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Diastereoselective One-Pot Synthesis of Tetrafunctionalized 2-Imidazolines

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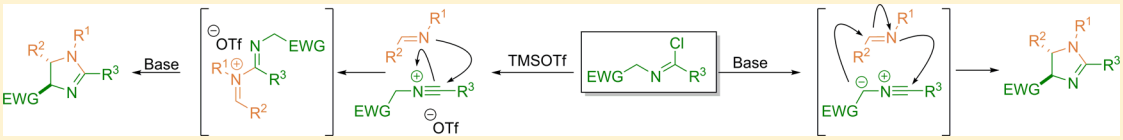
Supporting Information



ABSTRACT: A convenient *trans*-selective one-pot synthesis of tetrafunctionalized 2-imidazolines is described. Our approach to these valuable heterocyclic scaffolds involves a formal 1,3-dipolar cycloaddition between nitrile ylides or nitrilium triflates and imines. A detailed experimental study in combination with a high-level computational exploration of reaction routes reveals a plausible reaction pathway that accounts for the observed diastereoselectivity.

INTRODUCTION

2-Imidazolines are valuable heterocyclic compounds with a variety of applications in both catalysis and biology. Indeed, antihypertensive,[1] antihyperglycemic,[2] antidepressive,[3] antihypercholesterolemic,[4] and anti-inflammatory[5] activities have been reported. Important examples of C2-functionalized 2-imidazolines are the so-called nutlins (e.g., **1**, Figure 1), which have been associated with antitumor activities.[6] Furthermore, 2-imidazolines are also frequently used as chiral organocatalysts (e.g., **2**),[7] as chiral P,N-ligands in asymmetric transition-metal catalysis (e.g., **3**),[7a,8] and as precursors for *N*-heterocyclic carbenes (e.g., **4**).[9]

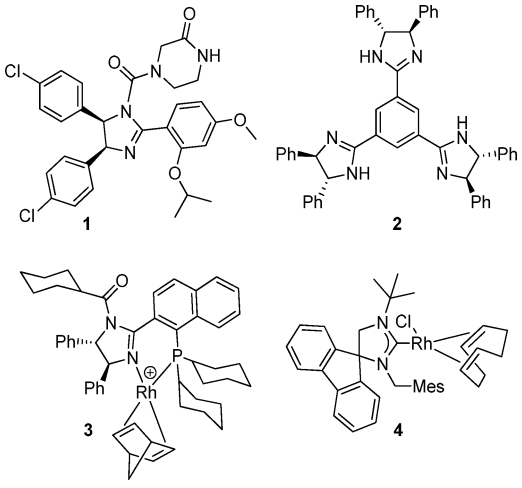


Figure 1. Tetrasubstituted 2-imidazolines as an antitumor compound (**1**), as chiral ligands for asymmetric catalysis (**2** and **3**), and as an NHC complex (**4**).

Several multistep approaches are known to synthesize highly functionalized 2-imidazolines.[7a,10] However, functionalization at the C2-position proves to be challenging. Currently, four direct methods are available as summarized in Scheme 1. One approach involves the Ugi-deprotection−cyclization strategy (**A**),[11] whereas a Pd-catalyzed carbonylative coupling procedure (**B**) toward tetrasubstituted 2-imidazolines has also been reported.[12] Alternatively, the Ritter reaction (**C**)[13] has been employed, and finally, a TMSCl mediated cycloaddition (**D**) has been effective.[14] However, all four approaches suffer from various limitations including the lack of relative stereocontrol.

We envisioned an alternative synthetic protocol based on a recently developed silver(I) acetate catalyzed three-component reaction. Starting from α-acidic isocyanides (**6**) and imines, generated in situ from aldehydes or ketones and amines (Scheme 2), trisubstituted 2-imidazolines (**9a**) are synthesized efficiently.[15] In this reaction, the silver ion coordinates to the isocyanide terminal carbon, thereby lowering the pK_a of the α-proton. After deprotonation of **6**, the resulting iminium ion (**7**) and the Ag(I)-dipole (**8**) undergo a subsequent rapid stepwise cyclocondensation to the desired 2-imidazolines (**9a**).

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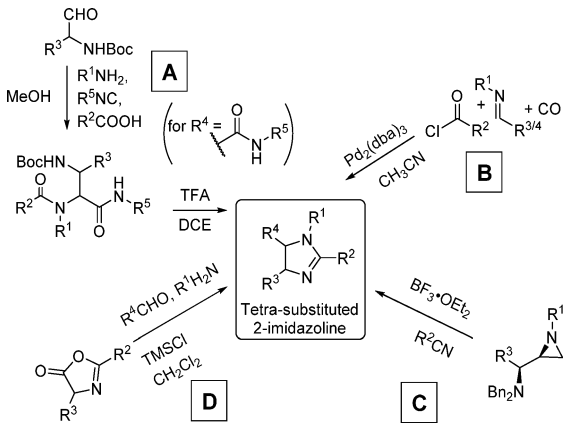
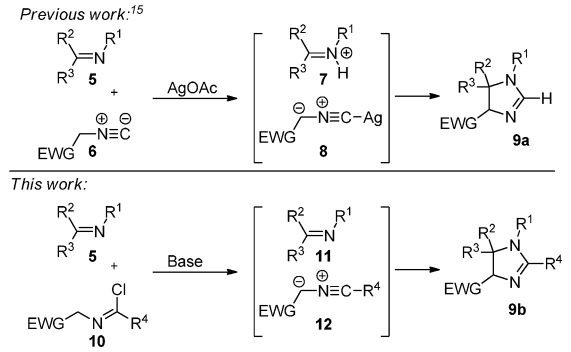
Scheme 1. Available Synthetic Methods toward the Synthesis of Tetrafunctionalized 2-Imidazolines



Scheme 2. One-Pot Synthesis of Tri- and Tetrafunctionalized 2-Imidazolines



We thus rationalized that the use of nitrile ylides (**12**) instead of silver dipoles (**8**) should allow an efficient direct one-pot synthesis of tetrasubstituted 2-imidazolines (**9b**) from readily available starting materials (Scheme 2). Nitrile ylides (**12**) are commonly used as reactive intermediates in 1,3-dipolar cycloadditions with a variety of dipolarophiles, such as CC, CO, CS, NN, and NO multiple bonds,[16] but imines are scarcely used as dipolarophiles.[17] The cycloaddition reaction of **12** with carbonyls has been reported to deliver highly functionalized oxazolines and served as basis for our investigations.[17b,18]

Thus, we report herein a highly diastereoselective cycloaddition of nitrile ylides with imines to efficiently yield tetrafunctionalized 3,4-*trans*-2-imidazolines. Computational explorations based on density functional theory (DFT) provide valuable insights into the possible reaction paths and rationalize the observed *trans* selectivity.

RESULTS AND DISCUSSION

Nitrile ylides **12** are available from imidoyl chlorides by 1,3-dehydrochlorination.[16a] The *p*-nitrobenzyl-substituted imidoyl chloride **14a** and imine **13a** were selected as convenient benchmark substrates to study the reaction.[17a] The electron-withdrawing *p*-nitro group on the imidoyl chloride seems essential, since nitrile ylides with electron-neutral or -donating substituents are known to dimerize to form pyrazines.[19] We were encouraged by our initial experiment, showing that reaction of a 1:1 mixture of **13a** and **14a** with triethylamine in dichloromethane at room temperature for 16 h gave the desired *cis*- and *trans*-2-imidazolines **16a** in 19% yield in a reasonable diastereomeric ratio (17:83) according to ^{1}H NMR analysis of the crude mixture (Table 1, entry 2). The major isomer was assigned as the *trans* configuration based on comparison of the measured ^{1}H NMR spectra with the calculated spectra (see ref 20 for details) and the observed lower oxidation rate of this isomer toward the corresponding imidazole.[20] We then investigated the efficiency of several bases for the synthesis of **16a** (Table 1).

Using 2,6-lutidine as the base gave **16a** in a comparable yield of 18% (entry 4). When the stronger base DBU was used, only decomposition of the starting materials was observed (entry 5). Although using *tert*-butoxides seems to result in faster formation of **16a**, the overall yield did not improve significantly (11−33%, entries 6−9), but especially with lithium and sodium *tert*-butoxide in CH_2Cl_2 (entries 6 and 7), excellent diastereoselectivities were obtained (*cis*/*trans* = <5:95). A similar trend was observed when disilazides were employed as bases. With lithium bis(trimethylsilyl)amide (LiHMDS) in CH_2Cl_2 we obtained **16a** in 31% yield with excellent diastereoselectivity (*cis*/*trans* = <5:95, entry 10), but in the more coordinating solvent THF the reaction did not occur (entry 10). With NaHMDS on the other hand, better yields and diastereomeric ratios were obtained in THF (31% yield, dr <5:95) compared to CH_2Cl_2 (6%, dr 17:83) (entries 12 and 13). The use of KHMDS in THF gave **16a** in a comparable yield and diastereoselectivity (entry 14).

Double *p*-nitrophenyl-functionalized imidoyl chlorides **14b** undergo a similar cyclocondensation with imine **13a** to give **16b** in 60% yield in a dr of 6:94 when D*i*PEA was used as the base (entry 15). Employing DBU gave an even better yield (95%), but the reaction proceeds somewhat less selectively (17:83), although still favoring formation of *trans*-**16b** (entry 16). Comparable selectivities (20:80) were observed when *p*-halogen phenyl-substituted aldimines **13b,c** react with **14b** giving the corresponding tetrasubstituted 2-imidazolines **16c** and **16d** in moderate yields (26−30%, entries 17 and 18).

To rationalize the experimental results toward the formation of **16a**, we resorted to DFT calculations (see the Computational Section for details) for the reaction between **13a** and **15** in CH_2Cl_2. The energy profile for the full system is depicted in Figure 2.

For the 1,3-dipolar cycloaddition of the in situ formed nitrile ylide **15** and imine **13a** to give **16a**, we considered both a concerted mechanism and a stepwise process in which the nucleophilic imine nitrogen attacks the nitrilium C atom, followed by cyclization. The concerted process for **16a** formation, however, is unlikely as the LUMO of dipole **15** has essentially no amplitude on C1, while on the other hand, the amplitude on C2 is large (Figure 3). As a consequence, HOMO−LUMO overlap between **13** and **15** can occur only through the evolving N−C2 bond. Therefore, a concerted process, in which the N−C2 and C−C1 bonds are formed in a single elementary step, is less feasible. In line with this insight, transition-state optimizations for the concerted mechanism consistently led to **TS-1** of the stepwise mechanism.

Consequently, the computations support a stepwise process. Thus, attack of the imine nitrogen on the nitrile ylide carbon gives the thermodynamically driven formation of intermediate **17** (−4.2 kcal·mol^{-1}). The activation energy for this addition step is just 12.2 kcal·mol^{-1} (**TS-1**) and constitutes, in fact, the rate-determining step. The subsequent cyclization favors formation of the *trans* isomer of **16a** ($\Delta E^{\ddagger}$ = 6.5 kcal·mol^{-1} (**TS-3**); ΔE −26.9 kcal·mol^{-1}) over that of the *cis* isomer ($\Delta E^{\ddagger}$

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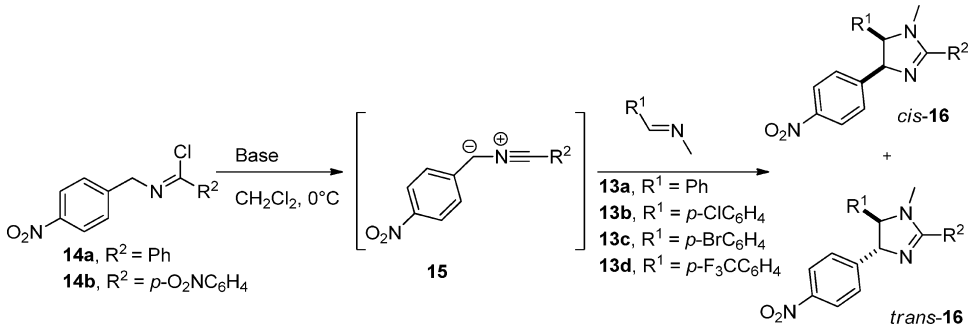
Table 1. Base Screening in the Synthesis of 2-Imidazolines 16



entry	imidoyl chloride	imine	base[a]	time (h)	product	dr[b] (*cis*:*trans*)	yield[c] (%)
1	**14a**	**13a**	none	16	**16a**		none
2	**14a**	**13a**	Et_3N	16	**16a**	17:83	19
3	**14a**	**13a**	D*i*PEA	16	**16a**	14:86	n.d.[d]
4	**14a**	**13a**	2,6-lutidine	16	**16a**	n.d.[e]	18
5	**14a**	**13a**	DBU	2	**16a**		none
6	**14a**	**13a**	LiO*t*Bu	2	**16a**	7:93	14
7	**14a**	**13a**	NaO*t*Bu	2	**16a**	<5:95	n.d.[d]
8	**14a**	**13a**	KO*t*Bu	2	**16a**	17:83	33
9[f]	**14a**	**13a**	KO*t*Bu	2	**16a**	20:80	11
10	**14a**	**13a**	LiHMDS	2	**16a**	<5:95	23
11[f]	**14a**	**13a**	LiHMDS	2	**16a**		none
12	**14a**	**13a**	NaHMDS	2	**16a**	17:83	6
13[f]	**14a**	**13a**	NaHMDS	2	**16a**	<5:95	31
14[f]	**14a**	**13a**	KHMDS	2	**16a**	10:90	23
15	**14b**	**13a**	D*i*PEA	3	**16b**	6:94	60
16	**14b**	**13a**	DBU	3	**16b**	17:83	95
17	**14b**	**13b**	DBU	3	**16c**	20:80	30
18	**14b**	**13c**	DBU	3	**16d**	20:80	26
19	**14b**	**13d**	DBU	3	**16e**	33:67	14

[a]Unless indicated otherwise, CH_2Cl_2 was used as the solvent. [b]Determined by ^1H NMR analysis from the crude reaction mixtures. [c]Yield after workup and column chromatography. [d]No product isolated after column chromatography. [e]The diastereomeric ratios could not be determined. [f]THF was used as solvent.

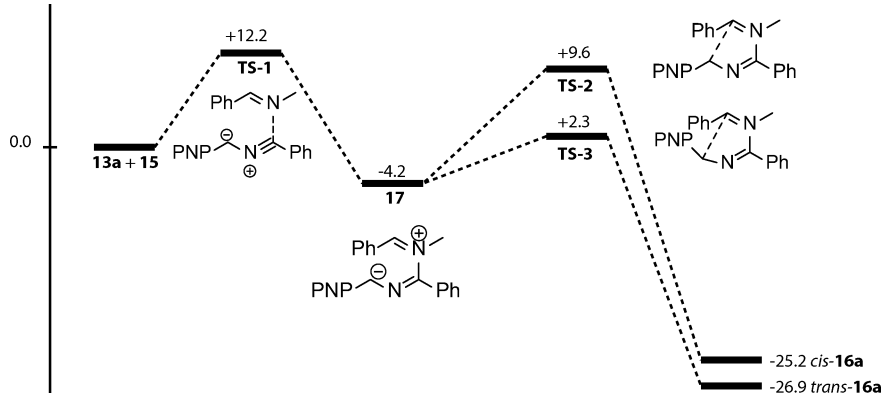


Figure 2. Relative ZORA-OLYP/TZ2P COSMO energies (kcal mol^{-1}) for the reaction between **13a** and **15** in CH_2Cl_2 to give *cis*-**16a** and *trans*-**16a**. PNP = *p*-nitrophenyl.

= 13.8 kcal·mol^{-1} (**TS-2**); ΔE −25.2 kcal·mol^{-1}). This agrees with the experimentally observed preferential formation of the *trans* isomer. However, it is also evident that subtle changes in base, solvent, counterion, and substituents play an important role in the ratio in which *cis*- and *trans*-**16a** are formed as illustrated by the results in Table 1.

In order to direct the reaction to exclusive formation of the *trans* diastereomer of **16** and to improve the yield, we envisioned the use of nitrilium ions **18** as suitable reactive intermediates for undergoing nucleophilic attack by the imines **19** (Scheme 3). The resulting incipient *N*-imidoyliminium ions **20** should, upon deprotonation, rapidly cyclize to give 2-imidazolines **21**. This "forced" stepwise protocol should allow for a better control of the reaction outcome.

Relatively stable nitrilium ions can be obtained from the corresponding imidoyl chloride following our recently developed protocol[21] utilizing TMSOTf as Lewis acid. We started with imidoyl chloride **14b**, having two strongly electron-

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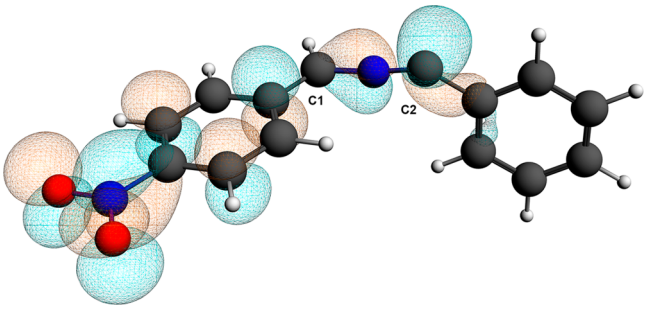
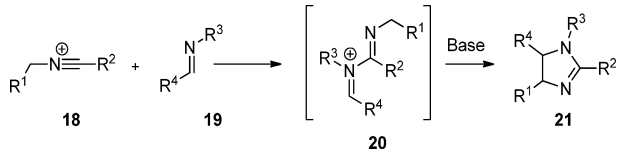


Figure 3. LUMO of nitrile ylide **15** in CH_2Cl_2 computed at ZORA-OLYP/TZ2P COSMO.

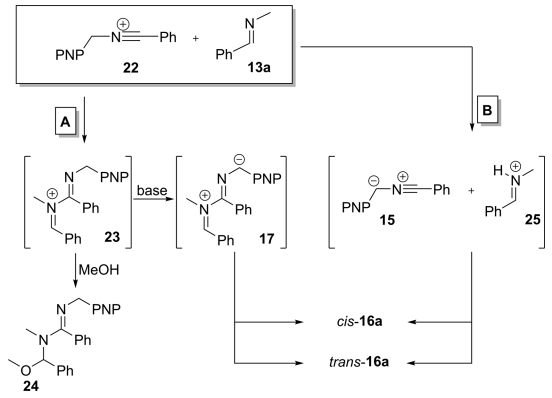
Scheme 3. Envisioned Protocol for the Stepwise Generation of 2-Imidazolines 21



withdrawing *p*-nitrophenyl substituents, for in situ generation of nitrilium ion **22**. After in vacuo removal of the solvent and excess TMSOTf and TMSCl at 0 °C, **22** was redissolved in either CH_2Cl_2 or THF, followed by addition of imine **13a** under basic conditions to promote the cyclocondensation toward 2-imidazoline **16b**. The results are summarized in Table 2. Possible competition between nucleophilic attack and deprotonation of nitrilium ion **22** by imine **13a** (pathway **B**, Scheme 4) is unlikely because no product formation was observed when the reaction was performed with 2 equiv of **13a** without additional base (entry 1, Table 2).

The results demonstrate that a reaction proceeding through nitrilium ions can indeed be optimized toward the selective formation of tetrafunctionalized *trans*-2-imidazolines **16b**. For example, excellent dr's (<5:95) in favor of *trans*-**16b** were obtained with D*i*PEA and 2,6-lutidine as the bases (entries 3 and 4). On the other hand, treatment of a solution of **22** and **13a** with *tert*-butoxides gave either a low yield (19%, entry 6) or led to decomposition of the starting material (entries 7 and 8). We were, however, pleased to find that *trans*-**16b** was formed almost exclusively (dr = <5:95) and in good yield (62%, entry 9) when LiHMDS in CH_2Cl_2 was used.[22]

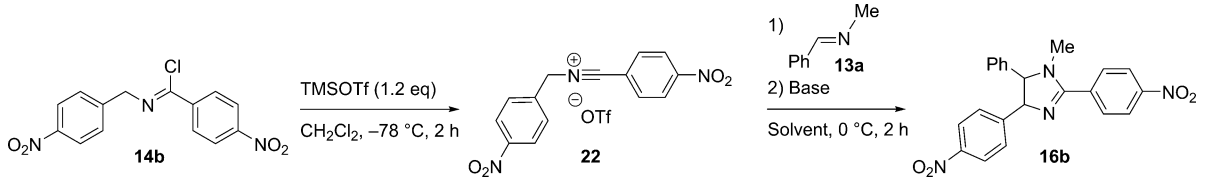
Scheme 4. Investigated Reaction Pathways



Additional experimental support for the envisioned stepwise process (pathway **A**, Scheme 4) of **22** by **13a** was obtained by mass spectrometry analysis of a 1:1 solution containing nitrilium ion **22** and imine **13a**, showing a major ESI-MS signal (*m*/*z* 358.1533) that corresponds to the stabilized intermediate *N*-imidoyliminium ion **23**. This is further corroborated by the observation of the ESI-MS peak corresponding to the pseudomolecular ion of the methoxy derivative **24** upon trapping **23** with methanol (Scheme 4).

Our computational analysis also points to pathway **A** involving the envisioned stepwise formation of **16a**. The energy profile of this analysis is depicted in Figure 4. The first step in this process is the nucleophilic attack of imine **13a** on to

Table 2. Base Screening in the Benchmark Reaction



entry	solvent	base	dr (*cis*:*trans*)[a]	yield[c] (%)
1	CH_2Cl_2	none[d]		
2	CH_2Cl_2	Et_3N	nd[b]	15
3	CH_2Cl_2	D*i*PEA	<5:95	28
4	CH_2Cl_2	2,6-lutidine	6:94	21
5	CH_2Cl_2	DBU	nd[b]	5
6	CH_2Cl_2	LiO*t*Bu	<5:95	19
7	CH_2Cl_2	NaO*t*Bu		none
8	CH_2Cl_2	KO*t*Bu		none
9	CH_2Cl_2	LiHMDS	<5:95	62
10	THF	LiHMDS		none
11	CH_2Cl_2	NaHMDS	20:80	42
12	THF	NaHMDS	20:80	38
13	THF	KHMDS		none

[a]Determined from the crude products using ^{1}H NMR analysis. [b]The diastereomeric ratios could not be determined. [c]Yield after workup and column chromatography. [d]Two equivalents of imine **13a** was used.

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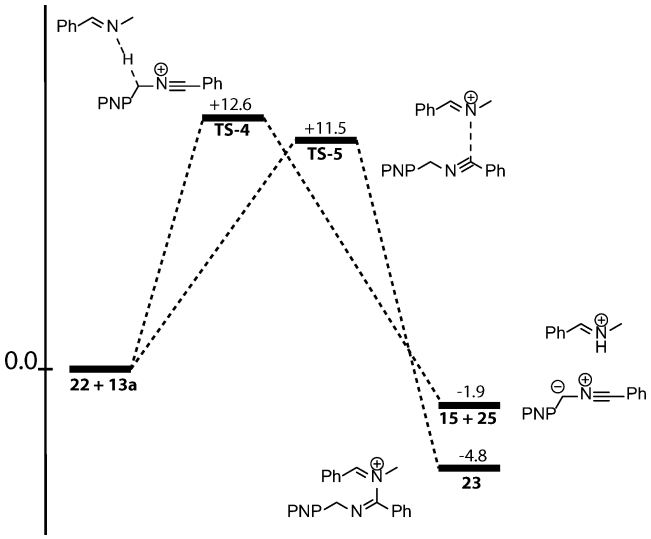

Figure 4. Relative ZORA-OLYP/TZ2P COSMO energies (kcal·mol^{-1}) for the reaction between **22** and **13a** in CH_2Cl_2 (see also Scheme 4).

nitrilium ion **22** upon which C−N bond formation takes place to render the −4.8 kcal·mol^{-1} favored adduct **23** with an overall barrier of 11.5 kcal·mol^{-1} (**TS-5**). The subsequent deprotonation of **23** by $HMDS^-$ to form **17** and HMDS (ΔE −54.1 kcal·mol^{-1}) is followed by cyclization (in similar fashion to Figure 2) to form *trans*-**16a** preferably. This pathway is both kinetically and thermodynamically favored over the alternative nitrile ylide pathway (Scheme 4, pathway **B**) to nitrile ylide **15** and iminium ion **25** ((ΔE −1.9; ($\Delta E^{\ddagger}$ 12.6 kcal·mol^{-1}(**TS−4**)),[23] subsequent deprotonation of **25** by $HMDS^-$ results in imine **13a** and **15** (ΔE −48.9 kcal·mol^{-1}), the starting materials for the computations in Scheme 2.

When the optimal conditions (Table 2, entry 9) were applied to the synthesis of **16a** (Figure 5), it became clear that this

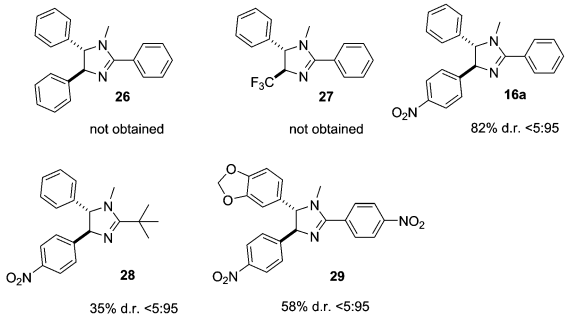

Figure 5. Various 2-imidazolines synthesized with the developed protocol.

method is superior over the direct cycloaddition. This is illustrated by the fact that **16a** was obtained in a much better yield of 82% compared to 23% obtained in the direct cycloaddition (Table 1, entry 10).

Some imines and imidoyl chlorides were combined using the optimized conditions (LiHMDS in CH_2Cl_2, Table 2, entry 9) for the production of several tetrasubstituted *trans*-2-imidazolines (Figure 5). The strongly electron-withdrawing *p*-nitrophenyl R^1 group proved essential for a successful reaction as phenyl- and trifluoromethyl-substituted reactants did not afford the desired 2-imidazolines (**26** and **27**, Figure 5). With the *p*-nitrophenyl R^1 group on the imidoyl chloride, R^2 was varied with phenyl and *tert*-butyl to give *trans*-**16a** exclusively in good yield (82%) and *trans*-**28** in moderate yield (35%). Finally, electron-rich imines could also be used, as the reaction with piperonal-derived methyl imine afforded *trans*-**29** in 58% yield.

CONCLUSION

In conclusion, we have shown that tetrasubstituted C2-functionalized 2-imidazolines can be efficiently formed from the 1,3-dipolar cycloaddition between nitrile ylides and imines. The reaction has a preference for the diastereoselective formation of the *trans* isomer. The ratio of *cis* vs *trans* is highly dependent on the substrates and reaction conditions. We furthermore demonstrated that the stepwise reaction between imines and nitrilium ions proceeds fully diastereoselectively and in better yields compared to the direct cycloaddition which makes this method superior over the direct cycloaddition. DFT calculations are in favor of a two-step cyclization mechanism accounting for preferential formation of the *trans* isomers in both protocols.

COMPUTATIONAL SECTION

All calculations have been performed using the Amsterdam Density Functional (ADF) program[24] using density functional theory (DFT) at OLYP/TZ2P for geometry optimizations and energies.[25] This approach has been shown to yield accurate geometries and barriers for organic reactions.[26] TZ2P is a large, uncontracted set of slater-type orbitals (STOs) of triple-ζ quality for all atoms, augmented with two sets of polarization functions, that is, p and d functions for hydrogen atoms and d and f functions for the other atoms. An auxiliary set of s, p, d, f, and g STOs was used to fit the molecular density and to represent the Coulomb and exchange potentials accurately in each self-consistent field cycle. Relativistic effects were taken into account explicitly using the zeroth-order regular approximation (ZORA).[27]

The reactions were modeled both in the gas phase and in dichloromethane. Solvation in dichloromethane has been simulated using the conductor-like screening model (COSMO).[28] In general, transition states (TSs) were determined by following the eigen mode with the negative force constant toward the saddle point on the potential energy surface. All stationary points were verified to be minima (zero imaginary frequencies) or TSs (one imaginary frequency) through vibrational analysis.

For the NMR calculations, we used the statistical average of (model) orbital potential (SAOP),[29] which has been shown to improve the description of NMR chemical shifts significantly with respect to GGA functionals.[30] For the computation of NMR parameters, we have used the ZORA-ET-pVQZ basis set, which is of quadruple-ζ quality and contains four sets of polarization functions.

EXPERIMENTAL SECTION

General Methods. Commercially available starting materials and reagents were used without further purification unless stated otherwise. Dichloromethane (ACS grade) and tetrahydrofuran (ACS grade) were purified and dried according to standard techniques. All reactions were carried out under an inert atmosphere of dry nitrogen. Standard syringe techniques were applied for transfer of air-sensitive reagents and dry solvents. Infrared (IR) spectra were measured as neat compounds, and wavelengths (ν) are reported in cm^{-1}. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded at 400.13 or 500.13 MHz and 100.62 or 125.78 MHz, respectively, with chemical shifts (δ) reported in ppm downfield from tetramethylsilane (TMS). Electrospray ionization (ESI) high-resolution mass spectrometry (Q-TOF analysis) was carried out in positive-ion mode (capillary potential of 4500 V). 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

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(silica on aluminum with fluorescence indicator). Compounds on TLC were visualized by UV detection (254 nm).

General Procedure A for the Synthesis of Imidazolines via the 1,3-Dipolar Cycloaddition. A flame-dried flask was charged with imidoyl chloride and dissolved in the appropriate solvent under inert atmosphere. Imine (1.2 equiv) was added, and the resulting mixture was cooled to 0 °C. Then base or a solution of base (1.2 equiv) was added dropwise. After disappearance of the starting material by TLC, the reaction was quenched by addition of equal volumes of saturated NH_4Cl and water. The aqueous layer was then extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The product was then purified by column chromatography with the indicated solvent.

*1-Methyl-4-(4-nitrophenyl)-2,5-diphenyl-2-imidazoline (**16a**).* According to general procedure A, reaction between imidoyl chloride **14a** (0.139g, 0.51 mmol), *N*-benzylidenemethanamine **13a** (0.053g, 0.35 mmol), and LiHMDS (450 μL, 1 M in ethylbenzene, 0.45 mmol) for 2 h followed by column chromatography (cyclohexane/EtOac 9:1 → 3:1) afforded *trans*-**16a** (42 mg, 23%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 8.21, (d, *J* = 8.7 Hz, 2H), 7.78−7.71 (m, 2H), 7.53−7.33 (m, 10H), 5.08 (d, *J* = 10.3 Hz, 1H), 4.22 (d, *J* = 10.3 Hz, 1H), 2.74 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 167.9, 150.9, 147.2, 140.3, 130.3, 129.1 (2C), 128.5 (2C), 128.4 (2C), 128.3, 127.7 (2C), 127.1, 123.7, 78.4, 77.0, 34.7. HRMS (ESI, 4500 V): calcd for $C_{22}H_{20}N_3O_2$ $(M + H)^+$ 358.1550, found 358.1535. IR (neat): ν (cm^{-1}) = 3377, 2972, 1556, 1423, 1379, 1099, 1045, 923, 879, 732. *cis*-**16a** ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) = 7.87 (d, *J* = 8.8 Hz, 2H), 7.75 (m, 2H), 7.49 (m, 5H), 7.09 (m, 3H), 6.93 (m, 2H), 5.67 (d, *J* = 11.2 Hz, 1H), 5.05 (d, *J* = 11.3 Hz, 1H), 2.79 (s, 3H).

*1-Methyl-2,4-bis(4-nitrophenyl)-5-phenyl-2-imidazoline (**16b**).* According to general procedure A, reaction between imidoyl chloride **14b** (0.052g, 0.16 mmol), *N*-benzylidenemethanamine **13a** (0.022 mL, 0.18 mmol), and DBU (27 μL, 0.18 mmol) for 3 h followed by column chromatography (cyclohexane/EtOac 4:1 → 1:1) afforded *trans*-**16b** (73 mg, 95%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 8.36 (d, *J* = 8.5 Hz, 2H), 8.22 (d, *J* = 8.5 Hz, 2H), 7.95 (d, *J* = 8.5 Hz, 2H), 7.52−7.38 (m, 5H), 7.36 (d, *J* = 7.3 Hz, 2H), 5.14 (d, *J* = 10.7 Hz, 1H), 4.26 (d, *J* = 10.7 Hz, 1H), 2.74 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 167.0, 150.0, 149.0, 147.4, 139.5, 137.0, 129.6 (2C), 129.3 (2C), 128.7, 127.7 (2C), 127.2, 123.9, 123.8, 78.5, 77.3, 34.7. IR (neat): ν (cm^{-1}) = 3354, 2972, 1379, 1178, 1086, 1045, 879, 627. HRMS (ESI, 4500 V): calcd for $C_{22}H_{19}N_4O_4$ $(M + H)^+$ 403.1401, found 403.1382.

*5-(4-Chlorophenyl)-1-methyl-2,4-bis(4-nitrophenyl)-2-imidazoline (**16c**).* According to general procedure A, reaction between imidoyl chloride **14b** (0.101g, 0.32 mmol), *N*-(4-chlorobenzylidene)-methanamine **13b** (0.053g, 0.35 mmol), and DBU (0.053g, 0.35 mmol) for 3 h followed by column chromatography (cyclohexane/EtOac 4:1) afforded *trans*-**16c** (41 mg, 30%) as an orange oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 8.37 (d, *J* = 8.7 Hz, 2H), 8.23 (d, *J* = 8.7 Hz, 2H), 7.94 (d, *J* = 8.7 Hz, 2H), 7.47−7.40 (m, 4H), 7.30 (d, *J* = 8.4 Hz, 2H), 5.08 (d, *J* = 10.8 Hz, 1H), 4.24 (d, *J* = 10.8 Hz, 1H), 2.74 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 166.2, 149.4, 149.1, 147.5, 138.0, 136.6, 134.7, 129.6 (2C), 129.6 (2C), 128.6 (2C), 127.7 (2C), 124.0 (2C), 123.9 (2C), 78.1, 77.2, 34.9. IR (neat): ν (cm^{-1}) = 2922, 2852, 1720, 1583 1516, 1065, 1013, 852, 725, 708, 573, 453. HRMS (ESI, 4500 V): calcd for $C_{22}H_{18}ClN_4O_4$ $(M + H)^+$ 437.1011, found 437.1013.

*5-(4-Bromophenyl)-1-methyl-2,4-bis(4-nitrophenyl)-2-imidazoline (**16d**).* According to general procedure A, reaction between imidoyl chloride **14b** (0.112 g, 0.35 mmol), *N*-(4-bromobenzylidene)-methanamine **13c** (0.076 g, 0.38 mmol), and DBU (0.057 μL, 0.38 mmol) for 3 h followed by column chromatography (cyclohexane/EtOac 4:1) afforded *trans*-**16d** (44 mg, 26%) as an orange oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 8.36 (d, *J* = 8.6 Hz, 2H), 8.22 (d, *J* = 8.6 Hz, 2H), 7.93 (d, *J* = 8.6 Hz, 2H), 7.59 (d, *J* = 8.3 Hz, 2H), 7.42 (d, *J* = 8.6 Hz, 2H), 7.24 (d, *J* = 8.3 Hz, 2H), 5.07 (d, *J* = 10.7 Hz, 1H), 4.23 (d, *J* = 10.7 Hz, 1H), 2.74 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 166.1, 149.5, 149.1, 147.5, 138.6, 136.7, 132.5 (2C), 129.6 (2C), 128.8 (2C), 127.6 (2C), 123.9 (2C), 123.8 (2C), 122.7, 78.1, 77.3, 34.9. IR (neat): ν (cm^{-1}) = 2920, 2849, 1581, 1514, 1107, 1064, 1009, 852, 700. HRMS (ESI, 4500 V): calcd for $C_{22}H_{18}BrN_4O_4$ $(M + H)^+$ 481.0506, found 481.0499.

*1-Methyl-2,4-bis(4-nitrophenyl)-5-(4-(trifluoromethyl)phenyl)-2-imidazoline (**16e**).* According to general procedure A, reaction between imidoyl chloride **14b** (0.080 g, 0.25 mmol), *N*-(4-trifluoromethylbenzylidene)methanamine **13d** (0.056 g, 0.30 mmol), and DBU (0.045 μL, 0.30 mmol) for 3 h followed by column chromatography (cyclohexane/EtOac 4:1) afforded *trans*-**16e** (17 mg, 14%) as an orange oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 8.38 (d, *J* = 8.7 Hz, 2H), 8.25 (d, *J* = 8.7 Hz, 2H), 7.96 (d, *J* = 8.7 Hz, 2H), 7.73 (d, *J* = 8.1 Hz, 2H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 8.6 Hz, 2H), 5.11 (d, *J* = 10.6 Hz, 1H), 4.35 (d, *J* = 10.6 Hz, 1H), 2.77 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 166.2, 149.1 (d, *J* = 4.6 Hz), 147.6, 143.5, 131.2, 130.9, 129.6 (2C), 127.7 (2C), 127.5 (2C), 126.4 (q, *J* = 3.6 Hz), 124.0 (2C), 123.9 (2C), 78.2, 77.1, 35.1. IR (neat): ν (cm^{-1}) = 2922, 2851, 1583, 1518, 1344, 1323, 1124, 1109, 1065, 1014, 853. HRMS (ESI, 4500 V): calcd for $C_{23}H_{18}F_3N_4O_4$ $(M + H)^+$ 471.1275, found 471.1290.

General Procedure B for the Synthesis of 2-Imidazolines via the Nitrilium Triflate Salts. A flame-dried Schlenk was charged with imidoyl chloride (1 equiv) that was dissolved in CH_2Cl_2 and cooled to −78 °C under inert atmosphere. Then TMSOTf (1.5 equiv) was added dropwise, and the resulting mixture was allowed to stir at this temperature. After 2 h, the reaction was allowed to warm to 0 °C, after which the solvent, excess TMSOTf, and formed trimethylsilyl chloride were removed in vacuo. The resulting nitrilium triflate was then redissolved at this temperature, after which imine (1.2 equiv) was added dropwise. After 30 min, base or a solution of base (1.2 equiv) was added dropwise to the solution. Upon disappearance of the starting material on TLC, the reaction was quenched by addition of equal volumes of saturated NH_4Cl and water. The aqueous layer was then extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The product was then isolated from the crude mixture by column chromatography.

*1-Methyl-2,4-bis(4-nitrophenyl)-5-phenyl-2-imidazoline (**16b**).* According to general procedure B, the reaction between **14b** (40 mg, 0.11 mmol) and TMSOTf (25 μL, 0.13 mmol) in CH_2Cl_2 (2 mL) afforded the nitrilium triflate that was dissolved in CH_2Cl_2 (2 mL) followed by dropwise addition of *N*-benzylidenemethanamine **13a** (17 μL, 0.13 mmol). Then LiHMDS (130 μL, 1 M in ethylbenzene, 0.13 mmol) was added dropwise and stirred for 3 h. Column chromatography (cyclohexane/EtOAc 2:1 → 1:1) afforded *trans*-**16b** as a yellow oil (28 mg, 62%).

*1-Methyl-4-(4-nitrophenyl)-2,5-diphenyl-2-imidazoline (**16a**).* According to general procedure B, reaction between **21** (30 mg, 0.10 mmol) and TMSOTf (20 μL, 0.12 mmol) in CH_2Cl_2 (2 mL) afforded the nitrilium triflate salt that was dissolved in CH_2Cl_2 (2 mL) followed by dropwise addition of *N*-benzylidenemethanamine **13a** (15 μL, 0.12 mmol). Then LiHMDS (120 μL, 1 M in ethylbenzene, 0.12 mmol) was added dropwise and the mixture stirred for 3 h. Column chromatography (cyclohexane/EtOAc 2:1 → 1:1) afforded *trans*-**16a** as a yellow oil (29 mg, 82%).

*2-tert-Butyl-1-methyl-4-(4-nitrophenyl)-5-phenyl-2-imidazoline (**28**).* According to general procedure B, the reaction between **21** (100 mg, 0.37 mmol) and TMSOTf (81 μL, 0.45 mmol) in CH_2Cl_2 (5 mL) afforded the nitrilium triflate salt that was dissolved in CH_2Cl_2 (5 mL) followed by dropwise addition of *N*-benzylidenemethanamine **13a** (52 μL, 0.45 mmol). Then LiHMDS (450 μL, 1 M in ethylbenzene, 0.45 mmol) was added dropwise and the mixture stirred for 3 h. Column chromatography (cyclohexane/EtOAc 2:1) afforded *trans*-**30** as a yellow oil (43 mg, 35%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.17 (d, *J* = 8.7 Hz, 2H), 7.44−7.29 (m, 5H), 7.25−7.21 (m, 2H), 4.86 (d, *J* = 9.2 Hz, 1H), 4.08 (d, *J* = 9.2 Hz, 1H), 2.84 (s, 3H), 1.46 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 173.2, 151.6, 147.2, 141.0, 129.7 (2C), 128.2, 127.5 (2C), 127.0 (2C), 123.8 (2C), 78.8, 75.7, 34.6, 33.9, 28.6 (3C). IR (neat): ν (cm^{-1}) = 3308, 2972, 2887,

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1558, 1379, 1275, 1086, 1045, 879, 621. HRMS (ESI, 4500 V): calcd for $C_{20}H_{24}N_3O_2$ $(M + H)^+$ 338.1863, found 338.1849.

*5-(Benzo[d][1,3]dioxol-5-yl)-1-methyl-2,4-bis(4-nitrophenyl)-2-imidazoline (**29**).* According to general procedure B, the reaction between **21** (30 mg, 0.06 mmol) and TMSOTf (0.08 mmol, 15 μL) in CH_2Cl_2 (2 mL) afforded the nitrilium triflate that was dissolved in CH_2Cl_2 (2 mL) followed by dropwise addition of a solution of *N*-(benzo[*d*][1,3]dioxol-5-ylmethylene)methanamine (0.08 mmol, 15 mg, in 1 mL CH_2Cl_2). Then LiHMDS (80 μL, 1 M in ethylbenzene, 0.08 mmol) was added dropwise and the mixture stirred for 16 h. Column chromatography (cyclohexane/EtOAc 2:1) afforded *trans*-**31** as a yellow oil (15.4 mg, 58%). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 8.36 (d, J = 8.6 Hz, 2H), 8.23 (d, J = 8.6 Hz, 2H), 7.92 (d, J = 8.6 Hz, 2H), 7.45 (d, J = 8.5 Hz, 2H), 6.92 (s, 1H), 6.84 (d, J = 7.9 Hz, 1H), 6.73 (d, J = 8.0 Hz, 1H), 6.04 (s, 2H), 5.09 (d, J = 10.7 Hz, 1H), 4.16 (d, J = 10.7 Hz, 1H), 2.72 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 165.9, 149.9, 149.0, 148.7, 148.0, 147.4, 139.9, 133.2, 129.6 (2C), 127.6 (2C), 123.9 (2C), 123.9 (2C), 121.1, 108.6, 106.9, 101.5, 78.4, 77.1, 34.6. IR (neat): ν (cm^{-1}) = 3292, 2972, 2889, 1427, 1379, 1192, 1066, 1045, 879, 579. HRMS (ESI, 4500 V): calcd for $C_{23}H_{19}N_4O_6$ $(M + H)^+$ 447.1299, found 447.1275.

MS Characterization of the Reactive Intermediates. *N-Benzylidyne-1-(4-nitrophenyl)methanaminium Ion (**22**).* HRMS (ESI, 4500 V): calcd for $C_{14}H_{11}N_2O_2$ (M^+) 239.0815, found 239.0812.

*Imine Adduct 1 (**23**).* HRMS (ESI, 4500 V): calcd for $C_{22}H_{20}N_3O_2$ (M^+) 358.1550, found 358.1533.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra of all new compounds and structural data and total energies of stationary points. This material is available free of charge via the Internet at http://pubs.acs.org/.

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Notes

The authors declare no competing financial interest.

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(20) The diastereomeric ratios were determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixtures. The assignment of the diastereoisomers was based on the different oxidation rates of the *cis* and *trans* isomers in air. It has been reported that *cis*-2-imidazolines oxidize in less than 1 day to the corresponding imidazoles compared to weeks for *trans* 2-imidazolines (see ref 15b). More evidence was obtained by comparison of the calculated ^{1}H NMR chemical shifts (SAOP/ET-pVQZ, see the Computational Section for full details) of the two protons bonded to C4 and C5 with the experimentally observed ones. These protons have distinct chemical shifts for both isomers in the NMR spectrum. The calculated shifts of *cis*-**16a** (*H*C4 expt 5.68 ppm, calcd 5.65 ppm; *H*C5 expt 5.05 ppm, calcd 4.98 ppm) and *trans*-**16a** (*H*C4 expt 5.08 ppm, calcd 5.20 ppm; *H*C5 expt 4.22 ppm, calcd 4.23 ppm) match perfectly.

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(22) The *cis* isomer was not observed in the ^{1}H NMR spectrum.

(23) Under kinetic control at 0 °C, the Arrhenius equation results in a ratio between pathways A and B of 2:1. Under thermodynamic control at 0 °C, the Boltzmann equation results in a product ratio of 208:1 for **23** vs **15**+**25**.

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