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Multicomponent Synthesis of 2-Imidazolines

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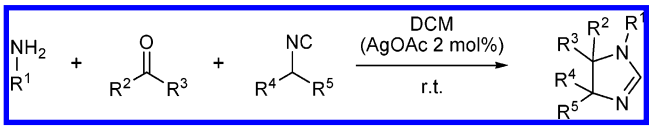

A multicomponent reaction (MCR) between amines, aldehydes, and isocyanides bearing an acidic α-proton gives easy access to a diverse range of highly substituted 2-imidazolines. The limitations of the methodology seem to be determined by the reactivity of the isocyanide and by the steric bulk on the in situ generated imine rather than by the presence of additional functional groups on the imine. Less reactive isocyanides, for example *p*-nitrobenzyl isocyanide **25a**, react successfully with amines and aldehydes, using a catalytic amount of silver(I) acetate. Some of the resulting *p*-nitrophenyl-substituted 2-imidazolines undergo air oxidation to the corresponding imidazoles. Differences in reactivity of the employed isocyanides are explained with use of DFT calculations. Difficult reactions with ketones instead of aldehydes as the oxo-compound in this MCR are promoted by silver(I) acetate as well.

Introduction

In the past decades, 2-imidazoline derivatives have attracted considerable interest because of their wide variety of biological activities. Several 2-imidazolines have a high affinity for imidazoline binding sites (IBS).[1] These IBS are being increasingly studied for their involvement in hypertension, regulation of blood pressure, insulin secretion control, and numerous human brain disorders such as depression, neurodegeneration, and opioid tolerance/dependence.[2] Moreover, a series of highly substituted *cis*-imidazoline analogues called Nutlins (Nutley inhibitors) has been successfully screened as inhibitors of MDM2, a protein that negatively modulates the transcriptional activity and stability of the p53 tumor suppressor protein.[3] Crystal structures show that the Nutlins mimic the interactions of the p53 peptide with MDM2 to a high degree. The 2-imidazoline core essentially acts as a fairly rigid replacement of the helical backbone of p53. Also, 2-imidazolines have been examined for their hormonal effects due to estrogen receptor modulation[4] as well as for their interaction with α2-adrenoceptors.[5] Studies have been reported on the possible application of 2-imidazolines as, among others, antihyperglycemic,[6] antiinflammatory,[7] antihypertensive,[5,8] and antihypercholesterolemic[9] agents. Furthermore, 2-imidazolines are widely used as convenient building blocks for the synthesis of biologically active molecules such as azapenams, (bis)dioxocyclams, diazapinones,[10] and 2,3-diamino acids.[11]

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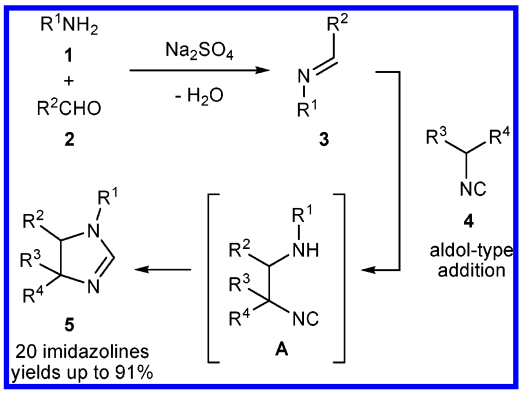
In addition to their pharmaceutical relevance, 2-imidazolines are becoming increasingly important in catalysis. They have been satisfyingly employed as chiral ligands in asymmetric catalysis.[12] More important, however, is their growing application as precursors for *N*-heterocyclic carbene (NHC) ligands.[13] These remarkably stable carbenes exhibit properties strikingly similar and even superior to those of the electron-rich organophosphanes PR_3.[14] Therefore, phosphorus ligands have often been advantageously replaced by NHCs as ligands in transition metal catalysis.[15] Nitrogen alkylation of 2*H*-2-imidazolines and subsequent deprotonation of the corresponding salts is an established and elegant way to generate saturated NHCs.[16]

Evidently, 2-imidazolines are interesting synthetic targets. Both medicinal chemists and researchers involved in catalysis will benefit from simple and flexible 2-imidazoline syntheses, which facilitate fast and efficient generation of diverse libraries of these compounds for high-throughput screening procedures. However, traditional linear synthetic approaches toward 2-imidazolines involve multiple steps and are rather limited in scope.[17] A powerful alternative strategy for the rapid introduction of molecular diversity involves multicomponent reactions (MCRs).[18] Recently, we reported a versatile multicomponent synthesis of 2*H*-2-imidazolines **5** from amines **1**, aldehydes **2**, and isocyanides **4** (Scheme 1).[17] The MCR probably involves an aldol-type addition of the isocyanide **4** to the in situ generated imine **3** followed by ring closure of intermediate **A**.[19] However, a concerted cyclization of **3** and **4** to produce **5** cannot be excluded.

The compatibility of a range of structurally different aldehydes and amines in this MCR was demonstrated, but the reaction seems to be critically dependent on the acidity of the isocyanide α-proton. So far, the method proved useful to prepare 4-disubstituted 2-imidazolines. Also, the yield of the MCR decreased notably when the rather bulky benzhydrylamine was used as amine component **1**. Finally, ketones were not tested yet as the oxo-component in the MCR. Here, we wish to report an extensive scope study addressing the following issues: (i) the influence of sterically demanding and/or more functionalized amines and aldehydes; (ii) further variation of the isocyanide component; and (iii) the application of ketones instead of aldehydes as the oxo-components in the MCR.

SCHEME 1. Multicomponent Synthesis of 2-Imidazolines



Results and Discussion

Steric factors were believed to cause the disappointing yields for MCRs with benzhydrylamine and isobutyraldehyde as the amine and aldehyde components, respectively. Bulky groups hinder the aldol-type addition of the isocyanide **4** to the in situ generated imine **3**. To investigate if these factors indeed determine the limitations of the MCR, a series of sterically more and less demanding amines and aldehydes was tested in combination with isocyanoacetate **4a** (Table 1).

The application of bulky amines such as *tert*-butylamine, 2,4,6-trimethylaniline, or benzhydrylamine results in diminished yields of **5** (**5hmr**, **5ins**, and **5jot**, respectively), unless a very small aldehyde like formaldehyde is used (**5c**−**e**). On the other hand, sterically demanding aldehydes such as pivaldehyde and mesitaldehyde react even more sluggishly. Not only do they give no detectable formation of 2-imidazoline in combination with the moderately bulky isopropylamine (**5*l*** and **5q**), a *tert*-butyl group on the aldehyde even slows down the reaction significantly when ammonia is used as the amine component (**5k**), although the isolated yield of **5k** was still reasonable after prolonged stirring at room temperature. Application of mesitaldehyde together with ammonia proved to be satisfying (**5p**). It is unlikely that low yields are due to sluggish imine formation, because in general, considerable amounts of imine could be recovered after the reaction. The presence of one or two moderately bulky groups on the in situ formed imine does not hinder the aldol-type addition (**5b**, **5f**, and **5g**), but surprisingly, combination of ammonia, paraformaldehyde, and **4a** furnished only the 2-oxazoline, resulting from a reaction between the in situ generated formaldehyde and isocyanoacetate **4a**.[20] In conclusion, the results presented in Table 1 indicate that steric congestion around the imine carbon indeed influences the aldol-type addition step of the 2-imidazoline formation (toward the

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TABLE 1. The Influence of Sterically Demanding Amine and Aldehyde Substituents[a,b]

1 2 4a (*anti*)-5 (*syn*)-5

	$R^1 = H$[c]	$R^1 = i$-Pr	$R^1 = t$-Bu	R^1 = Mes	$R^1 = CHPh_2$
$R^2 = H$[d]	**5a**, <5%[e,f]	**5b**, 70%	**5c**, 69%	**5d**, 65%	**5e**, 82%
$R^2 = i$-Pr	**5f**, 76% (68:32)	**5g**, 74% (75:25)	**5h**, 21% (anti)	**5i**, <5%[e]	**5j**, 13% (66:34)
$R^2 = t$-Bu	**5k**, 56%[g] (78:22)	***5l***, <5%[e]	**5m**, <5%[h]	**5n**, <5%[e]	**5o**, <5%[e]
R^2 = Mes	**5p**, 67% (anti)	**5q**, <5%[e]	**5r**, 15% (anti)	**5s**, <5%[e]	**5t**, 17% (74:26)

[a] Isolated yields and diastereomeric ratios are reported, unless stated otherwise. [b] Structures containing asymmetric carbons represent racemic compounds. [c] A solution of 2 N NH_3 in MeOH was used. [d] Paraformaldehyde was used. [e] In the ^1H NMR spectrum of the crude product, no 2-imidazoline could be observed. [f] The corresponding 2-oxazoline was isolated in quantitative yield. [g] Yield after stirring for 3 days. After a reaction time of 18 h, only 20% of **5k** could be isolated. [h] The corresponding 2-oxazoline was isolated in 10% yield.

proposed intermediate **A** in Scheme 1). Furthermore, they suggest that only one sterically demanding group on the in situ formed imine is allowed.

To synthesize 2-imidazolines susceptible to further manipulation, amines and aldehydes containing additional functional groups were tested in our MCR (Table 2). Although application of an α,β-unsaturated aldehyde proved successful before,[17] the use of acrolein **7** resulted in an unidentified mixture of polymers (entry 1). On the other hand, allylamine **9** furnished an imidazoline bearing a terminal alkene substituent suitable for, e.g., olefin metathesis or rhodium-catalyzed ring closure (entry 2).[21] The ease with which unprotected alcohols in both the amine and the aldehyde component can be accommodated is illustrated by entries 3−5. Because of insolubility of the imine derived from amine **18** and aldehyde **16** in DCM, the synthesis of 2-imidazoline **19** was performed in methanol.

Many studies are dedicated to the promising abilities of multivalent ligands and inhibitors for the manipulation of polyvalent interactions between biological entities.[22] It has been established that, in comparison with their monomeric counterparts, dimeric molecules often show higher biological activity. Therefore, we decided to investigate the potential of our MCR to access products containing multiple 2-imidazoline units connected by various tethers. Such bis-imidazolines would be valuable precursors for bidentate NHC ligands for transition metal catalysis as well. In Schemes 2 and 3, the synthesis of two different bis-imidazolines is illustrated. Reaction of hexane-1,6-diamine (**20**) with isobutyraldehyde (**10**) (2 equiv) and 9-isocyanofluorene (**4b**) (2 equiv) efficiently provides hexane-tethered bis-imidazoline **21**. With both ^1H and ^{13}C NMR measurements, no distinction between the two possible diastereomers could be made. Reaction of isophthalaldehyde (**22**) with isopropylamine (**6**) (2 equiv) and **4b** (2 equiv) gave bis-imidazoline **23** containing a somewhat more rigid tether. Again, the diastereomeric ratio could not be determined from the NMR data.

Because further variation of the isocyanide component in the multicomponent synthesis of 2-imidazolines would significantly increase the versatility of the reaction,

TABLE 2. Synthesis of 2-Imidazolines with Functionalized Amines and Aldehydes[a]

entry	amine	aldehyde	product (yield)[b]
1	**6**	**7**	**8** (0%)
2	**9**	**10**	**11** (91%)
3	**12**	*p*CH_2O **13**	**14** (83%)
4	**15**	**16**	**17** (68%)
5[c]	**18**	**16**	**19** (38%)[d]

[a] 9-Isocyanofluorene **4b** was used as the isocyanide component. For structure, see ref 17. [b] Isolated yields are reported. [c] Reaction was performed in methanol. [d] Yield after flash column chromatography and crystallization.

(21) The first example of a rhodium-catalyzed direct C−H insertion of 4,4-dimethyl-2-imidazoline to 3,3-dimethylbut-1-ene was reported in: Wiedemann, S. H.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2004**, *6*, 1685−1687.

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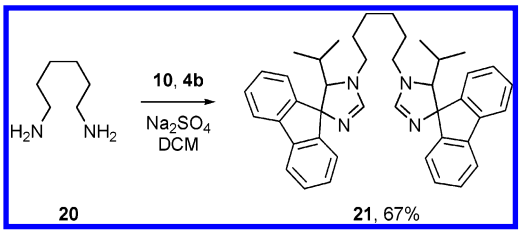
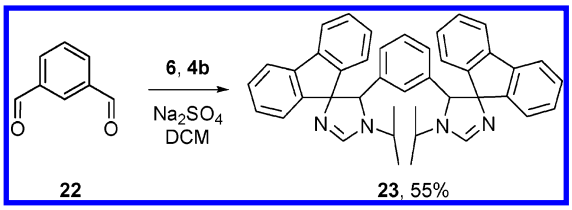
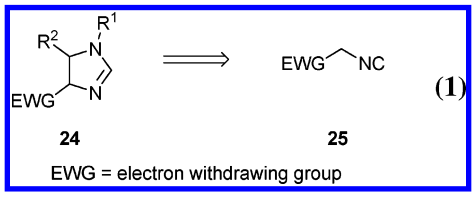
SCHEME 2. A Bis-imidazoline from Hexane-1,6-diamine



SCHEME 3. A Bis-imidazoline from Isophthalaldehyde



additional isocyanides with acidic α-protons were considered as well. To synthesize 4-monosubstituted 2-imidazolines **24**, we explored the use of isocyanides with the general structure **25** (eq 1).

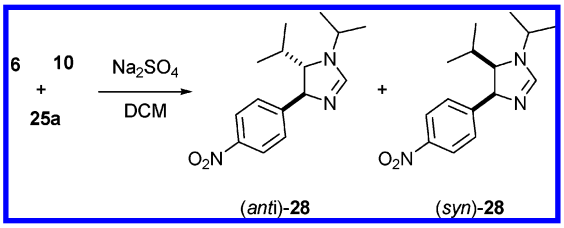


p-Nitrobenzyl isocyanide (**25a**) was envisioned as an isocyanide of type **25** that still contains a fairly acidic methylene unit. It was synthesized from the corresponding amine **26**, which was prepared according to a literature procedure[23] in two steps (overall yield 98%).

The first attempt to allow **25a** to react with the in situ generated imine of isopropylamine (**6**) and isobutyraldehyde (**10**) did not result in the formation of the desired product **28** (Table 3, entry 1). Only imine and isocyanide **25a** could be isolated. Also performing the reaction at a higher temperature was unsuccessful (entry 2). Instead of using even higher temperatures to obtain the 2-imidazoline **28**, another method was conceived. Several studies have been conducted on the increased acidity of α-protons of isocyanides coordinated to metals.[24] Transition metal catalyzed cycloadditions of various isocyanoacetates,[25] benzyl isocyanide,[26] and allyl isocyanide[27] to a range of electron-poor olefins or aldehydes have been reported. The cycloaddition to imines, however, required C=N bond activation by the introduction of a sulfonyl group on the imine nitrogen.[28] In 1999, Grigg et al. described the efficient silver(I) acetate catalyzed cycloaddition of methyl isocyanoacetate to Michael acceptors.[29] We envisioned silver(I) acetate as a suitable Lewis acid to activate *p*-nitrobenzyl isocyanide (**25a**). Indeed, one-pot reaction of **25a** with **6** and **10** in the presence of only 2 mol % of silver(I) acetate provided 2-imidazoline *anti*-**28** in 39% yield as a single diastereomer (Table 3, entry 3).

Besides *anti*-**28**, another product was isolated in 27% yield after flash column chromatography.[30] This product was identified as imidazole **29** (Scheme 5). Apparently, some of the initially formed imidazoline had been oxidized during the reaction or during workup/purification.[31]

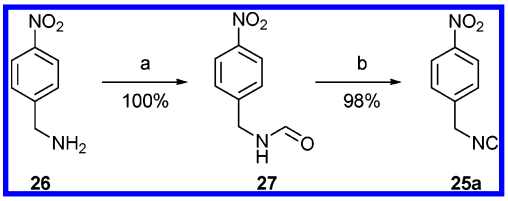
TABLE 3. Synthesis of 4-Monosubstituted 2-Imidazoline 28



entry	*T*, °C	catalyst	yield,[a] %
1	20	none	0[b]
2	60	none	0[b]
3	20	AgOAc[c]	39 (anti)[d,e]

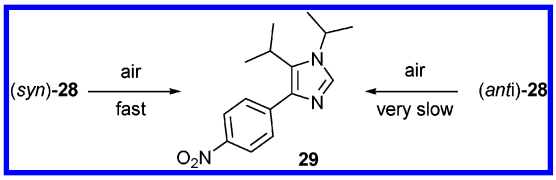
[a] Isolated yields are reported. [b] Only imine and isocyanide **25a** were recovered. [c] 2 mol % of AgOAc was used. [d] Relative stereochemistry was determined from the ^{1}H NMR coupling constants of H-4 and H-5. [e] Also the corresponding imidazole **29** was isolated in 27% yield.

SCHEME 4. Synthesis of *p*-Nitrobenzyl Isocyanide 25a[a]



[a] Reagents and conditions: (a) acetic formic anhydride, DCM, 0 °C to rt, 1 h; (b) $POCl_3$, Et_3N, THF, −78 to 0 °C, 1 h.

SCHEME 5. Air Oxidation of *p*-Nitrophenyl-Substituted Imidazolines *syn*-28 and *anti*-28



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(30) A second byproduct, isolated in only 7%, was characterized as the oxazoline formed by reaction of **25a** and **10**.

(31) For a recent example of the air oxidation of imidazolines to imidazoles see: Illgen, K.; Nerdinger, S.; Behnke, D.; Friedrich, C. *Org. Lett.* **2005**, *7*, 39−42.

SCHEME 6. Proposed Mechanism for the Silver(I)-Catalyzed Cycloaddition of 25a to Imines 31

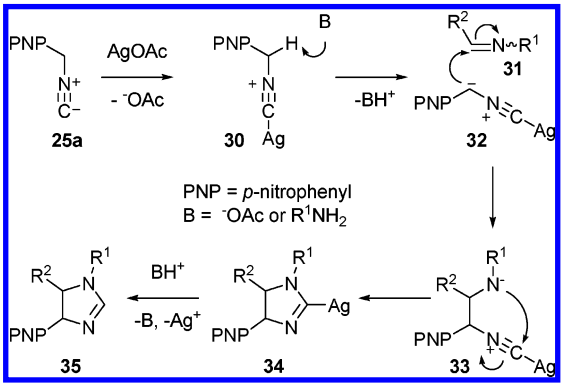
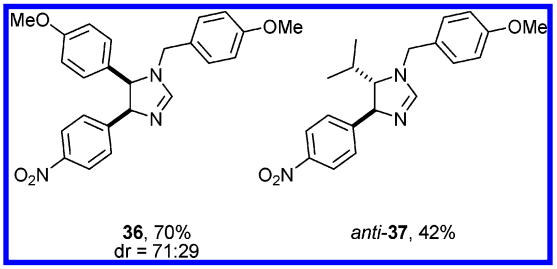


CHART 1. 4-Nitrophenyl-Substituted 2-Imidazolines



Because complete diastereoselectivity had never been observed before in our MCR, we reasoned that **29** should be formed from *syn*-**28**. To test this hypothesis, and to examine the factors causing the oxidation, both the MCR and subsequent workup were performed under exclusion of oxygen. Indeed, in the crude product a mixture of *anti*-**28** and *syn*-**28** could be observed in a ratio of 58:42 according to ^{1}H NMR. When this crude mixture was subjected to air, *syn*-**28** was rapidly oxidized to **29**, even in the absence of light. Also *anti*-**28** is not infinitely air-stable. After storing a purified sample for half a year under air, it contained about 75% of the oxidized product **29**. In conclusion, **29** is a product of the air oxidation of *syn*-**28** (fast) and/or *anti*-**28** (very slow) (Scheme 5). For this oxidation, neither silver(I) catalyst nor light is needed.

The proposed mechanism for the silver(I) catalyzed MCR with *p*-nitrobenzyl isocyanide (**25a**) is depicted in Scheme 6. It is believed that the activated isocyanide **30** is deprotonated by either the acetate anion or a trace of amine present in the reaction mixture (acting as base **B** after in situ imine formation). Then, the imine **31** is attacked by the deprotonated complex **32** to give aldol adduct **33**. Ring closure of the secondary amine followed by exchange of the silver(I) cation by a proton would provide the 2-imidazoline **35**. The formation of **34** from **31** and **32** may proceed via either a concerted cycloaddition or a stepwise mechanism. An alternative pathway would involve the aldol-type addition to an iminium ion intermediate.

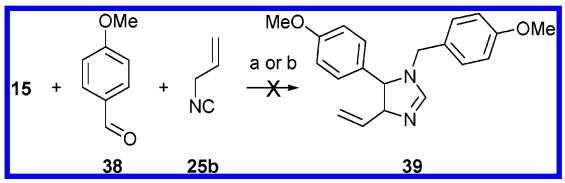
Variation of the amine and aldehyde substituents gave two more 4-nitrophenyl-substituted 2-imidazolines **36** and **37** in reasonable to good yields (Chart 1). According to NOESY measurements, for 2-imidazoline **36**, the syn-diastereomer was formed in excess. In the crude product **37**, both diastereomers *anti*-**37** and *syn*-**37** could be detected in a 62:38 ratio. However, after flash column chromatography only *anti*-**37** and the corresponding imidazole were isolated. Both diastereomers of **36** appeared to be much more air-stable. Nevertheless, after storing the mixture for months under air, both diastereomers were oxidized to the imidazole.

TABLE 4. Calculated Energy Differences between *syn*- and *anti*-Imidazolines

entry	compd	$\Delta E_{(syn)-(anti)}$,[a] kcal/mol
1	**28**	4.0
2	**36**	2.0
3	**37**	4.7

[a] BP86/TZP.

SCHEME 7. Attempts toward the Synthesis of 4-Vinyl-Substituted 2-Imidazoline 39[a]



[a] Reagents and conditions: (a) Na_2SO_4, DCM, rt, 18 h; (b) Na_2SO_4, AgOAc (2 mol %), DCM, rt, 18 h.

The air oxidation of 2-imidazolines could proceed via a radical stabilized by the *p*-nitrophenyl group. For the oxidation of both diatereomers, similar radical intermediates are expected. For the syn-diastereomers, the two substituents at C-4 and C-5 move away from each other during this radical formation (this reduces the steric repulsion), whereas for the anti-diastereomers, these groups move toward each other (this increases the steric repulsion). Formation of this radical intermediate should be faster from the syn-diastereomers than for the anti-diastereomers. This is supported by density functional theory (DFT)[32] calculations that show the *anti*-imidazolines to be more stable than their syn counterparts by 2−5 kcal/mol (Table 4).

Encouraged by the good results in the silver(I) catalyzed reactions of **25a**, allyl isocyanide **25b** was tested to synthesize more 2-imidazolines of type **24**. Combination of *p*-methoxybenzylamine (**15**), *p*-anisaldehyde (**38**), and **25b** without catalyst did not result in any imidazoline formation (Scheme 7). Addition of silver(I) acetate to the reaction mixture did not promote the cycloaddition. In both cases, only the imine derived from **15** and **38** was isolated after evaporation of the solvent and unreacted **25b**. Apparently, the reactivity of activated allyl isocyanide toward imines is considerably lower compared to that of **25a**.

To rationalize the differences in reactivity of the various isocyanides in our MCR, DFT (BP86/TZ2P) calculations proved helpful. The proposed mechanism for the aldol-type addition probably involves deprotonation of the isocyanide followed by attack of the anion to the (protonated) imine. Three aspects are important for understanding the reactivity: the proton affinity (PA) of the isocyanide (which correlates to the acidity), the orbital

(32) Koch, W.; Holthausen, M. C. *A Chemist's Guide to Density Functional Theory*; Wiley-VCH: Weinheim, Germany, 2000.

TABLE 5. Computed Proton Affinities (kcal/mol) of Isocyanides and Orbital Energies of the HOMOs (eV) and Contributions of p_z-Orbitals in HOMOs (%) of Their Anions[a,b]

entry	isocyanide	Ag^+ coordinated	PA, kcal/mol	ϵ_{HOMO},[a] eV	% $p_z(C_{anion})$
1	**4a**	no	181.4	−3.63	27.4
2	**4b**	no	180.3	−3.87	31.5
3	**4c**	no	190.3	−3.91	47.6
4	**25a**	no	181.9	−4.01	27.9
5	**25a**	yes	170.2	−4.63	27.3
6	**25b**	no	200.8	−3.01	36.9
7	**25b**	yes	179.5	−4.31	26.1

[a] BP86/TZ2P. [b] In all calculations, DCM was taken as the solvent.

energy of the highest occupied molecular orbital (HOMO) of its carbanion, and the contribution of carbanion orbitals in the HOMO. The PA of a molecule BH is defined as the system's enthalpy change for the reaction $BH \rightarrow B^- + H^+$, e.g., a smaller PA corresponds to a larger concentration of the B^- anion. The difference in energy between the HOMO of the attacking deprotonated complex and the lowest unoccupied orbital (LUMO) of the imine (or the iminium ion) determines the interaction between the two. Thus, the reactivity is governed by the $[B^-]$, the HOMO-LUMO gap, and the contribution of carbanion orbitals in the HOMO.

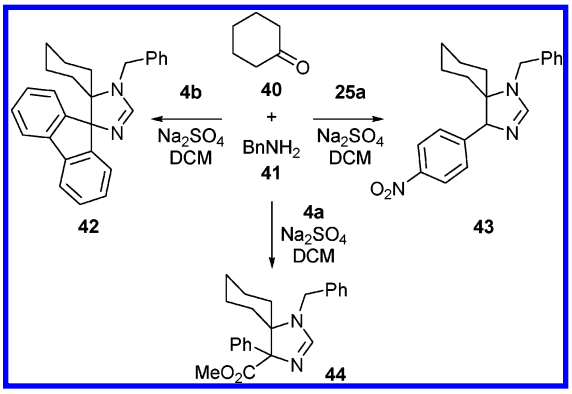
The computational setup for calculating PAs was validated against a series of organic and inorganic bases, for which experimental data are available.[33] It was shown that DFT gives both qualitatively and quantitatively good results for proton affinities.[34] Solvent effects (DCM) are properly taken into account by the COSMO model.[35] DFT calculations were performed for five different isocyanides: **4a**, **4b**, **25a**, **25b**, and methyl isocyanoacetate **4c**, which is also known to undergo cycloadditions with imines (Table 5).[19a]

The two isocyanides that display the highest reactivity in our MCR, **4a** and **4b** (entries 1 and 2), have similar values for the PA (ca. 181 kcal/mol),[36] HOMO orbital energy (ca. −3.7 eV), and contribution of carbanion (p_z) orbital in the HOMO (ca. 30%). These values can be taken as reference values for the reactivity of isocyanides in our MCR. Methyl isocyanoacetate **4c** (entry 3) has a larger contribution of carbanion orbitals in the HOMO, in fact the largest of all isocyanides we studied, and a HOMO orbital energy that is comparable to that of **4b** (entry 2). However, its proton affinity is almost 10 kcal/mol larger than that of **4a** and **4b**, which would result in a lower carbanion concentration and hence a lower reactivity. This is consistent with our previously reported experiments.[17]

Although its PA and contribution of the carbanion orbital in the HOMO are similar to those of **4a** (entry 1), *p*-nitrobenzyl isocyanide (**25a**) (entry 4) does not react with imines in the absence of silver(I). Its nonreactivity

(33) Bickelhaupt, F. M.; Buisman, G. J. H.; de Koning, L. J.; Nibbering, N. M. M.; Baerends, E. J. *J. Am. Chem. Soc.* **1995**, *117*, 9889−9899.
(34) Swart, M.; Bickelhaupt, F. M. Unpublished results.
(35) (a) Klamt, A.; Schüürmann, G. *J. Chem. Soc., Perkin Trans. 2* **1993**, 799−805. (b) Pye, C. C.; Ziegler, T. *Theor. Chem. Acc.* **1999**, *101*, 396−408.
(36) The measured pK_a of **4b** in DMSO (25 °C) is 12.3, see: Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456−463.

TABLE 6. MCRs with Cyclohexanone 40



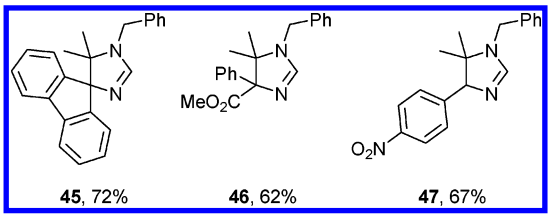
entry	isocyanide	catalyst	yield, %
1	**4b**	none	0[a]
2	**4a**	none	7
3	**25a**	none	0[a]
4	**4b**	AgOAc[b]	20
5	**4a**	AgOAc[b]	55
6	**25a**	AgOAc[b]	77

[a] Only imine and isocyanide were isolated. [b] 2 mol % of AgOAc was used.

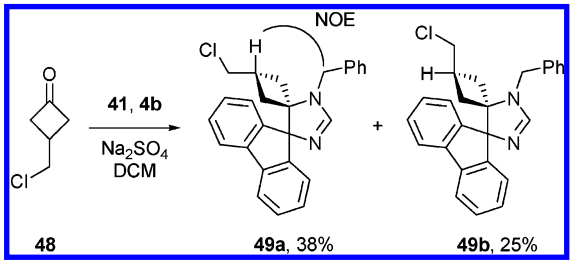
is ascribed to its HOMO being 0.4 eV lower in energy than that of **4a**. The activation by silver(I) has mainly an effect on the PA of **25a**, which is reduced by almost 12 kcal/mol (entry 5). Consequently, the concentration of carbanion increases significantly, which apparently compensates for the still rather poor ϵ_{HOMO} and causes the reaction to proceed after activation. Based on the HOMO orbital energy and the contribution of the carbanion p_z-orbital in it, allyl isocyanide (**25b**) should be able to react with imines, were it not for its very high PA, which is, in fact, the highest of the series. Preliminary results suggest that the PA of allyl groups may even be underestimated by our computational setup by up to 5 kcal/mol.[34] This makes it unlikely that any carbanions are present (entry 6). After activation by silver(I), the PA becomes comparable to that of **4a** or **4b**, which should be sufficient for reaction, but both the HOMO orbital energy and the contribution of the carbanion p_z-orbital in the HOMO decrease dramatically, by 1.3 eV and from 37% to 26%, respectively (entry 7). As a result, the carbanions will not be reactive toward imines. Furthermore, it was found that, for the anion of **25b**, not the isocyano group but the allyl group is the energetically favored coordination site for silver(I) (a difference of ca. 5 kcal/mol, see the Supporting Information for details). This thermodynamically more stable complex has a HOMO energy of −5.10 eV and a contribution of the carbanion p_z-orbital of only 22.9%. Therefore, nucleophilic attack would be even more hampered.

Instead of aldehydes, ketones also could be imagined as the oxo-components in the multicomponent synthesis of 2-imidazolines. However, both steric and electronic effects might decrease the reactivity of the in situ formed ketimines. The first attempts to apply cyclohexanone **40** in the MCR gave disappointing results (Table 6). With either 9-isocyanofluorene (**4b**) or *p*-nitrobenzyl isocyanide (**25a**), no 2-imidazoline was formed at all (entries 1 and 3). Employing isocyanoacetate **4a** as the isocyanide component gave the expected 5-disubstituted product,

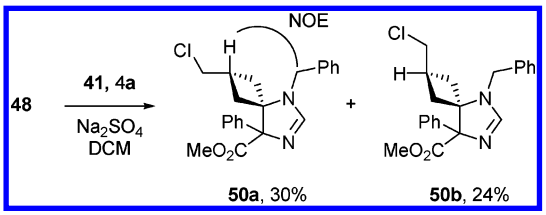
CHART 2. 2-Imidazolines Synthesized from Acetone with Silver(I) Acetate as Catalyst



SCHEME 8. Synthesis of 49a and 49b



SCHEME 9. Synthesis of 50a and 50b



albeit in only 7% yield (entry 2). Addition of a catalytic amount of silver(I) acetate appeared to be sufficient to activate the isocyanides to such an extent that reaction with the less electrophilic ketimines (as compared to the similar aldimines) is accelerated, which resulted in significantly increased yields (entries 4−6). The somewhat low yield for **42** is probably the result of steric factors. This is supported by experiments that combine acetone, benzylamine, and isocyanides (**4a**, **4b**, and **25a**) in the silver(I) catalyzed MCR, which furnished 2-imidazolines **45**−**47** (Chart 2). Even with 9-isocyanofluorene (**4b**) a good yield was obtained now.

When 3-(chloromethyl)cyclobutanone (**48**)[37] was applied, no additional catalyst was needed to perform the MCR (Scheme 8). Reaction of **48**, benzylamine (**41**), and 9-isocyanofluorene (**4b**) provided 2-imidazolines **49a** and **49b**, which contain a chloromethyl unit suitable for further derivatization, as a mixture of isomers. The identity of the trans-isomer **49a** was established by NOE measurements. Also isocyanoacetate **4a** gave good results when reacted with **48** and **41** (Scheme 9).[38] Again, NOE measurements were used for the identification of the trans-isomer **50a**. The relatively high reactivity of imines derived from cyclobutanone compared to the other ketimines can be accounted for by the release of ring strain, going from an sp^2 ring carbon to an sp^3 ring carbon.

Conclusions and Outlook

The scope of the multicomponent synthesis of 2*H*-2-imidazolines from isocyanides bearing acidic α-protons and in situ generated imines has been studied extensively. Three different isocyanides were used in combination with aldehydes and amines containing a variety of simple and functionalized side chains. The most important limitations are the steric bulk of the imine substituents and the reactivity of the isocyanide. Both the ease with which the isocyanide is deprotonated and the reactivity of the anion are important. Silver(I) catalysis appeared to be an excellent method to promote both difficult aldol-type additions to ketimines and reactions with *p*-nitrobenzyl isocyanide. The resulting *p*-nitrophenyl-substituted 2-imidazolines are relatively unstable to air. Both diastereomers are oxidized under air exposure (although with different rates) to the corresponding imidazoles. This MCR/oxidation procedure could be developed toward a useful and flexible imidazole synthesis additional to Sisko's methodology.[39] For the application of allyl isocyanide in the MCR, probably stronger activators for either the isocyanide or the imine are required.

Currently, we are investigating the activation of isocyanides with transition metals complexed to chiral ligands in order to achieve stereoselective aldol addition to in situ formed imines. Finally, different mono- and dimeric imidazolines are being used as precursors for *N*-heterocyclic carbenes containing two different C-backbone substituents.

Theory

DFT (BP86) calculations were performed with the Amsterdam Density Functional (ADF) program.[40] The MOs were expanded in large uncontracted sets of Slater-type orbitals,[41] which are of triple-ζ quality, augmented by one (TZP: 3d on C, N, O; 2p on H) or two sets of polarization functions (TZ2P: 3d and 4f on C, N, O; 2p and 3d on H; 5p and 4f on Ag); the 1s core shell of carbon, nitrogen, oxygen and the 1s−3d core shells of silver were treated by the frozen core (FC) approximation.[40b] 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 SCF cycle. For the silver-containing systems, (scalar) relativistic effects were taken into account with use of the zeroth-order regular approximation (ZORA).[40b,42]

Energies and gradients were calculated by using the local density approximation (LDA; Slater exchange and VWN correlation)[43] with nonlocal corrections due to Becke[44] (exchange) and Perdew[45] (correlation) added self-consistently. This xc-functional is one of the three best DFT functionals for the accuracy of geometries,[46] with an estimated unsigned error

(37) (a) Stevens, C. V.; de Kimpe, N. *J. Org. Chem.* **1996**, *61*, 2174−2178. (b) Rammeloo, T.; Stevens, C. V.; de Kimpe, N. *J. Org. Chem.* **2002**, *67*, 6509−6513.

(38) Application of the almost pure imine from **48** and **41** (prepared with $TiCl_4$, see ref 36b) resulted in even higher yields for **50a** (42%) and **50b** (33%).

(39) Sisko, J.; Kassick, A. J.; Mellinger, M.; Filan, J. J.; Allen, A.; Olsen, M. A. *J. Org. Chem.* **2000**, *65*, 1516−1524.

(40) (a) 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. (b) Fonseca Guerra, C.; Snijders, J. G.; te Velde, G.; Baerends, E. J. *Theor. Chem. Acc.* **1998**, *99*, 391−403. (c) ADF 2004.01; SCM, Theoretical Chemistry, Vrije Universiteit, Amsterdam, The Netherlands, http://www.scm.com.

(41) van Lenthe, E.; Baerends, E. J. *J. Comput. Chem.* **2003**, *24*, 1142−1156.

(42) van Lenthe, E.; Baerends, E. J.; Snijders, J. G. *J. Chem. Phys.* **1993**, *99*, 4597−4610.

(43) Vosko, S. H.; Wilk, L.; Nusair, M. *Can. J. Phys.* **1980**, *58*, 1200−1211.

(44) Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098−3100.

(45) Perdew, J. P. *Phys. Rev. B* **1986**, *33*, 8822−8824. Erratum: Perdew, J. P. *Phys. Rev. B* **1986**, *34*, 7406−7406.

of 0.009 Å in combination with the TZ2P basis set. Geometries were optimized by using analytical gradient techniques until the maximum gradient component was less than 1.0×10^{-4} atomic units. Vibrational frequencies were obtained through numerical differentiation of the analytical gradients.[40b]

Experimental Section

For general experimental methods, see the Supporting Information. Experimental details and characterization data for compounds **5g** and **5j** have been reported elsewhere.[17]

General Procedure I for the Synthesis of 2-Imidazolines. Reactions were carried out at a concentration of 1 M of amine, 1 M of aldehyde (or ketone), and 0.5 M of isocyanide in dry CH_2Cl_2, unless noted otherwise. Na_2SO_4 and the aldehyde were added, at room temperature, to a stirred solution of the amine. After the mixture was stirred for 2 h, the isocyanide was added and the reaction mixture was stirred at room temperature for an additional 18 h. The reaction mixture was then filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (PE:EtOAc:Et_3N = 2:1:0.01, gradient, unless stated otherwise).

Methyl 4-Phenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (5a). According to General Procedure I, reaction between NH_3 (2 M in MeOH, 2.3 mL, 4.6 mmol), *p*-formaldehyde (60 mg, 2.0 mmol), and **4a** (175 mg, 1.0 mmol), followed by flash column chromatography (EtOAc:MeOH:Et_3N = 1:0:0.01, gradient), did not afford **5a**, but the corresponding 2-oxazoline (235 mg, quant) as a yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.42−7.28 (m, 5H), 7.08 (s, 1H), 5.21 (d, J = 8.9 Hz, 1H), 4.28 (d, J = 8.9 Hz, 1H), 3.77 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 171.4 (C), 161.0 (CH), 136.2 (C), 128.8 (2 × CH), 128.5 (CH), 126.0 (2 × CH), 67.8 (C), 64.7 (CH_2), 53.5 (CH_3); IR (neat) 2956 (s), 1757 (s), 1257 (s), 1214 (s) cm^{-1}; MS (EI, 70 eV) *m/z* (%) =205 (0.5) [M]$^+$, 187 (100), 145 (68).

Methyl 1-Isopropyl-4-phenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (5b). According to General Procedure I, reaction between isopropylamine (118 mg, 2.0 mmol), *p*-formaldehyde (60 mg, 2.0 mmol), and **4a** (175 mg, 1.0 mmol), followed by flash column chromatography (EtOAc:MeOH:Et_3N = 1:0:0.01, gradient), afforded **5b** (173 mg, 70%) as a yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.40−7.19 (m, 5H), 6.98 (s, 1H), 4.27 (d, J = 9.6 Hz, 1H), 3.63 (s, 3H), 3.53−3.42 (m, 1H), 3.27 (d, J = 9.6 Hz, 1H), 1.15 (d, J = 6.6 Hz, 3H), 1.11 (d, J = 6.6 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 173.9 (C), 154.8 (CH), 143.1 (C), 128.4 (2 × CH), 127.3 (CH), 125.4 (2 × CH), 79.1 (C), 54.6 (CH_2), 52.8 (CH_3), 47.6 (CH), 21.14 (CH_3), 21.09 (CH_3); IR (neat) 2970 (s), 1726 (s), 1593 (s), 1254 (s), 1214 (s) cm^{-1}; HRMS (EI, 70 eV) calcd for $C_{14}H_{18}N_2O_2$ (M$^+$) 246.1368, found 246.1392.

Methyl 1-*tert*-Butyl-4-phenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (5c). According to General Procedure I, reaction between *tert*-butylamine (88 mg, 1.2 mmol), *p*-formaldehyde (36 mg, 1.2 mmol), and **4a** (98 mg, 0.56 mmol), followed by flash column chromatography, afforded **5c** (100 mg, 69%) as a yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.39−7.35 (m, 2H), 7.29−7.18 (m, 3H), 7.10 (s, 1H), 4.31 (d, J = 9.7 Hz, 1H), 3.62 (s, 3H), 3.30 (d, J = 9.7 Hz, 1H), 1.18 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 174.1 (C), 153.6 (CH), 143.4 (C), 128.5 (2 × CH), 127.4 (CH), 125.6 (2 × CH), 79.2 (C), 54.3 (CH_2), 52.9 (CH_3), 52.5 (C), 29.1 (3 × CH_3); IR (neat) 2972 (s), 1726 (s), 1592 (s), 1258 (s), 1236 (s), 1201 (s); HRMS (EI, 70 eV) calcd for $C_{15}H_{20}N_2O_2$ (M$^+$) 286.1893, found 286.1890.

Methyl 1-Mesityl-4-phenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (5d). According to General Procedure I, reaction between 2,4,6-trimethylaniline (270 mg, 2.0 mmol), *p*-formaldehyde (60 mg, 2.0 mmol), and **4a** (175 mg, 1.0 mmol), followed by flash column chromatography, afforded **5d** (209 mg, 65%) as a yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.76−7.50 (m, 6H), 7.15−7.11 (m, 2H), 4.94 (d, J = 9.8 Hz, 1H), 4.01 (s, 3H), 3.81 (d, J = 9.8 Hz, 1H), 2.52 (s, 3H), 2.50−2.29 (br s, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 173.7 (C), 155.7 (CH), 143.2 (2 × C), 137.8 (2 × C), 133.3 (C), 129.3 (2 × CH), 128.6 (2 × CH), 127.5 (CH), 125.5 (2 × CH), 80.4 (C), 58.7 (CH_2), 53.0 (CH_3), 20.8 (CH_3), 17.8 (2 × CH_3); IR (neat) 2951 (m), 2923 (m), 1729 (s), 1600 (s), 1576 (s), 1488 (s), 1263 (s), 1217 (s) cm^{-1}; HRMS (EI, 70 eV) calcd for $C_{20}H_{22}N_2O_2$ (M$^+$) 322.1681, found 322.1672.

Methyl 1-Benzhydryl-4-phenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (5e). According to General Procedure I, reaction between benzhydrylamine (366 mg, 2.0 mmol), *p*-formaldehyde (60 mg, 2.0 mmol), and **4a** (196 mg, 1.12 mmol), followed by flash column chromatography, afforded **5e** (340 mg, 82%) as a yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.34−7.30 (m, 2H), 7.25−7.08 (m, 12H), 7.00−6.85 (m, 1H), 6.82 (s, 1H), 5.32 (s, 1H), 4.24 (d, J = 9.8 Hz, 1H), 3.59 (s, 3H), 3.19 (d, J = 9.8 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 174.0 (C), 156.4 (CH), 142.8 (C), 139.8 (C), 139.8 (C), 129.3 (2 × CH), 129.0 (2 × CH), 128.6 (CH), 128.44 (CH), 128.40 (CH), 128.36 (2 × CH), 128.3 (2 × CH), 128.0 (CH), 127.9 (CH), 126.0 (2 × CH), 80.3 (C), 66.4 (CH), 58.6 (CH_2), 53.4 (CH_3); IR (KBr) 3025 (m), 1721 (s), 1595 (m), 1258 (s), 706 (s) cm^{-1}; HRMS (EI, 70 eV) calcd for $C_{24}H_{22}N_2O_2$ (M$^+$) 370.1681, found 370.1691.

Methyl 5-Isopropyl-4-phenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (5f). According to General Procedure I, reaction between NH_3 (2 M in MeOH, 2.3 mL, 4.6 mmol), isobutyraldehyde (154 mg, 2.1 mmol), and **4a** (192 mg, 1.1 mmol), followed by flash column chromatography, afforded **5f** (206 mg, 76%) as a 68:32 mixture of diastereomers as a yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.60−7.46 (m, 2H), 7.45−7.33 (m, 2H), 7.30−7.10 (m, 4H + 4H), 6.2 (br s, 1H + 1H), 4.53 (d, J = 3.2 Hz, 1H), 4.09 (d, J = 2.2 Hz, 1H), 3.64 (s, 3H), 3.62 (s, 3H), 2.45−2.35 (m, 1H), 1.55−1.40 (m, 1H), 1.01 (d, J = 6.9 Hz, 3H), 0.84 (d, J = 6.9 Hz, 3H), 0.71 (d, J = 6.6 Hz, 3H), 0.35 (d, J = 6.6 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 175.1 (C), 172.8 (C), 154.1 (CH), 153.3 (CH), 144.1 (C), 136.9 (C), 128.7 (CH), 128.4 (2 × CH), 128.1 (CH), 128.0 (CH), 127.5 (2 × CH), 126.3 (CH), 78.7 (C), 78.6 (CH), 76.6 (C), 71.7 (CH), 53.3 (CH_3), 52.9 (CH_3), 29.6 (CH), 29.1 (CH), 22.0 (CH_3), 21.8 (CH_3), 16.1 (CH_3), 16.0 (CH_3); IR (KBr) 3136 (m), 2938 (m), 1728 (s), 1221 (s) cm^{-1}; HRMS (EI, 70 eV) calcd for $C_{14}H_{18}N_2O_2$ (M$^+$) 246.1368, found 246.1352.

***anti*-Methyl 1-*tert*-Butyl-5-isopropyl-4-phenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (5h).** According to General Procedure I, reaction between *tert*-butylamine (146 mg, 2.0 mmol), isobutyraldehyde (144 mg, 2.0 mmol), and **4a** (190 mg, 1.09 mmol), followed by flash column chromatography, afforded *anti*-**5h** (59 mg, 21%) as a sticky yellow solid. ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.56−7.44 (m, 2H), 7.31−7.17 (m, 4H), 4.50 (d, J = 2.1 Hz, 1H), 4.48 (s, 3H), 1.58−1.49 (m, 1H), 1.27 (s, 9H), 0.74 (d, J = 7.2 Hz, 3H), 0.40 (d, J = 6.9 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 175.2 (C), 155.3 (CH), 137.5 (C), 128.2 (2 × CH), 127.9 (2 × CH), 127.5 (CH), 83.8 (C), 66.7 (CH), 53.4 (C), 52.7 (CH_3), 30.7 (3 × CH_3), 29.7 (CH), 20.0 (CH_3), 17.0 (CH_3); IR (neat) 2956 (m), 2914 (m), 2850 (m), 1745 (s), 1667 (s), 1217 (s) cm^{-1}; HRMS (EI, 70 eV) calcd for $C_{18}H_{26}N_2O_2$ (M$^+$) 302.1994, found 302.1998.

Methyl 5-*tert*-Butyl-4-phenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (5k). According to General Procedure I, reaction between NH_3 (2 M in MeOH, 2.0 mL, 4.0 mmol), pivaldehyde (172 mg, 2.0 mmol), and **4a** (175 mg, 1.0 mmol), followed by flash column chromatography, afforded **5k** (146 mg, 56%) as a 78:22 mixture of diastereomers as a white solid. ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.61−7.56 (m, 2H), 7.49−7.36 (m, 2H), 7.30−7.16 (m, 4H + 4H), 4.43 (d, J = 0.9 Hz, 1H), 4.02 (s, 1H), 3.67 (s, 3H), 3.65 (s, 3H), 0.99 (s, 9H), 0.60 (s, 9H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 174.8 (C), 172.7 (C), 153.1 (CH), 151.9 (CH), 144.3 (C), 136.3 (C), 128.3 (2 × CH), 128.00 (2 × CH), 127.97 (2 × CH), 127.8 (2 × CH), 127.4 (CH), 126.8 (CH), 84.1 (CH), 78.5 (C), 74.9 (CH), 52.9 (CH_3), 52.5 (CH_3), 34.8 (C), 34.5 (C), 27.2 (3 × CH_3), 27.1 (3 × CH_3)

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(one-quarternary C of minor diastereomer remained undetectable); IR (neat) 3186 (s, br), 2954 (s), 1732 (s), 1597 (s), 1254 (s) cm^{-1}; HRMS (EI, 70 eV) calcd for $C_{15}H_{20}N_2O_2$ (M^+) 260.1525, found 260.1523.

Methyl 1,5-Di-*tert*-butyl-4-phenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (5m). According to General Procedure I, reaction between *tert*-butylamine (146 mg, 2.0 mmol), pivaldehyde (172 mg, 2.0 mmol), and **4a** (175 mg, 1.0 mmol), followed by flash column chromatography, did not afford **5m**, but the corresponding 2-oxazoline (26 mg, 10%) as a single diastereomer (anti) as a yellow oil. ^1H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.83 (d, J = 7.2 Hz, 2H), 7.44−7.37 (m, 3H), 7.30−7.25 (m, 1H), 4.38 (s, 1H), 4.07 (s, 3H), 1.06 (s, 9H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 154.4 (C), 131.1 (C), 129.1 (CH), 128.5 (2 × CH), 126.5 (CH), 125.0 (2 × CH), 75.8 (CH), 60.4 (C), 60.1 (CH_3), 36.0 (C), 25.3 (CH_3); IR (neat) 2957 (s), 1741 (s), 1713 (s), 1250 (s), 1079 (s) cm^{-1}; HRMS (EI, 70 eV) calcd for $C_{15}H_{19}NO_3$ (M^+) 261.1365, found 261.1383.

***anti*-Methyl 5-Mesityl-4-phenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (5p).** According to General Procedure I, reaction between NH_3 (2 M in MeOH, 2.0 mL, 4.0 mmol), mesitaldehyde (296 mg, 2.0 mmol), and **4a** (175 mg, 1.0 mmol), followed by precipitation from Et_2O and PE, afforded *anti*-**5p** (216 mg, 67%) as a white solid. Mp 222−225 °C; ^1H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.18−7.09 (m, 3H), 6.98−6.93 (m, 3H), 6.71 (s, 1H), 6.35 (s, 1H), 6.34 (s, 1H), 3.62 (s, 3H), 2.58 (s, 3H), 2.05 (s, 3H), 1.65 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 175.1 (C), 152.3 (CH), 138.4 (C), 137.8 (C), 137.7 (C), 137.0 (C), 131.5 (C), 130.8 (CH), 129.0 (CH), 127.0 (2 × CH), 126.9 (CH), 126.8 (2 × CH), 81.0 (C)*, 64.5 (CH)*, 53.2 (CH_3), 21.4 (CH_3), 20.6 (CH_3), 20.3 (CH_3), The signals labeled with an asterisk could only be found using gs-HMBC and gs-HMQC measurements (for the spectra, see the Supporting Information); IR (neat) 3056 (s, br), 2949 (s), 2916 (s), 2853 (m), 1732 (s), 1597 (s), 1447 (s), 1232 (s) cm^{-1}; HRMS (EI, 70 eV) calcd for $C_{20}H_{22}N_2O_2$ (M^+) 322.1681, found 322.1666.

***anti*-Methyl 1-*tert*-Butyl-5-mesityl-4-phenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (5r).** According to General Procedure I, reaction between *tert*-butylamine (146 mg, 2.0 mmol), mesitaldehyde (296 mg, 2.0 mmol), and **4a** (175 mg, 1.0 mmol), followed by flash column chromatography, afforded *anti*-**5r** (58 mg, 15%) as a single diastereomer as a sticky white solid. ^1H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.27 (s, 1H), 7.15 (d, J = 5.9 Hz, 2H), 7.01−6.95 (m, 3H), 6.69 (s, 1H), 6.32 (s, 1H), 6.24 (br s, 1H), 3.66 (s, 3H), 2.63 (s, 3H), 2.08 (s, 3H), 1.80 (s, 3H), 1.18 (s, 9H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 175.0 (C), 153.9 (CH), 138.3 (C), 138.0 (C), 136.3 (C), 136.2 (C), 133.6 (C), 130.7 (CH), 128.9 (CH), 126.7 (2 × CH), 126.5 (CH), 125.7 (2 × CH), 85.5 (C), 61.4 (CH), 54.2 (C), 53.1 (CH_3), 29.2 (3 × CH_3), 21.3 (CH_3), 20.8 (CH_3), 20.6 (CH_3); IR (neat) 2974 (s), 1723 (s), 1597 (s), 1237 (s), 1212 (s), 1197 (s) cm^{-1}; HRMS (EI, 70 eV) calcd for $C_{24}H_{30}N_2O_2$ (M^+) 378.2307, found 378.2319.

Methyl 1-Benzhydryl-5-mesityl-4-phenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (5t). According to General Procedure I, reaction between benzhydrylamine (366 mg, 2.0 mmol), mesitaldehyde (296 mg, 2.0 mmol), and isocyanoacetate **4a** (180 mg, 1.03 mmol), followed by flash column chromatography, afforded **5t** (84 mg, 17%) as a 74:26 mixture of diastereomers as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.65−7.63 (m, 2H), 7.42−6.94 (m, 15H + 13H), 6.90 (s, 1H), 6.83 (s, 1H), 6.81 (s, 1H), 6.74 (s, 1H), 6.66 (s, 1H), 6.48 (s, 1H), 6.20 (s, 1H), 5.33 (s, 1H), 4.99 (s, 1H), 4.94 (s, 1H), 3.67 (s, 3H), 3.33 (s, 3H), 2.28 (s, 3H), 2.27 (s, 3H), 2.14 (s, 3H), 1.92 (s, 3H), 1.73 (s, 3H), 1.71 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 174.9 (C), 171.5 (C), 153.1 (CH), 152.9 (CH), 144.4 (C), 141.0 (C), 139.3 (C), 139.2 (C), 139.1 (C), 138.9 (C), 138.7 (C), 138.4 (C), 138.3 (C), 138.2 (C), 137.3 (C), 137.20 (C), 137.16 (C), 131.3 (CH), 130.6 (CH), 130.4 (C), 129.5 (CH), 129.4 (CH + CH), 129.2 (CH), 129.1 (CH), 128.90 (CH), 128.87 (CH), 128.86 (CH), 128.69 (CH), 128.67 (CH), 128.5 (CH), 128.30 (CH), 128.25 (CH), 127.9 (CH + CH), 127.8 (CH), 127.58 (CH), 127.56 (CH), 127.4 (CH), 127.33 (CH), 127.30 (CH + CH), 127.1 (CH), 126.8 (CH + CH), 126.7 (CH), 126.0 (CH), 124.9 (CH), 84.4 (C), 84.0 (C), 67.4 (CH), 64.1 (CH), 63.7 (CH), 63.3 (CH), 53.2 (CH_3), 51.9 (CH_3), 21.3 (CH_3), 20.9 (CH_3), 20.7 (2 × CH_3), 20.7 (CH_3), 20.4 (CH_3), the assignments of the several signals was confirmed by using gs-HMBC and gs-HMQC measurements. Due to the crowded aromatic region, not all 34 different aromatic CH signals could be assigned (for the spectra, see the Supporting Information); IR (neat) 3029 (m), 2950 (m), 1726 (s), 1594 (s), 1576 (s), 1493 (s), 1452 (s), 1225 (s), 1179 (s) cm^{-1}; HRMS (EI, 70 eV) calcd for $C_{33}H_{32}N_2O_2$ (M^+) 488.2464, found 488.2459.

2-Imidazoline 11. According to General Procedure I, reaction between allylamine (570 mg, 10.0 mmol), isobutyraldehyde (720 mg, 10.0 mmol), and **4b** (1.0 g, 5.24 mmol), followed by flash column chromatography, afforded **11** (1.439 g, 91%) as a brown oil. ^1H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.60−7.55 (m, 2H), 7.36−7.12 (m, 7H), 5.97−5.84 (m, 1H), 5.35−5.28 (m, 2H), 3.96 (dd, J = 15.5, 4.7 Hz, 1H), 3.71 (dd, J = 15.5, 7.8 Hz, 1H), 3.56 (d, J = 8.2 Hz, 1H), 0.79 (d, J = 6.8 Hz, 3H), 0.19 (d, J = 6.7 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 160.4 (CH), 150.9 (C), 145.7 (C), 140.6 (C), 140.5 (C), 133.3 (CH), 128.3 (2 × CH), 127.7 (CH), 127.0 (CH), 126.4 (CH), 124.4 (CH), 119.8 (CH), 119.7 (CH), 119.4 (CH_2), 83.6 (C), 73.6 (CH), 51.4 (CH_2), 29.9 (CH), 20.7 (CH_3), 19.9 (CH_3); IR (neat) 2960 (s), 2927 (m), 2869 (m), 1673 (s), 1609 (s), 1449 (s) cm^{-1}; HRMS (EI, 70 eV) calcd for $C_{21}H_{22}N_2$ (M^+) 302.1783, found 302.1779.

2-Imidazoline 14. According to General Procedure I, reaction between 2-aminoethanol (122 mg, 2.0 mmol), *p*-formaldehyde (60 mg, 2.0 mmol), and **4b** (191 mg, 1.0 mmol), followed by flash column chromatography (EtOAc:MeOH:Et_3N = 1:0:0.01, gradient), afforded **14** (218 mg, 83%) as a sticky yellow solid. ^1H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.58−7.55 (m, 4H), 7.36−7.17 (m, 5H), 3.51 (s, 2H), 3.44−3.40 (m, 2H), 3.36 (br s, 1H), 3.11 (t, J = 5.4 Hz, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 158.8 (CH), 149.7 (2 × C), 139.8 (2 × C), 129.1 (2 × CH), 128.5 (2 × CH), 124.0 (2 × CH), 119.7 (2 × CH), 79.2 (C), 59.1 (CH_2), 58.6 (CH_2), 49.4 (CH_2); IR (neat) 3177 (s, br), 3044 (m), 2924 (m), 2854 (m), 1663 (s), 1590 (s), 1449 (s), 1067 (s) cm^{-1}; HRMS (EI, 70 eV) calcd for $C_{17}H_{16}N_2O$ (M^+) 264.1263, found 264.1255.

2-Imidazoline 17. According to General Procedure I, reaction between *p*-methoxybenzylamine (274 mg, 2.0 mmol), *p*-hydroxybenzaldehyde (244 mg, 2.0 mmol), and **4b** (191 mg, 1.0 mmol), followed by flash column chromatography (EtOAc:MeOH:Et_3N = 1:0:0.01, gradient), afforded **14** (294 mg, 68%) as a yellow solid. Precipitation from ethyl acetate gave a white powder. Mp 245−248 °C; ^1H NMR (400 MHz, pyridine-d_5) δ (ppm) 11.28 (br s, 1H), 8.10 (s, 1H), 7.62−7.59 (m, 2H), 7.54 (s, 1H), 7.47 (d, J = 7.2 Hz, 1H), 7.36−7.29 (m, 4H), 7.17−7.08 (m, 2H), 7.03 (d, J = 8.3 Hz, 2H), 6.95 (d, J = 8.0 Hz, 2H), 6.85 (d, J = 8.2 Hz, 2H), 5.10 (s, 1H), 4.94 (br s, 1H), 4.76 (d, J = 14.4 Hz, 1H), 4.14 (d, J = 14.4 Hz, 1H), 3.68 (s, 3H); ^{13}C NMR (101 MHz, pyridine-d_5) δ (ppm) 160.0 (CH), 159.8 (C), 158.2 (C), 151.1 (C), 146.7 (C), 141.6 (C), 140.4 (C), 130.5 (2 × CH), 128.8 (2 × CH), 128.7 (CH), 128.6 (C), 128.3 (CH), 128.1 (CH), 127.2 (CH), 127.1 (CH), 125.8 (C), 125.0 (CH), 119.91 (CH), 119.86 (CH), 115.8 (2 × CH), 114.6 (CH), 85.6 (C), 72.9 (CH), 55.2 (CH_3), 49.8 (CH_2); IR (KBr) 3438 (s, br), 3035 (s), 2997 (s), 2928 (s), 1609 (s), 1588 (s), 1506 (s), 1249 (s) cm^{-1}; HRMS (EI, 70 eV) calcd for $C_{29}H_{24}N_2O_2$ (M^+) 432.1838, found 432.1850.

2-Imidazoline 19. According to General Procedure I, reaction between 3-amino-1-propanol (150 mg, 2.0 mmol), 4-hydroxybenzaldehyde (244 mg, 2.0 mmol), and **4b** (191 mg, 1.0 mmol) in MeOH, followed by flash column chromatography (EtOAc:Et_3N = 1:0.01, EtOAc:MeOH:Et_3N = 1:0.01:0.01, gradient) and crystallization from EtOAc and PE, afforded **16** (141 mg, 38%) as a white solid. Mp 190−193 °C; ^1H NMR (250 MHz, DMSO-d_6) δ (ppm) 9.12 (br s, 1H), 7.66 (s, 1H), 7.64−7.63 (m, 1H), 7.56−7.49 (m, 2H), 7.40−7.32 (m, 2H), 7.12−7.06 (m, 1H), 7.01−6.96 (m, 2H), 6.53 (d, J = 8.5 Hz, 2H), 6.36

(d, J = 8.5 Hz, 2H), 4.85 (s, 1H), 4.54 (br s, 1H), 3.50−3.45 (m, 2H), 3.43−3.31 (m, 1H), 3.04−2.94 (m, 1H), 1.74−1.64 (m, 2H); ^{13}C NMR (63 MHz, DMSO-d_6) δ (ppm) 159.8 (CH), 156.3 (C), 150.1 (C), 145.6 (C), 140.2 (C), 139.4 (C), 128.3 (CH), 127.8 (3 × CH), 127.7 (CH), 126.4 (CH), 126.2 (CH), 125.3 (C), 124.2 (CH), 119.5 (CH), 119.3 (CH), 114.5 (2 × CH), 84.2 (C), 72.5 (CH), 58.2 (CH_2), 42.3 (CH_2), 30.3 (CH_2); IR (KBr) 3420 (s, br), 3057 (s), 2933 (s), 1660 (s), 1515 (s), 1447 (s), 1267 (s), 1232 (s), 1047 (s) cm^{-1}; HRMS (EI, 70 eV) calcd for $C_{24}H_{22}N_2O_2$ (M^+) 370.1681, found 370.1690.

Bis-2-imidazoline 21. According to General Procedure I, reaction between hexane-1,6-diamine (116 mg, 1.0 mmol), isobutyraldehyde (144 mg, 2.0 mmol), and **4b** (350 mg, 1.83 mmol), followed by flash column chromatography, afforded **21** (370 mg, 67%) as a yellow solid. ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.68 (d, J = 7.3 Hz, 4H), 7.47−7.23 (m, 14H), 3.73 (d, J = 7.5 Hz, 2H), 3.43−3.27 (m, 4H), 2.00−1.80 (m, 6H), 1.70−1.50 (m, 4H), 0.89 (d, J = 6.8 Hz, 6H), 0.37 (d, J = 6.8 Hz, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 160.2 (2 × CH), 151.0 (2 × C), 145.8 (2 × C), 140.62 (2 × C), 140.56 (2 × C), 128.3 (4 × CH), 127.7 (2 × CH), 127.0 (2 × CH), 126.5 (2 × CH), 124.5 (2 × CH), 119.8 (2 × CH), 119.7 (2 × CH), 83.4 (2 × C), 73.8 (2 × CH), 48.3 (2 × CH_2), 29.6 (2 × CH), 27.8 (2 × CH_2), 27.2 (2 × CH_2), 20.4 (2 × CH_3), 20.1 (2 × CH_3); IR (neat) 2957 (s), 2932 (s), 2868 (m), 1605 (s), 1448 (s) cm^{-1}; HRMS (EI, 70 eV) calcd for $C_{42}H_{46}N_4$ (M^+) 606.3722, found 606.3779.

Bis-2-imidazoline 22. According to General Procedure I, reaction between isopropylamine (118 mg, 2.0 mmol), isophthalaldehyde (268 mg, 1.0 mmol), and **4b** (382 mg, 2.0 mmol), followed by flash column chromatography, afforded **22** (329 mg, 55%) as a yellow solid. ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.59 (s, 1H), 7.48 (s, 1H), 7.47−7.22 (m, 9H), 6.98−6.91 (m, 2H), 6.77−6.11 (m, 9H), 4.76 (s, 2H), 3.20−3.11 (m, 1H), 2.73 (br s, 1H), 1.53 (d, J = 6.9 Hz, 3H), 1.20 (d, J = 6.8 Hz, 3H), 1.15 (d, J = 6.4 Hz, 3H), 0.99 (d, J = 6.4 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 156.3 (CH), 156.2 (CH), 150.2 (C), 149.9 (C), 145.1 (2 × C), 140.7 (C), 140.4 (C), 140.0 (C), 139.8 (C), 135.74 (C), 135.68 (C), 128.4 (CH), 128.4 (CH), 127.90 (CH), 127.87 (CH), 127.8 (CH), 127.6 (CH), 127.3 (CH), 127.2 (CH), 126.25 (CH), 126.20 (CH), 126.16 (CH), 125.8 (CH), 125.7 (2 × CH), 123.9 (CH), 123.8 (CH), 119.5 (CH), 119.4 (CH), 119.3 (CH), 119.0 (CH), 84.2 (C), 84.0 (C), 72.3 (CH), 72.1 (CH), 46.5 (CH), 46.4 (CH), 22.3 (CH_3), 22.1 (CH_3), 20.3 (CH_3), 19.9 (CH_3); IR (neat) 3041 (m), 2968 (s), 1585 (s), 1448 (s), 1225 (s), 1197 (s) cm^{-1}; HRMS (EI, 70 eV) calcd for $C_{42}H_{38}N_4$ (M^+) 598.3096, found 598.3074.

1-(Isocyanomethyl)-4-nitrobenzene (25a). Acetic formic anhydride (13 mL) was added dropwise to a stirred solution of 4-nitrobenzylamine *(***26**) (6.7 g, 44.1 mmol) in 90 mL of dry CH_2Cl_2 at 0 °C. Stirring was continued for 1 h at room temperature. Evaporation of the solvent and acids at reduced pressure yielded **27** as a white solid. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 8.26 (s, 1H), 8.13 (d, J = 9.6 Hz, 2H), 7.41 (d, J = 9.6 Hz, 2H), 6.10 (br s, 1H), 4.59 (d, J = 7.6 Hz, 2H). To a stirred solution of crude **27** in 150 mL of dry THF at −78 °C was added Et_3N (34 mL, 240 mmol). After this $POCl_3$ (5.6 mL, 54 mmol) in 40 mL of dry THF was added dropwise and the reaction mixture was allowed to warm to 0 °C. After the solution was stirred for another 1 h, ice cold water (100 mL) was added. The mixture was extracted with Et_2O (3 × 80 mL). Drying with Na_2SO_4 followed by concentration in vacuo afforded **25a** (7.0 g, 98% over 2 steps) as an almost pure, light brown solid. Mp 98−101 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 8.21 (d, J = 8.1 Hz, 2H), 7.49 (d, J = 8.1 Hz, 2H), 4.71 (s, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 158.7 (C), 139.0 (C), 126.5 (2 × CH), 124.2 (2 × CH), 45.8 (C), 44.9 (t, J = 7.6 Hz, CH_2); IR (neat) 2157 (s), 1516 (s), 1351 (s) cm^{-1}; HRMS (EI, 70 eV) calcd for $C_8H_6N_2O_2$ (M^+) 162.0429, found 162.0432.

General Procedure II for the AgOAc-Catalyzed Synthesis of 2-Imidazolines. Reactions were carried out at a concentration of 1 M of amine, 1 M of aldehyde, and 0.5 M of isocyanide in dry CH_2Cl_2, unless stated otherwise. Na_2SO_4 and the aldehyde were added, at room temperature, to a stirred solution of the amine. After the solution was stirred for 2 h, the isocyanide and AgOAc (2 mol % relative to the isocyanide) were added and the reaction mixture was stirred at for an additional 18 h. The reaction mixture was filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (PE:EtOAc:Et_3N = 2:1:0.01, gradient).

1,5-Diisopropyl-4-(4-nitrophenyl)-4,5-dihydro-1*H*-imidazole (28). According to General Procedure II, reaction between isopropylamine (144 mg, 2.0 mmol), isobutyraldehyde (118 mg, 2.0 mmol), and **25a** (162 mg, 1.0 mmol) gave **28** as a mixture of diastereomers, together with some **29**. The ^{1}H NMR spectrum of this crude product is shown in the Supporting Information. When the NMR sample was subjected to air, oxidation of the syn-diastereomer to imidazole **29** could be seen. Flash column chromatography afforded *anti*-**28** (106 mg, 39%) as an orange oil and **29** (74 mg, 27%) as a sticky yellow solid. *anti*-**28**: ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 8.12 (d, J = 8.7 Hz, 2H), 7.31 (d, J = 8.7 Hz, 2H), 7.16 (d, J = 1.2 Hz, 1H), 4.76 (d, J = 6.3 Hz, 1H), 3.40−3.29 (m, 1H), 3.28 (dd, J = 6.4, 3.8 Hz, 1H), 2.00−1.86 (m, 1H), 1.31 (d, J = 6.8 Hz, 3H), 1.10 (d, J = 6.5 Hz, 3H), 0.88 (d, J = 6.9 Hz, 3H), 0.87 (d, J = 6.8 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 153.7 (CH), 152.6 (C), 146.9 (C), 127.5 (2 × CH), 123.8 (2 × CH), 71.2 (CH), 69.4 (CH), 46.3 (CH), 29.7 (CH), 22.2 (CH_3), 22.0 (CH_3), 17.8 (CH_3), 15.6 (CH_3); IR (neat) 2964 (m), 1592 (s), 1519 (s), 1344 (s) cm^{-1}; HRMS (EI, 70 eV) calcd for $C_{15}H_{21}N_3O_2$ (M^+) 275.1634, found 275.1625.

1,5-Diisopropyl-4-(4-nitrophenyl)-1*H*-imidazole (29): ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.21 (d, J = 8.8 Hz, 2H), 7.65 (d, J = 8.8 Hz, 2H), 7.60 (s, 1H), 4.48 (m, 1H), 3.38 (m, 1H), 1.54 (d, J = 6.8 Hz, 6H), 1.34 (d, J = 7.3 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 146.1 (C), 142.9 (C), 135.0 (C), 134.1 (CH), 133.7 (C), 128.9 (2 × CH), 123.4 (2 × CH), 47.4 (CH), 24.8 (CH), 24.3 (2 × CH_3), 21.7 (2 × CH_3); IR (neat) 2971 (m), 2934 (m), 1597 (s), 1515 (s), 1343 (s) cm^{-1}; HRMS (EI, 70 eV) calcd for $C_{15}H_{19}N_3O_2$ (M^+) 273.1477, found 273.1478.

1-(4-Methoxybenzyl)-5-(4-methoxyphenyl)-4-(4-nitrophenyl)-4,5-dihydro-1*H*-imidazole (36). According to General Procedure II, reaction between *p*-methoxybenzylamine (274 mg, 2.0 mmol), *p*-anisaldehyde (272 mg, 2.0 mmol), and **25a** (162 mg, 1.0 mmol), followed by flash column chromatography, afforded **36** (293 mg, 70%) as a 29:71 mixture of diastereomers as an orange/brown oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 8.14 (d, J = 8.6 Hz, 2H), 7.93 (d, J = 8.6 Hz, 2H), 7.452 (s, 1H), 7.448 (s, 1H), 7.32−6.84 (6H + 10H), 6.76 (d, J = 8.6 Hz, 2H), 6.63 (d, J = 8.6 Hz, 2H), 5.53 (d, J = 11.4 Hz, 1H), 5.06 (d, J = 10.4 Hz, 1H), 4.77 (d, J = 11.3 Hz, 1H), 4.48 (d, J = 14.5 Hz, 1H), 4.38 (d, J = 14.3 Hz, 1H), 3.99 (d, J = 10.2 Hz, 1H), 3.90−3.78 (m, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.82 (s, 3H), 3.72 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 159.7 (C), 159.32 (C), 159.29 (C), 159.0 (C), 157.9 (CH), 156.7 (CH), 150.6 (C), 147.3 (C), 147.2 (C), 146.5 (C), 131.2 (C), 129.5 (2 × CH), 129.4 (2 × CH), 129.1 (2 × CH), 128.7 (2 × CH + 2 × CH), 127.8 (C), 127.4 (2 × CH), 126.8 (C), 123.7 (2 × CH), 122.6 (2 × CH), 114.8 (2 × CH), 114.2 (2 × CH + 2 × CH), 113.6 (2 × CH), 79.2 (CH), 74.0 (CH), 71.4 (CH), 66.9 (CH), 55.31 (CH_3), 55.28 (CH_3), 55.24 (CH_3), 55.1 (CH_3), 48.8 (CH_2), 48.6 (CH_2), one quaternary C of the minor diastereomer could not be detected. Relative stereochemistry was assigned by using gs-HMBC and gs-NOESY measurements (for spectra, see the Supporting Information); IR (neat) 1610 (s), 1594 (s), 1513 (s), 1344 (s), 1248 (s) cm^{-1}; HRMS (EI, 70 eV) calcd for $C_{24}H_{23}N_3O_4$ (M^+) 417.1689, found 417.1681. After storing the product for about 6 months under air, only the corresponding **imidazole** (a yellow solid) was retrieved. Mp 172−178 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.97 (d, J = 9.1 Hz, 2H), 7.58−7.53 (m, 3H), 7.06 (d, J = 8.8 Hz, 2H), 6.90−6.82 (m, 4H), 6.74 (d, J = 8.8 Hz, 2H), 4.80 (s, 2H), 3.80 (s, 3H), 3.71 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 160.4 (C), 159.4 (C), 145.7 (C), 141.4 (C), 137.4 (CH), 136.2 (C), 132.0 (2 × CH), 131.2 (C), 128.5 (2 × CH), 128.0 (C), 126.3 (2 × CH), 123.6 (2 × CH),

121.5 (C), 114.8 (2 × CH), 114.2 (2 × CH), 55.32 (CH_3), 55.27 (CH_3), 48.4 (CH_2); IR (neat) 1612 (m), 1598 (m), 1513 (s), 1333 (s), 1250 (s), 1176 (m), 1100 (m), 1028 (m) cm^{-1}; HRMS (EI, 70 eV) calcd for $C_{24}H_{21}N_3O_4$ (M^+) 415.1532, found 415.1518.

1-(4-Methoxybenzyl)-5-isopropyl-4-(4-nitrophenyl)-4,5-dihydro-1*H*-imidazole (37). According to General Procedure II, reaction between *p*-methoxybenzylamine (274 mg, 2.0 mmol), isobutyraldehyde (118 mg, 2.0 mmol), and **25a** (162 mg, 1.0 mmol) gave **37** as a mixture of diastereomers, together with some of the corresponding imidazole. The ^1H NMR spectrum of this crude product is shown in the Supporting Information. Flash column chromatography afforded *anti*-**37** (150 mg, 42%) as an orange oil and the corresponding imidazole (40 mg, 11%) as a colorless oil. *anti*-**37**: ^1H NMR (250 MHz, $CDCl_3$) δ (ppm) 8.12 (d, J = 8.8 Hz, 2H), 7.25 (d, J = 8.7 Hz, 2H), 7.16−7.13 (m, 3H), 6.89 (d, J = 8.6 Hz, 2H), 4.86 (d, J = 6.8 Hz, 1H), 4.51 (d, J = 14.9 Hz, 1H), 4.12 (d, J = 14.9 Hz, 1H), 3.82 (s, 3H), 3.20 (dd, J = 6.9, 3.8 Hz, 1H), 2.10−1.93 (m, 1H), 0.98 (d, J = 6.8 Hz, 3H), 0.92 (d, J = 6.9 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 159.8 (C), 156.9 (CH), 152.7 (C), 147.3 (C), 129.6 (2 × CH), 128.4 (C), 128.1 (2 × CH), 124.1 (2 × CH), 114.6 (2 × CH), 71.1 (CH), 70.8 (CH), 55.7 (CH_3), 49.2 (CH_2), 29.4 (CH), 18.3 (CH_3), 16.6 (CH_3); IR (neat) 2959 (m), 1595 (s), 1514 (s), 1345 (s), 1248 (s) cm^{-1}; HRMS (EI, 70 eV) calcd for $C_{20}H_{23}N_3O_3$ (M^+) 353.1739, found 353.1749. **Imidazole**: ^1H NMR (250 MHz, $CDCl_3$) δ (ppm) 8.16 (d, J = 8.9 Hz, 2H), 7.64 (d, J = 8.9 Hz, 2H), 7.35 (s, 1H), 6.99 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 8.8 Hz, 2H), 5.08 (s, 2H), 3.73 (s, 3H), 3.22−3.29 (m, 1H), 1.17 (d, J = 7.3 Hz, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 159.5 (C), 146.3 (C), 142.9 (C), 137.8 (CH), 136.3 (C), 134.7 (C), 129.0 (2 × CH), 128.1 (2 × CH), 127.9 (C), 123.4 (2 × CH), 114.4 (2 × CH), 55.3 (CH_3), 49.1 (CH_2), 24.7 (CH), 21.7 (2 × CH_3); IR 2966 (m), 2934 (m), 1598 (m), 1514 (s), 1343 (s), 1249 (s) cm^{-1}; HRMS (EI, 70 eV) calcd for $C_{20}H_{21}N_3O_3$ (M^+) 351.1583, found 351.1600.

2-Imidazoline 42. According to General Procedure II, reaction between benzylamine (214 mg, 2.0 mmol), cyclohexanone (196 mg, 2.0 mmol), and **4b** (191 mg, 1.0 mmol), followed by flash column chromatography, afforded **42** (76 mg, 20%) as a brown oil. ^1H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.55−7.49 (m, 2H), 7.42−7.10 (m, 12H), 4.23 (s, 2H), 2.07−1.98 (m, 2H), 1.42−1.30 (m, 2H), 1.10−1.05 (m, 3H), 0.80−0.72 (m, 1H), 0.37−0.26 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 159.1 (CH), 147.7 (2 × C), 140.6 (2 × C), 138.8 (2 × C), 128.8 (CH), 128.1 (2 × CH), 127.7 (2 × CH), 127.6 (CH), 126.6 (2 × CH), 126.1 (2 × CH), 119.7 (2 × CH), 85.2 (C), 69.3 (C), 46.0 (CH_2), 32.5 (CH_2), 24.9 (2 × CH_2), 22.7 (2 × CH_2); IR (neat) 3061 (m), 3030 (m), 2932 (s), 2861 (m), 1675 (m), 1595 (s), 1449 (s) cm^{-1}; HRMS (EI, 70 eV) calcd for $C_{27}H_{26}N_2$ (M^+) 378.2096, found 378.2105.

2-Imidazoline 43. According to General Procedure II, reaction between benzylamine (214 mg, 2.0 mmol), cyclohexanone (196 mg, 2.0 mmol), and **25a** (162 mg, 1.0 mmol), followed by flash column chromatography, afforded **43** (267 mg, 77%) as a brown solid. Mp 130−136 °C; ^1H NMR (250 MHz, $CDCl_3$) δ (ppm) 8.09 (d, J = 8.8 Hz, 2H), 7.38−7.19 (m, 7H), 6.99 (s, 1H), 4.95 (s, 1H), 4.24 (d, J = 15.2 Hz, 1H), 4.14 (d, J = 15.2 Hz, 1H), 1.81−0.69 (m, 10H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 156.2 (CH), 147.2 (C), 147.0 (C), 138.3 (C), 129.6 (2 × CH), 128.8 (2 × CH), 127.7 (CH), 127.6 (2 × CH), 123.1 (2 × CH), 76.5 (CH), 67.4 (C), 45.6 (CH_2), 33.8 (CH_2), 30.2 (CH_2), 24.9 (CH_2), 23.1 (CH_2), 21.9 (CH_2); IR (neat) 2934 (s), 2855 (m), 1595 (s), 1518 (s), 1345 (s) cm^{-1}; HRMS (EI, 70 eV) calcd for $C_{21}H_{23}N_3O_2$ (M^+) 349.1790, found 349.1790.

2-Imidazoline 44. According to General Procedure II, reaction between benzylamine (214 mg, 2.0 mmol), cyclohexanone (196 mg, 2.0 mmol), and **4a** (185 mg, 1.05 mmol), followed by flash column chromatography, afforded **44** (212 mg, 55%) as a green/brown oil. ^1H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.87−7.83 (m, 2H), 7.39−7.24 (m, 8H), 7.11 (s, 1H), 4.48 (s, 2H), 3.77 (s, 3H), 2.14−2.06 (m, 1H), 1.82−1.50 (m, 2H), 1.44−1.12 (m, 6H), 0.91−0.89 (m, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 172.5 (C), 156.7 (CH), 138.7 (C), 137.2 (C), 128.8 (2 × CH), 128.66 (CH), 128.65 (CH), 127.6 (2 × CH), 127.5 (2 × CH), 127.2 (2 × CH), 85.2 (C), 70.9 (C), 52.3 (CH_3), 47.9 (CH_2), 31.9 (CH_2), 31.4 (CH_2), 24.8 (CH_2), 22.5 (CH_2) 21.8 (CH_2); IR (neat) 2926 (s), 1726 (s), 1605 (s), 1452 (s), 1238 (s), 1218 (s) cm^{-1}; HRMS (EI, 70 eV) calcd for $C_{23}H_{26}N_2O_2$ (M^+) 362.1994, found 362.1996.

2-Imidazoline 45. According to General Procedure II, reaction between benzylamine (214 mg, 2.0 mmol), acetone (116 mg, 2.0 mmol), and **4b** (191 mg, 1.0 mmol), followed by flash column chromatography, afforded **45** (244 mg, 72%) as a white solid. Mp 138−145 °C; ^1H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.65 (d, J = 7.5 Hz, 2H), 7.54 (d, J = 7.6 Hz, 2H), 7.45−7.21 (m, 10H), 4.32 (s, 2H), 1.11 (s, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 158.2 (CH), 147.0 (2 × C), 141.2 (2 × C), 137.6 (C), 128.6 (2 × CH), 128.1 (2 × CH), 128.0 (2 × CH), 127.5 (CH), 126.5 (2 × CH), 125.9 (2 × CH), 119.5 (2 × CH), 85.4 (C), 68.9 (C), 46.6 (CH_2), 22.6 (2 × CH_3); IR (neat) 3062 (s), 3031 (s), 2969 (s), 2927 (s), 2865 (m), 1674 (s), 1589 (s), 1462 (s), 1449 (s), 1385 (s), 1365 (s), 1263 (s), 1226 (s), 1153 (s) cm^{-1}; HRMS (EI, 70 eV) calcd for $C_{24}H_{22}N_2$ (M^+) 338.1783, found 338.1793.

Methyl 1-Benzyl-5,5-dimethyl-4-phenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (46). According to General Procedure II, reaction between benzylamine (214 mg, 2.0 mmol), acetone (116 mg, 2.0 mmol), and **4a** (175 mg, 1.0 mmol), followed by flash column chromatography, afforded **46** (201 mg, 62%) as a yellow oil. ^1H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.67−7.63 (m, 2H), 7.41−7.26 (m, 8H), 7.17 (s, 1H), 4.22 (s, 2H), 3.78 (s, 3H), 1.42 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 172.0 (C), 156.3 (CH), 138.0 (C), 137.0 (C), 128.7 (2 × CH), 127.7 (2 × CH), 127.62 (3 × CH), 127.60 (CH), 127.5 (2 × CH), 84.4 (C), 69.1 (C), 51.9 (CH_3), 46.0 (CH_2), 22.8 (CH_3), 22.2 (CH_3); IR (neat) 2924 (m), 1728 (s), 1600 (s), 1263 (s), 1231 (s) cm^{-1}; HRMS (EI, 70 eV) calcd for $C_{20}H_{22}N_2O_2$ (M^+) 322.1681, found 322.1683.

1-Benzyl-5,5-dimethyl-4-(4-nitrophenyl)-4,5-dihydro-1*H*-imidazole (47). According to General Procedure II, reaction between benzylamine (214 mg, 2.0 mmol), acetone (116 mg, 2.0 mmol), and **25a** (162 mg, 1.0 mmol), followed by flash column chromatography, afforded **47** (207 mg, 67%) as a brown oil. ^1H NMR (250 MHz, $CDCl_3$) δ (ppm) 8.23 (d, J = 8.7 Hz, 2H), 7.50 (d, J = 8.6 Hz, 2H), 7.45−7.29 (m, 5H), 7.05 (d, J = 1.3 Hz, 1H), 4.95 (s, 1H), 4.31 (d, J = 15.0 Hz, 1H), 4.21 (d, J = 15.0 Hz, 1H), 1.42 (s, 3H), 0.67 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 156.4 (CH), 147.4 (C), 147.3 (C), 137.8 (C), 128.8 (2 × CH), 128.6 (2 × CH), 127.8 (CH), 127.6 (2 × CH), 123.3 (2 × CH), 79.4 (CH), 66.0 (C), 46.4 (CH_2), 27.2 (CH_3), 21.0 (CH_3); IR (neat) 1593 (s), 1518 (s), 1346 (s) cm^{-1}; HRMS (EI, 70 eV) calcd for $C_{18}H_{19}N_3O_2$ (M^+) 309.1477, found 309.1479.

2-Imidazoline 49. According to General Procedure I, reaction between benzylamine (214 mg, 2.0 mmol), **48** (237 mg, 2.0 mmol), and **4b** (191 mg, 1.0 mmol), followed by flash column chromatography, afforded **49** (252 mg, 63%) as a 60:40 mixture of isomers as a light brown solid. ^1H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.59−7.56 (m, 2H + 2H), 7.39−7.13 (m, 12H + 12H), 4.55 (s, 2H), 4.0.43 (s, 2H), 3.14 (d, J = 5.3 Hz, 2H), 2.80 (d, J = 6.8 Hz, 2H), 2.35−2.00 (m, 3H + 4H), 1.72−1.63 (m, 2H), 1.25−1.15 (m, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 157.9 (CH), 157.7 (CH), 146.1 (2 × C), 145.6 (2 × C), 140.53 (2 × C), 140.52 (2 × C), 138.0 (C), 137.9 (C), 129.5 (2 × CH), 129.4 (2 × CH), 129.03 (2 × CH), 128.97 (2 × CH), 128.5 (2 × CH), 128.3 (CH), 128.2 (CH), 128.1 (2 × CH), 127.8 (2 × CH), 127.6 (2 × CH), 125.34 (2 × CH), 125.28 (2 × CH), 120.01 (2 × CH), 119.95 (2 × CH), 85.8 (C), 84.8 (C), 69.0 (C), 68.2 (C), 48.8 (CH_2), 48.7 (CH_2), 47.6 (CH_2), 46.9 (CH_2), 34.4 (2 × CH_2), 32.2 (2 × CH_2), 29.3 (CH), 28.1 (CH); assignment of relative stereochemistry was achieved by using gs-NOESY measurements (for spectra, see the Supporting Information); IR (KBr) 3029, (s), 2948 (s), 2914 (s), 2802 (s), 2749 (s), 2697 (s), 1598 (s), 1451 (s), 737 (s) cm^{-1}; HRMS (EI, 70 eV) calcd for $C_{26}H_{23}ClN_2$ (M^+) 398.1550, found 398.1540.

2-Imidazoline 50. According to General Procedure I, reaction between benzylamine (214 mg, 2.0 mmol), **48** (237 mg, 2.0 mmol), and **4a** (175 mg, 1.0 mmol), followed by flash column chromatography, afforded **50** (208 mg, 54%) as a 56:44 mixture of isomers as a yellow/brown oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.58−6.82 (m, 11H + 11H), 4.47 (d, J = 2.2 Hz, 2H), 4.43 (s, 2H), 3.67 (s, 3H), 3.65 (s, 3H), 3.35−3.22 (m, 2H), 3.20 (d, J = 5.4 Hz, 2H), 2.68−2.56 (m, 1H), 2.55−2.35 (m, 3H + 1H), 2.30−2.19 (1H), 1.96−1.82 (m, 1H + 1H), 1.80−1.68 (m, 1H), 1.49−1.43 (m, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 173.9 (C), 171.6 (C), 156.8 (CH), 156.5 (CH), 138.1 (C), 137.9 (C), 137.8 (C), 137.7 (C), 128.9 (2 × CH), 128.8 (2 × CH), 128.3 (2 × CH), 128.1 (2 × CH), 127.9 (4 × CH), 127.7 (CH), 127.4 (CH), 127.3 (2 × CH), 127.2 (CH), 127.1 (CH), 126.8 (2 × CH), 84.8 (C), 84.6 (C), 70.3 (C), 68.7 (C), 52.30 (CH_3), 52.27 (CH_3), 49.1 (CH_2), 49.7 (CH_2), 47.1 (CH_2), 46.4 (CH_2), 34.1 (CH_2), 33.9 (CH_2), 32.6 (CH_2), 31.7 (CH_2), 30.7 (CH), 28.2 (CH); assignment of relative stereochemistry was achieved by using gs-NOESY measurements (for spectra, see the Supporting Information); IR (neat) 3032 (m), 2954 (m), 2868 (m), 1743 (s), 1672 (s), 1634 (s), 1496 (s), 1455 (s), 1258 (s), 1215 (s), 1175 (s), 699 (s) cm^{-1}; HRMS (EI, 70 eV) calcd for $C_{22}H_{23}ClN_2O_2$ (M^+) 382.1397, found 382.1428.

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Supporting Information Available: General experimental methods, ^{1}H and ^{13}C spectra of all new compounds and of **25a**, and computational details that were not mentioned in the Theory section (including Cartesian coordinates and computed energies of optimized structures). This material is available free of charge via the Internet at http://pubs.acs.org.

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