.6:1)[b]
11	**10a**	Me_2	Bn	4	**44a**	54 (1.1:1)
12	**9a**	Bn_2	*t*Bu	5	**45a**	59 (2:1)

[a] Only one diastereomer was isolated, presumably the *E* isomer. [b] Two diastereomeric pairs were obtained.



Scheme 5. Accesses to spiroannelated and fused bicyclic cyclopropylamines.



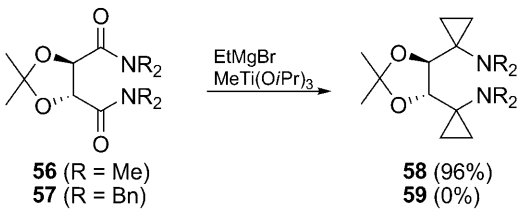
Scheme 6. Synthesis of dicyclopropylamines. For details, see Table 4.

Table 4. Synthesis of dicyclopropylamines (see Scheme 6).

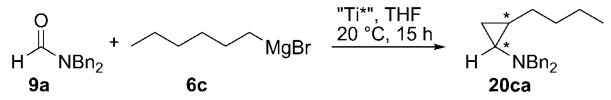
Entry	RX	R	*N*-Alkyl-*N*,*N*-diformylamine	Yield [%]	*N*,*N*-Dicyclopropylamine	Yield [%]
1	$(MeO)_2SO_2$	Me	**53a**	70	**54a**	67
2	$(EtO)_2SO_2$	Et	**53b**	71	**54b**	82
3	BuOMs	*n*Bu	**53c**	74	**54c**	53
4	AllBr	All	**53d**	52	**54d**	0
5	BnBr	Bn	**53e**	97	**54e**	57
6	4-$MeOC_6H_4CH_2Br$	4-$MeOC_6H_4CH_2$	**53f**	52	**54f**	53
7	$BrCH_2CO_2tBu$	$tBuO_2CCH_2$	**53g**	99	**55**	28

chiometric amount of a chiral titanium tetraalkoxide[22] prepared from an appropriately substituted chiral tetraphenyldioxolanedimethanol (TADDOL) ligand and a titanium tetraalkoxide.[23] Encouraged by this success, the development of similar conditions for the enantioselective cyclopropanation of *N*,*N*-dialkylcarboxamides was envisaged.

As a model system, the transformaton of *N*,*N*-dibenzylformamide (**9a**) with *n*-hexylmagnesium (**6c**) bromide was chosen (Scheme 8 and Table 2, entry 23). After initial optimization experiments, it was found that chiral titanium ligands generated from one equivalent of titanium tetraisopropoxide and one equivalent of either diamines, such as (1*R*,2*R*)-*N*,*N*′-bis(trifluoromethanesulfonyl)-1,2-diaminocyclohexane (DACH) **60** and (1*R*,2*R*)-*N*,*N*′-bis(trifluoromethanesulfonyl)-1,2-diaminodiphenylethane (DADPE) **61**, or the diol (*S*)-1,1′-bi-2-naphthol (BINOL) **62** did only furnish essentially racemic products (Table 5, entries 1–3) with concomitant loss of yield (52–65% vs. 87% for the variant with achiral methyltitanium triisopropoxide). In contrast, application of tetraphenyldioxolanedimethanol (TADDOL) **63** led to 2-butyl-*N*,*N*-dibenzylcyclopropylamine (**20ca**) in 59% yield with moderate enantiomeric excesses of 41% for the *Z* and 35% for the *E* isomer (entry 4). Further improvement of the enantiomeric excesses to 66% for the *Z* and 42% for the *E* isomer could be achieved, when the chiral titanium mediator was generated from two instead of one equivalent of TADDOL **63** (entry 5).

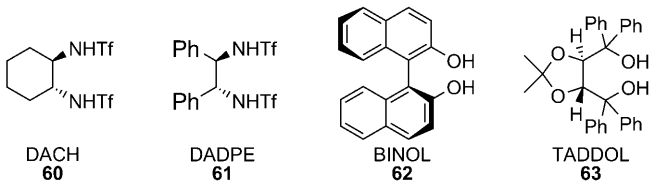


Scheme 7. Titanium-mediated cyclopropanation of (*R*,*R*)-tartaric acid derivatives.



Scheme 8. Enantioselective reductive cyclopropanation of carboxamide **9a** with **6c**. For details, see Table 5.

Table 5. Enantioselective reductive cyclopropanation of carboxamide **9a** with **6c** (see Scheme 8).



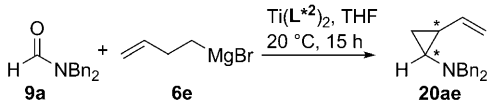
DACH **60** DADPE **61** BINOL **62** TADDOL **63**

Entry	"Ti"	Ligand	Yield **20ca** [%]	*Z*/*E*	*ee Z* isomer [%][a]	*ee E* isomer [%][a]
1	Ti(O*i*Pr)$_2$**L**	**60**	52	1:3.2	2	1
2	Ti(O*i*Pr)$_2$**L**	**61**	50	1:2.3	1	2
3	Ti(O*i*Pr)$_2$**L**	**62**	65	1:1.7	2	5
4	Ti(O*i*Pr)$_2$**L**	**63**	59	1:2.0	41	35
5	Ti**L**$_2$	**63**	57	1:5.0	66	42

[a] Enantiomeric excesses were determined after reductive debenzylation of **20ca**, thereby trapping the cyclopropylamine as a hydrotrifluoroacetate, and separation by analytical chiral-phase gas chromatography.

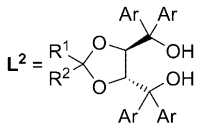
These results induced an attempt to optimize the enantioselectivity by systematic modification of the TADDOL ligand (Table 6). Switching from the two methyl substituents R^1 and R^2 on the dioxolane ring to the more bulky ethyl groups improved the enantiomeric excess slightly to 70% for the *Z* and 55% for the *E* isomer (Table 6, entry 2). Similar improvements were observed when one phenyl or one mesityl substituent (entries 4 and 5) was introduced on the dioxolane ring, whereas a spiroanellated five-membered ring (entry 3) did not increase the enantiomeric excesses. The highest enantioselectivities were obtained by application of a *tert*-butyl-substituted dioxolane derivative (entry 6) that gave rise to 84% enantiomeric excess for the *Z* isomer and 77% for the *E* isomer, but decreased the yield to 47%. Similar enantioselectivities (80% for the *Z* and 75% for the *E* isomer) were observed, when the aryl substituents on the diol moiety were changed from phenyl to the sterically more demanding 1-naphthyl groups, however, the yield went down even more to 38% (entry 7), whereas 3,5-dimethylphenyl- or 3,5-trifluoromethylphenyl substituents significantly decreased the enantioselectivities (entries 8 and 9). Since application of di-*tert*-butyl tartrate (entry 10) or 1,4-dimethoxy-1,1,4,4-tetraphenylbutane-2,3-diol (entry 11), respectively, only led to moderate enantiomeric excessses for both isomers, it can be concluded that close proximity of the chiral information and the titanium center is generally less important than steric bulk of the dioxolane substituents.

Similar results were observed for the reductive cyclopropanation of *N*,*N*-dibenzylformamide (**9a**) with 3-butenylmagnesium bromide (**6e**) (Scheme 9) in the presence of enantiomerically pure titanium bis(TADDOL)ates. Thus, application of tetraphenyldioxolanedimethanol as the ligand furnished the corresponding cyclopropylamine with an enantiomeric excess of 24% for the *E* isomer (Table 7, entry 1; the *ee* value of the *Z* isomer was not determined) and switching to the sterically more congested *tert*-butyl derivative significantly improved the enantiomeric excess to 62% (entry 2; the *ee* value of the *Z* isomer was not determined, but by comparison with the *ee* values for (*E*)-**20ca** and (*Z*)-**20ca** it is estimated to be 67%). It is noteworthy that, in



Scheme 9. Enantioselective reductive cyclopropanation of carboxamide **9a** with **6e** in the presence of chirally modified Ti(**L***^{2})$_2$. For details, see Table 7.

Table 6. Enantioselective reductive cyclopropanation of carboxamide **9a** with **6c** in the presence of chirally modified Ti(**L**^{2})$_2$ (see Scheme 8).



Entry	R^1	R^2	Ar	Yield **20ca** [%]	*Z*/*E*	*ee Z* isomer [%][a]	*ee E* isomer [%][a]
1	Me	Me	Ph	57	1:5.0	66	42
2	Et	Et	Ph	61	1:3.5	70	55
3	−(CH$_2$)−		Ph	64	1:2.8	65	50
4	Ph	H	Ph	55	1:3.0	73	62
5	Mes	H	Ph	55	1:2.7	71	65
6	*t*Bu	H	Ph	47	1:3.0	84	77
7	Me	Me	1-naphthyl	38	1:3.1	80	75
8	Me	Me	3,5-Me$_2$Ph	40	1:2.5	60	49
9	Me	Me	3,5-(CF$_3$)$_2$Ph	73	1:2.5	25	11
10			[b]	43	1:2.9	70	59
11			[c]	45	1:2.5	55	50

[a] Enantiomeric excesses were determined by comparison of the measured $[\alpha]_D^{20}$ values with the maximum $[\alpha]_D^{20}$ values extrapolated from the values for samples, for which the enantiomeric excesses were determined by chiral-phase gas chromatography (see footnote in Table 5). [b] Di-*tert*-butyl tartrate was used as the ligand **L**. [c] 1,4-Dimethoxy-1,1,4,4-tetraphenylbutane-2,3-diol was used as the ligand **L**.

Table 7. Enantioselective reductive cyclopropanation of carboxamide **9a** with **6e** in the presence of chirally modified Ti(**L***^{2})$_2$ (see Scheme 9).

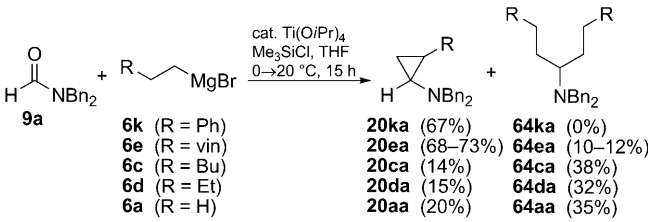
Entry	R^1	R^2	Ar	Yield **20ae** [%]	*Z*/*E*	*ee Z* isomer [%][a]	*ee E* isomer [%][b]
1	Me	Me	Ph	43	1:7.0	–	24
2	*t*Bu	H	Ph	45	1:7.0	–	62

[a] Enantiomeric excesses of the *Z* isomer were not determined. [b] Enantiomeric excesses of the *E* isomer were determined by ^{19}F-decoupled ^{1}H NMR spectroscopy of the (+)-Mosher ester obtained after hydroboration–oxidation of **20ae** and subsequent esterification with Mosher's acid chloride.

contrast to the corresponding cyclopropanations with *n*-hexylmagnesium bromide (**6e**) (see Scheme 8, Table 6), the diastereoselectivity in comparison with the achiral titanium reagent was not affected (1:7.0 for the chiral as well as the achiral reagent), and the chemical yield decreased only slightly (45–47% vs. 54% for the achiral reagent, see Table 2, entry 25).

Although the first asymmetric synthesis of 2-substituted cyclopropylamines by applying chirally modified titanium reagents could thus be achieved with acceptable enantioselectivities and in moderate yields, this success was hampered by the fact that equimolar amounts of the titanium mediator had to be used, probably due to the formation of an oligomeric, unreactive dialkoxytitanium oxide, which principally required two equivalents of the chiral ligand to form the active $Ti(\mathbf{L^2})_2$ species. Thus, the development of a catalytic variant of the titanium-mediated reductive cyclopropanation of *N*,*N*-dialkylcarboxamides in the presence of substoichiometric amounts of a chiral ligand is highly desirable.

It could be shown that the twofold alkylation of *N*,*N*-dialkylformamides with Grignard reagents that lack β-hydrogen atoms can be carried out with a catalytic amount of titanium reagent (3 mol%), if the intermediately formed titanium species is trapped with one equivalent of trimethylsilyl chloride.[24,25] Similarly, the cyclopropanation of *N*,*N*-dibenzylformamide (**9a**) with 2-phenylethylmagnesium bromide **6k** in the presence of 20 mol% of titanium tetraisopropoxide and one equivalent of trimethylsilyl chloride furnished *N*,*N*-dibenzyl-2-phenylcyclopropylamine (**20ka**) in 67% yield (*Z*/*E* = 1:2.0), and the reaction of **9a** with 3-butenylmagnesium bromide (**6e**) in the presence of 25 mol% of titanium tetraisopropoxide and one equivalent of trimethylsilyl chloride provided *N*,*N*-dibenzyl-2-ethenylcyclopropylamine (**20ea**) in 68–73% yield (*Z*/*E* = 1:7.0) with concomitant formation of the bisalkylation product **64** in 10–12% yield (Scheme 10).



Scheme 10. Reductive cyclopropanation of carboxamide **9a** with 2-substituted EtMgBr in the presence of a substoichiometric amount of $Ti(OiPr)_4$ and stoichiometric Me_3SiCl.

Encouraged by these results, similar reaction conditions were applied to an analogous cyclopropanation with β-hydrogen-containing alkylmagnesium halides. The reactions of *n*-hexyl-, *n*-butyl-, and ethylmagnesium bromide with **9a** under such conditions did indeed furnish the corresponding cyclopropylamines **20**, but in disappointingly low yields of only 14, 15, and 20%, respectively. The major products turned out to be the bisalkylation products **64** in 38, 32, and 35% yield, respectively (Scheme 10).

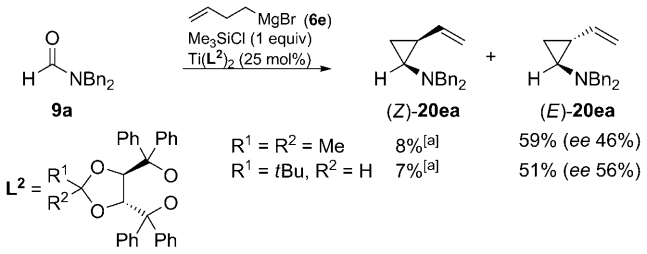
However, since the titanium-tetraisopropoxide-catalyzed cyclopropanation of *N*,*N*-dibenzylformamide (**9a**) with 3-butenylmagnesium bromide (**6e**) in the presence of trimethylsilyl chloride had furnished a satisfying yield of **20ea** (68–73%), a systematic evaluation was undertaken, in which the amount of titanium catalyst and the silyl additive was varied. It could be shown that further reduction of the amount of titanium tetraisopropoxide continuously decreased the quantity of cyclopropylamine **20ea** formed, with a lowest yield of 30% in the presence of 3 mol% titanium tetraisopropoxide (Table 8, entries 2–6). An increase in the amount of added trimethylsilyl chloride to two equivalents even led to a decrease of the yield to just 20% (entry 7). Additionally, several other alkylsilyl reagents were examined and found to either have virtually no effect on the yield (1,2-bis(chlorodimethysilyl)ethane, dichlorodimethylsilane, entries 8–10) or cause a significant decrease (*tert*-butyldimethylsilyl chloride, entry 11).

Table 8. Reductive cyclopropanation of carboxamide **9a** with **6e** in the presence of a substoichiometric amount of $Ti(OiPr)_4$ and stoichiometric silyl derivatives.

Entry	$Ti(OiPr)_4$ [mol%]	Si Additive ([equiv])	Yield **20ea** [%]
1	100	none	94
2	3	Me_3SiCl (1)	30
3	10	Me_3SiCl (1)	40
4	15	Me_3SiCl (1)	47
5	20	Me_3SiCl (1)	63
6	25	Me_3SiCl (1)	73
7	3	Me_3SiCl (2)	25
8	3	$(Me_2SiClCH_2)_2$ (1)	33
9	25	$(Me_2SiClCH_2)_2$ (1)	78
10	25	Me_2SiCl_2 (1)	71
11	25	$Me_2tBuSiCl$ (1)	34

As indicated by these results, the application of 25 mol% of titanium tetraisopropoxide and one equivalent of relatively inexpensive trimethylsilyl chloride as the silyl additive appeared to be the best conditions for a titanium-catalyzed variant of the reductive cyclopropanation of *N*,*N*-dialkylcarboxamides. Employing these conditions to the cyclopropanation of *N*,*N*-dibenzylformamide (**9a**) with 3-butenylmagnesium bromide (**6e**) in the presence of the chiral titanium bis(TADDOL)ates provided enantiomerically enriched *N*,*N*-dibenzyl-2-ethenylcyclopropylamine (**20ea**) in yields of 7–8% for the *Z* and 51–59% for the *E* isomer, the latter with an enantiomeric excess of up to 56%. In analogy to the noncatalyzed variant (see Scheme 9 and Table 7), the bis(TADDOL)ates with the *tert*-butyl substituent gave (*E*)-**20ea** with a higher, albeit only slightly, enantiomeric excess (56 vs. 46%) than the (TADDOL)ate with two methyl substituents (Scheme 11; the *ee* value of the *Z* isomer was not determined).

Although the enantioselectivities in this new asymmetric synthesis of 2-substituted cyclopropylamines remain moder-

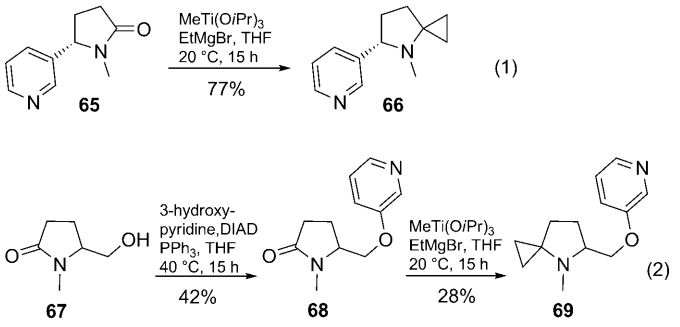


Scheme 11. Preparation of enantiomerically enriched cyclopropylamine **20ea**. [a] Enantiomeric excesses for the *Z* isomer were not determined.

ate, it constitutes the first enantioselective reductive cyclopropanation of carboxamides with substoichiometric quantities of the titanium mediator and sets the stage for potential further improvement of the enantioselectivities towards synthetically useful levels.

Application of the titanium-mediated cyclopropanation of *N,N*-dialkylcarboxamides in the synthesis of analogues of natural products and bioactive compounds: Having developed a reliable method with reproducible results for the transformation of *N,N*-dialkylcarboxamides into cyclopropylamines, a variety of applications towards drug development and natural product synthesis were considered. Thus, the titanium-mediated cyclopropanation does not only allow the transformation of known *N,N*-dialkylcarboxamide- and lactam-based biologically active compounds into potentially even more active cyclopropylamine analogues, but also the preparation of cyclopropylamine analogues of known biologically active compounds with methylene groups adjacent to a nitrogen atom.

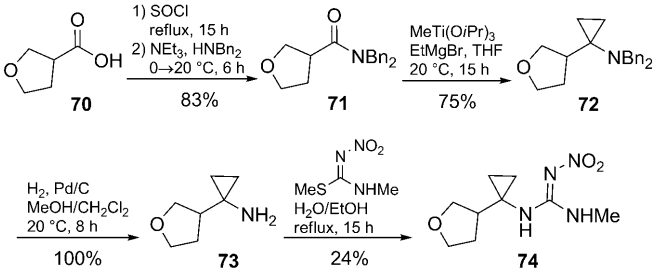
Among the variety of drugs that have an *N,N*-dialkylcarboxamide moiety, (*S*)-Cotinine **65**, a metabolite of nicotine with antidepressive activity, was chosen.[26] The lactam **65** was treated with ethylmagnesium bromide (**6a**) in the presence of methyltitanium triisopropoxide, and indeed, the spirocyclopropane derivative **66** could be isolated in 77% yield (Equation (1) in Scheme 12). Thus, Cotinine can be regarded as a prime example for the one-step modification of a biologically active substance without influencing the stereochemical features.



Scheme 12. Reductive cyclopropanation of the carbonyl groups in γ-lactams.

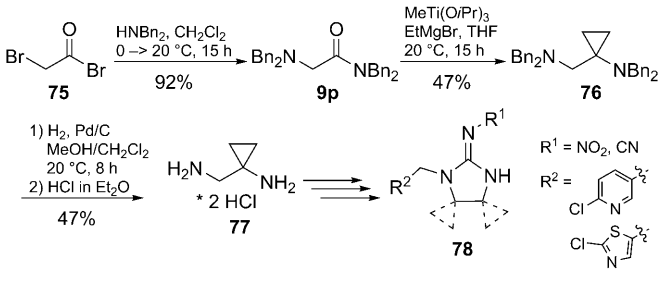
The importance of nicotinic acetylcholine receptor (nAChR) ligands arise from their significant therapeutic potential for the treatment of central nervous system (CNS) disorders such as Alzheimer's and Parkinson's disease as well as Tourette's syndrome.[27,28] 3-Pyridyl ether derivatives such as 3-(pyrrolidin-2-ylmethoxy)pyridine, which corresponds to **69** (Scheme 12) without the spirocyclopropane moiety, have been found to exhibit subnanomolar affinities towards nAChRs.[29] Due to its influence on the basicity on the adjacent nitrogen, a spirocyclopropanated analogue such as **69** might have a modified activity. Therefore, *N*-methyl-5-oxoprolinol **67**, obtained by esterification with concomitant *N*-methylation of 5-oxoproline[30] and subsequent reduction of the ester moiety,[31] was transformed with 3-hydroxypyridine in a Mitsunobu reaction to yield the pyridyl ether with a γ-lactam substructure **68**.[29] As expected, the methyltitanium-triisopropoxide-mediated cyclopropanation of **68** with ethylmagnesium bromide (**6a**) gave the desired spirocyclopropane derivative **69** in an unoptimized moderate yield of only 28% (Equation (2) in Scheme 12).

An interesting modification of the commercial insecticide Dinotefuran [*N''*-nitro-*N*-methyl-*N'*-(tetrahydrofuran-3-ylmethyl)guanidine] was conceived with the introduction of a cyclopropane ring instead of the originally present methylene group in the tetrahydrofuran ring. The preparation of **74** was achieved by starting with tetrahydrofuran-3-carboxylic acid (**70**) and its conversion to *N,N*-dibenzyltetrahydrofuran-3-carboxamide (**71**) through the acid chloride. Subsequent methyltitanium-triisopropoxide-mediated cyclopropanation of **71** succeeded in 75% yield to provide the corresponding *N,N*-dibenzylcyclopropylamine derivative **72**, which was debenzylated by hydrogenation over palladium on charcoal. Final condensation of the thus obtained cyclopropylamine **73** with methyl *N'*-nitro-*N*-methylimidothiocarbamate[32] gave the cyclopropylamine analogue **74** of Dinotefuran (Scheme 13).



Scheme 13. Synthesis of a spirocyclopropanated Dinotefuran analogue.

Imidacloprid is one of the most effective and widest used insecticides worldwide. In analogy to the derivatization of the insecticide Dinotefuran, Imidacloprid, which corresponds to **79** without the cyclopropane moiety (Scheme 14; $R^1 = NO_2$, X = NH, R^2 = 6-chloropyridin-3-yl) can be modified by attaching a spirocyclopropane moiety to either one of the two methylene groups in the imidazolidine ring. To-



Scheme 14. Spirocyclopropanated analogues of Imidacloprid.

wards that goal, bromoacetyl bromide (**75**) was treated with *N*,*N*-dibenzylamine to give *N*,*N*-dibenzylaminoacetic acid *N*′,*N*′-dibenzylamide (**9p**). Methyltitanium-triisopropoxide-mediated cyclopropanation of the latter with ethylmagnesium bromide (**6a**) provided the corresponding cyclopropylamine derivative **76** in a moderate yield of 47%, and catalytic hydrogenation over palladium on charcoal gave 1-(aminocyclopropyl)methylamine, which was best isolated as its bis(hydrochloride) **77**. However, further transformation into the two different spirocyclopropane derivatives **78** of Imidacloprid according to published procedures[33] was hampered by the fact that a successful, fourfold debenzylation of **78** only succeeded on a scale of up to 1.5 g and required 33 mol% of a highly active palladium catalyst.

Conclusion

The utility and broad scope of the titanium-mediated reductive cyclopropanation of *N*,*N*-dialkylcarboxamides has been demonstrated on numerous examples. Wide ranges of amides and Grignard reagents can be employed to give a variety of diversely substituted cyclopropylamines, which have great synthetic and even medicinal potential. Initially, the reagents and substrates were mixed at −78 °C, and the mixture was then warmed to ambient temperature and stirred for some time. However, this original version is inferior to the newer protocols according to which the Grignard reagent is added to the mixture of the respective *N*,*N*-dialkylcarboxamide and the titanium tetraisopropoxide or—preferably—methyltitanium triisopropoxide at ambient temperature. The reliability, efficiency, and unproblematic scalability of these protocols have made them a benchmark method for the synthesis of this class of compounds. An asymmetric version of this useful transformation has also been developed for the first time, thereby providing moderate levels of enantiocontrol and setting the stage for further exploratory research in this area of asymmetric synthesis.

Experimental Section

General procedure for the synthesis of cyclopropylamines by using titanium tetraisopropoxide (GP 1): A suspension of the respective alkylmagnesium bromide **6** (2.50 equiv, sol. in Et_2O) in anhydrous THF (5 mL per mmol of carboxamide) was cooled to −78 °C. A solution of $Ti(OiPr)_4$ (1.00 equiv) in anhydrous THF (0.5 mL per mmol of carboxamide) was added within 1 min. The mixture was stirred for 2 min before a solution of the respective *N*,*N*-dialkylcarboxamide **9**--**17** (1.00 equiv) in anhydrous THF (0.5 mL per mmol of carboxamide) was added within 1 min, which led to a yellow mixture. This mixture was stirred at −78 °C for 5 min, the cooling bath was removed, and the mixture was allowed to warm to 20 °C, upon which the mixture turned brown-black, and then it was stirred for the indicated time at 20 °C or first warmed to reflux, then stirred under reflux for the indicated time and recooled to 20 °C.

Workup, variant A: All volatile components (product, THF, Et_2O, *i*PrOH) were distilled off from the reaction mixture under reduced pressure (100 Torr) and condensed into a cold trap (−78 °C). The residue was either purified by column chromatography to give the corresponding cyclopropylamine, or it was transformed into the corresponding cyclopropylamine hydrochloride by acidification to pH 1 with HCl sol. (5–6 M in anhydrous Et_2O), filtered, and subsequently recrystallized from the indicated solvent.

Workup, variant B: The reaction mixture was hydrolyzed by addition of sat. NH_4Cl sol. (7.5 mL per 1.00 mmol of carboxamide) and H_2O (2.5 mL per 1.00 mmol of carboxamide), and the resulting mixture was stirred for 1–3 h until its color had changed from brown-black to white-yellow. The mixture was filtered, and the precipitate was washed with Et_2O (2× 1.5 mL per 1.00 mmol of carboxamide). The filtrate was made basic (pH > 11) by addition of 15% aq. NaOH sol. and extracted with Et_2O (3×2.5 mL per 1.00 mmol carboxamide). The combined organic extracts were washed with brine, dried ($MgSO_4$ or K_2CO_3), and concentrated under reduced pressure. The residue was either purified by column chromatography to give the corresponding cyclopropylamine, or it was acidified pH 1 with HCl sol. (5–6 M in anhydrous Et_2O), filtered, and the thus formed corresponding cyclopropylamine hydrochloride subsequently recrystallized from the indicated solvent.

Workup, variant C: The reaction mixture was hydrolyzed by addition of H_2O (10 mL per 10.0 mmol of carboxamide, stirred until a colorless precipitate had formed (1–3 h), filtered through a pad of Celite, and the filter cake was washed with the indicated solvent. The filtrate was extracted with the indicated solvent (3 times). The combined organic extracts were dried ($MgSO_4$, Na_2SO_4, or K_2CO_3) and the solvents concentrated under reduced pressure. The residue was purified by column chromatography.

Representative example: N,N-*dibenzyl*-N-*(1-ethylcyclopropyl)amine hydrochloride (**20ac**·HCl)*: According to GP 1, ethylmagnesium bromide (**6a**) (50.0 mmol in Et_2O/THF), $Ti(OiPr)_4$ (5.94 mL, 20.0 mmol), and *N*,*N*-dibenzylpropionamide (**9c**) (5.04 g, 19.9 mmol) in THF (200 mL) were allowed to react and stirred under reflux for 10 h. Workup according to variant B, transformation into the hydrochloride, and recrystallization from CH_2Cl_2/hexane (1:5) yielded 3.81 g (63%) of **20ac**·HCl as a colorless solid. M.p. 171 °C; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 11.2$ (br s, 1H), 7.65–7.77 (m, 4H), 7.05–7.33 (m, 6H), 4.07–4.29 (m, 4H), 1.98 (q, J = 7.4 Hz, 2H), 1.16–1.22 (m, 2H), 0.56 (t, J = 7.4 Hz, 3H), 0.25–0.35 ppm (m, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 131.93$ (CH), 129.58 (CH), 129.21 (C), 128.69 (CH), 56.88 (CH_2), 44.04 (C), 19.05 (CH_2), 8.78 (CH_2), 8.43 ppm (CH_3); MS (ESI): *m*/*z* (%): 266 (100) [M+H$^+$], 533 (42) [2M+H$^+$]; elemental analysis calcd (%) for $C_{19}H_{24}ClN$ (301.85): C 75.60, H 8.01; found: C 75.62, H 7.93.

General procedure for the synthesis of cyclopropylamines by using titanium tetraisopropoxide with inverse addition of the reactants (GP 2): A vigorously stirred solution of the respective *N*,*N*-dialkylcarboxamide **9**–**17** (1.00 equiv) and $Ti(OiPr)_4$ (1.10 equiv) in anhydrous THF (6 mL per 1.00 mmol of carboxamide) was treated with the respective alkylmagnesium bromide (2.50 equiv, sol. in Et_2O) within 20 s (the color of the mixture changed to brown-black and the temperature rose to around 45 °C). The reaction mixture was stirred at 20 °C for 10 h and then worked-up as described in GP 1, variants A–C.

Representative example: N-*cyclopropylpiperidine (**22aa**)*: According to GP 2, ethylmagnesium bromide (**6a**) (13 mmol in Et_2O/THF), $Ti(OiPr)_4$ (1.6 mL, 5.5 mmol), and *N*-formylpiperidine (**11a**) (0.57 g, 5.0 mmol) in THF (40 mL) were allowed to react for 10 h. Workup according to var-

iant B and purification of the residue by column chromatography (50 g silica, pentane/Et_2O 20:1, R_f = 0.31) yielded 0.47 g (74%) of **22aa** as a colorless liquid. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.41–2.56 (m, 4H), 1.31–1.52 (m, 7H), 0.30–0.40 ppm (m, 4H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 54.72 (CH_2), 39.20 (CH), 25.85 (CH_2), 24.51 (CH_2), 5.74 ppm (CH_2). For further characterization, the cyclopropylamine **22aa** was transformed into the corresponding solid hydrochloride **22aa**·HCl by treatment with sat. HCl sol. in Et_2O and the hydrochloride purified by recrystallization. M.p. 215–216 °C (dec.); elemental analysis calcd (%) for $C_8H_{16}ClN$ (161.67): C 59.43, H 9.98; found C 59.34, H 9.93.

General procedure for the synthesis of cyclopropylamines by using methyltitanium triisopropoxide (GP 3): A vigorously stirred solution of the respective *N,N*-dialkylcarboxamide **9**–**17** (1.00 equiv) and MeTi(O*i*Pr)$_3$ (1.20 equiv) in anhydrous THF (3 mL per 1.00 mmol of carboxamide) was treated with the respective alkylmagnesium bromide (2.00 equiv, sol. in Et_2O) within 20 s (the color of the mixture changed to brown-black and the temperature rose to around 45 °C), and the resulting mixture was stirred at 20 °C for the indicated time.

Workup, variant D: The reaction mixture was diluted with Et_2O (3 mL per 1.00 mmol of carboxamide) and the reaction then quenched by addition of H_2O (1 mL per 10.0 mmol of carboxamide). The resulting mixture was stirred until a colorless precipitate had formed (1–3 h), filtered through a pad of Celite, and the filter cake was washed with Et_2O (3 times). The filtrate was dried (Na_2SO_4 or K_2CO_3) and the solvents evaporated under reduced pressure. The residue was purified by column chromatography on silica gel. In specifically indicated cases, CH_2Cl_2 instead of Et_2O was used as the solvent for the workup without dilution of the reaction mixture before quenching.

Representative example: N,N-*dibenzyl*-N-*(2-phenylcyclopropyl)amine (**20ka**)*: According to GP 3, *N,N*-dibenzylformamide (**9a**) (2.25 g, 9.99 mmol), MeTi(O*i*Pr)$_3$ (2.88 g, 12.0 mmol), and 2-phenylethylmagnesium bromide (**6k**) (23.6 mL, 20.1 mmol, 0.85 M in THF) in anhydrous THF (30 mL) were stirred for 16 h. Workup according to variant D and purification by column chromatography (70 g silica, CH_2Cl_2) yielded 3.06 g (98%) of **20ka** as a colorless oil, a separable mixture of two diastereomers (*E*/*Z* = 2.3:1). (*Z*)-**20ka**: R_f = 0.74. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.09–7.45 (m, 15H), 3.62 (d, ^2J = 13.4 Hz, 2H), 3.35 (d, ^2J = 13.4 Hz, 2H), 2.19 (ddd, ^3J = 4.8, 7.0, 7.0 Hz, 1H), 2.10 (ddd, ^3J = 4.9, 7.0, 8.8 Hz, 1H), 1.04 (ddd, ^2J = 5.6 Hz, ^3J = 7.0 Hz, 8.8 Hz, 1H), 0.89 ppm (ddd, ^2J = 5.6 Hz, ^3J = 4.8, 4.9 Hz, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 138.33 (C), 138.22 (C), 129.49 (CH), 128.41 (CH), 127.83 (CH), 127.48 (CH), 126.68 (CH), 125.44 (CH), 57.30 (CH_2), 43.66 (CH), 23.75 (CH), 13.52 ppm (CH_2). (*E*)-**20ka**: R_f = 0.56. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.24–7.47 (m, 13H), 6.70–6.87 (m, 2H), 3.79 (d, ^2J = 13.5 Hz, 2H), 3.67 (d, ^2J = 13.5 Hz, 2H), 2.04 (ddd, ^3J = 3.2, 4.5, 7.5 Hz, 1H), 1.82 (ddd, ^3J = 3.2, 6.0, 9.2 Hz, 1H), 1.05 (ddd, ^2J = 4.3 Hz, ^3J = 4.5, 9.2 Hz, 1H), 0.97 ppm (ddd, ^2J = 4.3 Hz, ^3J = 6.0, 7.5 Hz, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 142.05 (C), 138.65 (C), 129.36 (CH), 128.06 (CH), 127.96 (CH), 126.85 (CH), 125.72 (CH), 125.32 (CH), 58.42 (CH_2), 47.57 (CH), 26.39 (CH), 17.57 ppm (CH_2).

General procedure for the synthesis of cyclopropylamines with reagent mixing at −78 °C using methyltitanium triisopropoxide generated in situ (GP 4): A solution of ClTi(O*i*Pr)$_3$ (1.00 equiv) in the indicated amount of anhydrous THF (2 mL per 1.00 mmol of ClTi(O*i*Pr)$_3$) was cooled to 0 °C and treated dropwise with MeLi (1.00 equiv, approximately 2.0 M sol. in Et_2O). The cooling bath was removed; the reaction mixture was stirred for 1 h and then cooled to −78 °C. The respective alkylmagnesium bromide (1.00 equiv) was added. The resulting mixture was warmed to the indicated temperature, treated with a solution of the respective *N,N*-dialkylcarboxamide **9**–**17** (1.00 equiv) in anhydrous THF (3–5 mL per 1.00 mmol), and stirred for the indicated time.

Workup, variant E: The reaction mixture was hydrolyzed by addition of H_2O (20 mL per 5.00 mmol of carboxamide) and sat. aq. $(NH_4)_2CO_3$ sol. (10 mL per 5.00 mmol of carboxamide), stirred until a colorless precipitate had formed (1–3 h), filtered through a pad of Celite, and the filter cake was washed with Et_2O. The filtrate was extracted with Et_2O (3 times). The combined organic extracts were dried (Na_2SO_4, $MgSO_4$, or K_2CO_3) and the solvents evaporated under reduced pressure. The residue was purified by column chromatography on silica gel.

Representative example: N,N-*dimethyl-2-[3-(trityloxy)propyl]cyclopropylamine (**38a**)*: According to GP 4, ClTi(O*i*Pr)$_3$ (2.50 mL, 5.00 mmol, 2.00 M in THF) and MeLi (3.21 mL, 5.00 mmol, 1.56 M in Et_2O) were allowed to react. The mixture was then treated with *N,N*-dimethylformamide (**10a**) (365 mg, 5.00 mmol) and 3-trityloxypentylmagnesium bromide (21.7 mL, 4.99 mmol, 0.23 M in THF) in anhydrous THF (20 mL), and was stirred at R.T. for 2 d. Workup according to variant E and purification by column chromatography (60 g silica, Et_2O) yielded 1.02 g (53%) of **38a** as a colorless oil, a separable mixture of two diastereomers (*E*/*Z* = 1.8:1). (*Z*)-**38a**: R_f = 0.77. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.19–7.49 (m, 15H), 3.10 (t, ^3J = 6.6 Hz, 2H), 2.29 (s, 6H), 1.69–1.87 (m, 1H), 1.50–1.55 (m, 1H), 1.21–1.37 (m, 1H), 0.62–0.72 (m, 1H), 0.51–0.59 (m, 1H), −0.05–0.03 ppm (m, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 144.52 (C), 128.69 (CH), 127.64 (CH), 126.74 (CH), 86.31 (C), 63.73 (CH_2), 45.80 (CH_3), 44.69 (CH), 30.58 (CH_2), 23.57 (CH_2), 18.66 (CH), 11.49 ppm (CH_2); IR (film): $\tilde{\nu}$ = 3059, 2937, 2813, 2768, 1490, 1448, 1073, 745, 705, 633 cm^{-1}; MS (DCI, NH_3): *m*/*z* (%): 386 (100) [M^++H], 243 (44) [Ph_3C^+], 142 (16) [M^+−CPh_3]; elemental analysis calcd (%) for $C_{27}H_{31}NO$ (385.55): C 84.11, H 8.10; found C 84.43, H 8.00. (*E*)-**38a**: R_f = 0.38. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.18–7.45 (m, 15H), 3.06 (t, ^3J = 7.0 Hz, 2H), 2.28 (s, 6H), 1.74 (ddt, ^3J = 7.0, 7.5, 6.5 Hz, 2H), 1.38 (ddt, ^2J = 14.0 Hz, ^3J = 7.5, 6.5 Hz, 1H), 1.21–1.26 (m, 1H), 1.16 (ddt, ^2J = 14.0, ^3J = 7.5, 6.5 Hz, 1H), 0.69–0.74 (m, 1H), 0.49–0.56 (m, 1H), 0.21–0.27 ppm (m, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 144.43 (C), 128.63 (CH), 127.67 (CH), 126.79 (CH), 86.27 (C), 63.34 (CH_2), 47.00 (CH), 44.98 (CH_3), 29.80 (CH_2), 29.31 (CH_2), 20.40 (CH), 13.77 ppm (CH_2); IR (film): $\tilde{\nu}$ = 3058, 2934, 2812, 2768, 1490, 1448, 1072, 745, 706, 633 cm^{-1}; MS (DCI, NH_3): *m*/*z* (%): 386 (100) [M^++H], 243 (32) [Ph_3C^+]; elemental analysis calcd (%) for $C_{27}H_{31}NO$ (385.55): C 84.11, H 8.10; found C 84.04, H 8.20.

General procedure for the twofold reductive cyclopropanation of *N*-alkyl-*N,N*-diformylamines with ethylmagnesium bromide in the presence of methyltitanium triisopropoxide (GP 5): Ethylmagnesium bromide (**6a**) (4.00 equiv) was added dropwise to a solution of the respective diformylamine **53** (1.00 equiv) and MeTi(O*i*Pr)$_3$ (2.40 equiv) in the indicated amount of anhydrous THF, and the mixture was stirred at 20 °C for 16 h. The reaction mixture was hydrolyzed by addition of H_2O (5 mL), stirred until a colorless precipitate had formed (1–3 h), filtered through Celite, and the precipitate was washed with Et_2O. The filtrate was extracted with Et_2O (3 times). The combined organic extracts were dried (K_2CO_3) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel.

In the cases of volatile products, concentrated aqueous HCl was added to the reaction mixture after hydrolysis, the mixture was filtered, and all liquid components were distilled off in vacuo. Et_2O (10 mL) and K_2CO_3 were added to the residue to liberate the amine, and the mixture was submitted to bulb-to-bulb distillation. The pure amine was obtained from this mixture of product and Et_2O by preparative-scale gas chromatography.

Representative example: N,N-*dicyclopropylethylamine (**54b**)*: According to GP 5, ethyl-*N,N*-diformylamine (**53b**)[20] (1.01 g, 10.0 mmol) and MeTi(O*i*Pr)$_3$ (5.76 g, 24.0 mmol) were treated with ethylmagnesium bromide (**6a**) (22.3 mL, 40.1 mmol, 1.80 M in Et_2O) in anhydrous THF (50 mL). Purification by preparative-scale gas chromatography (SE 30, column 2 m × 0.5 cm, 95 °C, R_T = 6.10 min) gave **54b** (82%, yield determined by gas chromatography of the mixture with Et_2O) as a colorless liquid. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.77 (q, J = 7.2 Hz, 2H), 1.81–1.89 (m, 2H), 1.12 (t, J = 7.2 Hz, 3H), 0.35–0.48 ppm (m, 8H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 50.81 (CH_2), 36.07 (CH), 11.42 (CH_3), 5.51 ppm (CH_2); IR (film): $\tilde{\nu}$ = 3092, 3011, 2968, 2931, 2874, 1446, 1362, 1217, 1024, 937, 822 cm^{-1}; MS (EI, 70 eV), *m*/*z* (%): 125 (39) [M^+], 110 (100) [M^+−CH_3], 96 (28) [M^+−C_2H_5], 84 (18) [M^+−C_3H_5], 82 (25) [$NC_5H_8^+$], 69 (27) [M^+−C_3H_5−CH_3], 68 (40) [$NC_4H_6^+$], 56 (57), 41 (94) [$C_3H_5^+$]; HRMS (EI): calcd for $C_8H_{15}N$: 125.1204 (correct HRMS); elemental analysis calcd (%) for $C_8H_{15}N$ (125.21): C 76.74, H 12.07, N 11.19; found C 76.75, H 12.16, N 11.09.

General procedure for the synthesis of chiral titanium bis(TADDOL)ates (GP 6): A solution of the respective ligand (2.00 equiv) in anhydrous benzene (2 mL per 1 mmol of ligand) was treated with $Ti(OiPr)_4$ (1.00 equiv). The reaction mixture was warmed to 40–45 °C and stirred at this temperature for 5 h. All volatile components were distilled off into a cold trap (liquid N_2), and the residue was dried under reduced pressure. The titanium bis(TADDOL)ates thus obtained can be stored for several weeks under an inert atmosphere.

General procedure for the enantioselective synthesis of cyclopropylamines (GP 7): A solution of the respective chiral titanium bis(TADDOL)ate (1.10 equiv, generated according to GP 6 or used as commercially available) in anhydrous THF (2.5–3 mL per 1.00 mmol of carboxamide) was treated with *N*,*N*-dibenzylformamide (1.50–2.50 mmol, 1.00 equiv). The respective alkylmagnesium bromide (2.20 equiv, sol. in Et_2O) was added dropwise. The reaction mixture was stirred for 15 h, then diluted with Et_2O (10 mL) and H_2O (1 mL) and stirred for an additional 1 h. The mixture was filtered, and the precipitate was washed with Et_2O (3×20 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$), and the solvents concentrated under reduced pressure. The residue was treated with pentane (5 mL), and the thus precipitating ligand was re-isolated by filtration. The filtrate was again concentrated under reduced pressure. The residue was purified by column chromatography on silica gel.

General procedure for the synthesis of cyclopropylamines in the presence of trialkylsilyl derivatives (GP 8): A solution of *N*,*N*-dibenzylformamide (1.00 equiv) in anhydrous THF (1 mL per 1.00 mmol of carboxamide) was treated with the desired amount of $Ti(OiPr)_4$ (3–100 mol%). The trialkylsilyl derivative (1.00 or 2.00 equiv) was added, and the resulting mixture was cooled to 0 °C. The respective alkylmagnesium bromide (2.20 equiv, sol. in Et_2O) was added dropwise, and the reaction mixture was stirred for 16 h while warming up to 20 °C. The mixture was diluted with Et_2O (5 mL), hydrolyzed by addition of H_2O (1 mL), and stirred for 1–2 h (a colorless precipitate formed). The reaction mixture was filtered, and the precipitate was washed with Et_2O (3×20 mL). The combined organic phases were washed with brine (5 mL), dried ($MgSO_4$), and the solvents evaporated under reduced pressure. The residue was purified by column chromatography on silica gel.

Representative examples for GP 6–8

Enantioselective synthesis of N,N-*dibenzyl-(2-butylcyclopropyl)amine (**20ca**) by using a stoichiometric amount of titanium reagent*: According to GP 6, the corresponding titanium bis(TADDOL)ate was generated from (4*R*,5*R*)-2-*tert*-butyl-4,5-bis(diphenylmethanol)-1,3-dioxolane (2.17 g, 4.40 mmol) and $Ti(OiPr)_4$ (645 μL, 2.20 mmol) and then converted according to GP 7 with *N*,*N*-dibenzylformamide (**9a**) (450 mg, 2.00 mmol) and *n*-hexylmagnesium bromide (**6c**). Workup and purification by column chromatography (100 g silica, Et_2O/pentane) gave 275 mg (47%) of **20ca** as a separable mixture of two diastereomers (*E*/*Z* = 3.0:1). The spectroscopic data correspond to the ones listed above. The enantiomeric excesses were determined by gas chromatography of the hydrotrifluoroacetates of (*Z*/*E*)-2-butylcyclopropylamine on a capillary column with the chiral-phase Lipodex E (2,6-di-*O*-pentyl-3-*O*-butyryl-γ-cyclodextrin at 100 °C. (*Z*)-**20ca**: R_f = 0.30 (Et_2O/pentane 1:100), $[\alpha]_D^{20} = -19.1°$ (*c* = 1.2, $CHCl_3$; 84% *ee*). (*E*)-**20ca**: R_f = 0.12 (Et_2O/pentane 1:100), $[\alpha]_D^{20} = -17.7°$ (*c* = 1.8, $CHCl_3$; 77% *ee*).

Enantioselective synthesis of N,N-*dibenzyl-2-(ethenylcyclopropyl)amine (**20ae**) using a stoichiometric amount of titanium reagent*: According to GP 6, the corresponding titanium bis(TADDOL)ate was generated from (4*R*,5*R*)-2-*tert*-butyl-4,5-bis(diphenylmethanol)-1,3-dioxolane (1.63 g, 3.30 mmol) and $Ti(OiPr)_4$ (484 μL, 1.65 mmol) and then converted according to GP 7 with *N*,*N*-dibenzylformamide (**9a**) (338 mg, 1.50 mmol) and 3-butenylmagnesium bromide (**6e**). Workup and purification by column chromatography (100 g silica, Et_2O/pentane) gave 166 mg (43%) of **20ae** as a separable mixture of two diastereomers (*E*/*Z* = 7.0:1). The spectroscopic data correspond to the ones described above. The enantiomeric excess was determined by analysis of the ^1H NMR spectrum of the (+)-Mosher ester of the 2-hydroxyethyl derivative obtained by hydroboration-oxidation of **20ae**. (*Z*)-**20ae**: $[\alpha]_D^{20}$: R_f = 0.38 (Et_2O/pentane 1:100). Because of the high diastereoselectivity, neither optical rotation nor the enantiomeric excess of the minor isomer could be determined. (*E*)-**20ae**: R_f = 0.20 (Et_2O/pentane 1:100), $[\alpha]_D^{20} = +4.21°$ (*c* = 1.4, $CHCl_3$; 62% *ee*). The enantiomeric excess was determined by analysis of the ^1H NMR spectrum of the (+)-Mosher ester of the 2-hydroxyethyl derivative obtained by hydroboration–oxidation of (*E*)-**20ae**.

Catalytic enantioselective synthesis of N,N-*dibenzyl-2-(ethenylcyclopropyl)amine (**20ae**) in the presence of trimethylsilyl chloride*: According to GP 6, but using only 50 mol% of $Ti(OiPr)_4$ (367 μL, 1.25 mmol) and (4*R*,5*R*)-2-*tert*-butyl-4,5-bis(diphenylmethanol)-1,3-dioxolane (1.24 g, 2.51 mmol), the corresponding titanium bis(TADDOL)ate was generated and then converted according to GP 8 with *N*,*N*-dibenzylformamide (**9a**) (1.13 g, 5.02 mmol), trimethylsilyl chloride (610 μL, 5.00 mmol) and 3-butenylmagnesium bromide (**6e**). Workup and purification by column chromatography (100 g silica, Et_2O/pentane 100:1) gave 758 mg (58%) of **20ae** as a separable mixture of two diastereomers (*E*/*Z* = 7.0:1). The spectroscopic data correspond to the ones listed above. The enantiomeric excess was determined by analysis of the ^1H NMR spectrum of the (+)-Mosher ester of the 2-hydroxyethyl derivative obtained by hydroboration–oxidation of **20ae**. (*Z*)-**20ae**: Because of the high diastereoselectivity, neither optical rotation nor the enantiomeric excess of the minor isomer could be determined. (*E*)-**20ae**: $[\alpha]_D^{20} = +3.80°$ (*c* = 0.8, $CHCl_3$; 56% *ee*).

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