Proximal Ester Assistance vs. Stereoelectronic Prohibition in Catalytic *N*-Acyliminium Ion Reactions: Stereoselective Formation of Aza-Heterocycles with Two Contiguous Quaternary-Tertiary Stereocenters

Moussa Saber, Sébastien Comesse,* Vincent Dalla,* Pierre Netchitaïlo, Adam Daïch

Laboratoire de Chimie, URCOM, EA 3221, CNRS-INC3M FR3038, UFR des Sciences et Techniques, Université du Havre, BP: 540, 25 Rue Philipe Lebon, 76058 Le Havre Cedex, France
Fax +33(2)32744391; E-mail: sebastien.comesse@univ-lehavre.fr; E-mail: vincent.dalla@univ-lehavre.fr

Received 16 June 2011

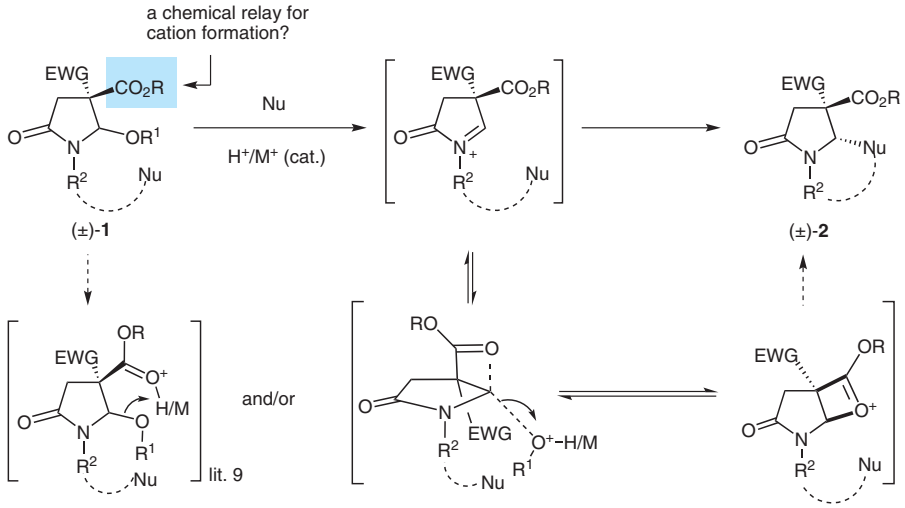
Abstract: The catalytic intramolecular and intermolecular α-amidoalkylation of deactivated *N*,*O*-acetals equipped with either two ester groups or both an ester and a cyano groups α to the reactive center has been developed. Reactions in the cyano ester series proceeded under harsher reaction conditions than those in the diester series, but furnished products with two contiguous quaternary and tertiary stereocenters with high to complete diastereocontrol. The reactivity trends and stereoselectivity profiles exhibited by these reactions may be consistent with a relay mode exerted by the ester arm(s), which might possibly direct the catalyst delivery and/or stabilize the raising carbenium ion through anchimeric bridging.

Key words: catalysis, bistrifluoromethanesulfonimide, *N*-acyliminium, directing effect and relay mode, diastereocontrol

Amongst common methods that readily generate *N*-acyliminium ions,[1] the acid-promoted activation of N,O-acetals is cornerstone.[2] Our group and others have recently documented novel catalytic systems for related α-amidoalkylation reactions.[3–7] In most cases, structurally simple, and then relatively reactive N,O-acetals were used. Catalytic *N*-acyliminium ion chemistry let the challenge of using substrates with high density of steric and electronic deactivating elements largely unmet. Therefore, one of the privileged directions in this field aims at evaluating new challenging substrates. We realized that this exercise might be addressed through the use of the generic substrates **1** represented in Scheme 1. With a quaternary center flanked by two electron-withdrawing groups (EWG = CO_2R, CN) resident to the N,O-acetalic carbon, this novel and readily available substrate class[8] is at first glance regarded as stereoelectronically deactivated towards electrophilic catalysis and therefore represents a suitable model for our preliminary study.

Likewise, several groups have recently shown that, in the presence of superacidic reagents such as triflic acid and $Sn(NTf_2)_4$, the electrophilic activation of an alkene to produce a transient carbocation intermediate could be relayed by a proximal ester function owing to the intrinsic basicity and nucleophilicity of the ester carbonyl.[9]

We then questioned whether this paradigm might also be effective for generating *N*-acyliminium ions from compounds **1** as well as carbenium ions from related alcohol derivatives in a more general prospect.[10] This would permit overcoming the inherent stereoelectronic deactivation exerted by the two proximal EWG groups and make substrates **1** amenable to a challenging catalytic *N*-acylimini-



Scheme 1 Ester-assisted vs. stereoelectronic prohibition of *N*-acyliminium ion formation–trapping under catalytic activation mode

SYNLETT 2011, No. 16, pp 2425–2429
Advanced online publication: 13.09.2011
DOI: 10.1055/s-0030-1260311; Art ID: B11011ST

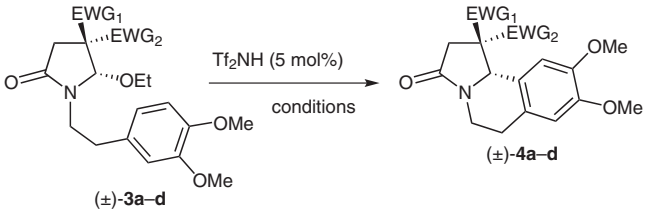
um ion alkylation to produce compounds **2**, as illustrated in Scheme 1.

Such an operation would be an elegant challenge in its own right, yet pointing out new vistas in alkylative chemistry. Moreover, it is also worth mentioning that these novel reactions would furnish Mannich-type adducts that bear two contiguous quaternary and tertiary stereocenters. We advance herein our preliminary efforts towards establishing this endeavor, with a highly efficient Tf_2NH-catalyzed intramolecular and intermolecular α-amidoalkylation of these novel N,O-acetals.

The requisite substrates (see compounds **3a–d** in Table 1, **5a–c** in Table 2, and **11a–c** in Scheme 2) were readily prepared according to our previously reported, unprecedented, and completely stereoselective formal [3+2]-cycloaddition protocol.[8,11] With a set of functionalized and novel subunits in hand, we embarked in the catalytic studies. The unique ability of Tf_2NH in catalytic *N*-acyliminium ion chemistry[4] prompted us to use this superacid for the present study. The capacity of these substrates to undergo an efficient yet challenging alkylation process was initially examined with the intramolecular Friedel–Crafts-type α-amidoalkylation of the substrates **3b–d** activated with an electron-rich aromatic nucleus (Table 1). While the presence of two ester substituents in substrate **3b** markedly retarded the cyclization to **4b** in comparison to that of the succinimide analogue **3a** (Table 1, entry 1 vs. entry 2), we were delightful to discover that the catalytic room-temperature cyclization was still feasible (Table 1, entry 2).[12] This result highlights the great value of Tf_2NH in *N*-acyliminium chemistry[4] since more than three equivalents TFA were required for the reaction of **3b** to proceed in refluxing acetonitrile.[8] Rewardingly, **4b** could be quantitatively produced within minutes in refluxing toluene in the presence of only 1 mol% Tf_2NH (Table 1, entry 3). Repeating the cyclization with the dicyano substrate **3c** in refluxing acetonitrile left the starting material untouched after 24 hours (Table 1, entry 4), thus firmly establishing a fundamental effect of the ester function. Remarkably, **4c** could be obtained in good yield at higher temperature (Table 1, entry 5).

At this juncture we felt that cyano ethyl esters should provide a good handle to shed more light into the effect exerted by the ester arm and therefore we evaluated their performance under Tf_2NH catalysis. Hence, repeating the room-temperature protocol using **3d** also led to no conversion (Table 1, entry 6), thus showcasing the importance of the two ester functions for an efficient process to occur under mild conditions. Pleasingly, conducting the reaction of **3d** in refluxing acetonitrile restored an excellent reaction profile, quantitatively returning **4d** with excellent diastereoselectivity favoring the *trans* adduct (Table 1, entry 7); this is in line with the contribution of a bridging effect from the ester as hypothesized in Scheme 1.[13,14] The *trans* stereochemistry of **4d** was established by X-ray single-crystal analysis after selective crystallization of the major isomer from MeCN–EtOAc (50:50, Figure 1).[15] It has to be noticed that this stereoselectivity is insensitive to

Table 1 Catalytic Intramolecular α-Amidoalkylations of Substrates **3a–d**



Entry	EWG_1, EWG_2	Conditions	Yield (%)[a]
1[b]	**3a** H, H	CH_2Cl_2, r.t., 1 h	**4a** 90
2	**3b** CO_2Et, CO_2Et	MeCN, r.t., 36 h	**4b** 93
3[c]	**3b** CO_2Et, CO_2Et	toluene, 110 °C, 20 min	**4b** 95
4	**3c** CN, CN	MeCN, 82 °C, 24 h	0
5[d]	**3c** CN, CN	toluene, 110 °C, 24 h	**4c** 80
6	**3d** CO_2Et, CN	MeCN, r.t,. 48 h	0
7	**3d** CO_2Et, CN	MeCN, 82 °C, 40 min	**4d** 94[e]
8[c]	**3d** CO_2Et, CN	toluene, 110 °C, 20 min	**4d** 95[e]
9	**3d** CO_2Et, CN	toluene, 60 °C, 15 h[f]	**4d** 96[e]

[a] Isolated yields are given.
[b] Compound **3a** is a methoxyaminal.
[c] 1 mol% Tf_2NH was used.
[d] The reaction was incomplete and the remaining **3c** was recovered.
[e] Compound **4d** was obtained as a mixture of two diastereomers in a 95:5 ratio.
[f] Reaction time nonoptimized.

the temperature and solvent, since ca. 95:5 *trans*/*cis* ratios were consistently obtained over a broad range of temperature (from 60 °C to 110 °C) in either MeCN or toluene (Table 1, entries 7–9). From this preliminary set of results a reactivity and stereoselectivity profile, in perfect accordance with our working hypothesis, is clearly observed: CO_2R, CO_2R > CO_2R, CN (high *trans* stereoselectivity) > CN, CN (Scheme 1). Beside the ability of the ester function located in compounds **3b**,**c** to impart high catalytic activity and good stereocontrol, the unusual thermal stability of this N,O-acetals/*N*-acyliminium ions system is another remarkable feature that further exemplifies its synthetic value.

Having clearly established an ester effect in this Friedel–Crafts-type cyclization, we wondered whether such an effect could be useful to overcome the even greater difficul-

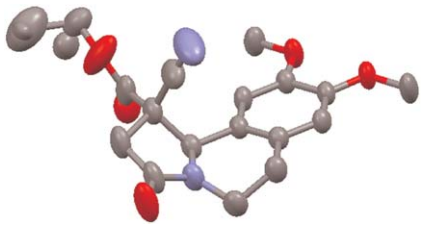


Figure 1 Ellipsoid model plot of compound **4d**. The hydrogen atoms were omitted for clarity.

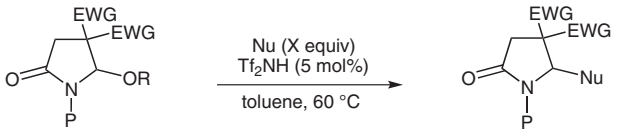
ties associated with an intermolecular α-amidoalkylation process. The challenging aspect of these reactions was immediately confirmed by the inability of the dicyano substrate **5a** to engage an allylation (Table 2, entry 1) or indoylation (not shown) process under conditions that permitted an intramolecular cyclization (see entry 5 in Table 1). In stark contrast, when the dimethyl esters **5b**,**c** were reacted with an array of C- and O-nucleophiles in the presence of 5 mol% Tf_2NH in toluene, the catalytic couplings were all efficient at only 60 °C (Table 2, entries 2–6).[16]

When the allylation of cyano ester substrates **11a**,**b** was carried out in refluxing toluene,[17] compounds **12** and **13** were isolated in fairly good yields and in this case with a remarkable >95 de (Scheme 2), which again accounts for the anchimeric participation of the ester function (Scheme 1).[13] Using a panel of π-nucleophiles a promising scope and uniformly perfect stereocontrol was found for this catalytic amidoalkylation (see formation of compounds **14** and **15** in Scheme 2).[18] The stereochemistry of compound **15** was established to be *trans* by chemical correlation as followed. A Knoevenagel reagent **16** was prepared and engaged with *N*-benzyl bromoacetamide under our previously reported[11] reaction conditions (Scheme 3). This led to an expected formal [3+2] lactam cycloadduct in an excellent yield, the ^1H NMR and ^{13}C NMR spectra of which were identical in all respects with those of compound **15** produced by the *N*-acyliminium approach as described in Scheme 2. Given the *trans* stereochemical assignment previously determined for similar cycloadducts,[11] we assume that the stereochemistry of compound **15** produced by this *N*-acyliminium ion based catalytic strategy is *trans* (i.e., consistent with incorporation of the nucleophile *syn* relative to the cyano group). The stereochemistry of compounds **12**–**14** is proposed by analogy which is supported by the *trans* stereoselectivity also displayed by the intramolecular approach.

The uniform *trans* stereoselectivity observed herein compares favorably with similar alkylations of 4,5-diacetoxy pyrrolidin-2-ones, where the stereoselectivity has been shown to be highly dependent on the nature of the nucleophile.[6d,19] This again supports the idea of a bridging stabilization of the ester function in this work. Moreover, the functional array presented by the coupling products shown in Table 2 and Scheme 2 is also noteworthy. It offers numerous prospects for further elaboration such as, for example, ring-closing metathesis (in the case of compounds **7**–**10** and **12**) and intramolecular hydroarylation (in the case of **14** and **15** and related compounds).

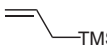
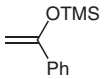
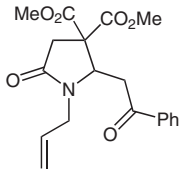
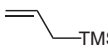
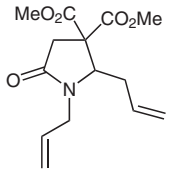
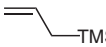
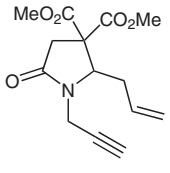
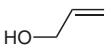
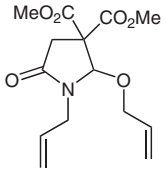
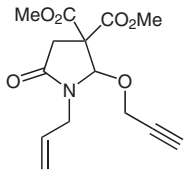
To summarize, we have demonstrated that stereoelectronically deactivated N,O-acetals bearing two electron-withdrawing groups in the vicinity of the acetalic carbon iminium precursors can undergo an acid-catalyzed alkylation with interesting catalytic activity, provided the resident quaternary carbon bears at least one ester function. Based on the general trends and highly stereoselective profile of this chemistry, a mechanism wherein the ester carbonyl anchimerically relays the raising cation might reasonably be postulated. In the case where the substrates bear two ester functions, preprotonation of one ester group followed by *syn* intramolecular H^+ delivery to the alkoxy leaving group might also be involved as an alternative synergistic relay mode[9] (see Scheme 1). We be-

Table 2 Catalytic Intermolecular a-Amidoalkylations of Substrates **5a–c**

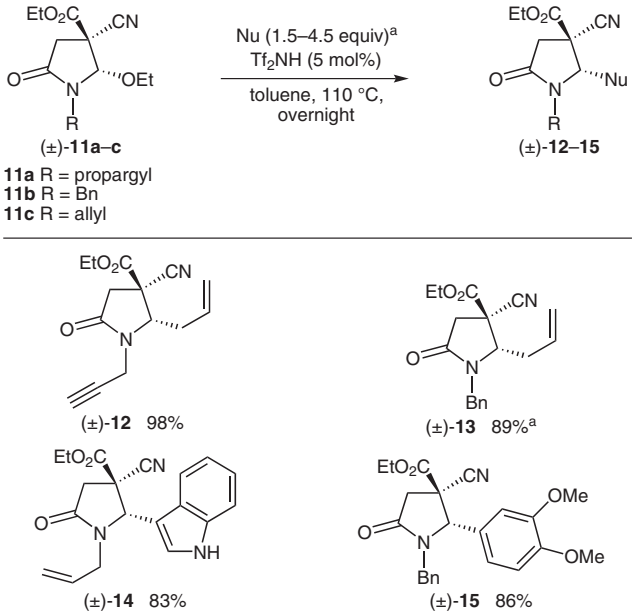


5a EWG = CN, R = Et
5b,**c** EWG = CO_2Me, R = Me

6–10

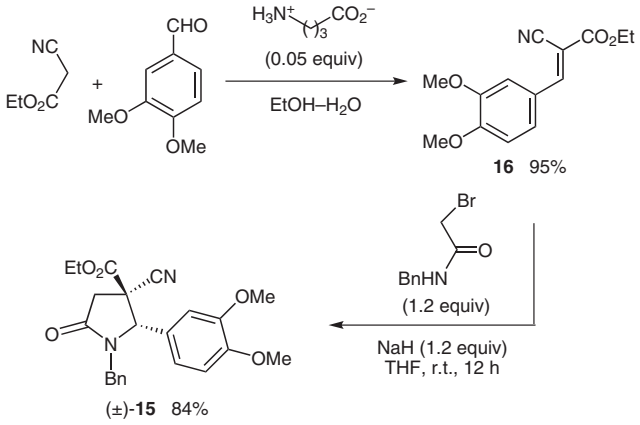
Run	Substrate **5** (P)[a]	Nu (equiv)	Product **6–10**	Yield (%)[b]
1[c]	**5a** (Bn)	 (4.5 equiv)	–[d]	–
2	**5b** (All)	 (3 equiv)	 **6**	75
3	**5b** (All)	 (2.2 equiv)	 **7**	93
4	**5c** (Propar)	 (2.2 equiv)	 **8**	96
5	**5b** (All)	 (3.5 equiv)	 **9**	>99
6	**5b** (All)	 (3.5 equiv)	 **10**	>99

[a] For abbreviations used for P groups, see (**a**) Bn: benzyl, (**b**) All: allyl, (**c**) Propar: propargyl.
[b] Isolated yields are given.
[c] Reaction conditions: 110 °C over 24 h.
[d] Compound **5a** was completely recovered.



Scheme 2 Preliminary scope of the highly stereoselective Tf_2NH-catalyzed amidoalkylation of gem-4-cyanoester 5-ethoxy pyrrolidin-5-ones. [a] 4.5 Equiv of allyltrimethylsilane were used; 1.5 equiv of indole and 1,2-dimethoxybenzene were used.

lieve these findings improve the knowledge of cationic chemistry and therefore may open new directions in this field. Further mechanistic work aimed at gaining a deeper understanding of the reaction mechanism is currently under way in our laboratory.



Scheme 3 Determination of the stereochemistry of compound **15** by chemical correlation

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

We are grateful to the University of Le Havre for the aid 'ATER position', attributed to one from us (M. S.) and to Miss Aurore Grand for experimental contribution. We thank Dr. Morgane Sanselme for her generous support in X-ray crystallographic analysis of **4d**.

References and Notes

(1) (a) For authoritative reviews on *N*-acyliminium ion chemistry, see: Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817. (b) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431.

(2) For two recent exhaustive reviews on the intermolecular amidoalkylation of N,O-acetals, see: (a) Yazici, A.; Pyne, S. G. *Synthesis* **2009**, 339. (b) Yazici, A.; Pyne, S. G. *Synthesis* **2009**, 513.

(3) Pin, F.; Comesse, S.; Garrigues, B.; Marchalin, Š.; Daich, A. *J. Org. Chem.* **2007**, *72*, 1181.

(4) (a) Ben Othman, R.; Bousquet, T.; Othman, M.; Dalla, V. *Org. Lett.* **2005**, *7*, 5335. (b) Tranchant, M. J.; Moine, C.; Ben Othman, R.; Bousquet, T.; Othman, M.; Dalla, V. *Tetrahedron Lett.* **2006**, *47*, 4477.

(5) Ben Othman, R.; Affani, R.; Tranchant, M. J.; Antoniotti, S.; Duñach, E.; Dalla, V. *Angew. Chem. Int. Ed.* **2010**, *49*, 776.

(6) For some other recent reports on catalytic amidoalkylation of N,O-acetals: (a) Okitsu, O.; Suzuki, R.; Kobayashi, S. *J. Org. Chem.* **2001**, *66*, 809. (b) Camilo, N. S.; Pilli, R. A. *Tetrahedron Lett.* **2004**, *45*, 2821. (c) de Godoy, L. A. F.; Camilo, N. S.; Pilli, R. A. *Tetrahedron Lett.* **2006**, *47*, 7853. (d) Ben Othman, R.; Bousquet, T.; Fousse, A.; Othman, M.; Dalla, V. *Org. Lett.* **2005**, *7*, 2825; and references therein. (e) Kinderman, S. S.; Wekking, M. M. T.; van Maarseveen, J. H.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *J. Org. Chem.* **2005**, *70*, 5519.

(7) For impressive catalytic enantioselective approaches, see: (a) Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 13404. (b) Raheem, I. T.; Thiara, P. S.; Jacobsen, E. N. *Org. Lett.* **2008**, *10*, 1577. (c) Peterson, E. A.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2009**, *48*, 6328. (d) Muratore, M. C.; Holloway, C. A.; Pilling, A. W.; Storer, R. I.; Trevitt, G.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 10796.

(8) Moussa, S.; Comesse, S.; Dalla, V.; Daïch, A.; Sanselme, M.; Netchitaïlo, P. *Synlett* **2010**, 2197.

(9) (a) Grau, F.; Heumann, A.; Duñach, E. *Angew. Chem. Int. Ed.* **2006**, *45*, 7285. (b) Paz Muñoz, M.; Lloyd-Jones, G. C. *Eur. J. Org. Chem.* **2009**, 516.

(10) For a recent series of papers reporting diastereoselective alkylation of chiral alcohol derivatives bearing an adjacent ester group, see: (a) Rubenbauer, P.; Bach, T. *Adv. Synth. Catal.* **2008**, *350*, 1125. (b) Stadler, D.; Bach, T. *J. Org. Chem.* **2009**, *74*, 4747. (c) Rubenbauer, P.; Bach, T. *Chem. Commun.* **2009**, 2130. (d) Cozzi, P. G.; Benfatti, F. *Angew. Chem. Int. Ed.* **2010**, *49*, 256.

(11) For related studies in our group, see: Comesse, S.; Sanselme, M.; Daïch, A. *J. Org. Chem.* **2008**, *73*, 5566.

(12) **Typical Procedure for the Preparation of 4a–d**
To a solution of an *N*,*O*-acetal **3a–d** (0.4 mmol) in a freshly distilled solvent as indicated in Table 1 (1.5 mL) was added dropwise a 0.5 M CH_2Cl_2 solution of $HNTf_2$ (40 μL, 0.02 mmol, 0.05 equiv). The reaction was stirred at the temperature indicated in Table 1 and followed by TLC. At the end of the reaction, the solution was quenched at r.t. by a 5% aq solution of $NaHCO_3$, and the aqueous phase was extracted two times with EtOAc (3 mL). The combined organic layers were dried over $MgSO_4$, the solvent was removed under vacuum, and the residue was then purified by silica gel chromatography to provide the desired tricycles **4a–d**.
Physical Data for 4b
Isolated as white solid (recrystallized from Et_2O); mp 157–159 °C; yield 95% (EtOAc–cyclohexane, 40:60). IR (KBr): 1728, 1691 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.84 (t, *J* = 7.0 Hz, 3 H), 1.36 (t, *J* = 7.0 Hz, 3 H), 2.60 (d, *J* = 16.4

Hz, 1 H), 2.79–3.03 (m, 3 H), 3.05 (d, *J* = 16.4 Hz, 1 H), 3.62–3.84 (m, 2 H), 3.84 (s, 6 H), 4.29–4.50 (m, 3 H), 5.54 (s, 1 H), 6.57 (s, 1 H), 7.30 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7, 14.3, 28.6, 37.8, 40.1, 60.9, 62.0, 26.6, 110.8, 110.5, 123.6, 127.9, 147.7, 148.4, 168.9, 169.8, 170.7.

(13) A simple steric bias (ester > cyano) could also be considered as an alternative or competitive mechanism, in line with ref. 10.

(14) Analytical data and copy of the ^{1}H NMR spectrum for compound **4d** are provided in the Supporting Information.

(15) Full crystallographic data have been deposited at the Cambridge Crystallographic Data Centre; CCDC reference number 833548 for the major diastereoisomer of product **4d**. Copies of the data can be obtained free of charge at the following address: http://www.ccdc.cam.ac.uk.

(16) For typical procedure for the preparation of **6**–**10**, see the Supporting Information.

(17) When these allylations were performed at 60 °C overnight, around 25% conversion into the desired product was observed, thus confirming the importance of the two ester functions for an efficient process under mild conditions in the intermolecular reactions too.

(18) For typical procedure for the preparation of **12**–**15**, see the Supporting Information.

(19) For a representative paper, see: Louwrier, S.; Ostendorf, M.; Boom, A.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1996**, *52*, 2603.