JOC Article
pubs.acs.org/joc

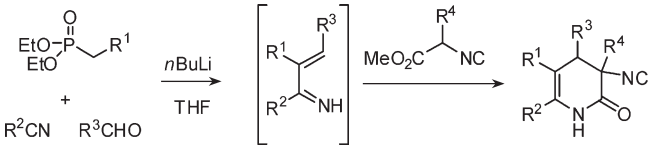
Scope and Limitations of an Efficient Four-Component Reaction for Dihydropyridin-2-ones

Rachel Scheffelaar,[†] Monica Paravidino,[†] Anass Znabet,[†] Rob F. Schmitz,[†] Frans J. J. de Kanter,[†] Martin Lutz,[§] Anthony L. Spek,[§] Célia Fonseca Guerra,[‡] F. Matthias Bickelhaupt,*[,‡] Marinus B. Groen,[†] Eelco Ruijter,*[,†] and Romano V. A. Orru*[,†]

[†]*Department of Chemistry & Pharmaceutical Sciences, Vrije Universiteit Amsterdam, De Boelelaan 1083, 1081 HV Amsterdam, The Netherlands,* [‡]*Amsterdam Center for Multiscale Modeling (ACMM), Vrije Universiteit AmsterdamDe Boelelaan 1083, 1081 HV Amsterdam, The Netherlands, and* [§]*Bijvoet Center for Biomolecular Research, Crystal and Structural Chemistry, Utrecht University, Padualaan 8, 3584 CH, Utrecht, The Netherlands.*

orru@few.vu.nl; e.ruijter@few.vu.nl; fm.bickelhaupt@few.vu.nl

Received December 22, 2009



A broad range of isonitrile-functionalized 3,4-dihydropyridin-2-ones could be prepared using a four-component reaction between phosphonates, nitriles, aldehydes, and isocyanoacetates. The reaction involves initial formation of a 1-azadiene intermediate which is trapped in situ by an isocyanoacetate to give the desired heterocyclic scaffold through cyclocondensation. The full scope and limitations of this four-component reaction are described. Variation of the nitrile and aldehyde inputs proved to be extensively possible, but variation of the phosphonate input remains limited. Regarding the isocyanoacetate, α-aryl isocyanoacetates give moderate to high yields and result in a complete diastereoselectivity for the 3,4-*cis* isomer. α-Alkyl isocyanoacetates gave the corresponding dihydropyridin-2-ones in moderate yields, most of them as mixtures of diastereomers. Elevated temperatures during cyclocondensation generally increased the yield and resulted in a change of the diastereomeric ratio in favor of the *cis*-diastereomer. In addition to isocyanoacetates, a limited number of other α-acidic esters resulted in the formation of dihydropyridin-2-ones, albeit in much lower yield. Computational studies show that the observed difference in yield cannot be simply correlated to specific physical properties (including acidity) of the different α-acidic esters.

Introduction

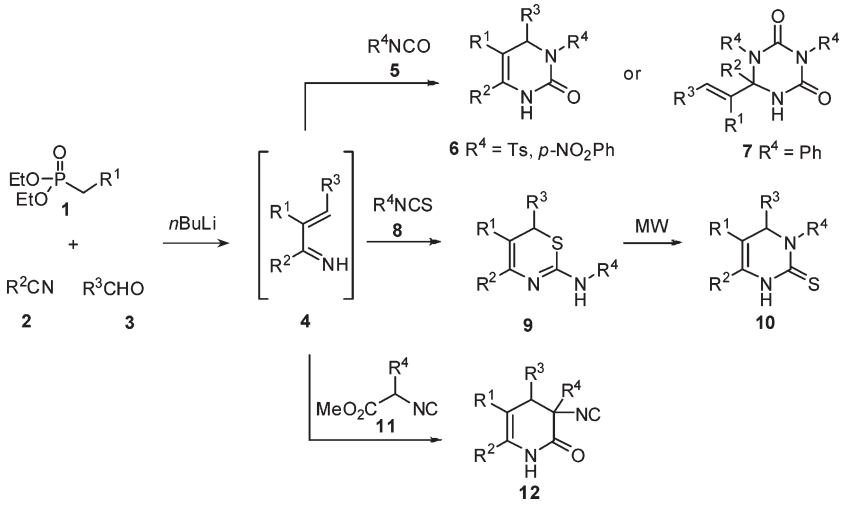
Organic synthesis has reached a high level of sophistication. Multistep, sequential synthesis allows access to many complex and challenging synthetic targets. However, the present synthetic methodology does not meet the standards set to future purposes. Certain constraints, including economic, societal, and environmental factors, force the synthetic community to conceive novel procedures and synthetic concepts to optimize efficiency. Ideally, the target molecule is prepared in one pot from readily available starting materials in one simple operation. Consequently, multicomponent reactions (MCRs) receive significant attention since they are well suited for the rapid construction of various valuable scaffolds.[1]

Parallel automated synthesis and combinatorial chemistry allow the generation of large numbers of compounds. However, experiences in combinatorial chemistry-based drug discovery in the past decades have shown that the amount of relevant hits is not directly proportional to the number of compounds screened, primarily because of the limited

(1) (a) Orru, R. V. A.; de Greef, M. *Synthesis* **2003**, 1471–1499. (b) Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89. (c) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3210. (d) Zhu, J. P. *Eur. J. Org. Chem.* **2003**, *7*, 1133–1144. (e) Jacobi von Wangelin, A.; Neumann, H.; Gördes, D.; Klaus, S.; Strübing, D.; Beller, M. *Chem.—Eur. J.* **2003**, *9*, 4286–4294. (f) Simon, C.; Constantieux, T.; Rodriguez, J. *Eur. J. Org. Chem.* **2004**, 4957–4980. (g) Ramón, D. J.; Yus, M. *Angew. Chem.* **2005**, *117*, 1628–1661. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602−1634. (h) Sunderhaus, J. D.; Martin, S. F. *Chem.—Eur. J.* **2009**, *15*, 1300–1308. (i) Ganem, B. *Acc. Chem. Res.* **2009**, *42*, 463–472.

DOI: 10.1021/jo902613j Published on Web 02/02/2010

SCHEME 1. 1-Azadienes as Important Intermediates for Diversity-Oriented Synthesis

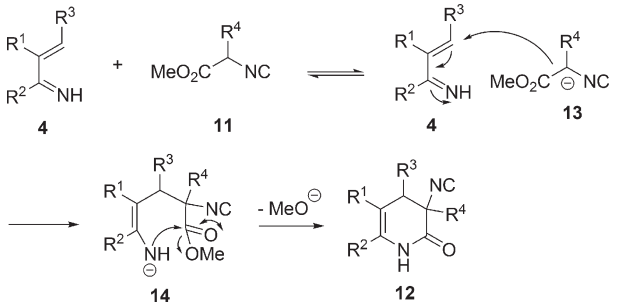


structural diversity in these compound collections.[2,3] In recent years, the importance of structural diversity generation in drug discovery is increasingly recognized. The need for more molecular diversity is also generally accepted in the design and development of novel ligand systems for homogeneous catalysis.[4]

Multicomponent chemistry is an ideal tool to generate both complexity and diversity, especially when a versatile reaction intermediate is envisaged. Furthermore, when the product of an MCR has a synthetic handle for another multicomponent reaction, additional complexity will be created. Such a strategy fits well in the concept of diversity-oriented synthesis (DOS).[2,5]

Recently, we have contributed with several examples in this area.[6,7] The common factor in the reported reactions is the application of an in situ generated 1-azadiene intermediate **4** that can be trapped by isocyanates **5** or isothiocyanates **8** to afford functionalized 3,4-dihydropyrimidine-2-ones **6**, triazinane diones **7**, 2-aminothiazines **9**, and dihydropyrimidine-2-thiones **10** (Scheme 1). 1-Azadiene intermediates **4** are obtained by reaction of phosphonates **1**, nitriles **2**, and aldehydes **3** via a Horner−Wadsworth−Emmons (HWE) reaction.[8] Recently, we reported in a communication an

SCHEME 2. Proposed Mechanism of the DHP-2-one MCR

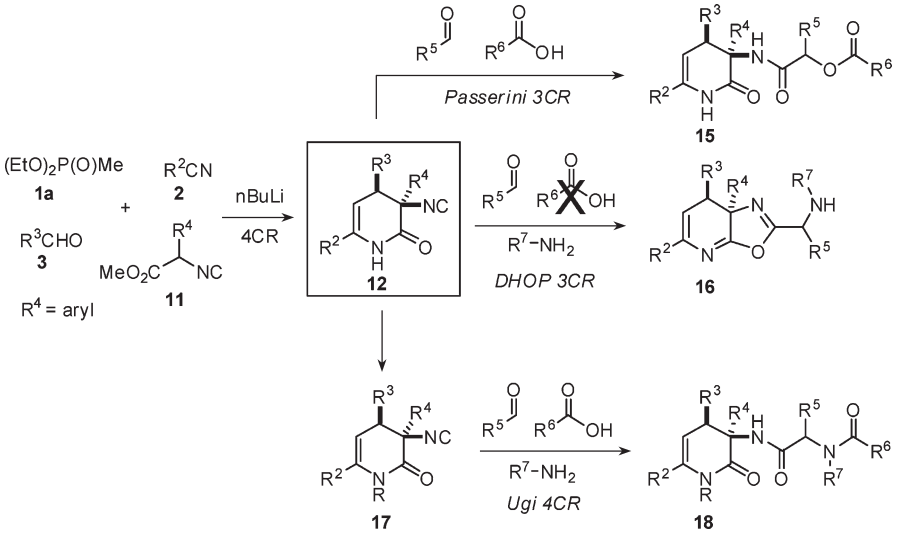


elaboration of this chemistry by examining isocyanoacetates **11** as the fourth component to gain access to isonitrile-containing 3,4-dihydropyridin-2-ones **12** (3,4 DHP-2-ones).[9] The reaction most likely involves a Michael-type attack of anion **13** to 1-azadiene **4** followed by lactamization of intermediate **14** (Scheme 2).

This is the first multicomponent reaction leading to isonitrile-functionalized heterocyclic products. That the isocyanide group is not reactive under these conditions is surprising, since this is a very reactive functional group in numerous multicomponent reactions.[10] A [4 + 1]-cycloaddition leading to pyrrole-type structures would be a conceivable reaction pathway.[11] The selective formation of the 3,4-DHP-2-one scaffold is remarkable, since other reactions such as 1,2 additions leading to β-lactams[12] and either imidazoline[10] or oxazole formation[13] could occur.

(2) Spring, D. R. *Org. Biomol. Chem.* **2003**, *1*, 3867–3870.
(3) Hann, M. M.; Leach, A. R.; Harper, G. *J. Chem. Inf. Comput. Sci.* **2001**, *41*, 856–864.
(4) Breit, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 6816–6825. and references therein.
(5) (a) Schreiber, S. L. *Science* **2000**, *287*, 1964–1969. (b) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46–48. (c) Tan, D. S. *Nature Chem. Biol.* **2005**, *1*, 74–84. (d) Spandl, R. J.; Bender, A.; Spring, D. R. *Org. Biomol. Chem.* **2008**, *6*, 1149–1158. (e) Galloway, W. R. J. D.; Bender, A.; Welch, M.; Spring, D. R. *Chem. Commun.* **2009**, 2446–2462. (f) Nielsen, T. E.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 48–56.
(6) Groenendaal, B.; Ruijter, E.; Orru, R. V. A. *Chem. Commun.* **2008**, 5474.
(7) (a) Vugts, D. J.; Jansen, H.; Schmitz, R. F.; De Kanter, F. J. J.; Orru, R. V. A. *Chem. Commun.* **2003**, 2594–2595. (b) Vugts, D. J.; Koningstein, M. M.; Schmitz, R. F.; De Kanter, F. J. J.; Groen, M. B.; Orru, R. V. A. *Chem.—Eur. J.* **2006**, *12*, 7178–7189. (c) Glasnov, T. N.; Vugts, D. J.; Koningstein, M. M.; Desai, B.; Fabian, W. M. F.; Orru, R. V. A.; Kappe, C. O. *QSAR Comb. Sci.* **2006**, *25*, 509. (d) Groenendaal, B.; Vugts, D. J.; Schmitz, R. F.; de Kanter, F. J. J.; Ruijter, E.; Groen, M. B.; Orru, R. V. A. *J. Org. Chem.* **2008**, *73*, 719. (e) Groenendaal, B.; Ruijter, E.; de Kanter, F. J. J.; Lutz, M.; Spek, A. L.; Orru, R. V. A. *Org. Biomol. Chem.* **2008**, *6*, 3158.
(8) (a) Shin, W. S.; Lee, K.; Oh, D. Y. *Tetrahedron Lett.* **1995**, *36*, 281–282. (b) Lee, K.; Oh, D. Y. *Synthesis* **1991**, 213–214.
(9) Paravidino, M.; Bon, R. S.; Scheffelaar, R.; Vugts, D. J.; Znabet, A.; Schmitz, R. F.; De Kanter, F. J. J.; Lutz, M.; Spek, A. L.; Groen, M. B.; Orru, R. V. A. *Org. Lett.* **2006**, *8*, 5369–5372.
(10) (a) Bon, R. S.; Hong, C.; Bouma, M. J.; Schmitz, R. F.; De Kanter, F. J. J.; Lutz, M.; Spek, A. L.; Orru, R. V. A. *Org. Lett.* **2003**, *5*, 3759–3762. (b) Bon, R. S.; Van Vliet, B.; Sprenkels, N. E.; Schmitz, R. F.; De Kanter, F. J. J.; Stevens, C. V.; Swart, M.; Bickelhaupt, F. M.; Groen, M. B.; Orru, R. V. A. *J. Org. Chem.* **2005**, *70*, 3542–3553. (c) Elders, N.; Schmitz, R. F.; de Kanter, F. J. J.; Ruijter, E.; Groen, M. B.; Orru, R. V. A. *J. Org. Chem.* **2007**, *72*, 6135–6142.
(11) Bedjequelal, K.; Bienaymé, H.; Poigny, S.; Schmitt, Ph.; Tam, E. *QSAR Comb. Sci.* **2006**, *25*, 504–508.
(12) (a) Hata, S.; Iwasawa, T.; Iguchi, M.; Yamada, K.; Tomioka, K. *Synthesis* **2004**, *9*, 1471–1475. (b) Cainelli, G.; Panunzio, M.; Giacomini, D.; Di Simone, B.; Camerini, R. *Synthesis* **1994**, *8*, 805–808. (c) Oare, D. A.; Henderson, M. A.; Sanner, M. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 132–157.

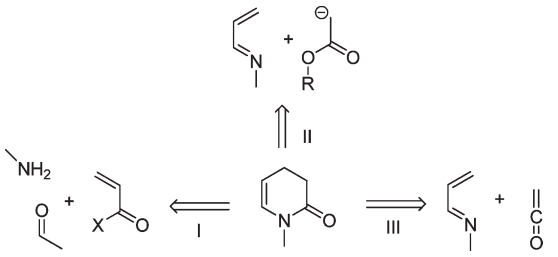
SCHEME 3. Isonitrile-Based Follow-up Chemistry on the DHP-2-one Scaffold



The presence of the isonitrile functionality in the MCR product allows isocyanide-based multicomponent follow-up chemistry, further increasing the complexity. Recently, we have demonstrated this by performing the well-known Passerini and Ugi MCRs on the DHP-2-one scaffold. For the Passerini reaction this resulted in a small series of conformationally constrained depsipeptides of type **15**.[14] The Ugi reaction gave not the expected product but rather the unprecedented dihydrooxazolopyridine (DHOP) scaffold **16** (Scheme 3).[15] The Ugi reaction can be performed after alkylation of the DHP-2-one amide, making highly functionalized conformationally constrained peptide mimics **18** accessible by applying a peptidic alkylating agent (Scheme 3).[16]

Besides the possibility for follow-up chemistry, 3,4-DHP-2-ones are conformationally similar to dihydropyridines, making them good candidates for the development of calcium channel modulators.[17] Moreover, the dihydropyridinone skeleton has often been used in natural product synthesis.[18]

SCHEME 4. Schematic Representation of Different Methods for the Synthesis of 3,4-DHP-2-ones (Substituents Are Removed for Clarity)



Several methods for the preparation of 3,4-DHP-2-ones have been reported in literature. The most commonly used method is the aza-annulation of enamines and α,β-unsaturated carboxylic acid derivatives (Scheme 4, route I).[18–20] Moreover, several 1-azadiene-based syntheses have been reported, using α-metalated acetate derivatives (Scheme 4, route II),[12a,b,21] or oxazolones[22] as reaction partners. These reactions usually follow a Michael addition/lactamization sequence (like the proposed mechanism in Scheme 2). DHP-2-ones have furthermore been synthesized by reacting 1-azadienes with ketenes giving a formal hetero-Diels–Alder reaction (Scheme 4, route III).[23]

In addition, an asymmetric *N*-heterocyclic carbene-catalyzed aza-Diels–Alder synthesis resulting in the formation of enantioenriched DHP-2-ones has been reported.[24] Furthermore, a base-induced rearrangement of ketene-*N*,

(13) (a) Bonne, D.; Dekhane, M.; Zhu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 2485–2488. (b) Elders, N.; Ruijter, E.; De Kanter, F. J. J.; Groen, M. B.; Orru, R. V. A. *Chem.—Eur. J.* **2008**, *14*, 4961–4973.

(14) Paravidino, M.; Scheffelaar, R.; Schmitz, R. F.; De Kanter, F. J. J.; Groen, M. B.; Ruijter, E.; Orru, R. V. A. *J. Org. Chem.* **2007**, *72*, 10239–10242.

(15) Scheffelaar, R.; Paravidino, M.; Muilwijk, D.; Lutz, M.; Spek, A. L.; De Kanter, F. J. J.; Orru, R. V. A.; Ruijter, E. *Org. Lett.* **2009**, *11*, 125–128.

(16) Scheffelaar, R.; Klein Nijenhuis, R. A.; Paravidino, M.; Lutz, M.; Spek, A. L.; Ehlers, A. W.; De Kanter, F. J. J.; Groen, M. B.; Orru, R. V. A.; Ruijter, E. *J. Org. Chem.* **2009**, *74*, 660–668.

(17) Ochoa, E.; Suarez, M.; Verdecia, Y.; Pita, B.; Martin, N.; Quinteiro, M.; Seoane, C.; Soto, J. L.; Duque, J.; Pomes, R. *Tetrahedron* **1998**, *54*, 12409–12420.

(18) Stille, J. R.; Barta, N. S. In *Studies in Natural Products Chemistry*; Ata-ur-Rahman, Ed.; Elsevier Science: Amsterdam, 1996; Vol. 18, pp 315–389.

(19) (a) Wagman, A. S.; Wang, L.; Nuss, J. M. *J. Org. Chem.* **2000**, *65*, 9103–9113. (b) Karpov, A. S.; Rominger, F.; Müller, T. J. J. *Org. Biomol. Chem.* **2005**, *3*, 4382–4391. (c) Paulvannan, K.; Chen, T. *J. Org. Chem.* **2000**, *65*, 6160–6166. (d) Pilipecz, M. V.; Varga, T. R.; Mucsi, Z.; Scheiber, P.; Nemes, P. *Tetrahedron* **2008**, *64*, 5545–5550.

(20) (a) Rodríguez, H.; Suárez, M.; Pérez, R.; Petit, A.; Loupy, A. *Tetrahedron Lett.* **2003**, *44*, 3709–3712. (b) Verdecia, Y.; Suárez, M.; Morales, A.; Rodríquez, E.; Ochoa, E.; González, L.; Martín, N.; Quinteiro, M.; Seoane, C.; Soto, J. L. *J. Chem. Soc. Perkin Trans. 1* **1996**, 947–951. (c) Světlik, J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1315–1318.

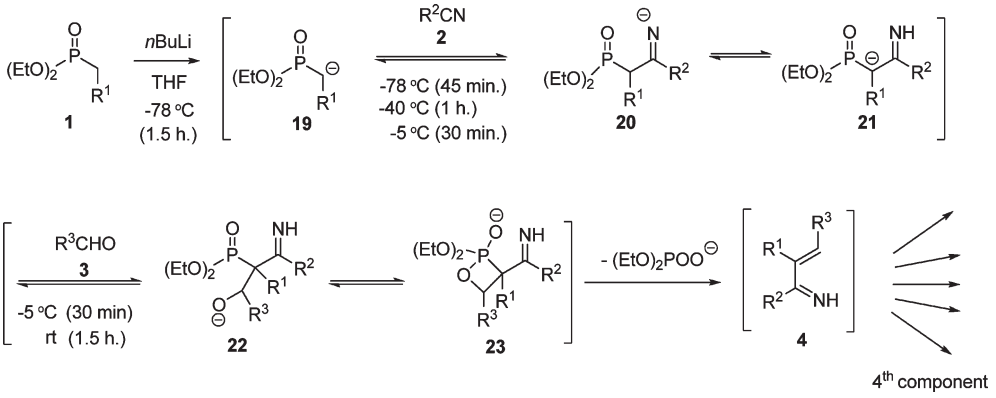
(21) (a) Komatsu, M.; Yamamoto, S.; Ohshiro, Y.; Agawa, T. *Tetrahedron Lett.* **1981**, *22*, 3769–3772. (b) Krishnan, K.; Singh, A.; Singh, B.; Kumar, S. *Synth. Commun.* **1984**, *14*, 219–226.

(22) (a) Sain, B.; Sandhu, J. S. *J. Heterocycl. Chem.* **1986**, *23*, 1007–1010. (b) Yadav, L. D. S.; Kapoor, R. *Synlett* **2008**, 2348–2354. (c) Yadav, L. D. S.; Kapoor, R. *Tetrahedron Lett.* **2008**, *49*, 4840–4844. (d) Jiang, J.; Qing, J.; Gong, L.-Z. *Chem.—Eur. J.* **2009**, *15*, 7031–7034.

(23) (a) Brady, W. T.; Shieh, C. H. *J. Org. Chem.* **1983**, *48*, 2499–2502. (b) Elliott, M. C.; Monk, A. E.; Kruiswijk, E.; Hibbs, D. E.; Jenkins, R. L.; Jones, D. V. *Synlett* **1999**, 1379–1382. (c) Sakamoto, M.; Miyazawa, K.; Kuwabara, K.; Tomimatsu, Y. *Heterocycles* **1979**, *12*, 231–237. (d) Kobayashi, S.; Semba, T.; Takahashi, T.; Yoshida, S.; Dai, K. *Tetrahedron* **2009**, *65*, 920–933.

(24) He, M.; Struble, J. R.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 8418–8420.

SCHEME 5. Mechanism of the Formation of 1-Azadiene 4 Involving a HWE Reaction



O-acetals to DHP-2-ones was published.[25] However, the variation possibilities and the opportunity for isocyanide-based follow-up chemistry make our novel multicomponent strategy unique.

The reaction already proved to be quite flexible with respect to the nitriles and aldehydes used, whereas the isonitrile input was thus far limited to rather α-acidic isocyanoacetates possessing an aromatic α-substituent.[9]

Herein we wish to report a full scope study including the variation of the phosphonate and isocyanoacetate components. Also the reactivity of α-acidic isocyanoacetates compared to other α-acidic esters will be discussed. Furthermore, experimental evidence of the proposed mechanism will be given.

Results and Discussion

The first step in the DHP-2-one synthesis is the generation of 1-azadiene intermediate **4**. For this, phosphonate **1** is deprotonated by *n*-BuLi at −78 °C, followed by addition of the nitrile **2** to afford **21**, the starting material for the HWE reaction (Scheme 5). The reaction mixture is gradually warmed to −5 °C, after which the aldehyde **3** is added. Increasing the temperature to rt allows the formation of 1-azadiene **4** with diethylphosphate as the byproduct. As discussed in the Introduction, **4** can be trapped by a fourth component to afford different heterocyclic scaffolds. Of particular interest for this work is the use of isocyanoacetates **11** to trap **4**, thus affording 3,4 DHP-2-ones of type **12** (Scheme 2).

Various phosphonates **1**, nitriles **2**, aldehydes **3**, and isocyanoacetates **11** were tested. The isocyanoacetates (racemic) are readily available in three steps from the corresponding amino acids using a procedure recently described by our group.[10] All phosphonates, nitriles, and aldehydes used were commercially available.

From our previous study, it had become clear that the phosphonate component showed limited variation possibilities.[7b] The best results were obtained using diethyl methylphosphonate **1a**, and initial experiments were therefore performed using this component. The one-pot reaction of **1a** and various nitriles, aldehydes, and aromatic isocyanoacetates is presented in Table 1 (entries 1−13). In all examples, a complete selectivity for the 3,4-*cis*-diastereomer was observed.

Aliphatic, aromatic, as well as heteroaromatic nitriles proved to be good reaction partners. Concerning the carbonyl component, aromatic, heteroaromatic, and α,β-unsaturated aldehydes gave good to excellent yields. Highly electron-deficient aldehydes such as *p*-nitrobenzaldehyde **3d** were shown to be an exception since no product formation was observed. Moreover, no aliphatic aldehydes could be used, since they lead to aldol-type products resulting from self-condensation (entry 10) and from nucleophilic attack of the isocyanoacetate to the aldehyde (entry 11).

To investigate the diastereoselectivity of the reaction, also the commercially available optically pure aldehyde (−)-myrtenal **3g** was used (entry 9) since this input proved to give an excellent asymmetric induction in the dihydropyrimidine MCR (Scheme 6a).[7b] However, in the present MCR no asymmetric induction was observed, and a 1:1 mixture of diastereomers was obtained (Scheme 6b). The absence of stereoinduction may be caused by the difference in mechanism of the two multicomponent pathways. In the present reaction, it is proposed that the stereocenters are formed in the first bond-forming step achieving intermediate **29**, whereas in the dihydropyrimidine case these are formed in the cyclization step (to obtain **27**). More conformational freedom in the former reaction is therefore probably the reason for the absence of stereoinduction.

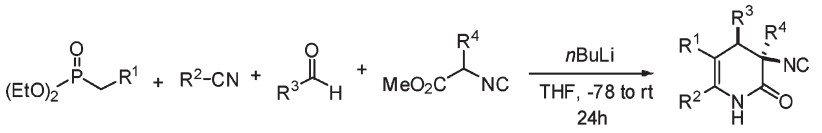
Another point of diversity is the R^1 substituent that is derived from the phosphonate component. In a previous study, we found that besides phosphonate **1a** only diethyl ethylphosphonate **1b** is a suitable reaction partner for 1-azadiene formation.[7b] However, both examples investigated using nitriles **2a** and **2c** gave only moderate yields (entries 15 and 16, Table 1).

The majority of the above experiments were performed using isocyanoacetate **11a**, which is an excellent reaction partner in the 4CR because of the high α-acidity. For the same reason, **11b** (R^4 = PCP, entries 12 and 13) also gave good results. The cyclocondensation reaction was also accomplished using the less α-acidic isocyanoacetate **11c** (R^4 = H, entry 14). However, this reaction resulted in the formation of the expected 3,4-DHP-2-one **12n** in only 19% yield (*trans*:*cis* = 67:33) along with 18% of **32**, derived from the subsequent conjugate addition of deprotonated **12n** to the 1-azadiene **30** still present followed by hydrolysis (Scheme 7). DHP-2-one **32** was isolated as a single diastereomer.

The results indicate that the cyclocondensation proceeds less efficient in these cases, probably due to the lower acidity

(25) Breuning, M.; Häuser, T. *Tetrahedron* **2007**, *63*, 934–940.

TABLE 1. One-Pot Reaction between Various Phosphonates 1, Nitriles 2, Aldehydes 3, And Isocyanoacetates 11*



1 2 3 11 12

Entry	Phosphonate (R^1)		Nitrile (R^2)		Aldehyde (R^3)		Isocyano-acetate (R^4)		DHP-2-one	Yield %[a,b] (*dr*)
1	H	**1a**	Ph	**2a**	PMP	**3a**	Ph	**11a**	**12a**	64
2	H	**1a**	*i*Pr	**2b**	PMP	**3a**	Ph	**11a**	**12b**	57
3	H	**1a**	2-furyl	**2c**	PMP	**3a**	Ph	**11a**	**12c**	76
4	H	**1a**	Ph	**2a**	Ph	**3b**	Ph	**11a**	**12d**	98
5	H	**1a**	Ph	**2a**	PCP	**3c**	Ph	**11a**	**12e**	72
6	H	**1a**	Ph	**2a**	PNP	**3d**	Ph	**11a**	**12f**	0
7	H	**1a**	Ph	**2a**		**3e**	Ph	**11a**	**12g**	36
8	H	**1a**	Ph	**2a**		**3f**	Ph	**11a**	**12h**	64
9	H	**1a**	Ph	**2a**		**3g**	Ph	**11a**	**12i**	77
10	H	**1a**	Ph	**2a**	*i*Pr	**3h**	Ph	**11a**	**12j**	0
11	H	**1a**	Ph	**2a**	*t*Bu	**3i**	Ph	**11a**	**12k**	0
12	H	**1a**	Ph	**2a**	PMP	**3a**	PCP	**11b**	**12l**	60
13	H	**1a**	Ph	**2a**	Ph	**3b**	PCP	**11b**	**12m**	60
14	H	**1a**	Ph	**2a**	PMP	**3a**	H	**11c**	**12n**	32 (63:37)[c,d]
15	Me	**1b**	Ph	**2a**	Ph	**3b**	Ph	**11a**	**12o**	12
16	Me	**1b**	2-furyl	**2c**	Ph	**3b**	Ph	**11a**	**12p**	25

*All reactions were carried out using 0.2 M phosphonate, 1.2 equiv of *n*-BuLi, 1.1 equiv of nitrile, aldehyde, and isocyanoacetate. [a]Isolated yields. [b]In case no diastereomeric ratio is reported, only the 3,4-*cis*-diastereomer was observed in the ^{1}H NMR of the crude product. [c]For this reaction, the 1-azadiene was added slowly to a solution of the isocyanoacetate. The general order of addition resulted in 19% (*trans*/*cis* 67:33) of **12n** and 18% of **32**. [d]The relative stereochemistry (*trans*/*cis*) was determined by NOESY experiments and the ^3J between H3 and H4 (12.4 Hz for the *trans*-**12n** and 6.7 Hz for *cis*-**12n**). PMP = *p*-methoxyphenyl, PNP = *p*-nitrophenyl, PCP = *p*-chlorophenyl.

of the isocyanoacetate. Formation of **32** was completely prevented using a reverse addition strategy, resulting in the formation of **12n** in 32% yield as a mixture of diastereomers (*trans*:*cis* = 63:37).

Further variation of the isocyanoacetate component was investigated by applying isocyanoacetates bearing aliphatic R^4-substituents. Phosphonate **1a**, nitrile **2a**, and aldehyde **3b** were reacted with several α-alkyl isocyanoacetates leading to DHP-2-ones **12q**−**u** (Table 2, entries 1−5) in poor to reasonable yields. In these examples (except for DHP-2-one **12s**), inseparable mixtures of diastereomers were obtained.[26]

The propensity of varying the nitrile and aldehyde components was demonstrated using isocyanoacetate **11h** (entries 6−9). Surprisingly, by changing either the nitrile or the aldehyde component a higher preference for the *cis*-diastereomer was achieved. The use of 1-cyclohexene-1-carboxaldehyde **3f** (entry 8) afforded only the *cis*-diastereomer. The yields, however, were all lower compared to DHP-2-one **12u** (entry 5).

The lower yields of α-alkyl isocyanoacetates in comparison with the α-aryl isocyanoacetates can be explained, like for isocyanoacetate **11c**, by the lower acidity of the α-proton decreasing the reaction rate and giving rise to the formation of side products.[27]

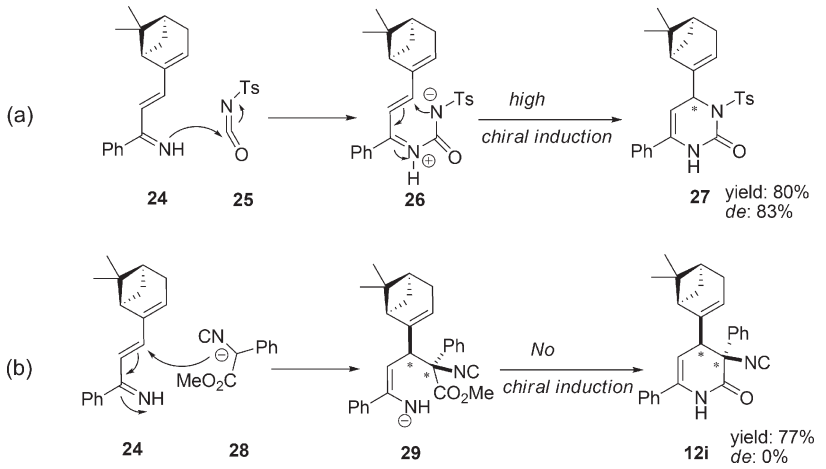
Because of the modest yields, an optimization study was performed using **1a**, **2a**, **3b**, and isocyanoacetate **11g** (Table 3). Performing the cyclocondensation at elevated temperatures proved successful in increasing the yield. Moreover, the diastereoselectivity increased in favor of the *cis*-isomer. Concentration of the reaction mixture and the use of a catalytic amount of Ag^I did not lead to an increase in yield. Ag^I is expected to coordinate to the isonitrile, thereby increasing the α-acidity of the isocyanoacetate.[28] This expected higher reactivity did not result in improved yield, although a rather high selectivity was obtained for the *cis*-diastereomer.

(26) Only in the case of DHP-2-one **12r** it was possible to get some pure fractions of both diastereomers.

(27) No clear side products could be isolated, although multiple spots on thin-layer chromatography were visible.

(28) (a) Grigg, R.; Lansdell, M. I.; Thornton-Pett, M. *Tetrahedron* **1999**, *55*, 2025–2044. (b) Soloshonok, V. A.; Kacharov, A. D.; Avilov, D. V.; Ishikawa, K.; Nagashima, N.; Hayashi, T. *J. Org. Chem.* **1997**, *62*, 3470–3479.

SCHEME 6. (a) Asymmetric Induction Obtained in the Dihydropyrimidine MCR with Optically Pure (−)-Myrtenal. (B) the Absence of Asymmetric Induction in the DHP-2-one MCR with Optically Pure (−)-Myrtenal[a]



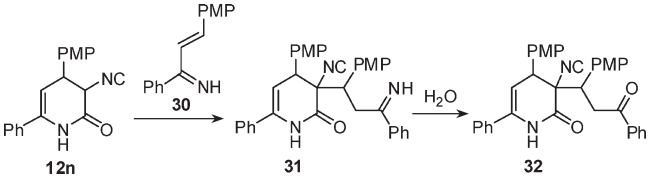
[a]Only the 3,4-*cis* stereoisomers are formed; de 0% refers only to the asymmetric induction of the chiral aldehyde.

TABLE 2. MCR of Phosphonate 1a and Various Nitriles 2 and Aldehydes 3 with α-Alkyl Isocyanoacetates 11 at rt and Reflux

Entry	Nitrile (R^2)	Aldehyde (R^3)	Isocyanoacetate (R^4)		DHP-2-one	Yield %[a], rt (*cis*:*trans*)	Yield %[a], Δ[b] (*cis*:*trans*)
1	Ph	Ph	Me	**11d**	**12q**	31 (56:44)	41 (56:44)
2	Ph	Ph	Et	**11e**	**12r**	30 (63:37)	41 (71:29)
3	Ph	Ph	*i*Pr	**11f**	**12s**	10 (*cis*)	29 (*cis*)
4	Ph	Ph	*i*Bu	**11g**	**12t**	47 (59:41)	55 (77:23)
5	Ph	Ph	Bn	**11h**	**12u**	62 (61:39)	65 (83:17)
6	*i*Pr	Ph	Bn	**11h**	**12v**	20 (85:15)	20 (*cis*)
7	2-furyl	Ph	Bn	**11h**	**12w**	37 (81:19)	61 (77:23)
8	Ph		Bn	**11h**	**12x**	18 (*cis*)	49 (*cis*)
9	Ph	PMP	Bn	**11h**	**12y**	41 (71:29)	58 (83:17)

[a]Isolated yields. Assignment of the *cis*- and *trans*-diastereomers will be further discussed in the paragraph about structural analysis. [b]After addition of the isocyanoacetate, the mixture was heated to reflux and the mixture was stirred at this temperature for 1 night. PMP = *p*-methoxyphenyl.

SCHEME 7. Follow-up Michael Addition of 12n−30



Since the yield and the diastereoselectivity were improved by using elevated temperatures, all previous reactions were performed utilizing these optimized conditions (Table 2). This indeed resulted in an improved yield for most of the reactions. Moreover, the diastereomeric ratio changed in favor of the *cis*-diastereomer in the majority of examples that were tested.

The stereoselectivity in this multicomponent reaction can likely be explained by steric considerations. Since the stereochemistry is presumably introduced in the first bond-forming step (Michael-type addition), the diastereomeric preference is based on kinetic grounds and the steric bulk in the transition state of this step becomes important. There seems to be a trend in steric bulk of the α-substituent of the isocyanoacetate with the diastereoselectivity obtained. When combining α-aryl isocyanoacetates with aromatic as well as α,β-unsaturated aldehydes, a complete selectivity for the *cis*-diastereomer is achieved.[29] However, isocyanoacetate

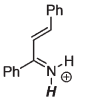
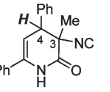
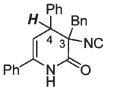
TABLE 3. Investigated Conditions of the Cyclocondensation Step Using 1a, 2a, 3b, and 11g

conditions[a]	yield[b] (%)	dr (*cis*:*trans*)
rt	47	59:41
reflux	55	77:23
concentrated 2×[c]	46	59:41
AgOAc (2 mol %)	14	91:9

[a]The different conditions depicted are the conditions after addition of the isocyanoacetate. [b]Isolated yields. [c]The product is concentrated to half its volume after 1-azadiene formation.

(29) The high diastereoselectivity of reactions involving α-aryl isocyanoacetates may also be the result of π-interaction in the transition state, apparently favoring in the *cis*-diastereomer.

TABLE 4. Proton Affinity Energies (kcal/mol) of Molecules B*H* in the Gas Phase and THF[a]

	MeO*H*		 **12q**		 **12u**	
			cis	*trans*	*cis*	*trans*
Gas phase	387	250	340	338	335	334
THF	214	179	203	201	199	199

[a]Computed at (COSMO-)BP86/TZ2P.

11h possessing a benzyl α-substituent did not give this stereoselectivity (Table 2, entry 5). A possible rationalization is that the steric bulk of the phenyl group is further away from the chiral reaction center. The other α-alkyl isocyanoacetates (**11d**,**e**,**g**) are apparently also less sterically congested, resulting in mixtures of diastereomers (Table 2, entries 1, 2, and 4). The steric background of the selectivity is furthermore supported by the fact that reaction of isocyanoacetate **11f** (possessing an isopropyl group as the α-substituent; Table 2, entry 3) resulted in the exclusive formation of the *cis*-diastereomer. No clear explanation can be given for the fact that a pronounced preference for the *cis*-diastereomer was obtained upon changing R^2 (nitrile) from phenyl to isopropyl or a 2-furyl (Table 2, entries 5−7). The exclusive formation of the *cis*-diastereomer when applying aldehyde **3f** (Table 2, entry 8) can be explained by the more sterically demanding properties of the cyclohexen-1-yl substituent compared to benzaldehyde.

Increasing the temperature during the cyclocondensation leads to a higher excess of the *cis*-diastereomer for DHP-2-ones **12r**,**t**,**u**,**v**,**y**. Epimerization of the C4 center of the DHP-2-one may account for this observation, leading to the thermodynamic product distribution. Alkaline species in the reaction mixture, including the 1-azadiene and methoxide, are feasible initiators. This epimerization does not occur when refluxing the purified product in THF for one night, which indicates the necessity of an external base. To prove the tendency of epimerization under the reaction conditions, a crude reaction mixture of **12u** with a diastereomeric ratio (dr) of 61:39 was refluxed for an additional night, resulting once more in a diastereomeric ratio of 76:24. DHP-2-ones **12q** and **12w** did not show a difference in dr at rt or reflux conditions, which indicates that this is already the thermodynamic ratio.

To rationalize if alkaline species like methoxide and the 1-azadiene are indeed able to deprotonate the DHP-2-one at the C4 position, proton affinity (PA) energies have been calculated, using the ADF program,[30] in the gas phase and in THF using density functional theory (DFT) at BP86/TZ2P in combination with the COSMO approach to simulate solvation. The proton affinity (PA) energy of a molecule B*H* is defined as the system's energy change for the reaction $BH \rightarrow B^- + H^+$. This means, the smaller the PA energy the higher the concentration of B^-, the higher the acidity of the compound B*H*. Therefore, to be a good base, the PA energy has to be higher than (or at least in the same range as) the PA energy of the DHP-2-one (proton at the C4 center). Table 4 shows the PA energy of MeO*H*, 1-azadieneH^+, and DHP-2-ones **12u** and **12q** (*cis* and *trans* conformations are calculated). These results suggest that in the gas phase as well as in THF, methoxide is sufficiently basic to deprotonate the C4 position of the DHP-2-one, while the 1-azadiene is not.

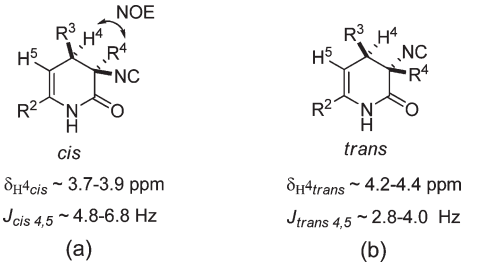


FIGURE 1. NOE correlations and H4−H5 coupling constants generally observed for the *cis*- and *trans*-diastereomers of DHP-2-ones **12** possessing aliphatic R^4-substituents.

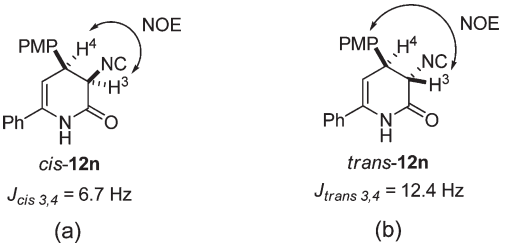


FIGURE 2. NOE correlations and H3−H4 coupling constants observed for the *cis*- and *trans*-diastereomers of **12n**.

Structural Analysis. X-ray crystal structure determination of DHP-2-one **12d** unambiguously confirmed the *cis*-relationship between the isocyanide group and R^3 (phenyl).[9] Furthermore, NOESY experiments of all DHP-2-ones possessing an aromatic R^4 substituent confirm the same stereochemical relationship. In these cases, a clear NOE correlation is visible between proton H4 and the *ortho* protons of the aromatic R^4 group (Figure 1a).

The use of α-alkyl isocyanoacetates in this MCR typically leads to the formation of inseparable diastereomeric mixtures. To deduce which peaks are derived from which diastereomer and thereby determine the diastereomeric ratio, NOESY experiments were also performed for all DHP-2-ones with aliphatic R^4 substituents. In all examples the major diastereomer showed a strong NOE correlation between proton H4 and the R^4 substituent, which is indicative for the *cis*-diastereomer

(30) Te Velde, G.; Bickelhaupt, F. M.; Baerends, E. J.; Fonseca Guerra, C.; Van Gisbergen, S. J. A.; Snijders, J. G.; Ziegler, T. *J. Comput. Chem.* **2001**, *22*, 931–967.

(31) The other diastereomer showed only a weak correlation (or none at all), which is expected for the *trans*-diastereomer (Figure 1b).

SCHEME 8. DHP-2-one 4CR with α-Acidic Esters As Fourth Component

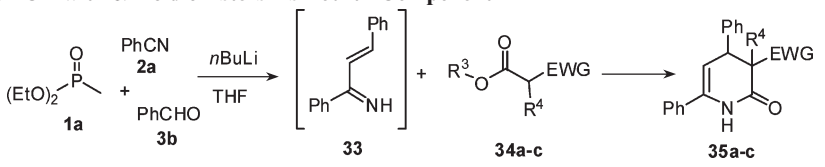


TABLE 5. MCR of Phosphonate 1a, Nitrile 2a, Aldehyde 3b, and α-Acidic Esters 34a−c and Isocyanoacetates 11a and d (as a Comparison)

entry	ester	EWG	R^3	R^4	DHP-2-one	yield (%) (*cis*:*trans*)
1	**34a**	CO_2Me	Me	Me	**35a**	17 (1:1)
2	**34b**	CN	Et	Ph	**35b**	7 (*cis*)
3	**34c**	CO_2Me	Me	Ph	**35c**	0
4	**11a**	NC	Me	Ph	**12d**	98 (*cis*)
5	**11d**	NC	Me	Me	**12q**	31 (56:44)

(Figure 1a).[31] This is supported by the observed difference in ^{1}H NMR chemical shifts of the H4 protons.

Proton H4 of the minor (*trans*) diastereomer appeared significantly more downfield compared to the major one (*cis*) (generally for α-alkyl isocyanoacetates: δ(minor) = 4.2−4.4 ppm, δ(major) = 3.7−3.9 ppm).[32] This higher chemical shift in the *trans* diastereomer might be explained by the orientation of proton H4 in the deshielding region of the anisotropy cone of the isocyanide (Figure 1b).

In all examples, there is also a distinct difference in coupling constants between protons H4 and H5 of both diastereomers. This coupling is typically around 4.8−6.8 Hz for the major (*cis*) diastereomer and 2.8−4.0 Hz for the minor (*trans*) diastereomer.[33] Indeed, the torsion angle H4−C4−C5−H5 (−40.5(12)°) derived from the molecular structure of the *cis*-diastereomer of DHP-2-one **12u** (R^4 = Bn) in the crystal (see Figure S1 in the Supporting Information)[34] corresponds with this generally observed H4/H5 coupling constants of the major *cis*-diastereomers (4.8−6.8 Hz).[35]

DHP-2-one **12n** (R^4 = H) is also formed as a mixture of two diastereomers (63:37). The major and minor diastereomers could be assigned by NOESY experiments as well. There is a clear NOE correlation between proton H3 and H4 for the minor diastereomer that is absent for the major. This correlation would be expected for the *cis*-diastereomer as indicated in Figure 2a. The major diastereomer shows a NOE correlation between proton H3 and the *ortho* protons of the *p*-methoxyphenyl substituent, indicative for the *trans*-diastereomer (Figure 2b).

Furthermore, there is a notable difference in coupling constants between protons H3 and H4 (J (minor, *cis*) = 6.7 Hz; J (major, *trans*) = 12.4 Hz). These coupling constants are consistent with the dihedral angles of 52° and 177°, respectively, derived from the COSMO-optimized structures in THF (DFT: BP86/TZ2P).[35]

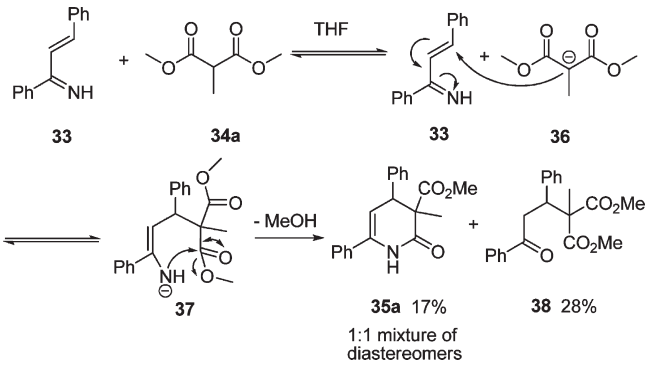
Application of Other α-Acidic Esters. Since α-isocyano esters proved to be good reaction partners in the DHP-2-one MCR, other α-acidic esters (**34a−c**) were considered as the fourth, cyclizing component, as well (Scheme 8). By applying **34a−c** in a similar procedure as described above, DHP-2-one scaffolds possessing a different functionality at the C3 position are expected. This evidently gives the possibility for functionalization by different follow-up reactions than the isocyanide-based reactions reported before.[14−16]

Although initially a similar α-reactivity of **34a−c** compared to **11a** and **d** is expected, the former generates the corresponding DHP-2-ones in much lower yields (0−17% compared to 31−98%, respectively, Table 5).

DHP-2-one **35a** was obtained in 17% yield (Table 5, entry 1) together with 28% of ketone **38**, which is plausibly formed by hydrolysis of enamine intermediate **37** (Scheme 9). The formation of ketone **38** is an important result regarding the mechanism of the DHP-2-one MCR. It strongly suggests a stepwise Michael type attack/lactamization pathway instead of a concerted cycloaddition. Unfortunately, attempts to facilitate the lactamization by performing the reaction at elevated temperatures (60 °C) did not lead to better results. Compound **35a** was obtained as a 1:1 diastereomeric mixture, suggesting that during lactamization the amine cannot discriminate between the two ester functionalities.

The isolation of **35a** and **38** (total yield 45%) using malonate **34a** indicate that the α-reactivity is not the limiting

SCHEME 9. Proposed Mechanism for the Formation of DHP-2-one 35a and Ketone 38



(32) Protons H4 of *cis*-DHP-2-ones with aromatic R^4 substituents (δ = 4.0−4.6 ppm) appear more downfield than those of DHP-2-one with aliphatic R^4 substituents, probably because in the former case these protons are deshielded by the aromatic R^4 substituent.

(33) For *cis*-DHP-2-ones with aromatic R^4 substituents the coupling constant between protons H4 and H5 is generally between 4.0 and 6.0 Hz.

(34) (a) The cis-diastereomer was selectively crystallized from a solution containing a 83:17 (cis:trans) mixture of diastereomers; (b) CCDC 751206 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(35) This assumption is made based on the standard Karplus Curve; see: *Basic One- and Two-Dimensional NMR Spectroscopy*, 3rd revised ed.; Friebolin, H., Ed.; Wiley-VCH: Weinheim, 1998.

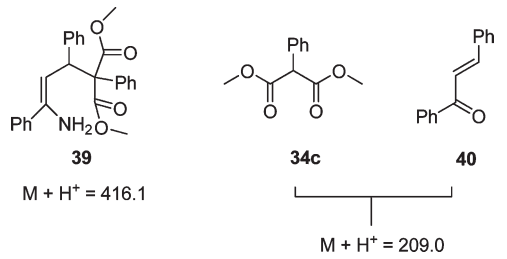


FIGURE 3. Masses observed in the LCMS of the crude reaction mixture of entry 3, Table 4, and their proposed structures.

factor using this reaction input. Most likely, the increased steric bulk, resulting from the substitution of a linear isonitrile (in **11d**) for a methyl ester (in **34a**), results in a more sluggish lactamization of **37**.

DHP-2-one **35b**[36] (Table 5, entry 2), was formed in 7% yield together with various side products, which could not be identified. Remarkably, DHP-2-one **35c** (Table 5, entry 3) was not formed at all according to LC−MS analysis of the crude reaction mixture (ESI, 60% MeOH in H_2O). Examination of the masses of all peaks indicate the presence of enamine **39** ($M + H^+ = 416.1$) (Figure 3). Moreover, three peaks were observed with a mass of 209.0 which may originate from dimethyl phenylmalonate **34c** and 1,3-diphenyl-2-propenone **40**, formed by hydrolysis of the intermediate 1-azadiene. The formation of enamine **39** provides additional support for our proposed mechanism.

The poor results by applying **34b**,**c** compared to isonitrile equivalents **11a**,**d** may originate from the differences in acidity and reactivity of the α-acidic esters. To investigate this in more detail, we calculated the proton affinity energies (in the gas phase and THF), the orbital energy of the highest occupied molecular orbital (HOMO) of its carbanion, and the percentage of the $2p_z$ orbital on the reacting carbon atom in the HOMO of the carbanion ($\%2p_z$).[37] Thus, a lower PA energy is associated with a higher carbanion abundance (active species), whereas a higher HOMO energy (ε_{HOMO}) and carbanion localization ($\%2p_z$) leads to a higher intrinsic reactivity of the carbanion. Although in previous studies[10b] we found a reasonable correlation using similar calculations, in this case, neither the trends in each of the parameters PA energy, ε_{HOMO}, and $\%2p_z$ nor combinations thereof led to a consistent correlation with the experimental yields. This strongly suggests that other factors are decisive for the differences in yield, such as, a more subtle interplay between electronic and steric factors along the reaction coordinates and/or the onset of alternative competing pathways. These issues are to be tackled in future computational studies focusing on the exploration of the conceivable network of competing mechanistic pathways toward DHP-2-ones and their kinetic and thermodynamic parameters.

(36) Although the stereochemistry of DHP-2-one **35b** was not determined using NOE experiments, it is expected to have the same *cis*-diastereoselectivity as the DHP-2-ones prepared with α-aryl isocyanoacetates. The coupling constant between H4 and H5 is 4.4 Hz, which is similar to its isonitrile variant (4.5 Hz). In addition, the chemical shift value of the H4 proton is identical (4.34 vs 4.32 ppm).

(37) A table with these values is presented in the Supporting Information. In addition to the mentioned α-acidic esters, the same parameters are calculated for **11c** and **34a**.

Conclusion

The new 4CR described here provides access to a broad range of functionalized DHP-2-ones. Variation of the nitrile (R^2) and aldehyde (R^3) inputs proved to be extensively possible but variation of the phosphonate (R^1) input remains limited. The use of the chiral aldehyde, (−)-myrtenal, did not result in any stereoinduction. When using aromatic isocyanoacetates (R^4) the DHP-2-ones were obtained in moderate to high yields with a complete *cis*-diastereoselectivity. The use of aliphatic isocyanoacetates (R^4 = alkyl) gave the products in moderate to reasonable yields generally as mixtures of diastereomers. However, elevated temperatures during the cyclocondensation typically resulted in higher yields and an improved diastereomeric ratio in favor of the *cis*-diastereomer. This is most likely the result of epimerization of the C4 stereocenter leading to the thermodynamically more stable isomer.

The use of α-acidic esters other than α-isocyano esters (malonate and α-cyanoacetate) also proved possible, although these reactions afforded the corresponding DHP-2-ones in much lower yields. Computational results can not yet explain the observed difference in reactivity. Future efforts will focus on developing a deeper understanding of reaction mechanisms based on experimental and computational findings as a tool in novel multicomponent reaction design.

Experimental Section

General Information. All reactions were carried out under an inert atmosphere of dry argon. Standard syringe techniques were applied for transfer of air-sensitive reagents and dry solvents. Melting points are uncorrected. Infrared (IR) spectra are measured in KBr, and wavelengths (ν) are reported in cm^{-1}. ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded at 250.13 or 400.13 MHz and 62.90 or 100.62 MHz, respectively, with chemical shifts (δ) reported in ppm down field from tetramethylsilane. Peak assignment was also done with the aid of *gs*-COSY, *gs*-HMQC, and *gs*-HMBC measurements. Assignment of relative stereochemistry was achieved using gs-NOESY measurements. Electron impact (EI) mass spectrometry was carried out with an electron ionization voltage of 70 eV. MS (ESI) spectra were recorded on a liquid chromatograph mass spectrometer. Chromatographic purification refers to flash chromatography using the indicated solvent (mixture) and silica gel (40−63 μm, 60 Å). Thin layer chromatography was performed using silica plates (silica on aluminum with fluorescence indicator). Compounds on TLC were visualized by UV-detection. THF was dried and distilled from sodium benzophenone ketyl prior to use. Benzonitrile was dried with $MgSO_4$ and then distilled from P_2O_5 under reduced pressure. Isobutyronitrile and 2-furaldehyde were both distilled prior to use. Other commercially available reagents were used as purchased. Experimental details of compounds **12a**−**n** have been reported elsewhere.[9]

General Procedure I for the Synthesis of 3,4-Dihydropyridin-2-ones. All reactions were carried out at a concentration of 0.2 M of phosphonate **1**, 0.24 M of *n*-BuLi, 0.22 M of nitrile **2**, 0.22 M of aldehyde **3**, and 0.22 M of isocyanoacetate **11** (or malonate/cyanoacetate **34**) in dry THF. A 1.0 mmol portion of the limiting reaction component, the phosphonate, was used. of *n*-BuLi (1.2 equiv, 1.6 M solution in hexane) was added at −78 °C to a stirred solution of phosphonate in THF. After the mixture was stirred at −78 °C for 1.5 h, the nitrile (1.1 equiv) was added and the mixture was then stirred at −78 °C for 45 min, at −40 °C for 1 h,

and at −5 °C for 30 min. The aldehyde (1.1 equiv) was added, and after being stirred at −5 °C for 30 min, the mixture was allowed to warm to rt and stirred for 1.5 h. Finally, the isocyanoacetate (or malonate/cyanoacetate) (1.1 equiv) was added, and the mixture was stirred overnight either at rt or at reflux. The reaction mixture was concentrated in vacuo (water bath at rt) and the crude product purified by column chromatography.[38]

3,4-Dihydropyridin-2-one 12o. According to general procedure I, reaction between phosphonate **1b**, *n*-BuLi, benzonitrile **2a**, benzaldehyde **3b**, and isocyanoacetate **11a**, followed by column chromatography (*c*-hexane/EtOAc = 9:1→8:2) afforded **12o** as a yellow solid (43 mg, 0.12 mmol, 12%): mp 178−180 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.69−7.66 (m, 2H), 7.50−7.37 (m, 11H), 7.26−7.18 (m, 3H), 3.97 (s, 1H), 1.67 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 163.8 (C), 161.5 (C), 136.8 (C), 135.3 (C), 134.2 (C), 131.1 (C), 129.7 (CH), 129.3 (3 CH), 129.2 (4 CH), 129.1 (2 CH), 128.8 (CH), 128.4 (2 CH), 125.8 (2 CH), 113.0 (C), 70.4 (C), 56.6 (CH), 18.0 (CH_3); IR (KBr) 2141 (w), 1691 (s), 1494 (w), 1447 (w), 1385 (w), 1372 (w), 1280 (w), 1266 (w), 766 (w), 752 (m), 698 (m); HRMS (EI, 70 eV) calcd for $C_{25}H_{20}N_2O$ (M^+) 364.1570, found 364.1575.

3,4-Dihydropyridin-2-one 12q. According to general procedure I, reaction between phosphonate **1a**, *n*-BuLi, benzonitrile **2a**, benzaldehyde **3b**, and isocyanoacetate **11c**, followed by column chromatography (*c*-hexane/ EtOAc = 9:1→8:2) afforded **12q** at rt as a yellow solid (88 mg, 0.31 mmol, 31%, *cis*:*trans* = 56:44) and at reflux as a orange solid (118 mg, 0.41 mmol, 41%, *cis*:*trans* = 56:44:. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49−7.33 (m, 11H + 11H), 5.64−5.62 (m, 1H + 1H), 4.24 (d, J = 4.0 Hz, 1H, minor), 3.79 (d, J = 4.8 Hz, 1H, major), 1.73 (s, 3H, major), 1.46 (s, 3H, minor); ^{13}C NMR (63 MHz, $CDCl_3$) δ 167.0 (C, minor), 166.2 (C, major), 160.9 (C, major), 159.7 (C, minor), 137.2 (C), 136.8 (C), 136.4 (C), 135.6 (C), 133.7 (2 C), 129.8 (2 CH), 129.7 (2 CH), 129.3 (4 CH), 129.2 (2 CH), 128.9 (2 CH), 128.8 (2 CH), 128.6 (2 CH), 125.3 (2 CH), 125.2 (2 CH), 105.2 (CH, major), 105.0 (CH, minor), 63.2 (C, minor), 63.0 (C, major), 50.5 (CH, major), 49.8 (CH, minor), 24.5 (CH_3, major), 20.2 ppm (CH_3, minor); IR (KBr) 2148 (w), 2130 (m), 1687 (s), 1655 (m), 759 (m), 700 (m); HRMS (EI, 70 eV) calcd for $C_{19}H_{16}N_2O$ (M^+) 288.1257, found 288.1254.

3,4-Dihydropyridin-2-one 35a. According to general procedure I, reaction between phosphonate **1a**, *n*-BuLi, benzonitrile **2a**, benzaldehyde **3b**, and dimethyl methylmalonate **34a** followed by column chromatography (*c*-hexane→*c*hexane/EtOAc 8:2) afforded at rt **35a** as an orange foam (56 mg, 0.17 mmol, 17%, *cis*:*trans* = 50:50) and **38** as a white foam (101 mg, 0.28 mmol, 28%). **35a**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.97 (br s, 1H + 1H), 7.51−7.22 (m, 10H + 10H), 5.67 (dd, J = 1.4, 5.17 Hz, 1H), 5.55 (d, J = 2.2 Hz, 1H), 4.41 (d, J = 5.20 Hz, 1H), 3.88 (d, J = 3.91 Hz, 1H), 3.77 (s, 3H), 3.43 (s, 3H), 1.61 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3 (C), 171.3 (C), 171.0 (C), 170.8 (C), 139.7 (C), 137.9 (C), 137.3 (C), 137.1 (C), 135.1 (C), 134.8 (C), 129.6 (CH), 129.5 (CH), 129.4 (2 CH), 129.4 (6 CH), 129.1 (2 CH), 128.7 (2 CH), 128.1 (2 CH), 125.6 (2 CH), 125.5 (2 CH), 106.9 (CH), 105.8 (CH), 55.0 (C), 54.6 (C), 53.2 (CH_3), 52.4 (CH_3), 50.9 (CH), 47.1 (CH), 21.2 (CH_3), 17.5 (CH_3); HRMS (EI, 70 eV) calcd for $C_{20}H_{19}NO_3$ (M^+) 321.1359, found 321.1371. **38**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93−7.91 (m, 2H), 7.53−7.37 (m, 3H), 7.26−7.15 (m, 5H), 4.19 (X part of ABX, J_{AX} = 3.0 Hz, J_{BX} = 11.0 Hz, 1H), 3.76 (A part of ABX, J_{AB} = 17.1 Hz, J_{AX} = 11.0 Hz, 1H), 3.76 (s, 3H), 3.65 (s, 3H), 3.57 (B part of ABX, J_{AB} = 17.1 Hz, J_{BX} = 3.0 Hz, 1H), 1.44 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.8 (C), 172.1 (C), 171.9 (C), 139.1 (C), 137.1 (C), 133.0 (CH), 129.4 (2 CH), 128.6 (2 CH), 128.3 (2 CH), 128.2 (2 CH), 127.4 (CH), 58.1 (C), 52.6 (2 CH_3), 45.7 (CH), 41.2 (CH_2), 19.69 (CH_3); MS (ESI) 377.1 (M + Na^+), 355.1 (M + H^+), 209 ($C_{15}H_{13}O^+$).

3,4-Dihydropyridin-2-one 35b. According to general procedure I, reaction between phosphonate **1a**, *n*-BuLi, benzonitrile **2a**, benzaldehyde **3b**, and ethyl phenylcyanoacetate **34b**, followed by column chromatography (*c*-hexane→*c*hexane/EtOAc 8:2), afforded at rt **35b** as a white foam (23 mg, 0.07 mmol, 7%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.69 (br s, 1H), 7.52−7.35 (m, 10H), 7.32−7.18 (m, 5H), 5.76 (dd, J = 1.6, 4.4 Hz, 1H), 4.34 (d, J = 4.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.2 (C), 137.8 (C), 137.0 (C), 134.4 (C), 134.0 (C), 130.1 (CH), 129.6 (2 CH), 129.3 (3 CH), 129.2 (2 CH), 129.1 (2 CH), 128.8 (CH), 127.58 (2 CH), 125.6 (2 CH), 117.1 (C), 105.9 (CH), 56.5 (C), 50.8 (CH); HRMS (EI, 70 eV) calcd for $C_{24}H_{18}N_2O$ (M^+) 350.1414, found 350.1423.

Acknowledgment. This work was performed with financial support from the Netherlands Organization for Scientific Research (NWO, VICI grant). M. C. Smoluch (Vrije Universiteit Amsterdam) is kindly acknowledged for HRMS measurements. M.L. and A.L.S. were financially supported by NWO-CW. F.M.B. and C.F.G. thank the National Research Combination - Catalysis (NRSC-C) for a postdoctoral fellowship for C.F.G. and The Netherlands Organization for Scientific Research (NWO-CW and NWO-NCF) for further financial support.

Supporting Information Available: Detailed experimental procedures for compounds **12p** and **12r**−**y** and X-ray crystallographic data for compound **12u**. Copies of ^{1}H NMR and ^{13}C NMR spectra for compounds **12o**−**y**, **35a**, **35b**, and **38** and Cartesian coordinates and total energies for compounds **12q** (*cis* and *trans*), **12u** (*cis* and *trans*), 1-azadiene, MeOH, **11a**,**c**,**d**, and **34a**−**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

(38) Major and minor peaks in the ^{1}H NMR and ^{13}C NMR are denoted where possible.