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Olefin exchange-mediated cyclopropanation of nitriles with homoallylic alcohols

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ABSTRACT

We report herein olefin exchange-mediated cyclopropanation of nitriles with homoallylic alcohols. The use of homoallylic alcohols is central to the successful implementation.

Since Kulinkovich and co-workers discovered an efficient cyclopropanation of carboxylic esters in 1989,[1] the Kulinkovich reaction has been extended to other carboxylic acid derivatives to provide convenient access to heteroatom-substituted cyclopropanes.[2] For example, the Szymoniak group developed the preparation of aminocyclopropanes by adaptation of the Kulinkovich reaction to nitriles with aid of a Lewis acid.[3a] The successful cyclopropanation reactions of nitriles with homologs other than the ethyl Grignard reagent and an intramolecular version of unsaturated nitriles by the action of the cyclohexyl Grignard reagent were also reported.[3,4,5a] Addition of a Lewis acid is typically required to promote ring closure, but is unnecessary in the case of intramolecular reactions or in the presence of a suitable chelating substituent.[4] A variant involving the use of diethylzinc and lithium iodide also appeared.[5b,c] In contrast, attempts to implement the olefin exchange-mediated procedure[6] to intermolecular coupling of nitriles and α-olefins (such as 1-hexene and 1-octene) proved to be futile, presumably because the low-valent titanium species reacts with the nitrile prior to olefin exchange.[3d,4,7a,b] We report herein the first example of an intermolecular Kulinkovich cyclopropanation between nitriles and homoallylic alcohols.

Over the years, we examined low-valent titanium-mediated cyclopropanation reactions of several carboxylic acid derivatives, such as esters, amides, carbonates, imides, nitriles, vinylogous esters and amides, and *N*-acylpyrroles, under previously developed ligand (olefin) exchange conditions. Initial investigations on nitriles were unsuccessful under these conditions, and the high affinity of nitriles for low-valent titanium species was presumed to thwart the requisite olefin exchange.[7a] Other laboratories also made similar observations, and competition between intra- and intermolecular cyclopropanation reactions of ω-vinyl tethered nitriles was particularly informative.[3d,4,8] Nitriles are indeed more reactive substrates than esters and amides in the Kulinkovich reactions, and the greater reactivity of nitriles has allowed chemoselective preparation of functionalized aminocyclopropanes bearing esters and amides.[3e] These results prompted us to explore directing effects of homoallylic alcohols (alkoxides), because formation of a temporary tether between a hydroxyl group and an alkoxytitanium species could increase the rate of olefin exchange,[7b,c] as well as control diastereoselectivity.[9] The synthetic utility of these substrate-directed reactions has been demonstrated by us and other laboratories.[10–12]

When a titanium-mediated coupling reaction of homoallylic alcohol **1** and nitrile **2** was performed under typical olefin exchange reaction conditions involving slow addition of the cyclohexyl Grignard reagent at 0 °C or room temperature,[9,13,14] a complex mixture of **3a** and **4a** was formed only in low yields, along with the dimerization product of **1**[10] (Scheme 1, entry 1). A modest improvement in yields was observed when the Grignard reagent was added at −78 °C (Scheme 1, entries 2–5). These results were in contrast with successful coupling reactions between **1** and vinylogous esters or *N*-acylpyrroles under identical conditions.[7b,c]

A satisfactory solution was found by changing the order of addition, that is, pre-mixing of titanium isopropoxide and the cyclohexyl Grignard reagent at −78 °C, followed by addition of a

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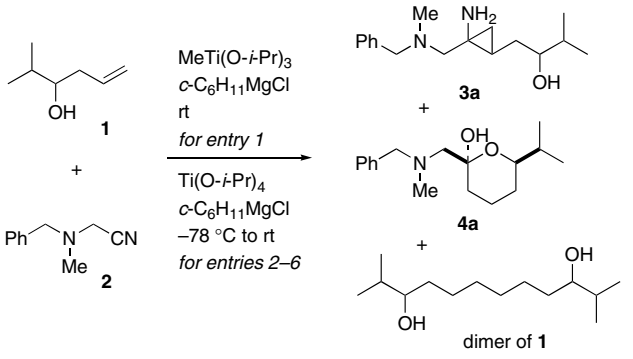
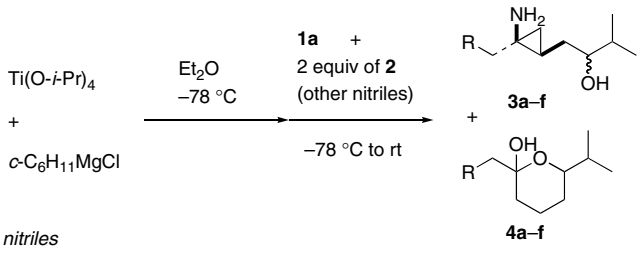


entry	2	Grignard	solvent	yields (%) 3a	4a	dimer
1	1 equiv	4 equiv	THF	8	20	21
2	1 equiv	4 equiv	THF	16	24	0
3	1 equiv	3 equiv	Et_2O	19	24	0
4	2 equiv	3 equiv	Et_2O	20	22	0
5	2 equiv	3 equiv	THF	11	14	0
6	2 equiv	4 equiv	THF	17	16	0

Scheme 1. Coupling between homoallylic alcohols and nitriles.

mixture of **1** and **2**, followed by subsequent warming of the resulting mixture to room temperature. Additionally, use of 2 equiv of a nitrile and 2 equiv of Ti(O-*i*-Pr)$_4$ further increased overall yields (Procedures A and B in Scheme 2).

Formation of both aminocyclopropanes and cyclic hemiacetals is conspicuous and likely to arise from the common intermediates (see **A** in Scheme 3); an excess of Ti(O-*i*-Pr)$_4$ or *i*-PrOMgCl might serve as a mild Lewis acid to promote the three-membered ring



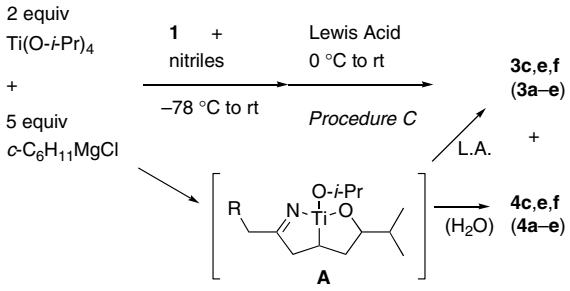
Conditions A:
1 equiv of Ti(O-*i*-Pr)$_4$
3 equiv of *c*-C_6H_{11}MgCl

entry	nitrile	products (%)	
1	**2**	**3a** (39)	**4a** (31)
2	**6**	**3b** (14)	**4b** (46)
3	**7**	**3c** (27)	**4c** (34)
4	**8**	**3d** (26)	**4d** (37)
5	**9**	**3e** (15)	**4e** (24)
6	**10**	**3f** (20)	**4f** (19)

Conditions B:
2 equiv of Ti(O-*i*-Pr)$_4$
5 equiv of *c*-C_6H_{11}MgCl

entry	nitrile	products (%)	
7	**2**	**3a** (43)	**4a** (40)
8	**6**	**3b** (30)	**4b** (50)
9	**7**	**3c** (57)	**4c** (35)
10	**8**	**3d** (34)	**4d** (33)
11	**9**	**3e** (33)	**4e** (30)
12	**10**	**3f** (30)	**4f** (38)

Scheme 2. An improved method for coupling between homoallylic alcohols and nitriles.



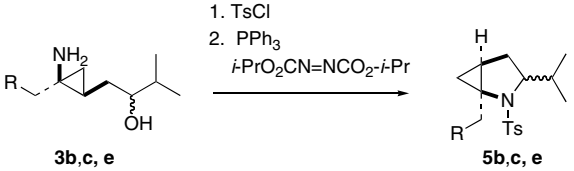
entry	nitrile	$BF_3{\cdot}Et_2O$	TMSOTf	products (%)
1	**9**	3 equiv		**3e** (54) + **4e** (0)
2			3 equiv	**3e** (57) + **4e** (35)
3			6 equiv	**3e** (67) + **4e** (28)
4	**7**		3 equiv	**3c** (65) + **4c** (26)
5			6 equiv	**3c** (75) + **4c** (11)
6	**10**		6 equiv	**3f** (42) + **4f** (27)

Scheme 3. Use of Lewis acids in coupling between homoallylic alcohols and nitriles.

forming step, since increasing amounts of Ti(O-*i*-Pr)$_4$ raised relative proportions of aminocyclopropanes (Procedure B). Noteworthy are negligible influences on the product ratios by a heteroatom in the nitrile substrates (**9** and **10** vs **2** and **6**–**8**), especially as the final ring closure was documented to require addition of a Lewis acid (e.g., $BF_3{\cdot}Et_2O$) in the absence of a suitable chelating substituent.[3,4] Benzonitrile is also amenable to this cyclopropanation procedure, whereas cyclopropanation of aromatic nitriles was reported to be less efficient than that of aliphatic counterparts.[3c]

Next we examined the efficacy of an external Lewis acid in maximizing the yield of aminocyclopropanes (Scheme 3). TMSOTf was found to be suitable in promoting cyclopropanation in good overall yields (Procedure C), although substantial amounts of **4** were present even when the reactions were allowed to run longer.[15,16] The Szymoniak group demonstrated the utility of $BF_3{\cdot}Et_2O$ for this purpose. In our own studies addition of $BF_3{\cdot}Et_2O$ prior to aqueous workup resulted in the lower material balance due to complex reaction mixtures (entry 1 vs entry 2 in Scheme 3).

The *trans*-dialkyl stereochemistry of **3b**, **3c**, and **3e** was firmly established by clean formation of pyrrolidines **5b**, **5c**, and **5e**, respectively, by standard methods (73–95%): (1) N-tosylation; (2) the Mitsunobu reaction (Eq. 1). By analogy the remaining aminocyclopropanes **3a**, **3d**, and **3f** were tentatively assigned to possess the *trans*-dialkyl stereochemistry. The disappointing lack of 1,3-diastereocontrol in the directed cyclopropanation was surprising: **3a**, **3e**, and **3f** were obtained as ca. 1:1, 2:1, and 1.4:1 diastereomeric mixtures, respectively.[9] Formation of **3b**–**d** was also not selective, but the exact ratios could not be ascertained due to the presence of an additional stereocenter.

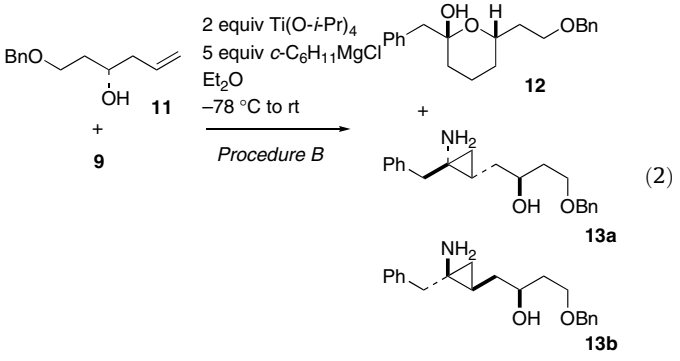


(1)

A lack of 1,3-diastereocontrol, as well as the formation of both cyclopropylamines and hydroxypyrans, is unsatisfactory in sharp contrast to the 1,3-diastereoselective hydroxycyclopropanation of homoallylic alcohols with esters.[9] The 1,3-diastereoselectivity issue can be bypassed by employing primary or achiral tertiary alcohols in place of secondary alcohols. Interestingly, only aminocyclopropanes were obtained from the use of tertiary homoallylic alcohols.[17]

When an alcohol of **1** was protected as the corresponding TIPS or benzyl ether, no coupling product (either **3** or **4**) was found in the reaction mixture. Thus, the presence of an effective directing group such as a homoallylic alcohol is necessary for the successful titanium-mediated coupling of nitriles and terminal olefins.

Although the afore-mentioned investigations were performed with racemic substrates, coupling of two segments bearing multi-stereocenters is also possible by employing readily available, nonracemic homoallylic alcohols. Such an example of segment coupling is illustrated in Eq. 2: union of **9** and **11** delivered **12** (41%) and a 1.4:1 mixture of **13a** and **13b** (31%).



(2)

In summary, olefin exchange-mediated cyclopropanation of nitriles has been developed by employing homoallylic alcohols. Although cyclopropanation of nitriles had previously been reported by direct adaptation of the Kulinkovich reaction, an olefin exchange-mediated variant was elusive. Central to the successful implementation is the use of homoallylic alcohols, which has been found in a growing number of titanium-mediated carbon–carbon bond forming reactions. Optimization is currently in progress to better control the product ratios of hydroxypyrans to aminocyclopropanes.

Acknowledgment

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15. TMSCl was also utilized successfully, but the resulting reactions were slightly less clean than those with TMSOTf.
16. *Representative procedure C*: To a cooled (−78 °C) solution of Ti(O-*i*-Pr)$_4$ (171 mg, 0.6 mmol) in ether (1 mL) was added dropwise a 2 M solution of *c*-$C_6H_{11}MgCl$ in ether (0.75 mL, 1.5 mmol). After the resulting bright-yellow reaction mixture had been stirred at −78 °C for 45 min, a solution of homoallylic alcohol **1** (35 mg, 0.3 mmol) and nitrile **9** (70 mg, 0.6 mmol) in ether (1.2 mL) was added at once. The reaction mixture was stirred at −78 °C for an additional 45 min, allowed to warm to room temperature, stirred at room temperature for 5 h, and then cooled to 0 °C. TMSOTf (0.33 mL, 1.8 mmol) was added dropwise at 0 °C. The resulting mixture was stirred at room temperature for 5 h and quenched at 0 °C by addition of 10% NaOH (4 mL). The aqueous layer was separated and extracted with Et_2O (5 × 5 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexanes–EtOAc 5:1→2:1, followed by CH_2Cl_2–methanol–25% NH_4OH 50:1:0→10:1:0.04) to afford hydroxypyran **4e** (20 mg, 28%) and aminocyclopropane **3e** (47 mg, 67%).
17. Kim, K.; Cha, J. K., unpublished results.