Facile Preparation of Cyclopropylamines from Carboxamides

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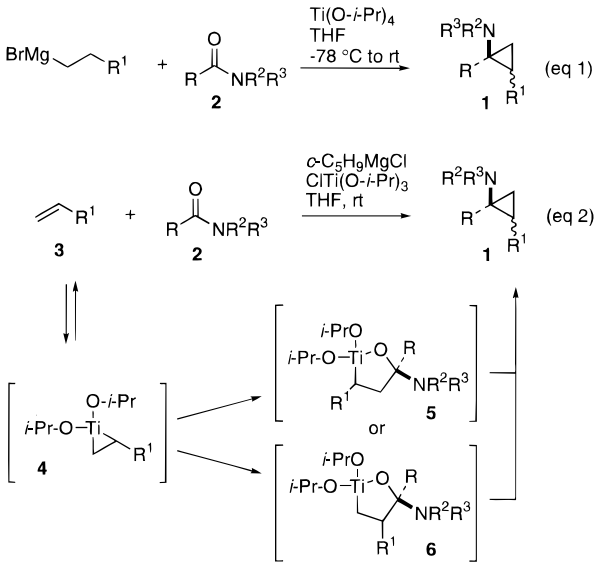
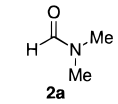
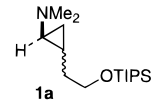
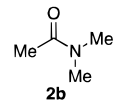
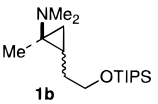
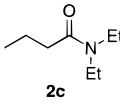
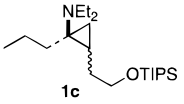
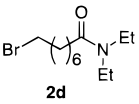
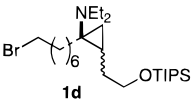
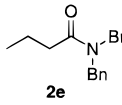
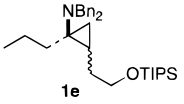
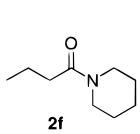
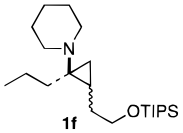
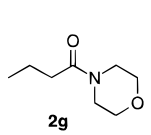
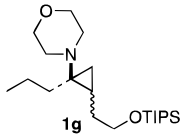
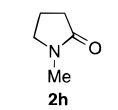
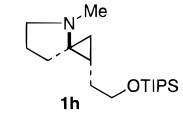
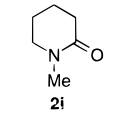
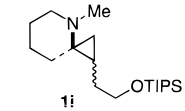
Recently, we developed a facile preparation of cyclopropanols and cyclopropanone hemiketals by Ti(II)-mediated coupling of terminal olefins and alkyl carboxylates or ethylene carbonate.[1] This new hydroxycyclopropanation, in turn, evolved from the original Kulinkovich procedure.[2−4] More recently appeared de Meijere's adaptation of the original protocol to *N*,*N*-dialkylamides leading to a facile preparation of *N*,*N*-dialkylcyclopropylamines **1** (eq 1).[3b,5] This recent publication prompted us to report our variant of utilizing Ti(II)-mediated coupling of *N*,*N*-dialkylamides and monosubstituted olefins (eq 2).



When commercially available cyclopentylmagnesium chloride (4.5 equiv) was added slowly (during 30 min) at room temperature to a THF solution of amide **2** (1.0 equiv), olefin **3** (1.5 equiv), and $ClTi(O\text{-}i\text{-}Pr)_3$ or $Ti(O\text{-}i\text{-}Pr)_4$ (1.5 equiv), the cyclopropylamine **1** was isolated in moderate to excellent yield. As can be seen from additional examples in Table 1, this aminocyclopropanation appears to be general and is anticipated to tolerate the presence of other functional groups in the olefin and carboxamide partners. In the case of amides **2a**−**2d**, the formation of the products (**1a**−**1d**) was accompanied by a minute (≤5%) amount of the acyclic ketones derived from hydrolysis of the presumed intermediates **5** (vide infra). Diastereoselectivity of the aminocyclopropane formation is moderate. With the exception of *N*,*N*-dimethylformamide (**2a**) and 1-methyl-2-pyrrolidinone (**2h**), the stereochemistry of the major products, **1b**−**g**,**i**, has the siloxyethyl side chain (R^1) in the β-configuration, i.e., *syn* to the dialkylamino substituent. The stereo-

Table 1. Intermolecular Aminocyclopropanation of *N*,*N*-Dialkylamides with 4-(Triisopropylsiloxy)-1-butene

Amide	Product[a,b]	Yield / ds[c]
 **2a**	 **1a**	61% (1:2.2)[d]
 **2b**	 **1b**	68% (6.3 : 1)[e]
 **2c**	 **1c**	56% (5.3 : 1)
 **2d**	 **1d**	60% (7.6 : 1)[e]
 **2e**	 **1e**	54% (1.3 : 1)
 **2f**	 **1f**	69% (7.3 : 1)
 **2g**	 **1g**	77% (3.1 : 1)
 **2h**	 **1h**	21%(46%)[f] (1.0 : 0)
 **2i**	 **1i**	79% (6.2 : 1)

[a] With the exception of **1h**, the cyclopropylamine products were isolated as a mixture of *cis* and *trans* diastereomers. See text for their stereochemical assignment. [b] In the case of **2a**−**d**, the formation of the products **1a**−**d** was accompanied by a small amount of acyclic ketones derived from **5**. For details, see text. [c] Except for **1b** and **1d**, the reported diastereoselectivity was based on isolation yield. [d] The major isomer of **1a** has the siloxyethyl chain in the α-configuration. [e] Determined by GC. [f] Yield in parentheses is based on the consumed **2h**.

(1) (a) Lee, J.; Kang, C. H.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1996**, *118*, 291. (b) Lee, J.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1996**, *118*, 4198. (c) Lee, J.; Kim, Y. G.; Bae, J.; Cha, J. K. *J. Org. Chem.* **1996**, *61*, 4878. See also: (d) Lee, J.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1995**, *117*, 9919.

(2) (a) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A.; Prityts kaya, T. S. *Zh. Org. Khim.* **1989**, *25*, 2244. (b) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A.; Savchenko, A. I.; Prityts kaya, T. S. *Zh. Org. Khim.* **1991**, *27*, 294. (c) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A. *Synthesis* **1991**, 234. (d) Kulinkovich, O. G.; Vasilevskii, D. A.; Savchenko, A. I.; Sviridov, S. V. *Zh. Org. Khim.* **1991**, *27*, 1428. (e) Kulinkovich, O. G.; Sorokin, V. L.; Kel'in, A. V. *Zh. Org. Khim.* **1993**, *29*, 66. (f) Kulinkovich, O. G.; Savchenko, A. I.; Sviridov, S. V.; Vasilevskii, D. A. *Mendeleev Commun.* **1993**, 192.

(3) (a) de Meijere, A.; Kozhushkov, S. I.; Spaeth, T.; Zefirov, N. S. *J. Org. Chem.* **1993**, *58*, 502. (b) Chaplinski, V.; de Meijere, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 413.

(4) See also: (a) Corey, E. J.; Rao, S. A.; Noe, M. C. *J. Am. Chem. Soc.* **1994**, *116*, 9345. (b) Kasatkin, A.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 6079. (c) Kasatkin, A.; Kobayashi, K.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1996**, *37*, 1849 and references cited therein.

(5) Only a few general methods have previously been developed for the preparation of substituted cyclopropylamines: Vilsmaier, E. In *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; Wiley: Chichester, 1987; Chapter 22.

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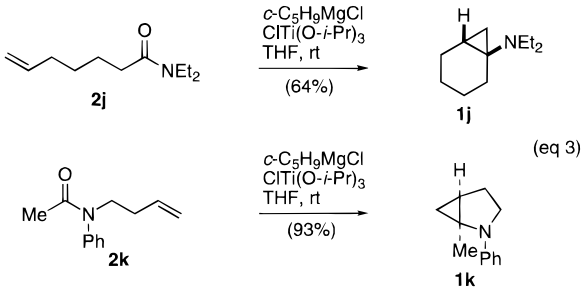
chemical assignment of **1a** (both isomers), **1c** (both isomers), **1h**, and **1i** (the major isomer) is based on difference NOE measurements; that of the remaining compounds was made by analogy and on the basis of their TLC behavior.[6]

The intramolecular cyclopropanation of the ω-vinylamides **2j** and **2k** (eq 3) also took place smoothly to provide the respective bicyclic cyclopropylamines **1j** and **1k** in fair to excellent yield.



(eq 3)

Not surprisingly, primary and secondary amides do not undergo the aminocyclopropanation process. For example, acetamide and 2-piperidinone were recovered unchanged under otherwise identical reaction conditions, while the olefin partner underwent reduction and reductive dimerization. α,β-Unsaturated amides also failed to give the corresponding cyclopropylamines.[7]

With regard to the reaction mechanism, the olefin-exchange route[1a−c] is thought to generate the postulated titanacyclopropane intermediate **4**. This key intermediate reacts with the amide carbonyl group to furnish the corresponding titanaoxacyclopentane adduct(s) **5** and/or **6**, which is then converted to the product **1**. The different reaction course of the carboxamides *vis-a-vis* carboxylates (which afford the cyclopropanols as the reaction product)[1] can be attributed, to a large extent, to the oxophilicity of titanium. As part of our mechanistic studies as to which of the two Ti−C bonds of **4** undergoes the insertion with the carbonyl group, we explored the possibility of trapping or interrupting the presumed titanaoxacyclopentane intermediate(s) [**5** and/or **6**] prior to "cycloreversion". The reaction products containing 68% (6.3:1 ds) of **1b** and 4% of **7** (i.e., the hydrolysis product of the intermediate **5**) were obtained from **2b** and **3** under the above-mentioned reaction conditions (employed for Table 1). When the reaction was quenched (H_2O) immediately after the gradual addition of the Grignard reagent, **1b** (64%; 6.4:1 ds) and **7** (14%) were isolated.[8] Even when the Grignard reagent was added rapidly (in 30 s), followed by immediate quenching, the aminocyclopropane **1b** was isolated in 47% (3.3:1 ds), along with **7** (8%)! The last experiment indicates that the aminocyclopropanation proceeds rapidly at room temperature.[9,10] Although the unequivocal elucidation of regioselectivity (i.e., **5** and/or **6**) in the Ti−C bond insertion step is not possible at this time,[11] our examples represent the first interception of the titanaoxacyclopentane adducts **5** from *N*,*N*-dialkylamides when *N*-alkyl groups are Me or Et.

(eq 4)

a. slow (20 min) Grignard addition; 24 h delay prior to quench.	68% (6.3 : 1 ds)	4%
b. slow (20 min) Grignard addition; 10 min delay prior to quench.	64% (6.4 : 1 ds)	14%
c. fast (30 sec) Grignard addition; no delay prior to quench.	47% (3.3 : 1 ds)	8%

In summary, we have developed a new, general method for the synthesis of *N*,*N*-dialkylcyclopropylamines by Ti(II)-mediated coupling of terminal olefins and *N*,*N*-dialkylcarboxamides. While reaction yields are moderate, useful functional groups can be conveniently introduced into the otherwise inaccessible target compounds. Other key features include the simplicity of operation and the ready availability of inexpensive reagents. Further mechanistic and synthetic studies are currently in progress.

Acknowledgment. We are grateful to the National Institutes of Health (GM35956) for generous financial support and an NIH Research Career Development Award (1990−1995; GM-00575 to J.K.C.). J.L. also thanks The University of Alabama for a graduate fellowship. We are indebted to Dr. Ken Belmore for the difference NOE measurements.

Supporting Information Available: Representative experimental procedure and characterization/spectral data (25 pages).

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(6) In all cases, R_f values (on silica gel) of the major and minor isomers are drastically different, and the isomers having the siloxyethyl chain in the β-configuration, i.e., *syn* to the dialkylamino substituent, move further. For example, the R_f value of the major isomer of **1c** in 7:1 hexane−EtOAc is 0.73, while that of the minor isomer is only 0.35.

(7) Cf. (a) Seebach, D.; Schiess, M. *Helv. Chim. Acta* **1982**, *65*, 2598. (b) Seebach, D.; Beck, A. K.; Schiess, M.; Widler, L.; Wonnacott, A. *Pure Appl. Chem*. **1983**, *55*, 1807. (c) Bertschart, C.; Seebach, D. *Helv. Chim. Acta* **1987**, *70*, 2215.

(8) (a) The mixture containing the major product **1b**-β and the ketone **7** was treated with $NaBH_4$ to convert **7** to the corresponding alcohol so as to facilitate separation from **1b**. (b) Diastereoselectivity was measured by GC.

(9) In several examples, de Meijere et al. heated the reaction mixture in THF under reflux using the original Kulinkovich protocol.[3b] In our hands, however, the reaction of **2e** with ethyl or hexyl Grignard reagents, reported to require heating, readily took place at room temperature in comparable yields. In any event, we believe that the postulated intermediate **4** has only a transient lifetime.

(10) (a) In contrast to amides **2a**−**d**, **2e**−**i** gave none of the ketones derived from hydrolysis of **5** or **6**. (b) None of the methyl-branched ketone, the hydrolysis product of the intermediate **6**, was detected in any of the interception experiments with amide **2a**−**i**. These results do not necessarily exclude the intermediacy of **6**, but rather its transient nature may have precluded the detection.

(11) In our previous paper, (ref 1 and see also ref 4a), we had favored selective insertion of the ester carbonyl group between Ti and the more substituted carbon on the basis of the reductive dimerization product of the starting olefin. However, it is noteworthy that, in the case of zirconocene−alkene complexes, the coupling with aldehydes is known to take place with the opposite orientation to that with alkenes: Takahashi, T.; Suzuki, N.; Hasegawa, M.; Nitto, Y.; Aoyagi, K.; Saburi, M. *Chem. Lett*. **1992**, 331.