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Titanium-Mediated Alkylative Coupling of *N*-Acylpyrroles

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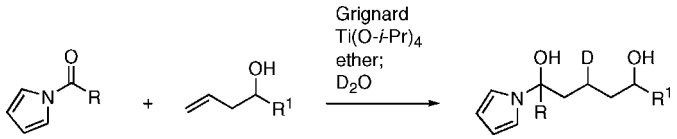
ABSTRACT



Inter- and intramolecular titanium-mediated coupling reactions of *N*-acylpyrroles are reported for convenient functionalization of terminal olefins. Comparison with the Kulinkovich reaction of esters and other carboxylic acid derivatives is also included.

Since the discovery in 1989 by Kulinkovich and co-workers of an efficient cyclopropanation of carboxylic esters mediated by low-valent titanium species,[1] the combined use of titanium alkoxides and Grignard reagents has emerged as a versatile synthetic method. By building on the presumed intermediacy of the key dialkoxytitanacyclopropane or (η^2-alkene)titanium complex (e.g., **I**), which is generated in situ from a Grignard reagent, the Kulinkovich reaction has been extended to other carboxylic acid derivatives to provide convenient access to heteroatom-substituted cyclopropanes.[2,3] Also available is 1,2-bisfunctionalization of olefins, alkynes, or allenes.[3,4] We herein report a further extension of the titanium-mediated coupling reactions to *N*-acylpyrroles and comparison with those of carboxylic esters.

A precedent for 1,2-bisfunctionalization of monosubstituted olefins among our own studies stems from titanium-mediated cyclization of ω-vinyl tethered imides: the titanaoxacyclopentane intermediate **II** proved to be sufficiently stable and amenable to functionalization (e.g., oxidation by molecular oxygen) (Scheme 1).[5] Failure of cyclopropane formation from imides could be attributed to the nonbasicity of their nitrogen. We were particularly interested in identifying suitable acyl derivatives that would display the imide-type reactivity toward the Kulinkovich reaction intermediates and, at the same time, afford the ketone coupling products. Because of the known stability of their tetrahedral intermediates, *N*-acylpyrroles[6] or *N*-acylindoles[7] seemed particularly well-suited for such 1,2-bisfunctionalization of terminal olefins. Mg^{2+}/Ti^{4+} counterions were expected to help bestow stability on the intermediates.[6] Indeed, treatment of *N*-acylpyrrole **1A** with 2.2−3.0 equiv of ethylmagnesium bromide in the presence of Ti(O-*i*-Pr)$_4$ (1.1−1.5 equiv) in ether at room temperature, followed by addition of D_2O and subsequent aqueous workup (or direct silica gel column chromatography), gave pyrrolyl carbinol **2Aa** in 92% yield (Table 1, entry 1).[8] When isopropylmagnesium bromide was employed in place of the ethyl Grignard reagent, the corresponding carbinol **2Ab** was obtained in 62% yield,

(1) (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.; Sorokin, V. L.; Kel'in, A. V. *Zh. Org. Khim.* **1993**, *29*, 66. (d) Kulinkovich, O. G.; Savchenko, A. I.; Sviridov, S. V.; Vasilevskii, D. A. *Mendeleev Commun.* **1993**, 230.

(2) Kulinkovich, O. G. *Russ. Chem. Bull., Int. Ed.* **2004**, *53*, 1065.

(3) (a) Kulinkovich, O. G.; de Meijere, A. *Chem. Rev.* **2000**, *100*, 2789. (b) Sato, F.; Urabe, H.; Okamoto, S. *Chem. Rev.* **2000**, *100*, 2835.

(4) Sato, F.; Urabe, H. In *Titanium and Zirconium in Organic Synthesis*; Marek, I., Ed.; Wiley-VCH: Weinheim, 2002; Chapter 9.

(5) (a) Lee, J.; Ha, J. D.; Cha, J. K. *J. Am. Chem. Soc.* **1997**, *119*, 8127. (b) Sung, M. J.; Lee, C.-W.; Cha, J. K. *Synlett* **1999**, 561. (c) Kim, S.-H.; Kim, S.-I.; Lai, S.; Cha, J. K. *J. Org. Chem.* **1999**, *64*, 6771.

(6) Evans, D. A.; Borg, G.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 3188.

(7) Arai, E.; Tokuyama, H.; Linsell, M. S.; Fukuyama, T. *Tetrahedron Lett.* **1998**, *39*, 71.

(8) (a) At least two runs were performed for each experiment, and average yields are given in Table 1. (b) Less effective were Weinreb amides (e.g., *N*-methoxy-*N*-methylamides), which gave substantial amounts of cyclopropanols in addition to ketones (corresponding to **2A**): Lee, J. C.; Cha, J. K. Unpublished results.

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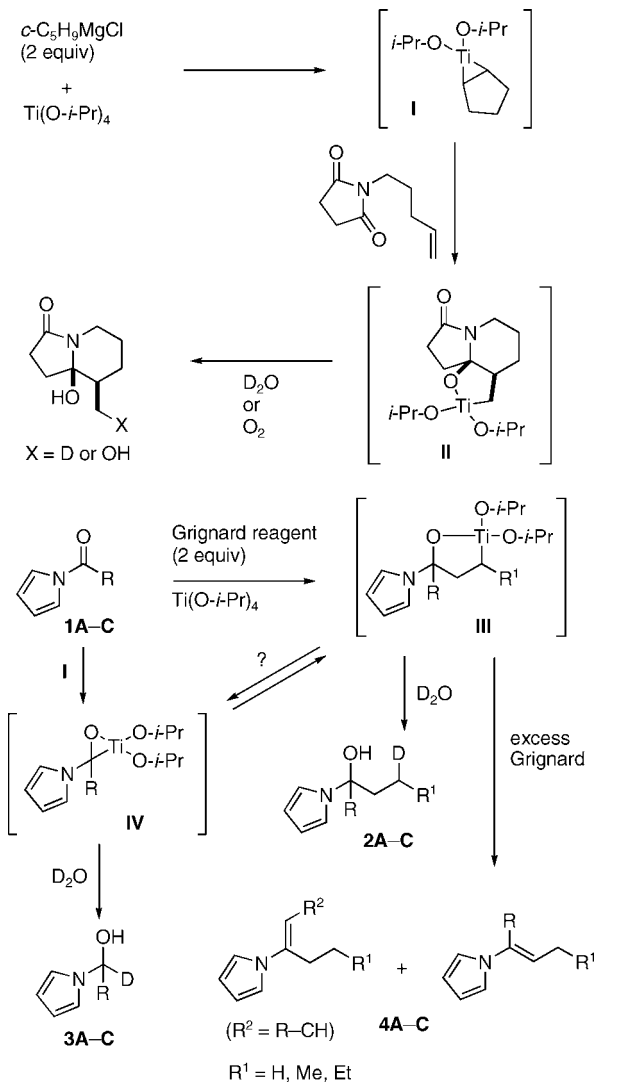
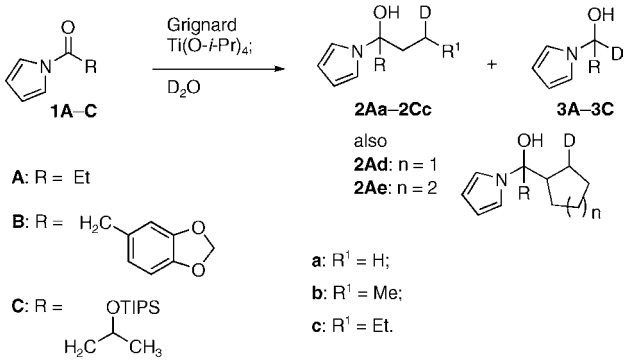
Scheme 1. Reaction Pathways for Coupling of Imides and *N*-Acylpyrroles



along with 10% yield of **3A** (Table 1, entry 2). Similarly, **2Ac** (72%) and **3A** (7%) were obtained by use of *n*-butylmagnesium bromide (Table 1, entry 3). Use of cyclopentyl and cyclohexyl Grignard reagents was not surprisingly ineffective and gave larger amounts of **3A** (41% and 35%), along with poor yields of **2Ad** and **2Ae**, respectively (Table 1, entries 4 and 5). Interestingly, entry 5 was the only case where partial deuterium incorporation was observed in the product (i.e., **2Ae**).

Except for the ethyl Grignard reagent (Table 1, entries 1, 6, and 9), other reagents produced varying amounts of the reduction byproducts **3A**−**C**. Their unexpected formation might be related in part to the ketone-like reactivity of *N*-acylpyrroles,[6] as pyrroles are π-excessive heterocycles due to the nitrogen lone pair delocalization. A competition experiment between **1A** and methyl propionate utilizing a 1:2 mixture of Ti(O-*i*-Pr)$_4$ and a Grignard reagent as the limiting reagents (to eliminate possible concentration effects) indeed established the greater reactivity of *N*-acylpyrroles compared to esters. It should be pointed out that Marek had

Table 1. Intermolecular Coupling of *N*-Acylpyrroles



entry	*N*-acyl pyrrole	Grignard reagent	products (% yield) 2A−C	+	3A−C
1	**1A**	**a**: ethyl	**2Aa**: R^1 = H (92)		**3A** (0)
2	**1A**	**b**: *i*-Pr	**2Ab**: R^1 = Me (62)		**3A** (10)
3	**1A**	**c**: *n*-Bu	**2Ac**: R^1 = Et (72)		**3A** (7)
4	**1A**	**d**: *c*-C_5H_9	**2Ad**: n = 1 (29)		**3A** (41)
5	**1A**	**e**: *c*-C_6H_{11}	**2Ae**: n = 2 (8)		**3A** (35)
6	**1B**	**a**: ethyl	**2Ba**: R^1 = H (83)		**3B** (0)
7	**1B**	**b**: *i*-Pr	**2Bb**: R^1 = Me (52)		**3B** (16)
8	**1B**	**c**: *n*-Bu	**2Bc**: R^1 = Et (58)		**3B** (10)
9	**1C**	**a**: ethyl	**2Ca**: R^1 = H (78)		**3C** (<2)
10	**1C**	**b**: *i*-Pr	**2Cb**: R^1 = Me (52)		**3C** (20)
11	**1C**	**c**: *n*-Bu	**2Cc**: R^1 = Et (54)		**3C** (26)

reported the absence of cyclohexanol (no titanaoxirane involvement) from treatment of cyclohexanone with Ti(O-*i*-Pr)$_4$ (1 equiv) and the isopropyl Grignard reagent (2 equiv).[9] Upon addition of D_2O to the reaction mixture, however, complete deuterium incorporation into **3A**−**C** is suggestive of the intermediacy of **IV** (which could exist as a dimer).[10−12] The precise mechanism for formation of **IV** (**3A**−**C**) is unknown; either ligand exchange between **1A**−**C** and **I** or an electron-transfer pathway by a low-valent titanium species might be operating. At present, an alternate pathway **III** → **IV** cannot be ruled out. Use of an increasingly large excess (i.e., >2 equiv per titanium isopropoxide) of the Grignard reagent resulted in a sharp drop-off of deuterium incorporation in **2A**−**C** attributable to subsequent β-H abstraction; surprisingly, instead of **3A**−**C**, *N*-(alkenyl)pyrroles **4A**−**C** were produced in up to 25−30% yields as an inseparable mixture of both regioisomers.[13]

(9) Morlender-Vais, N.; Soldovnikova, N.; Marek, I. *J. Chem. Soc., Chem. Commun*. **2000**, 1849.

(10) Six, Y. *Eur. J. Org. Chem*. **2003**, 1157.

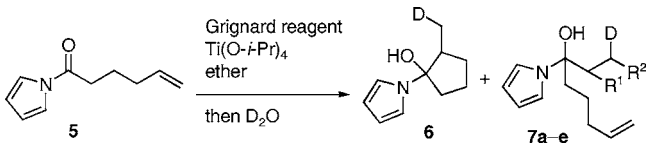
(11) Cf.: (a) Eisch, J.; Gitua, J. N.; Otieno, P. O.; Shi, X. *J. Organomet. Chem*. **2001**, *624*, 229. (b) Eisch, J.; Gitua, J. N. *Organometallics* **2003**, *22*, 24.

(12) Cf. (a) Erker, G.; Rosenfeldt, F. *J. Organomet. Chem*. **1982**, *224*, 29. (b) Erker, G.; Dorf, U.; Czisch, P.; Petersen, J. L. *Organometallics* **1986**, *5*, 668. (c) Waymouth, R. M.; Clauser, K. R.; Grubbs, R. H. *J. Am. Chem. Soc*. **1986**, *108*, 6385. (d) Negishi, E.-i.; Takahashi, T. *Bull. Chem. Soc. Jpn*. **1998**, *71*, 755.

(13) Side-product formation was increased in proportion to an excess amount of the Grignard reagent. Each regioisomer is predominantly (8:1) the (*E*)-isomer by comparison of the chemical shift to that of related compounds: Tarasova, O. A.; Schmidt, E. Y.; Albanov, A. I.; Mikhaleva, A. I.; Brandsma, L.; Trofimov, B. A. *Zh. Org. Khim*. **1999**, *35*, 1530.

Intramolecular and intermolecular coupling reactions of *N*-acylpyrroles and terminal olefins were next examined under the typical olefin exchange modification procedure.[8,14,15] Both products **6** and **7a**−**e** were obtained from **5** (Table 2); the product ratios were dependent on the nature

Table 2. Intramolecular Coupling of ω-Vinyl *N*-Acylpyrroles

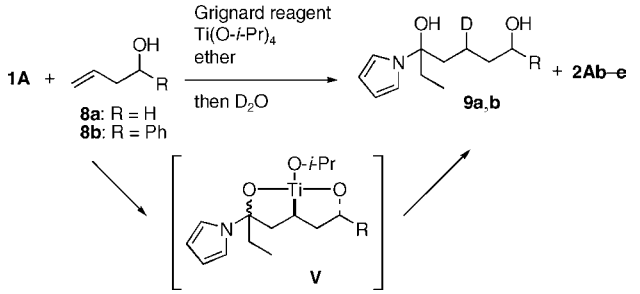


entry	Grignard reagent	**7**: R^1 and R^2	**6**:**7a**−**e** (combined % yield)
1	ethyl	**7a**: $R^1 = R^2 = H$	1:9 (78)
2	*i*-propyl	**7b**: $R^1 = H$, $R^2 = Me$	3:2 (70)
3	*n*-butyl	**7c**: $R^1 = H$, $R^2 = Et$	3:2 (72)
4	cyclopentyl	**7d**: R^1, $R^2 = (CH_2)_3$	4:1 (64)
5	cyclohexyl	**7e**: R^1, $R^2 = (CH_2)_4$	9:1 (79)

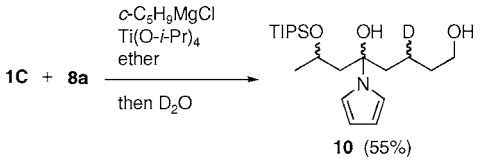
of the Grignard reagents, and the combined yields were moderate to good (64−79%). Preferential formation of **7a** by the action of ethylmagnesium bromide was not surprising (Table 2, entry 1). However, when other Grignard reagents were employed, the unexpected generation of significant amounts of the intermolecular products **7b**−**e** was observed (Table 2, entries 2−5). This observation is in sharp contrast to efficient cyclization of vinyl tethered esters, amides, carbonates, and imides that proceeds with little intermolecular reaction.[5,14] Also noteworthy is the remarkable difference between cyclopentyl and cyclohexyl Grignard reagents in the resulting product ratios (Table 2, entries 4 and 5).[16] The higher affinity of the presumed dialkoxytitanacyclopropane intermediates (e.g., **I**) for *N*-acylpyrroles, even in the presence of terminal olefins, may account for inefficient olefin exchange and thus the unexpected findings. The presence of unsaturation (e.g., C═C) might promote formation of the titanaoxapentane intermediates by coordination to a low-valent titanium species and could eliminate or reduce the reduction product corresponding to **3A**−**C**.[11]

A similar result was observed for coupling of **1A** and monosubstituted olefins (such as 1-hexene and 1-triisopyl-siloxy-3-butene) to afford the desired pyrrolyl carbinols admixed with the Grignard reagent-derived counterparts (i.e., **2Ad** and **2Ae**) only in low (20−35%) yields. We chose to utilize homoallylic alcohols **8a**,**b** since an internal hydroxy group could help increase the rate of olefin exchange so as to improve the reaction efficiency.[17,18] Reaction of **8a**,**b** with a 3:1 mixture of Grignard reagents and Ti(O-*i*-Pr)$_4$ (1 equiv) afforded the desired products **9a**,**b** (Table 3), accompanied

Table 3. Coupling of *N*-Acylpyrroles and Homoallylic Alcohols



entry	Grignard reagent	**8a**,**b**	T (°C)	**9a**,**b** + **2Ab**−**e** (% yield)
1	cyclopentyl	**8a**	0	46 + (**2Ad**) 26
2	cyclopentyl	**8a**	rt	55 + (**2Ad**) 19
3	cyclohexyl	**8a**	rt	59 + (**2Ae**) 11
4	isopropyl	**8b**	0	60 + (**2Ab**) 18
5	isopropyl	**8b**	rt	68 + (**2Ab**) 17
6	*n*-butyl	**8b**	0	39 + (**2Ac**) 44
7	*n*-butyl	**8b**	rt	51 + (**2Ac**) 33
8	cyclopentyl	**8b**	0	50 + (**2Ad**) 36
9	cyclopentyl	**8b**	rt	70 + (**2Ad**) 16
10	cyclopentyl	**8b**	50	37 + (**2Ad**) 45
11	cyclohexyl	**8b**	rt	64 + (**2Ae**) ~5



by rather significant amounts of **2Ab**−**e**. No reduction product **3A** was found in the crude reaction mixture. Presumably due to directing effects by the internal hydroxyl group, the nature of the Grignard reagents appeared to have relatively little influence on the yields of **9a**,**b**. Overall, room temperature was found to be optimal. Comparable results were also obtained from **1C** and **8a** to afford **10** (55%).

With regard to the synthetic utility of the coupling products, the ω-hydroxy ketone **11** was obtained in nearly quantitative yield by treatment of **9a** with DBU (0.05 equiv) in THF (Scheme 2).[6] Disappointingly, a preliminary study on oxidation of the presumed intermediate **V** (where the presumed major diastereomer is shown) by molecular oxygen in the absence or presence of an additive met with limited success to afford an easily separable mixture of **12** (34%)

(14) (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.

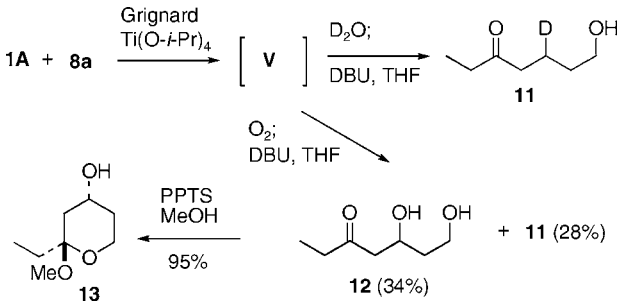
(15) For related reactions of ketones with $Cp_2Ti(PMe_3)_2$, see: (a) Hewlett, D. F.; Whitby, R. J. *J. Chem. Soc., Chem. Commun.* **1990**, 1684. (b) Kablaoui, N. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 3182. (c) Mandal, S. K.; Amin, S. R.; Crowe, W. E. *J. Am. Chem. Soc.* **2001**, *123*, 6457. See also: (d) Quan, L. G.; Cha, J. K. *Tetrahedron Lett.* **2001**, *42*, 8567.

(16) For other examples of a significant difference in the reactivity between cyclopentyl and cyclohexyl Grignard reagents, see: (a) Lecornué, F.; Ollivier, J. *J. Chem. Soc., Chem. Commun.* **2003**, 584. (b) Laroche, C.; Bertus, P.; Szymoniak, J. *Tetrahedron Lett.* **2003**, *44*, 2485.

(17) (a) Quan, L. G.; Kim, S.-H.; Lee, J. C.; Cha, J. K. *Angew. Chem., Int. Ed.* **2002**, *41*, 2160. (b) Masalov, N.; Feng, W.; Cha, J. K. *Org. Lett.* **2004**, *6*, 2365.

(18) For related uses of homoallylic alcohols, see: (a) Savchenko, A. I.; Kulinkovich, O. G. *Zh. Org. Khim.* **1997**, *33*, 913. (b) Isakov, V. E.; Kulinkovich, O. G. *Synlett* **2003**, 967.

Scheme 2. Synthetic Applications



and **11** (28%). Upon exposure of **12** to pyridinium *p*-toluenesulfonate (PPTS) in methanol, tetrahydropyran **13** was isolated in 95% yield.

In summary, we have developed inter- and intramolecular titanium-mediated coupling reactions of *N*-acylpyrroles toward 1,2-bisfunctionalization of terminal olefins. The known remarkable stability of the pyrrolyl carbinols should be useful in subsequent elaboration. Optimization of oxygenation is currently in progress to develop new approaches to functionalized tetrahydropyrans and 1,3,5-triols. Formation of the reduction products **3A**−**C** might help shed light on the mechanism of the Kulinkovich reactions of carboxylic acid derivatives. Further mechanistic and synthetic studies are currently in progress.

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Supporting Information Available: Representative experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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