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Organocatalysis

Synthesis of 1,5-Ring-Fused Imidazoles from Cyclic Imines and TosMIC – Identification of in situ Generated *N*-Methyleneformamide as a Catalyst in the van Leusen Imidazole Synthesis

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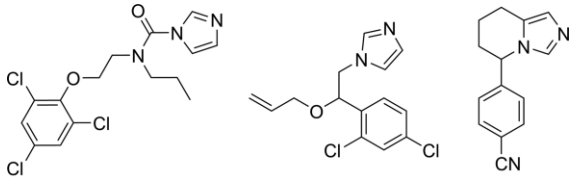
In memory of Prof. Rolf Huisgen

Abstract: Imidazoles fused with a cyclic system in 1,5-position were synthesized via the van Leusen imidazole synthesis employing saturated aliphatic tricycles including an imine function in the base catalyzed cycloaddition reaction with *p*-toluenesulfonyl-methyl isocyanide (TosMIC). Thereby, *N*-(tosylmethyl)formamide, a decomposition product of TosMIC, was found to act as a promoter of this reaction leading to considerably reduced reaction times and improved yields. Mechanistic studies revealed that *N*-(tosylmethyl)formamide is transformed into *N*-methyleneformamide acting as a catalyst in this reaction under the applied basic conditions. Being a Michael acceptor, the employed imines add to this compound, thus being transformed into iminium ions. The so formed intermediates facilitate the first step of the van Leusen imidazole synthesis, which is the addition of deprotonated TosMIC to the iminium subunit. *N*-methyleneformamide is finally reformed during the overall reaction and can thus be considered as an organocatalyst of the studied cycloaddition reaction.

Introduction

Imidazole rings are a common structural motif present in many natural products, medicinal drugs, and chemical compounds.[1] Thus, imidazole rings are found for example in numerous anticancer, antibacterial, antiparasitic, antihistaminic, antihypertensive, antineuropathic, and antifungal drugs.[2] Crop protection agents containing an imidazole heterocycle, for instance Prochloraz (**1**) or Imazalil (**2**) (Figure 1), are widely applied to maintain crop quality and quantity.[1a,3]

Since the first imidazole syntheses by Debus and Radziszewski in the 19th century, a multitude of synthetic methods for the preparation of imidazoles has evolved.[4] A common approach for the preparation of imidazoles is the van Leusen imidazole synthesis which is based on the 1,3-cycloaddition of tosylmethyl isocyanide (TosMIC) with imines under basic conditions.[4c,5] By this method, a large variety of either 1,5-di-, or 1,4,5-tri-substituted imidazoles employing acyclic imines as starting materials has been synthesized.[5,6] In contrast, examples in which the van Leusen imidazole synthesis has been applied to the construction of imidazoles displaying a fused ring system originating from 1,5-position are less common which is likely due to the fact that cyclic imines are less abundant than their acyclic counterparts.



1 **2** **3**

Figure 1. Structures of Prochloraz (**1**), Imazalil (**2**) and Fadrozole (**3**).

Exhibiting an imine subunit, pyrazine-2(1*H*)one derivatives have been employed in cycloaddition reactions with TosMIC yielding the corresponding ring fused systems that served as intermediates for the development of anticancer agents.[7] Further examples for the construction of 1,5-ring-fused imidazoles by means of TosMIC are found in syntheses of imidazobenzodiazepine and imidazo β-carboline derivatives.[8–10] Furthermore, also nitrogen containing heteroaromatic compounds like quinolone, isoquinoline, and quinoxaline formally displaying a C=N subunit have successfully been employed in the synthesis of the corresponding *N*-fused imidazo heterocycles employing TosMIC (Figure 2).[11]

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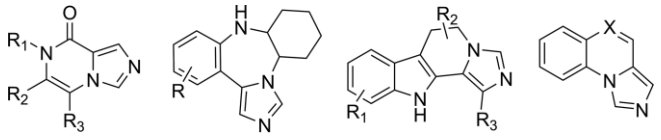


4 5 6 7

Figure 2. Structures of 1,5-ring-fused imidazoles synthesized from TosMIC and pyrazine-2(1*H*)ones (**4**);[7] benzodiazepines (**5**);[9] β-carboline derivatives (**6**)[10] and nitrogen containing heteroaromatics (**7**).[11]

Though, *N*-fused imidazoles with a saturated aliphatic cycle in 1,5-position are of great interest as for example Fadrozole (**3**), a non-steroidal aromatase inhibitor used for the treatment of breast cancer,[12] cycloaddition reactions of basic cyclic imines devoid of any additional functionalities have not been explored in the van Leusen imidazole synthesis, except for a cycloaddition reaction with 4-azahomoadamant-4-ene.[13]

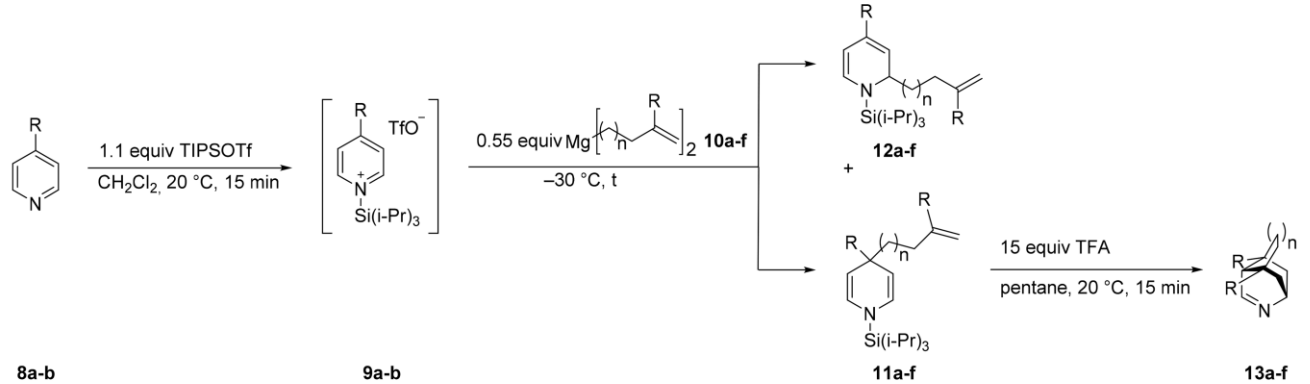
It is likely to be attributed to the limited availability of appropriate cyclic imines which are devoid of any additional unsaturation that cycloaddition reactions of this type of compounds with TosMIC for the preparation of the respective *N*-fused imidazoles have hardly been explored so far. We have repeatedly reported on the synthesis of this kind of alicyclic imines by acid catalyzed intramolecular cycloaddition reactions of 4,4-disubstituted 1,4-dihydropyridines (1,4-DHPs) with one of the 4-substituents serving as dienophile.[14] The tricyclic imines resulting from these reactions exhibiting a highly defined geometry are to be considered as valuable building blocks for the construction of drug like compounds, as they represent scaffolds of high rigidity encompassing well defined trajectories for individual substituents. To further improve the versatility of these building blocks, we now intended to utilize the imine function for the anellation of an imidazole ring by the van Leusen imidazole synthesis to introduce a polar subdomain in this otherwise apolar compounds.

Results and Discussion

As starting material for the anellation of an imidazole ring, we intended to use tricyclic imines which are symmetric, possess substituents R at bridge heads of different size (CH_3, C_6H_5), and vary with regard of the length of the "upper bridge" (n = 0–2). Therefore, compounds **13a**–**13f** should be employed for this purpose. For the synthesis of these compounds, **13a**–**13f**, the synthetic procedure developed for the construction of related, but non-symmetrically substituted tricyclic imines should be followed.[14a] Accordingly, in the first step appropriately 4,4-disubstituted 1,4-dihydropyridines should be prepared via reaction of *N*-silylpyridinium ions with bisorganomagnesium compounds. An acid catalyzed intramolecular hetero-Diels-Alder-reaction of these 4,4-disubstituted 1,4-dihydropyridines – with one 4-substituent exhibiting a double bond serving as dienophile – should finally furnish the respective tricyclic imines.

Hence, for the synthesis of the required 1,4-DHPs **11a**–**11f**, following a published procedure, 4-methylpyridine **8a** or 4-phenylpyridine **8b** were treated with TIPSOTf (1.1 equiv., in CH_2Cl_2 at 20 °C for 15 min) to generate the corresponding pyridinium ions **9a**–**9b** which were then trapped by addition of

Table 1. Synthesis of symmetric tricyclic imines **13a–f**.



8a-b **9a-b** **11a-f** **13a-f**

Entry	Starting material	R	Reagent	n	R	t (h)	Products 11	Products 12	NMR yield (%)[a] 11	NMR yield (%)[a] 12	Isol. yield (%) 11a-f	Isol. yield (%) 13a-f
1	**8a**	Me	**10a**	0	Me	16	**11a**	**12a**	59	17	55	76
2	**8b**	Ph	**10b**	0	Ph	16	**11b**	**12b**	26	16	19	94
3	**8a**	Me	**10c**	1	Me	16	**11c**	**12c**	40	–[b]	37	62
4	**8b**	Ph	**10d**	1	Ph	16	**11d**	**12d**	66	20	52	95
5	**8a**	Me	**10e**	2	Me	18	**11e**	**12e**	49	–[b]	50	78
6	**8b**	Ph	**10f**	2	Ph	48	**11f**	**12f**	–[c]	–[c]	55	74

[a] The yield of **11** and **12** in the crude product and the product ratio were determined using ^{1}H NMR spectroscopy with 2,4,6-collidine as internal standard. Isol. yields surpassing the NMR-yield are within error deviations.[16] [b] Not determinable due to low signal intensity. [c] Not determined.

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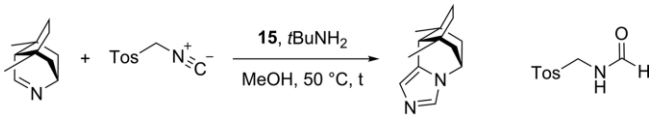
the respective bisorganomagnesium species **10a**–**10f** (–30 °C). However, for economic reasons here only 0.55 equivalents instead of 1.1 equiv. of the organometallic reagents were used in contrast to the literature procedure.[14a] As in related cases,[14,15] these reactions resulted in mixtures of the regioisomeric 1,2- and 1,4-addition products, i.e. of **11a**–**11f** and **12a**–**12f**. In these mixtures according to ^{1}H NMR quantification based on the use of an internal standard, the desired 1,4-addition products **11a**–**11e** clearly prevailed in each case over the respective 1,2-addition products **12a**–**12e**. Thus, the ^{1}H NMR yields for **11a**–**11e** amounted to 26–66 % whereas for **12a**–**12e,** they ranged from values partly too low for an accurate determination (<1 %) to up to 20 %. In line with these results, **11a**–**11e** could finally be isolated in yields from 19–55 %. Dihydropyridine **11f**, for which the crude product had not been analyzed by ^{1}H NMR, was isolated in a yield of 55 %, indicating that also this addition reaction had proceeded in favor of the 1,4-addition product.

The successive intramolecular hetero-Diels-Alder reaction of **11a**–**11f** could finally be accomplished by subjecting the obtained 4,4-disubstituted 1,4-dihydropyridines **11a**–**11f** to TFA (15 equiv.) in pentane (at 20 °C for 15 min), i.e. reaction conditions published for related cycloaddition reactions before.[14a] That way the desired tricyclic imines **13a**–**13f** were obtained in good to excellent yields (Table 1, entries 1–6: 62–95 %).

Next, we focused on the anellation of an imidazole ring to the imine function of the synthesized tricyclic imines **13a**–**13f** to generate the desired condensation products, imidazole derivatives **14**. This we intended to perform as already mentioned afore according to the so called van Leusen imidazole synthesis, in which imines are reacted with TosMIC in the presence of a base to give the corresponding imidazole derivative.[5]

When imine **13c**, chosen as a model compound, was treated with TosMIC (1.5 equiv.) in MeOH and subsequently with *t*BuNH$_2$ (2.0 equiv., 20 °C) and stirred for 14 h at 50 °C (Table 2 entry 1), the desired imidazole **14c** could be obtained, yet only in a yield of 29 %. Upon extension of the reaction time to 96 h, the yield rose to moderate 49 % (Table 2, entry 2). Assuming that an increased amount of deprotonated TosMIC might raise the reaction rate thus reducing the required reaction time, in a next attempt 6 equivalents of the base were employed under otherwise identical reaction conditions (50 °C, 14 h). However, the amount of formed product **14c** dropped to 19 % (Table 2, entry 3) indicating that a higher concentration of the base had an adverse effect. Therefore, the original ratio of TosMIC to *t*BuNH$_2$ of 1.5:2 was restored and the amount of TosMIC and *t*BuNH$_2$ relative to imine **13c** was doubled (Table 2, entry 4). This led to an improved, but still mediocre yield of 37 % (Table 2, entry 4). To our surprise, when the reaction was carried out with another batch of TosMIC under the initial reaction conditions (1.5 equiv. TosMIC, 2 equiv. *t*BuNH$_2$, 14 h), the yield improved from 29 % to 40 % (Table 2, compare entries 5 and 1). Careful analysis of the batch of TosMIC employed in this reaction revealed that about 2/3 of the reagent had undergone conversion into *N*-(tosylmethyl)formamide (**15**) by addition of water and only 1/3 of the reagent had remained unchanged. This result suggested that *N*-(tosylmethyl)formamide (**15**) has a positive effect on the imidazole formation given the fact that the actual quantity of TosMIC utilized was only about 1/3 of the calculated 1.5 equiv. whereas the yield of imidazole **14c** was still higher than that for the reaction with pure TosMIC (Table 2, compare entries 5 and 1). Accordingly, at next an experiment was performed which was identical with the first reaction (Table 2, entry 1) with pure TosMIC (1.5 equiv.) except that in addition 3 equiv. of *N*-(tosylmethyl)formamide (**15**) were added prior to heating to 50 °C for 14 h (Table 2, entry 6). In this case, a yield of 44 % was reached for imidazole **14c** which was significantly better than the result of the original reaction without *N*-(tosylmethyl)formamide (**15**), (Table 2, entry 1) and similar to that performed with the impure TosMIC sample (Table 2, entry 5). Although the amount of TosMIC and *N*-(tosylmethyl)-formamide (**15**) had notably been raised as compared to the formerly conducted experiment (Table 2, compare entries 5 and 6), the yield remained roughly unchanged. Hence, it seemed reasonable that the effect mediated by *N*-(tosylmethyl)formamide (**15**) might also depend on the amount of the base

Table 2. Optimization of the synthesis of imidazole **14c**.



13c **14c** **15**

Entry	TosMIC [equiv.]	base [equiv.]	**15** [equiv.]	t [h]	Isol. Yield [%]
1	1.5	*t*BuNH$_2$ (2)	0	14	29
2	1.5	*t*BuNH$_2$ (2)	0	96	49
3	1.5	*t*BuNH$_2$ (6)	0	14	19
4	3.0	*t*BuNH$_2$ (4)	0	14	37
5	n.d.[a]	*t*BuNH$_2$ (2)	n.d.[a]	14	40
6	1.5	*t*BuNH$_2$ (2)	3	14	44
7	1.5	*t*BuNH$_2$ (6)	3	14	91
8	1.5	*n*BuNH$_2$ (6)	3	14	48
9	1.5	DBU (6)	3	14	84

[a] The exact amount of TosMIC and **15** employed is unknown as a partially decomposed sample of TosMIC (the amount formally corresponding to 1.5 equiv.) containing also **15** was used. ^{1}H NMR spectroscopy indicated the amount of TosMIC in the mixture to be ca. 1/3 that of **15** ca. 2/3.

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present. Therefore, the last reaction (Table 2, entry 6) was repeated with 6 instead of 3 equivalents of tBuNH$_2$ with the other reaction conditions remaining unchanged. In that case (1.5 equiv. TosMIC, 3 equiv. formamide **15**, 6 equiv. tBuNH$_2$), imidazole **14c** was isolated in an excellent yield of 91 %, suggesting that for the positive effect of formamide **15** on the imidazole formation indeed a sufficient amount of the base is required. Thus, in this reaction, the base tBuNH$_2$ might not only be required for the deprotonation of the cycloaddition reagent TosMIC, but also for a so far unknown activation of formamide **15**.

To verify whether other bases also might be suitable for this reaction, tBuNH$_2$ was substituted by *n*-butylamine or by 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU) (Table 2, entries 8–9). With nBuNH$_2$, the yield significantly decreased to only 48 %, whereas DBU proofed to be a suitable base as well and a very good yield (84 %) was achieved. However, as it is known that TosMIC does not decompose in the presence of tBuNH$_2$[5] and the best yield in our experiments was obtained with this base, tBuNH$_2$ was chosen as base for all future experiments. Next, for the so far developed reaction conditions, ^{1}H NMR experiments were performed in the presence of 1,3,5-trimethoxybenzene as internal standard over a period of 20.5 h (Figure 3, solid line) to get an estimate in what quantity the starting material **13c** is consumed and the product **14c** is formed.

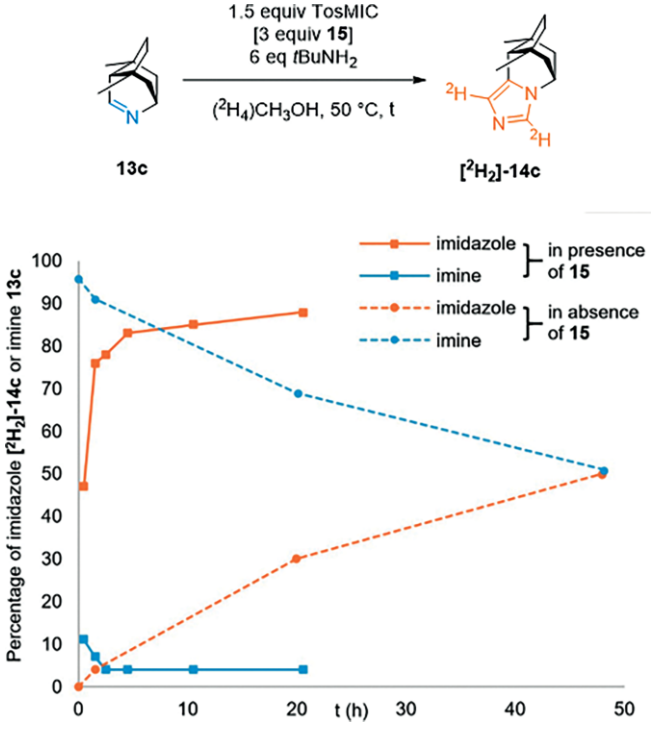

Figure 3. Time course of the imidazole formation in the absence and in the presence of *N*-(tosylmethyl)formamide (**15**). The percentage of **13c** and **[^{2}H$_2$]-14c** in the reaction mixture was determined by ^{1}H NMR spectroscopy applying 1,3,5-trimethoxybenzene as internal standard.

Because of the need of (^{2}H$_4$)CH$_3$OH as a deuterated solvent, these ^{1}H NMR experiments, however, did not reflect the signals of TosMIC, but of its deuterated analogue [^{2}H$_2$]-TosMIC (exchange of protons of CH$_2$ group) and finally also those of the double deuterated form of the final product, **[^{2}H$_2$]-14c**. In case of the reaction of **13c** with TosMIC in the presence of *N*-(tosylmethyl)formamide (**15**), the percentage of the product **[^{2}H$_2$]-14c** was fast-growing. An amount of 47 % and 76 % had been reached after 0.5 h and 1.5 h, respectively thereafter it took 19 h to further raise to 88 % (after 20.5 h). Interestingly, the share of remaining imine **13c** had dropped within 0.5 h to a value as low as 11 %. Thereafter, it lowered to 4 % within a reaction time of 2.5 h from whereon no further significant change could be observed. Due to the fact that a good ^{1}H NMR yield for imidazole **[^{2}H$_2$]-14c** could already be observed after a reaction time of 1.5 h, this reaction time was considered sufficient for any further reaction to be performed.

In contrast, the reaction of imine **13c** with [^{2}H$_2$]-TosMIC to give imidazole **[^{2}H$_2$]-14c** performed in the absence of formamide **15** (Figure 3, dashed line) proceeded much slower. After 1.5 h, just 4 % of imidazole **[^{2}H$_2$]-14c** had formed. This amount rose slowly to 51 % within 48 h, which equals the quantity that had been reached within only 0.5 h in the prior experiment with formamide **15**, clearly demonstrating the promoting effect of this compound (**15**). Intriguingly, in case of the cycloaddition reaction of **14c** with TosMIC executed in the presence of formamide **15,** a large gap between the amount of remaining starting material **13c** and formed product **[^{2}H$_2$]-14c** exists, the sum of the share of both compounds being distinctly below 100 %. This phenomenon was most pronounced at the beginning of the reaction and became continuously less with increasing reaction time. In the absence of formamide **15,** no such discrepancy could be observed (see Figure 3). This clearly points to the formation of some intermediate during the reaction performed in the presence of *N*-(tosylmethyl)formamide (**15**), though at this point due to the complexity of the ^{1}H NMR spectra no such compound could be identified.

Next, the reaction conditions established for the cycloaddition of **13c** with TosMIC in the presence of *N*-(tosylmethyl)-formamide (**15**) were applied to the tricyclic imines **13a**–**13b** and **13d**–**13f**. In order to get insight in the promoting effect of *N*-(tosylmethyl)formamide (**15**), these reactions were also performed in the absence of *N*-(tosylmethyl)formamide (**15**).

In both cases, the consumption of imine and formation of imidazole was quantified directly by ^{1}H NMR at the time point given. For this reason, the reactions were carried out in (^{2}H$_4$)CH$_3$OH again. When imine **13a** was treated with TosMIC (1.5 equiv.) in the presence of formamide **15** (3 equiv.) and tBuNH$_2$ (6 equiv.) for 1.5 h at 50 °C, the desired imidazole **[^{2}H$_2$]-14a** was formed to 51 % with no imine **13a** remaining (Table 3, entry 1). When in the same reaction formamide **15** was omitted, the ^{1}H NMR yield of imidazole **[^{2}H$_2$]-14a** dropped to 25 %, and 45 % of the starting material **13a** was found to be still present. The results obtained for the reactions of imines **13b**–**13d** with TosMIC leading to **[^{2}H$_2$]-14b**–**14d** (for the sake of completeness data of the formation of **[^{2}H$_2$]-14c** described above have been included here, too) highlight the positive effect of *N*-(tosylmethyl)formamide (**15**) even better. Thus, the yields for imidazoles **[^{2}H$_2$]-14b**–**14d** amounted to 46–76 % when formamide **15** was present, whereas only negligible amounts were identified when **15** was absent and large amounts of starting materials,

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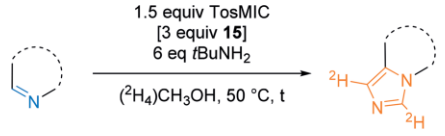
Table 3. Synthesis of various imidazoles.



13 14

Entry	Imine struct. R	Imine struct. no.	Imidazole struct. R	Imidazole struct. no.	t (h)	Percentage according to ^{1}H NMR (%)[a] in absence of 15: Imine 13	in absence of 15: Imidazole 14	in presence of 15: Imine 13	in presence of 15: Imidazole 14
1	Me	13a	Me	[$^2H_2$]-14a	1.5	45	25	0	51 (63)[b]
					3	–	–	0	53
2	Ph	13b	Ph	[$^2H_2$]-14b	1.5	98	traces	8	46 (59)[b]
					3	–	–	6	46
3	Me	13c	Me	[$^2H_2$]-14c	1.5	91[b]	4[b]	7[b]	76[c] (91)[b,c]
4	Ph	13d	Ph	[$^2H_2$]-14d	1.5	90	traces	32	48 / 59[d] (56)[b]
					3	–	–	30	53
5	Me	13e	Me	[$^2H_2$]-14e	6 d	92	2	78	14[e]
6	Ph	13f	Ph	[$^2H_2$]-14f	6 d	82	2	83	12[e]
7		13g		[$^2H_2$]-14g	1.5	0	41	0	21[e]
8		13h		[$^2H_2$]-14h	1.5	25	66	0	83
						72[f]	23[f]	0[f]	86[f]

[a] The amount of **13** and **14** in the crude reaction mixture was determined using ^{1}H NMR spectroscopy with 1,3,5-trimethoxybenzene as internal standard. [b] Isolated yield after purification (given in parentheses). The experiment was carried out in non-deuterated methanol leading to a non-deuterated imidazole. [c] Identical to data given in Figure 3; isolated yield identical to data given in Table 2. [d] Yield determined after aqueous workup (addition of 1,3,5-trimethoxybenzene as internal standard to the crude reaction mixture, evaporation of $(^2H_4)CH_3OH$, redissolving in CH_2Cl_2 and twofold washing with brine) using ^{1}H NMR spectroscopy. [e] In consequence of the low yields obtained, only analysis by ^{1}H NMR and ESI-HRMS was conducted for these products. [f] Reaction at 25 °C.

imines **13b**-**d**, remained unchanged (Table 3, entries 2–4). To ensure that the moderate ^{1}H NMR yields for the syntheses of imidazoles **[$^2H_2$]-14a**–**14b**,**d** in the presence of **15** were not due to an insufficient reaction time, these were repeated, setting the reaction time to 3 h. Yet, the quantities for unreacted imines **13a**–**13b**,**d** and formed imidazoles **[$^2H_2$]-14a**–**14b**,**d** remained virtually unchanged (Table 3, entries 1, 2 and 4) which is in line with what had been observed when studying the time course of the transformation of **13c** into **[$^2H_2$]-14c** (Figure 3). Similar to this transformation described in Figure 3, also the sum of the quantities of unreacted imine and formed imidazole was distinctly lower than 100 %, in particular for the transformations of imines **13a**–**13b** into imidazoles **[$^2H_2$]-14a**–**14b**. Remarkably, when the synthesis of imidazoles **14a**–**14d** was carried out in non-deuterated methanol (in the presence of **15**), the yields achieved after purification for the, in consequence non-deuterated imidazoles **14a**–**14d** were higher (56–91 % vs. 46–76 %; see Table 3, entries1–4) than those observed in the ^{1}H NMR experiments [in ($^2H_4$)CH_3OH] afore. This is likely to be attributed to a so far unknown precursor of **14a**–**14d** which upon workup is at least partially transformed in the respective imidazole derivative. This was exemplarily verified by subjecting the ^{1}H NMR experiment with imidazole **[$^2H_2$]-14d** (reaction time 1.5 h) to an aqueous workup. Thereupon, the yield for **[$^2H_2$]-14d** determined by ^{1}H NMR out of the crude reaction product rose from 48 % to 59 %, now being in good accord with the isolated yield of 56 % (Table 3, entry 4). By crystallization and subsequent X-ray crystallography of the non-deuterated imidazole **14d** the unique structure of these imidazoles was corroborated (Figure 4).

In contrast to the results described above, the yields obtained in the syntheses of imidazoles **[$^2H_2$]-14e**–**f** from imines **13e**–**13f** were quite disappointing. Monitoring the reactions by TLC revealed that within 1.5 h no detectable amount of product had formed independent of the absence or presence of formamide **15**. When the reaction time was extended to 6 d for the formation without *N*-(tosylmethyl)formamide (**15**), still only minute amounts of imidazole derivatives **[$^2H_2$]-14e**–**14f** could be detected (ca. 2 %, Table 3, entries 5–6). In contrast, the yield for these compounds was distinctly higher when formamide **15** was present in the reaction mixture, though still low with values of 14 % and 12 % for **[$^2H_2$]-14e** and **[$^2H_2$]-14f**, respectively**.** Hence, despite the poor outcome of these reactions, the positive effect of formamide **15** was still clearly evident.

The poor yields obtained for the cycloaddition reaction performed with the cyclic imines **13e**–**13f** appear quite astonishing, considering the close structural similarity of these compounds with the imines **13a**–**13d**, for which the yields for the cycloaddition products, the imidazole derivatives **[$^2H_2$]-14a**–**14d** had been quite satisfying. Clearly, this phenomenon must

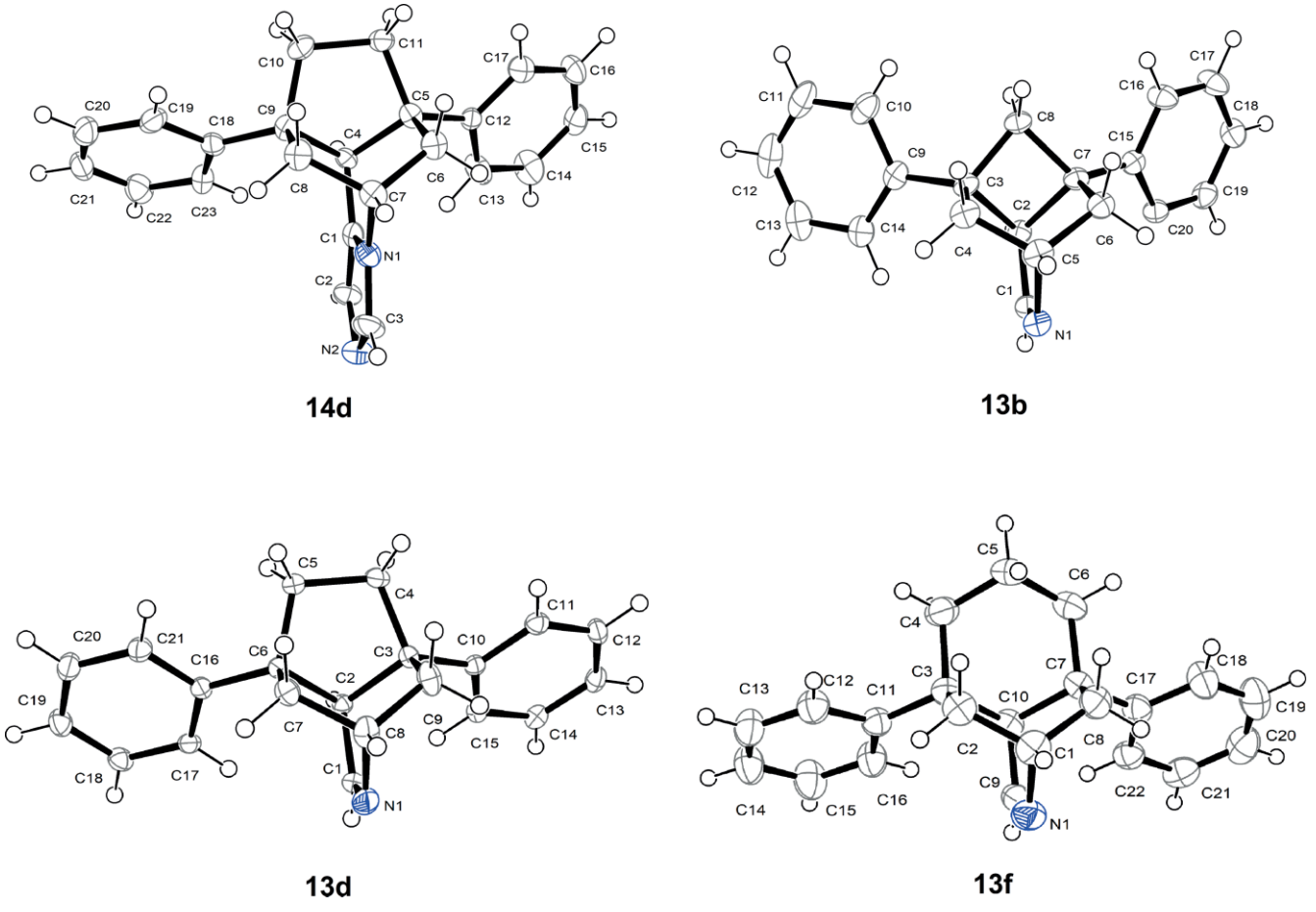


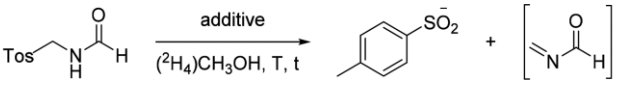
Figure 4. X-ray crystal structures of imidazole **14d** and tricyclic imines **13b**, **13d** and **13f**.[17]

be associated with the continuous enlargement of the "upper bridge", from a CH_2, to a CH_2CH_2, and finally a $CH_2CH_2CH_2$ unit upon the transition from **13a**–**13b** to **13c**–**13d** and finally to **13e**–**13f**. As a result of the increasing size of this bridge, the adjacent bridgehead substituents should be pushed towards the imine function, thus increasing the shielding and associated with that reducing the reactivity of the latter. The assumed change of the orientation of the aforementioned bridgehead substituents could be verified by X-ray structures obtained for the phenyl-substituted imines **13b**, **13d**, and **13f**. These clearly show that with the increasing size of the "upper bridge" the bridgehead substituents are getting closer to the imine function.

Finally, the effect of *N*-(tosylmethyl)formamide (**15**) on the cycloaddition reaction of imines **13a**–**13f** with TosMIC should exemplarily also be studied for some imines structurally different from **13a**–**13f**. As such 2,3,4,5-tetrahydropyridine (**13g**) and 3,4-dihydroisoquinoline (**13h**) were selected. In case of the reaction with imine **13g**, the starting material was fully consumed within 1.5 h, independent of whether formamide **15** was present or not. However, this time the yield of the cycloaddition product **[$^2H_2$]-14g** was higher when **15** was absent (41 %) than when it was present (21 %). Possibly, formamide **15** mediates decomposition reactions in this case as a multitude of side products was detected by ^{1}H NMR, which might be associated with the dynamic character of imine **13g** existing in mono- and trimeric form.[18] However, the positive effect of *N*-(tosylmethyl)formamide (**15**) in the cycloaddition reaction with TosMIC became again evident when 3,4-dihydroisoquinoline (**13h**) was used as starting material. Employing the standard conditions, the ^{1}H NMR yield for the product **[$^2H_2$]-14h** amounted to 83 % when formamide **15** was present and to 66 % when it was absent. Thereby, according to the ^{1}H NMR data in the first case the starting material had been completely consumed (0 %, **13h**) and in the latter 25 % remained unchanged (reaction time 1.5 h). The positive effect of *N*-(tosylmethyl)formamide (**15**) became even more apparent, when the conversion of imine **13h** into **[$^2H_2$]-14h** was performed at a reduced temperature of 25 °C instead of 50 °C. Then, after the same reaction time (1.5 h) only 23 % of the imine **13h** had been transformed into product **[$^2H_2$]-14h** when **15** was absent, but 86 % in its presence (^{1}H NMR yields, Table 3, entry 8).

Next, to shed some light on the fate and possibly on the function of *N*-(tosylmethyl)formamide **15** in the above described cycloaddition reaction, a series of control experiments was performed. First, formamide **15** dissolved in $(^2H_4)CH_3OH$ was kept for 1.5 h at 50 °C in the absence of any additive and further in the presence of TosMIC (0.5 equiv.), tricylic imine **13c** (0.33 equiv.), or *t*$BuNH_2$ (2.0 equiv.) (Table 4, entries 1–4). According to the subsequently performed ^{1}H NMR analysis of the respective reactive mixtures, formamide **15** remained completely unchanged when no additive or TosMIC was present, or was accompanied with minute amounts of the decomposition product **16** (ca. 1 %; **16** was identified in a subsequent reaction) when tricyclic imine **13c** was present. However, when *tert*-butylamine was added (Table 4, entry 4) only minor amounts of **15** (4 %) remained unchanged after 1.5 h and new species had formed. One of these could be identified as *p*-toluenesulfinic acid **16**, the share of which amounted to 96 %. Thereby, the base-induced decomposition of formamide **15** proceeds rather fast, as about 35 % of this compound had been converted into *p*-toluenesulfinic acid **16** even at the lower temperature of 25 °C within 7 min (Table 4, entry 5).

Table 4. Reactions of *N*-(tosylmethyl)formamide **15** under varying conditions.



15 **16** **17**

Entry	Additive (equiv)	T [°C]	t (min)	^{1}H NMR ratio **15**:**16**
1	none	50	90	100:0
2	TosMIC (0.5)	50	90	100:0
3	**13c** (0.33)	50	90	99:1
4	*t*$BuNH_2$ (2)	50	90	4:96
5	*t*$BuNH_2$ (2)	25	7	65:35
6	TosMIC (0.5) *t*$BuNH_2$ (2)	50	90	6:94
7	**13c** (0.33) *t*$BuNH_2$ (2)	50	90	2:98
8	Cs_2CO_3 (1)	25	20	2:98

To check whether TosMIC or imine **13c** might influence the *t*$BuNH_2$ induced decomposition of formamide **15**, control experiments were performed, in which in addition to *t*$BuNH_2$ either TosMIC or imine **13c** was present (Table 4, entries 6–7). The decay of formamide **15** turned out to be largely independent from these additives. However, new signals appeared in the ^{1}H NMR spectra (as compared to the reactions without these additives) indicating that from **15** derived decomposition products might have reacted with TosMIC and tricyclic imine **13c**, respectively. Yet, attempts to identify the newly formed species remained unsuccessful due to the high complexity of the ^{1}H NMR spectra and the low amounts of the respective compounds present.

According to Xia et al.,[19] *N*-(tosylmethyl)formamide (**15**) upon treatment with Cs_2CO_3 (in toluene, at 70 °C) undergoes a decomposition reaction yielding *p*-toluenesulfinate **16** and *N*-methyleneformamide (**17**). Thereby the formation of the latter had only become evident from a by-product that had formed via its participation in a Michael addition reaction. Hence, it seemed reasonable to assume that also upon treatment of formamide **15** with *t*$BuNH_2$ (as it is e.g. the case in the reaction listed in Table 4, entry 4) besides *p*-toluenesulfinate (**16**) also *N*-methyleneformamide (**17**) is generated, though also as a rather short-lived intermediate.

A first hint that *N*-methyleneformamide **17** may also have formed under the reaction conditions used for the cycloaddition of imines **13** with TosMIC, i.e. when *t*$BuNH_2$ in $(^2H_4)CH_3OH$ is applied as a base, came from an MS analysis (ESI-HRMS, see SI). A reaction product obtained by treatment of imine **13c** with formamide **15** and *t*$BuNH_2$ (Table 4, entry 7) showed a MS signal attributable to an adduct consisting of imine **13c** and *N*-methyleneformamide **17**.

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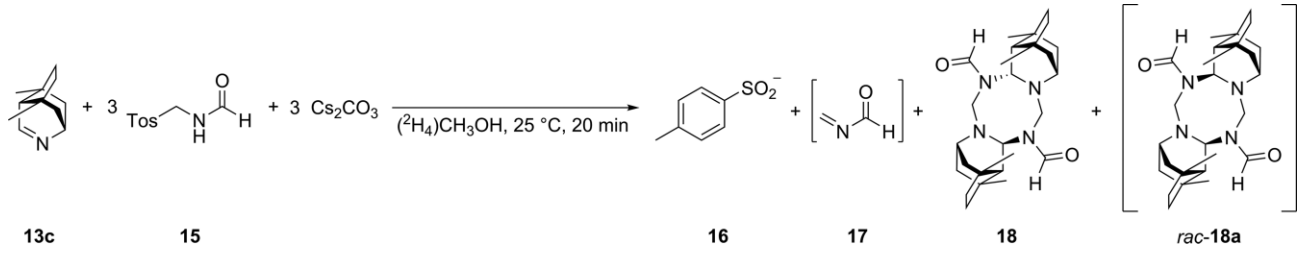
Next, $tBuNH_2$ should be substituted by Cs_2CO_3 in the cycloaddition reactions of imine **13c** with TosMIC. That way, so our hope, consecutive reactions of *N*-methyleneformamide (**17**) might be shifted towards intermediates important for the cycloaddition reaction with TosMIC, as no competing reactions with $tBuNH_2$ as nucleophile could take place.

A control experiment performed in this context, in which *N*-(tosylmethyl)formamide **15** was treated with Cs_2CO_3 in $(^2H_4)CH_3OH$ at 25 °C, revealed that also under these reaction conditions and within 20 min, **15** is almost quantitatively transformed in *p*-toluenesulfinic acid salt **16** (Table 4, entry 8). Though still no evidence for the formation of *N*-methyleneformamide (**17**) was found. However, when the decomposition experiment of *N*-(tosylmethyl)formamide **15** by Cs_2CO_3 in $(^2H_4)CH_3OH$ at 25 °C was performed in the presence of imine **13c** (Scheme 1), a new compound could be detected and isolated. This compound could be identified as the dimer **18**[20] the structure of which comprising a unique 1,3,5,7-tetrazoctane ring could be unequivocally established by X-ray crystallography (Figure 5). As can be seen from the structure of dimer **18**, this compound is the result of the combination of two molecules of the tricyclic imine **13c** with two molecules of *N*-methyleneformamide **17**. Accordingly, upon decomposition of formamide **15** besides *p*-toluenesulfinic acid **16** (compare to Table 4, entry 8), *N*-methyleneformamide **17** must have formed. Still, the existence of *N*-methyleneformamide **17** itself could not be corroborated, which might indicate that it is prone to rapid consecutive reactions under the reaction conditions given.

Interestingly, later on dimer **18** (and what is thought to be its racemic diastereomer *rac*-**18a**) could also be identified in the ^1H NMR spectra of experiments performed before (see supporting information). In particular, these were the control experiment when the decomposition of formamide **15** by $tBuNH_2$ had been studied in presence of imine **13c** (Table 4, entry 7) as well as the experiments in which the reactions time course under the original reaction conditions had been monitored by ^1H NMR (Figure 3, reaction with *N*-(tosylmethyl)formamide **15**; NMR taken after 0.5 h). Obviously also $tBuNH_2$ similar to Cs_2CO_3 appears to lead to the formation of *N*-methyleneformamide **17** upon fragmentation of *N*-(tosylmethyl)formamide (**15**).

Based on the above described results, the following mechanism for the catalytic effect of *N*-(tosylmethyl)formamide **15** on the synthesis of imidazoles seems plausible (Scheme 2). In the first step, *N*-(tosylmethyl)formamide (**15**) is cleaved by *tert*-butylamine to give *p*-toluenesulfinic acid **16** besides *N*-methyleneformamide **17**. By acting as a Michael acceptor methyleneformamide **17** reacts with imine **13c** to the iminium ion **19**, which exists in a reversible equilibrium with the isolated dimer **18** (and *rac*-**18a**) which has been isolated. Then TosMIC adds to this derivative, the thus activated intermediate iminium ion **19** – which possibly exists in an equilibrium with a cyclic oxadiazene species – to give the addition product **20**. Retro-Michael addition releases *N*-methyleneformamide **17** which is now available for a new reaction cycle. The nitrogen centered anion **21** that has been liberated by the retro-Michael addition should then successively react to imidazole **14c**, as it has been proposed by van Leusen et al. for the formation of imidazoles from imines and TosMIC, where a species analogous to **21** has been postulated as primary addition product.[5] According to this rationale, *N*-methyleneformamide **17** acts as a catalyst for the activation of the imine function thus accelerating the imidazole synthesis.



Scheme 1. Cs_2CO_3-induced decomposition of *N*-(tosylmethyl)formamide **15** in presence of imine **13c**.

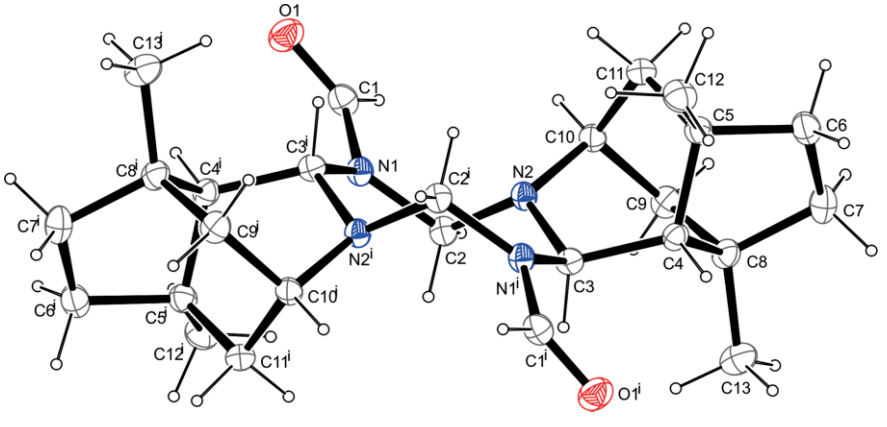


Figure 5. X-ray crystal structure of dimer **18**.[17]

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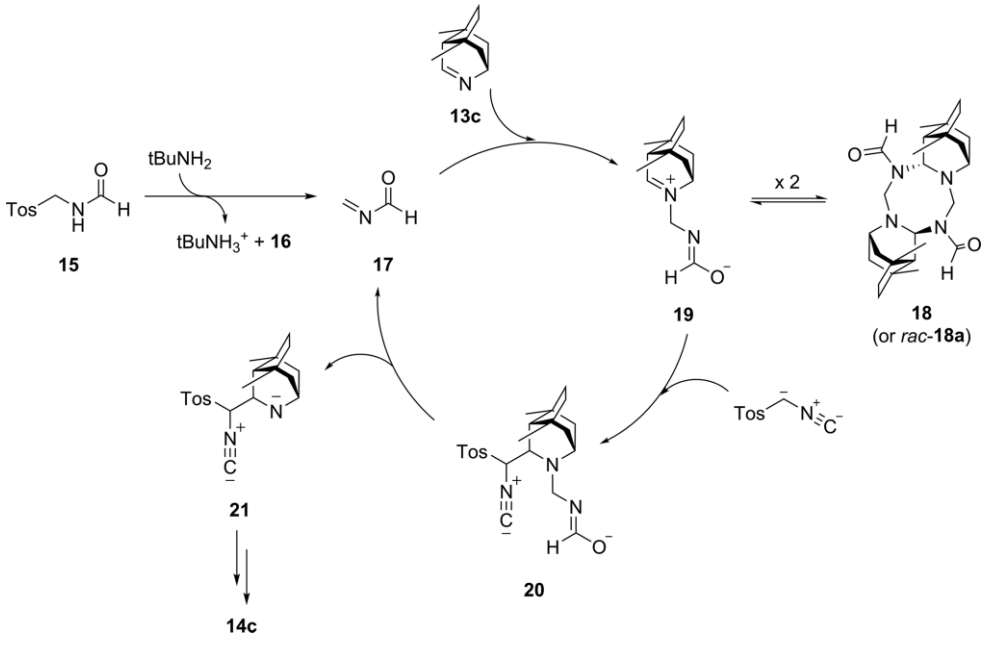
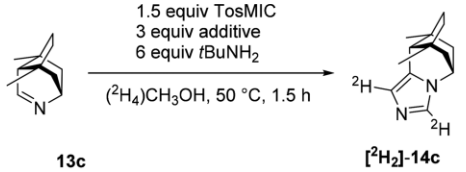


Scheme 2. Rationale for the promoting effect of *N*-(tosylmethyl)formamide (**15**).

Finally, to ensure the promoting effect for the imidazole syntheses arises from *N*-methyleneformamide **17** and not from another decomposition product of *N*-(tosylmethyl)formamide **15**, *p*-toluenesulfinic acid **16** and the most obvious hydrolysation products of *N*-methyleneformamide (**17**), i.e. formaldehyde and formamide, were studied for their effects on the formation of imidazole **14c** under the standard conditions (Table 5, entries 1–3). None of the tested compounds led to a reasonable effect and the starting imine **13c** remained largely unchanged. Interestingly, also the attempt to mimic the function of *N*-methyleneformamide **17** with acrolein in the course of the imidazole synthesis proved to be unsuccessful (Table 5, entry 4). As it seems, acrolein, due to its high reactivity, is prone to extensive side reactions leading to consumption of starting material **13c** and of TosMIC, that way interfering with the formation of the desired imidazole **14c**. This highlights nicely the unique function of *N*-methyleneformamide **17** as a catalyst that activates the imine function in the van Leusen imidazole synthesis.

Table 5. Control experiments to affirm *N*-methyleneformamide (**17**) as catalyst.



13c → **[$^2H_2$]-14c**

Entry	additive	Percentage according to ^{1}H NMR (%)[a]	
		13c	**[$^2H_2$]-14c**
1	**16** (Na^+ salt)	93	4
2	formaldehyde	82	8
3	formamide	88	3
4	acrolein	68	4

[a] The amount of **13c** and **[$^2H_2$]-14c** in the crude reaction mixture was determined using 1H NMR spectroscopy with 1,3,5-trimethoxybenzene as internal standard.

Conclusion

In summary, a small set of imidazoles fused with a cyclic system in 1- and 5-position, starting from saturated aliphatic tricycles incorporating an imine functional group and TosMIC has been synthesized. By serendipity, *N*-(tosylmethyl)formamide was identified as a pre-catalyst for the imidazole synthesis, leading to significantly increased yields and shortened reaction times. Mechanistic studies suggest that by a *tert*-butylamine induced decomposition of *N*-(tosylmethyl)formamide, *N*-methyleneformamide is generated. Being a Michael acceptor, *N*-methyleneformamide (**17**) acts as an organocatalyst of these reactions by reacting with the imines, thus forming the corresponding iminium ions **19**, that are activated for the nucleophilic attack by TosMIC. This appears to be the first time an activation of imines for imidazole synthesis via cycloaddition with TosMIC is described which is likely to possess great potential for the employment of less reactive imines for the construction of 1,5-disubstituted imidazoles via the van Leusen imidazole synthesis. Accordingly, further studies exploring the scope of this method, the use of methyleneformamide (**17**) as an organocatalyst on an expanded set of acyclic and cyclic imines in the van Leusen imidazole synthesis can be expected to become a rewarding endeavor.

Experimental Section

Anhydrous reactions were performed under an argon atmosphere in vacuo-dried glassware. All solvents were distilled prior to use and dry THF, Et_2O, 1,4-dioxane and CH_2Cl_2 were prepared under a nitrogen atmosphere according to standard procedures.[21] All purchased chemicals were used without further purification. TLC was performed with plates from Merck KGaA (silica gel 60 F_{254} or aluminum oxide 60 F_{254} on aluminum sheets, neutral). For purification via flash chromatography (FC) silica gel 60 (40–63 μm mesh size) from Merck KGaA or activated basic alumina Brockmann I (150 μm

mesh size) from Sigma-Aldrich adjusted to Brockmann III activity grade[22] prior to use were employed. Melting points were determined with a BÜCHI 510 melting point apparatus. All melting points are uncorrected. Infrared spectra were recorded with a Perkin Elmer Paragon 1000 and a Jasco FT/IR-410. Solid substances were measured as KBr pellets and oils as film on NaCl. HRMS were obtained with a Finnigan MAT 95 (EI) and a Finnigan LTQ FT (ESI). ^{1}H and ^{13}C NMR spectra were acquired with a Avance III HD Bruker BioSpin (400 or 500 MHz), referenced to the solvent residual peak as internal standard and analyzed with MestReNova (Version 12.0.0–20080; Mestrelab Research S.L.; released 26.09.2017).[23]

2,3,4,5-Tetrahydropyridine **13g**[24] and *N*-(tosylmethyl)formamide **15**[19] were synthesized according to the literature.

Synthesis of 4,4-disubstituted *N*-triisopropylsilyl-1,4-dihydropyridines (general procedure/ GP1)

The 4-substituted pyridine derivatives were dissolved in CH_2Cl_2 (0.86 mL/mmol) and TIPSOTf (1.1 equiv.) was added. Prior to cooling to –30 °C and subsequent dropwise addition of the R_2Mg solution (0.55 equiv.) the solution was stirred at r.t. for 15 min. After the time given the reaction was quenched by addition of water (10 mL/mmol) followed by extraction of the aqueous layer with CH_2Cl_2 (3 × 10 mL/mmol). The combined organic layers were dried with $MgSO_4$ and the solvent was removed under vacuum. Quantitative determination of the dihydropyridines in the crude product was achieved by ^{1}H NMR spectroscopy using 2,4,6-collidine as internal standard. The oxidation of side products was realized by stirring of the crude product under air for the specified period of time, followed by purification by FC.

Synthesis of symmetric tricyclic imines (general procedure / GP2)

The symmetric tricyclic imines were prepared in analogy to the literature.[14a]

TFA (15 equiv.) was added to a solution of the 4,4-disubstituted *N*-triisopropylsilyl-1,4-dihydropyridine (1.0 equiv.) in pentane (10 mL/mmol) in one portion and the resulting mixture was stirred for 15 min at 20 °C. The reaction was quenched by the addition of K_2CO_3 (8 equiv.) and a 1:1 mixture of 2 M $HCl_{aq.}$ and EtOH (40 mL/mmol) was added. The solution was washed with pentane (6 × 20 mL/mmol) and adjusted to pH = 9 with K_2CO_3. The aqueous layer was extracted with CH_2Cl_2 (4 × 20 mL/mmol), the organic layers were combined, dried with Na_2SO_4, and the solvent was removed under vacuum. The crude product was purified by FC.

Synthesis of symmetric tricyclic imidazoles (general procedure / GP3)

To a solution of TosMIC (1.5 equiv.) in methanol (6.7 mL/mmol) the imine (1.0 equiv.) and subsequently *N*-(tosylmethyl)formamide (3 equiv.) was added at 20 °C. The resulting mixture was treated with *t*BuNH$_2$ (6 equiv.), stirred for 1.5 h at 50 °C and then allowed to reach 20 °C. The solvent was removed under vacuum, the residue was dissolved in CH_2Cl_2 (20 mL/mmol) and washed with saturated aqueous NaCl solution (20 mL/mmol) twice. The organic layer was dried with $MgSO_4$, the solvent removed under vacuum and the crude product was purified by FC.

NMR experiments

The ^{1}H NMR experiments to study the formation of the imidazoles (Figure 3; Table 3, Table 5) and to explore the function of *N*-(tosylmethyl)formamide **15** (Table 4; Scheme 1) were carried out on the basis of GP3 in $(^2H_4)CH_3OH$. The concentrations of the reagents used were identical to those described in GP3 and as follows: Imines **13a**–**13h** (0.1 mmol/mL), TosMIC (0.15 mmol/mL), *N*-(tosylmethyl)formamide **15** (0.3 mmol/mL), *t*BuNH$_2$ (0.6 mmol/mL). After the reaction time indicated the crude reaction mixtures were cooled to 20 °C and analyzed by ^{1}H NMR spectroscopy. Quantification of the imines **13a**–**13h** and the imidazoles **14a**–**14h** in the crude reaction mixture was achieved by ^{1}H NMR spectroscopy with 1,3,5-trimethoxybenzene as internal standard. Assignment of the imine and imidazole protons was accomplished by means of reference spectra given in this publication or in literature.

Preparation of bis(organo)magnesium solutions 10c–f

The bis(organo)magnesium solutions employed in the synthesis of the 4,4-disubstituted *N*-triisopropylsilyl-1,4-dihydropyridines were prepared according to our previously published procedure.[14a] The utilized organic halides (3-bromoprop-1-en-2-yl)benzene,[25] 4-bromo-2-methylbut-1-ene,[26] 1-bromo-3-phenylbut-3-ene[27] (synthesis via 3-phenylbut-3-en-1-ol[28]), 5-bromo-2-methylpent-1-ene[29] and (5-chloropent-1-en-2-yl)benzene[30] were synthesized according to literature. 3-Bromo-2-methyl-1-propene was purchased.

Magnesium turnings (1.5 equiv.) were covered with THF (0.13 mL/mmol) and a solution of the organic halide (1.0 equiv.) in THF (0.8 mL/mmol) was added dropwise to keep the reaction mixture boiling mildly. After complete addition stirring was continued for 1 h at 20 °C followed by addition of 1,4-dioxane (1.1 equiv.) and further stirring for 1 h at 20 °C. The resulting suspension was centrifuged (30 min, 3000 *g*), the supernatant was separated and the remaining slurry was suspended in Et_2O to retrieve the same volume as before. Centrifugation was repeated (30 min, 3000 *g*) and the supernatants were combined. The concentrations of the bis(organo)magnesium solutions were determined according to a procedure of Chong et al.[31]

Deviating from this, bis(2-methylallyl)magnesium **10a** and bis(2-phenylallyl)magnesium **10b** were synthesized as reported below.

Bis(2-methylallyl)magnesium 10a

3-Bromo-2-methylpropene (1.0 equiv., 2 M in THF) was added to magnesium powder (1.2 equiv., 3 M in THF) over a period of 2 h at 0 °C. The reaction mixture was kept at 0 °C for 2 h, subsequently stirred at 20 °C for 12 h followed by addition of 1,4-dioxane (1.1 equiv.) and further stirring for 1 h at 20 °C. The resulting suspension was centrifuged (30 min, 3000 *g*), the supernatant was separated and the remaining slurry was suspended in Et_2O to retrieve the same volume as before. Centrifugation was repeated (30 min, 3000 *g*) and the supernatants were combined.

Bis(2-phenylallyl)magnesium 10b

To a suspension of Rieke magnesium (preparation in analogy to literature;[32] 0.57 M in THF; 1 equiv.) was added (3-bromoprop-1-en-2-yl)benzene (0.40 equiv.) dropwise. The mixture was kept at 20 °C for 1 h followed by addition of 1,4-dioxane (0.55 equiv.) and further stirring for 1 h at 20 °C. The resulting suspension was centrifuged (30 min, 3000 *g*) and the supernatant was separated.

4-Methyl-4-(2-methylallyl)-1-triisopropylsilyl-1,4-dihydropyridine 11a

Synthesis according to GP1 from 4-picoline (305 mg, 3.27 mmol, 318 µL), TIPSOTf (1.10 g, 3.59 mmol, 0.97 mL) and bis(2-methylallyl)magnesium **10a** (0.09 m in THF/Et_2O 1:1, 1.80 mmol, 20.0 mL). The reaction was stopped after 16 h. Quantitative determination indicated 590 mg (59 %) of dihydropyridine **11a** followed by stirring under air for 2 d. Purification by FC (Al_2O_3-basic, activity III, pentane) afforded **11a**.

Colorless oil (552 mg, 55 %); R_f = 0.95 (Al_2O_3; pentane); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.93 (d, J = 8.2 Hz, 2 H, 2 × NC*H*CH),

4.76 (dq, J = 2.9/1.5 Hz, 1 H, $CCH_2CCH_2^b$), 4.66–4.61 (m, 1 H, $CCH_2CCH_2^a$), 4.29 (d, J = 8.2 Hz, 2 H, 2 × NCHC*H*), 1.97 (d, J = 0.7 Hz, 2 H, CCH_2C), 1.77 (dd, J = 1.4/0.8 Hz, 3 H, CH_2CCH_3), 1.30–1.18 (m, 3 H, 3 × C*H*$(CH_3)_2$), 1.07 (d, J = 7.2 Hz, 18H, 3 × CH$(CH_3)_2$), 1.05 (s, 3 H, CHCC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.6 ($CHCCH_2C$), 127.5 (NCH), 113.1 (CCH_2CCH_2), 108.6 (NCH*C*H), 53.9 ($CHCCH_2$), 34.4 (CH*C*), 34.2 ($CHCCH_3$), 25.0 ($CHCCH_2CCH_3$), 18.0 (3 × CH$(CH_3)_2$), 11.6 (3 × *C*H$(CH_3)_2$); IR (film): $\tilde{\nu}$ = 3072, 3043, 2945, 2868, 1670, 1601, 1464, 1369, 1288, 1088, 1065, 1016, 970, 883, 733, 689, 660 cm^{-1}; HRMS (EI): *m/z* $[M]^+$ calcd. for $C_{19}H_{35}NSi$: 305.2533, found 305.2583.

4-Phenyl-4-(2-phenylallyl)-1-triisopropylsilyl-1,4-dihydropyridine 11b

Synthesis according to GP1 from 4-phenylpyridine (1.38 g, 8.89 mmol), TIPSOTf (3.00 g, 9.78 mmol, 2.6 mL) and bis(2-phenylallyl)magnesium **10b** (0.10 m in THF, 4.89 mmol, 50.0 mL). The reaction was stopped after 16 h. Quantitative determination indicated 996 mg (26 %) of dihydropyridine **11b** followed by stirring under air for 2 d. Purification by FC (Al_2O_3-basic, activity III, pentane) afforded **11b**.

Orange solid (723 mg, 19 %); R_f = 0.41 (Al_2O_3; pentane); m.p. 59 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.38 (m, 2 H, 2 × CHCCC*H*CHCH), 7.35–7.28 (m, 4 H, 2 × CHCCCHC*H*CH, 2 × C_{alkene}CCH), 7.25–7.16 (m, 3 H, 2 × C_{alkene}CCHC*H*, C_{alkene}CCHCHC*H*), 7.13 (tt, J = 7.3/1.2 Hz, 1 H, CHCCCHCHC*H*), 5.89 (d, J = 8.2 Hz, 2 H, 2 × NCH), 5.28 (d, J = 1.9 Hz, 1 H, $CCH_2CCH_2^b$), 5.03–4.98 (m, 1 H, $CCH_2CCH_2^a$), 4.35 (d, J = 8.3 Hz, 2 H, 2 × NCHC*H*), 2.99 (s, 2 H, CCH_2C), 1.27–1.13 (m, 3 H, 3 × C*H*$(CH_3)_2$), 1.05 (d, J = 7.2 Hz, 18H, 3 × CH$(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.5 (CHCCCHCHCH), 147.0 (C_{alkene}CCH), 144.0 (C_{alkene}CCH), 128.2 (CHCCCH*C*HCH), 127.9 (C_{alkene}CCH*C*H), 127.7 (NCH), 127.1 (C_{alkene}CCH), 126.7 (C_{alkene}CCHCH*C*H), 126.6 (CHCC*C*HCHCH), 125.3 (CHCCCHCH*C*H), 116.7 (CCH_2CCH_2), 106.7 (NCH*C*H), 49.0 (CCH_2CCH_2), 42.8 (CCH_2CCH_2), 18.0 (3 × CH$(CH_3)_2$), 11.5 (3 × *C*H$(CH_3)_2$); IR (film): $\tilde{\nu}$ = 3643, 3325, 3271, 3055, 3022, 2927, 2864, 1946, 1871, 1803, 1599, 1495, 1444, 1032, 758, 700 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $C_{29}H_{40}NSi$ 430.2925, found 430.2926.

4-Methyl-4-(3-methylbut-3-en-1-yl)-1-triisopropylsilyl-1,4-dihydropyridine 11c

Synthesis according to GP1 from 4-picoline (1.14 g, 12.3 mmol, 1.2 mL), TIPSOTf (4.14 g, 13.5 mmol, 3.6 mL) and bis(3-methylbut-3-en-1-yl)magnesium **10c** (0.25 m in THF/Et_2O 1:1, 6.77 mmol, 27.0 mL). The reaction was stopped after 16 h. Quantitative determination indicated 1.57 g (40 %) of dihydropyridine **11c**. Purification by FC (Al_2O_3-basic, activity III, pentane) afforded **11c**.

Colorless solid (1.45 g, 37 %); R_f = 0.97 (Al_2O_3; pentane); m.p. 33 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.03–5.96 (m, 2 H, 2 × NCH), 4.65 (q, J = 1.1 Hz, 2 H, $CH_2CH_2CCH_2$), 4.21–4.15 (m, 2 H, 2 × NCHC*H*), 2.04–1.94 (m, 2 H, $CHCCH_2CH_2$), 1.72 (t, J = 1.0 Hz, 3 H, $C_{alkene}CH_3$), 1.29–1.18 (m, 5 H, 3 × C*H*$(CH_3)_2$, $CHCCH_2$), 1.08 (d, J = 7.2 Hz, 18H, 3 × CH$(CH_3)_2$), 1.03 (s, 3 H, $CHCCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.8 ($CH_2CH_2CCH_3$), 128.3 (NCH), 108.6 ($CH_2CH_2CCH_2$), 107.8 (NCH*C*H), 44.0 ($CHCCH_2$), 34.9 ($CH_2CH_2CCH_2$), 33.8 ($CHCCH_3$, CH*C*), 23.2 ($CHC(CH_2)_2CCH_3$), 18.0 (3 × CH$(CH_3)_2$), 11.6 (3 × *C*H$(CH_3)_2$); IR (KBr): $\tilde{\nu}$ = 3091, 3041, 2945, 2866, 1668, 1647, 1599, 1464, 1377, 1286, 1109, 1078, 1045, 1016, 972, 881, 746, 733, 689, 663, 619, 513 cm^{-1}; HRMS (EI): *m/z* $[M]^+$ calcd. for $C_{20}H_{37}NSi$ 319.2690, found 319.2692.

4-Phenyl-4-(3-phenylbut-3-en-1-yl)-1-triisopropylsilyl-1,4-dihydropyridine 11d

Synthesis according to GP1 from 4-phenylpyridine (534 mg, 3.44 mmol), TIPSOTf (1.16 g, 3.78 mmol, 1.05 mL) and bis(3-phenylbut-3-en-1-yl)magnesium **10d** (0.20 m in THF/Et_2O 1:1, 1.89 mmol, 9.6 mL). The reaction was stopped after 16 h. Quantitative determination indicated 1.01 g (66 %) of dihydropyridine **11d** followed by stirring under air for 4 d. Purification by FC (Al_2O_3-basic, activity III, pentane) afforded **11d**.

Yellow solid (788 mg, 52 %); R_f = 0.52 (Al_2O_3; pentane); m.p. 54 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.46–7.42 (m, 2 H, 2 × C_{alkene}CCH), 7.41–7.38 (m, 2 H, 2 × CHCCC*H*CHCH), 7.34–7.29 (m, 4 H, 4 × CCCHC*H*CH), 7.27–7.23 (m, 1 H, C_{alkene}CCHCHC*H*), 7.14 (tt, J = 7.3/1.3 Hz, 1 H, CHCCCHCHC*H*), 6.19 (d, J = 8.3 Hz, 2 H, 2 × NCH), 5.31 (d, J = 1.4 Hz, 1 H, $CH_2CH_2CCH_2^b$), 5.11 (d, J = 1.4 Hz, 1 H, $CH_2CH_2CCH_2^a$), 4.44 (d, J = 8.3 Hz, 2 H, 2 × NCHC*H*), 2.66–2.57 (m, 2 H, $CH_2CH_2CCH_2$), 1.86–1.78 (m, 2 H, $CH_2CH_2CCH_2$), 1.30 (sep, J = 7.5 Hz, 3 H, 3 × C*H*$(CH_3)_2$), 1.12 (d, J = 7.4 Hz, 18H, 3 × CH$(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 152.4 (CHCC*C*HCHCH), 149.5 (C_{alkene}CCH), 141.6 (C_{alkene}CCH), 128.5 (NCH), 128.3 (CCCHC*H*CH)*, 128.2 (CCCH*C*HCH)*, 127.3 (C_{alkene}CCHCHC*H*), 126.8 (CHCCCHCHCH), 126.2 (C_{alkene}C*C*H), 125.4 (CHCCCHCH*C*H), 111.6 ($CH_2CH_2CCH_2$), 106.2 (NCH*C*H), 41.9 ($CCH_2CH_2CCH_2$), 41.8 ($CH_2CH_2CCH_2$), 32.4 ($CH_2CH_2CCH_2$), 18.1 (3 × CH$(CH_3)_2$), 11.6 (3 × *C*H$(CH_3)_2$) Signals indicated by * cannot be assigned unambiguously and are interchangeable; IR (KBr): $\tilde{\nu}$ = 3082, 3051, 2949, 2866, 1664, 1597, 1464, 1444, 1288, 1076, 1047, 976, 881, 777, 740, 692, 665, 632, 523, 498 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $C_{30}H_{42}NSi$ 444.3081, found 444.3088.

4-Methyl-4-(4-methylpent-4-en-1-yl)-1-triisopropylsilyl-1,4-dihydropyridine 11e

Synthesis according to GP1 from 4-picoline (521 mg, 5.59 mmol, 0.54 mL), TIPSOTf (1.88 g, 6.15 mmol, 1.7 mL) and bis(4-methylpent-4-en-1-yl)magnesium **10e** (0.21 m in THF/Et_2O 1:1, 3.07 mmol, 15.0 mL). The reaction was stopped after 18 h. Quantitative determination indicated 907 mg (49 %) of dihydropyridine **11e**. Purification by FC (Al_2O_3-basic, activity III, pentane) afforded **11e**.

Colorless oil (935 mg, 50 %); R_f = 0.93 (Al_2O_3; pentane); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.00–5.95 (m, 2 H, 2 × NCH), 4.68–4.61 (m, 2 H, $CH_2CH_2CCH_2$), 4.20–4.13 (m, 2 H, 2 × NCHC*H*), 1.99 (t, J = 7.6 Hz, 2 H, $CH_2CH_2CCH_2$), 1.69 (s, 3 H, $C_{alkene}CH_3$), 1.48–1.39 (m, 2 H, $CH_2CH_2CH_2$), 1.28–1.18 (m, 3 H, 3 × C*H*$(CH_3)_2$), 1.14–1.03 (m, 2 H, $CHCCH_2$), 1.08 (d, J = 7.4 Hz, 18 H, 3 × CH$(CH_3)_2$), 1.00 (s, 3 H, $CHCCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.8 ($CH_2CH_2CCH_3$), 128.0 (NCH), 109.5 ($CH_2CH_2CCH_2$), 108.1 (NCH*C*H), 45.6 ($CHCCH_2$), 38.5 ($CH_2CH_2CCH_2$), 33.8 ($CHCCH_3$, CH*C*), 24.3 ($CH_2CH_2CH_2$), 22.6 ($C_{alkene}CH_3$), 18.0 (3 × CH$(CH_3)_2$), 11.6 (3 × *C*H$(CH_3)_2$); IR (film): $\tilde{\nu}$ = 3072, 3039, 2945, 2895, 2868, 1668, 1606, 1462, 1383, 1286, 1076, 1016, 970, 883, 731, 688, 665 cm^{-1}; HRMS (EI): *m/z* $[M - CH_3]^+$ calcd. for $C_{20}H_{36}NSi$ 318.2612, found 318.2603.

4-Phenyl-4-(4-phenylpent-4-en-1-yl)-1-triisopropylsilyl-1,4-dihydropyridine 11f

Synthesis according to GP1 from 4-phenylpyridine (818 mg, 5.27 mmol), TIPSOTf (1.78 g, 5.80 mmol, 1.56 mL) and bis(3-phenylbut-3-en-1-yl)magnesium **10f** (0.19 m in THF/Et_2O 1:1, 2.90 mmol, 15.5 mL). The reaction was stopped after 48 h. Quantitative determination was omitted followed by stirring under air for 2 d. Purification by FC (Al_2O_3-basic, activity III, pentane) afforded **11f**.

Yellow solid (1.31 g, 55 %); R_f = 0.63 (Al_2O_3; pentane); m.p. 61 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.41–7.35 (m, 4 H, 2 × CHCCC*H*CHCH, 2 × C_{alkene}CCH) 7.33–7.28 (m, 4 H, 4 × CCCHC*H*CH), 7.26–7.20 (m, 1 H, C_{alkene}CCHCHC*H*), 7.12 (tt, J = 7.3/1.3 Hz, 1 H, CHCCCHCHC*H*), 6.09–6.02 (m, 2 H, 2 × NCH), 5.25 (d, J = 1.5 Hz, 1 H, $CH_2CH_2CCH_2^b$), 5.06 (dt, J = 1.4/1.3 Hz, 1 H, $CH_2CH_2CCH_2^a$), 4.35–4.30 (m, 2 H, 2 × NCHC*H*), 2.55 (t, J = 7.4 Hz, 2 H, $CH_2CCH_2CH_2$), 1.73–1.65 (m,

2 H, $CH_2CCH_2CH_2CH_2$), 1.61–1.54 (m, 2 H, $CH_2CH_2CH_2$), 1.28–1.18 (m, 3 H, $3 \times CH(CH_3)_2$), 1.06 (d, J = 7.4 Hz, 18 H, $3 \times CH(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 152.7 (CHCCCHCHCH), 149.1 ($C_{alkene}C$), 141.9 ($C_{alkene}C$), 128.3 (CCCHCHCH)*, 128.1 (CCCHCHCH)*, 128.1 (NCH), 127.3 ($C_{alkene}CCHCHCH$), 126.8 (CHCCCHCHCH), 126.3 ($C_{alkene}CCH$), 125.3 (CHCCCHCHCH), 112.0 ($CH_2CH_2CCH_2$), 106.5 (NCHCH), 41.8 (NCHCHC), 35.9 ($CH_2CH_2CCH_2$), 24.8 ($CH_2CH_2CH_2$), 18.0 ($3 \times CH(CH_3)_2$), 11.5 ($3 \times CH(CH_3)_2$) Signals indicated by * cannot be assigned unambiguously and are interchangeable; IR (KBr): $\tilde{\nu}$ = 3049, 2949, 2864, 1666, 1626, 1601, 1491, 1460, 1387, 1288, 1078, 1057, 976, 883, 766, 744, 694, 665, 631 cm^{-1}; HRMS (EI): m/z $[M]^+$ calcd. for $C_{31}H_{43}NSi$ 457.3160, found 457.3170.

1,7-Dimethyl-4-azatricyclo[3.3.1.0^{2,7}]non-3-ene 13a

Synthesis according to GP2 from dihydropyridine **11a** (622 mg, 2.04 mmol) and TFA (3.48 g, 30.5 mmol, 2.34 mL) in pentane (20 mL). Purification by FC (Al_2O_3-basic, activity III, pentane/CH_2Cl_2/MeOH 88.5:10:1.5) afforded imine **13a**.

Yellow oil (230 mg, 76 %); R_f = 0.35 (Al_2O_3; pentane/CH_2Cl_2/MeOH 88.5:10:1.5); ^1H NMR (400 MHz, $CDCl_3$): δ = 8.08 (d, J = 3.8 Hz, 1 H, NCHCH), 4.46 (tt, J = 3.1/1.9 Hz, 1 H, $NCH(CH_2)_2$), 2.48 (d, J = 3.7 Hz, 1 H, NCHCH), 1.71 (dt, J = 9.0/2.3 Hz, 1 H, CCH_2^bC), 1.58 (dd, J = 12.6/2.1 Hz, 2 H, $2 \times NCHCH_2^b$), 1.29 (d, J = 9.0 Hz, 1 H, CCH_2^aC), 0.94 (s, 6 H, $2 \times CH_3$), 0.82–0.75 (m, 2 H, $2 \times NCHCH_2^a$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.1 (NCHCH), 56.5 ($NCH(CH_2)_2$), 50.9 (NCHCH), 49.3 (CCH_2C), 37.8 ($NCH(CH_2)_2$), 34.9 (CCH_2), 26.6 (CH_3); IR (film): $\tilde{\nu}$ = 3388, 2997, 2947, 2920, 2860, 1672, 1610, 1450, 1375, 1342, 1282, 1151, 1016, 719 cm^{-1}; HRMS (EI): m/z $[M]^+$ calcd. for $C_{10}H_{15}N$ 149.1199, found 149.1203.

1,7-Diphenyl-4-azatricyclo[3.3.1.0^{2,7}]non-3-ene 13b

Synthesis according to GP2 from dihydropyridine **11b** (700 mg, 1.63 mmol) and TFA (2.81 g, 24.4 mmol, 1.89 mL) in pentane (16 mL). Purification by FC (Al_2O_3-basic, activity III, pentane/CH_2Cl_2/MeOH 87:10:3) afforded imine **13b**.

Colorless solid (417 mg, 94 %); R_f = 0.34 (Al_2O_3; pentane/CH_2Cl_2/MeOH 87:10:3); m.p. 95 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 8.57 (d, J = 3.7 Hz, 1 H, NCHCH), 7.33–7.26 (m, 4 H, CCCHCHCH), 7.21–7.15 (m, 2 H, CCCHCHCH), 7.08–7.01 (m, 4 H, CCCHCHCH), 4.76–4.69 (m, 1 H, $NCH(CH_2)_2$), 3.34 (d, J = 3.6 Hz, 1 H, NCHCH), 2.78 (dt, J = 9.0/2.2 Hz, 1 H, CCH_2^bC), 2.15–2.06 (m, 3 H, $2 \times NCHCH_2^b$, CCH_2^aC), 1.35 (d, J = 13.5 Hz, 2 H, $2 \times NCHCH_2^a$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.7 (NCHCH), 147.1 ($CCCH_2$), 128.6 (CCHCHCH), 126.3 (CCHCHCH), 125.1 (CCHCHCH), 56.6 ($NCH(CH_2)_2$), 48.9 (NCHCH), 45.6 (CCH_2C), 42.4 (CH_2C), 40.2 ($NCH(CH_2)_2$); IR (KBr): $\tilde{\nu}$ = 3051, 3020, 2960, 2926, 2846, 1610, 1599, 1495, 1444, 1340, 1205, 1070, 752, 700, 540, 482 cm^{-1}; HRMS (EI): m/z $[M]^+$ calcd. for $C_{20}H_{19}N$ 273.1512, found 273.1514.

3,6-Dimethyl-9-azatricyclo[4.3.1.0^{3,7}]dec-8-ene 13c

Synthesis according to GP2 from dihydropyridine **11c** (2.32 g, 7.26 mmol) and TFA (20.7 g, 109 mmol, 13.9 mL) in pentane (72 mL). Purification by FC (Al_2O_3-basic, activity III, pentane/CH_2Cl_2/MeOH 88:10:2) afforded imine **13c**.

Yellow oil (735 mg (62 %); R_f = 0.58 (Al_2O_3; pentane/CH_2Cl_2/MeOH 88:10:2); ^1H NMR (500 MHz, $CDCl_3$): δ = 8.20 (d, J = 4.1 Hz, 1 H, NCHCH), 4.14 (p, J = 2.6 Hz, 1 H, $NCH(CH_2)_2$), 2.11 (d, J = 4.1 Hz, 1 H, NCHCH), 1.67–1.60 (m, 2 H, $2 \times CCH_2^bCH_2$), 1.57–1.50 (m, 2 H, $2 \times CCH_2^aCH_2$), 1.43–1.37 (m, 2 H, $2 \times NCHCH_2^b$), 1.21–1.15 (m, 2 H, $2 \times NCHCH_2^a$), 0.94 (s, 6 H, $2 \times CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.2 (NCHCH), 56.9 (NCHCH), 55.2 ($NCH(CH_2)_2$), 42.7 ($NCH(CH_2)_2$), 42.2 (CH_2C), 39.8 (CH_2CH_2), 28.7 (CH_3); IR (film): $\tilde{\nu}$ = 2997, 2947, 2866, 2360, 1616, 1454, 1375, 1340, 1304, 1172, 1097, 997 cm^{-1}; HRMS (EI): m/z $[M]^+$ calcd. for $C_{11}H_{17}N$ 163.1356, found 163.1365.

3,6-Diphenyl-9-azatricyclo[4.3.1.0^{3,7}]dec-8-ene 13d

Synthesis according to GP2 from dihydropyridine **11d** (3.11 g, 7.00 mmol) and TFA (12.0 g, 105 mmol, 8.0 mL) in pentane (70 mL). Purification by FC (Al_2O_3-basic, activity III, pentane/CH_2Cl_2/MeOH 88.5:10:1.5) afforded imine **13d**.

Beige solid (1.92 g, 95 %); R_f = 0.42 (Al_2O_3; pentane/CH_2Cl_2/MeOH 88.5:10:1.5); m.p. 140 °C; ^1H NMR (400 MHz, CD_2Cl_2): δ = 8.62 (d, J = 3.8 Hz, 1 H, NCHCH), 7.36–7.25 (m, 8 H, CCHCHCH, CCHCHCH), 7.22–7.16 (m, 2 H, CCHCHCH), 4.30 (p, J = 2.7 Hz, 1 H, $NCH(CH_2)_2$), 3.50 (d, J = 3.8 Hz, 1 H, NCHCH), 2.25–2.12 (m, 4 H, CH_2CH_2), 2.08–2.00 (m, 2 H, $2 \times NCHCH_2^b$), 1.80–1.72 (m, 2 H, $2 \times NCHCH_2^a$); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 169.9 (NCHCH), 150.6 ($CCCH_2$), 129.0 (CCHCHCH), 126.3 (CCHCHCH), 126.2 (CCHCHCH), 55.4 ($NCH(CH_2)_2$), 50.7 (CH_2C), 50.1 (NCHCH), 45.2 ($NCH(CH_2)_2$), 40.9 (CH_2CH_2); IR (KBr): $\tilde{\nu}$ = 3080, 3053, 2999, 2943, 2929, 2864, 1618, 1601, 1579, 1493, 1446, 1338, 1302, 1080, 906, 764, 712, 700, 546 cm^{-1}; HRMS (EI): m/z $[M]^+$ calcd. for $C_{21}H_{21}N$ 287.1669, found 287.1676.

3,7-Dimethyl-10-azatricyclo[5.3.1.0^{3,8}]undec-9-ene 13e

Synthesis according to GP2 from dihydropyridine **11e** (850 mg, 2.55 mmol) and TFA (4.40 g, 38.2 mmol, 2.95 mL) in pentane (26 mL). Purification by FC (Al_2O_3-basic, activity III, pentane/CH_2Cl_2/MeOH 88:10:2) afforded imine **13e**.

Yellow oil (353 mg, 78 %); R_f = 0.30 (Al_2O_3; pentane/CH_2Cl_2/MeOH 88:10:2); ^1H NMR (400 MHz, $CDCl_3$): δ = 8.38 (d, J = 4.2 Hz, 1 H, NCHCH), 4.22–4.16 (m, 1 H, $NCH(CH_2)_2$), 1.74 (d, J = 4.2 Hz, 1 H, NCHCH), 1.54–1.44 (m, 2 H, $CH_2CH_2CH_2$), 1.40–1.30 (m, 4 H, $2 \times NCHCH_2^b$, $2 \times CCH_2^bCH_2$), 1.12–1.00 (m, 4 H, $2 \times NCHCH_2^a$, $2 \times CCH_2^aCH_2$), 0.81 (s, 6 H, $2 \times CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.5 (NCHCH), 55.9 ($NCH(CH_2)_2$), 53.1 (NCHCH), 37.7 ($CH_2CH_2CH_2$), 35.7 ($NCH(CH_2)_2$), 32.9 (CH_2C), 32.1 (CH_3), 19.1 ($CH_2CH_2CH_2$); IR (film): $\tilde{\nu}$ = 3049, 2997, 2924, 2864, 2843, 1614, 1456, 1375, 1336, 1309, 1178, 1076, 1014, 984, 895, 708 cm^{-1}; HRMS (ESI): m/z $[M + H]^+$ calcd. for $C_{12}H_{20}N$ 178.1590, found 178.1590.

3,7-Diphenyl-10-azatricyclo[5.3.1.0^{3,8}]undec-9-ene 13f

Synthesis according to GP2 from dihydropyridine **11f** (600 mg, 1.31 mmol) and TFA (2.26 g, 19.7 mmol, 1.5 mL) in pentane (13 mL). Purification by FC (Al_2O_3-basic, activity III, pentane/CH_2Cl_2/MeOH 88:10:2) afforded imine **13f**.

Colorless solid (293 mg, 74 %); R_f = 0.20 (Al_2O_3; pentane/CH_2Cl_2/MeOH 88:10:2); m.p. 193 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.40 (d, J = 3.7 Hz, 1 H, NCHCH), 7.40–7.34 (m, 4 H, CCHCHCH), 7.34–7.27 (m, 4 H, CCHCHCH), 7.16 (tt, J = 7.2/1.4 Hz, 2 H, CCHCHCH), 4.41–4.33 (m, 1 H, $NCH(CH_2)_2$), 3.47 (d, J = 3.7 Hz, 1 H, NCHCH), 2.11–1.98 (m, 4 H, $NCH(CH_2)_2$), 1.90 (qt, J = 13.6/3.7 Hz, 1 H, $CH_2CH_2^bCH_2$), 1.84–1.69 (m, 3 H, $2 \times CCH_2^bCH_2$, $CH_2CH_2^aCH_2$), 1.49 (dt, J = 13.3/4.0 Hz, 2 H, $2 \times CCH_2^aCH_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.8 (NCHCH), 151.8 ($CCCH_2$), 128.5 (CCHCHCH), 126.3 (CCHCHCH), 125.9 (CCHCHCH), 54.6 ($NCH(CH_2)_2$), 45.1 (NCHCH), 41.4 (CCH_2), 40.1 ($CH_2CH_2CH_2$), 36.8 ($NCH(CH_2)_2$), 19.9 ($CH_2CH_2CH_2$); IR (KBr): $\tilde{\nu}$ = 3055, 3022, 2939, 2918, 2846, 1610, 1495, 1442, 1354, 1286, 1082, 1026, 901, 756, 702, 548 cm^{-1}; HRMS (ESI): m/z $[M + H]^+$ calcd. for $C_{22}H_{24}N$ 302.1903, found 302.1902.

3,5-Dimethyl-7(1,5)imidazolatricyclo[3.2.1.0^{3,6}]octaphan 14a

Synthesis according to GP3 from imine **13a** (37 mg, 0.25 mmol), TosMIC (72 mg, 0.37 mmol), *N*-(tosylmethyl)formamide (157 mg, 0.736 mmol) and $tBuNH_2$ (109 mg, 1.47 mmol, 0.16 mL) in methanol (2.5 mL). Purification by FC (SiO_2, EtOAc/MeOH/NEt_3 93:5:2) afforded imidazole **14a**.

Colorless oil (29 mg, 63 %); R_f = 0.23 (SiO_2, EtOAc/MeOH/NEt_3 93:5:2); ^1H NMR (500 MHz, $CDCl_3$): δ = 7.48 (s, 1 H, NCHN), 6.80 (s,

1 H, CCHN), 4.62 (br s, 1 H, NC*H*(CH_2)$_2$), 2.75 (s, 1 H, CCHC), 1.90 (dd, *J* = 12.8/2.7 Hz, 2 H, NCH(CH_2^b)$_2$), 1.74 (dt, *J* = 9.3/2.1 Hz, 1 H, CCH_2^bC), 1.46 (d, *J* = 9.3 Hz, 1 H, CCH_2^aC), 1.29–1.21 (m, 2 H, NCH(CH_2^a)$_2$), 0.97 (s, 6 H, 2 × CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 130.6 (NCHN), 129.9 (*C*CHN), 122.6 (*C*CHN), 50.7 (N*C*H(CH_2)$_2$), 49.1 (CCH_2C), 45.1 (*C*CHC), 41.9 (NCH(CH_2)$_2$), 40.0 (CCH_3), 25.3 (CH_3); IR (film): $\tilde{\nu}$ = 3374, 2944, 2860, 1671, 1479, 1455, 1397, 1374, 1333, 1275, 1234, 1193, 1109, 1091, 953, 936, 799, 658 cm^{-1}; HRMS (ESI): *m/z* [M + H]$^+$ calcd. for $C_{12}H_{17}N_2$ 189.1386, found 189.1385.

3,5-Diphenyl-7(1,5)imidazolatricyclo[3.2.1.0^{3,6}]octaphan 14b

Synthesis according to GP3 from imine **13b** (200 mg, 0.732 mmol), TosMIC (214 mg, 1.10 mmol), *N*-(tosylmethyl)formamide (468 mg, 2.19 mmol) and *t*BuNH_2 (324 mg, 4.39 mmol, 0.46 mL) in methanol (7.5 mL). Purification by FC (SiO_2, EtOAc/MeOH/NEt_3 93:5:2) afforded imidazole **14b**.

Colorless solid (134 mg, 59 %); R_f = 0.31 (SiO_2, EtOAc/MeOH/NEt_3 93:5:2); m.p. 162 °C; ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.63 (s, 1 H, NCHN), 7.29–7.22 (m, 4 H, CCHC*H*), 7.16 (tt, *J* = 7.4/1.3 Hz, 2 H, CCHCHC*H*), 7.11–7.05 (m, 4 H, CC*H*CH), 7.00 (s, 1 H, CCHN), 4.90 (br s, 1 H, NC*H*(CH_2)$_2$), 3.74 (s, 1 H, CCHC), 2.76 (dt, *J* = 9.2/2.2 Hz, 1 H, CCH_2^bC), 2.41 (dd, *J* = 13.2/3.2 Hz, 2 H, NCH(CH_2^b)$_2$), 2.28 (d, *J* = 9.2 Hz, 1 H, CCH_2^aC), 1.81–1.73 (m, 2 H, NCH(CH_2^a)$_2$); ^{13}C NMR (125 MHz, CD_2Cl_2): δ = 147.8 (*C*CHCH), 131.7 (NCHN), 130.5 (*C*CHN), 128.9 (CCH*C*H), 126.8 (CCHCH*C*H), 125.5 (*C*CHCH), 122.5 (*C*CHN), 51.3 (N*C*H(CH_2)$_2$), 46.6 (*C*CH_2), 45.5 (CCH_2C), 45.1 (*C*CHC), 44.6 (NCH(CH_2)$_2$); IR (KBr): $\tilde{\nu}$ = 3103, 3024, 2937, 1676, 1603, 1493, 1479, 1444, 1398, 1327, 1288, 1230, 1209, 1092, 943, 756, 698, 660, 528 cm^{-1}; HRMS (ESI): *m/z* [M + H]$^+$ calcd. for $C_{22}H_{21}N_2$ 313.1699, found 313.1697.

3,6-Dimethyl-8(1,5)imidazolatricyclo[4.2.1.0^{3,7}]nonaphan 14c

Synthesis according to GP3 from imine **13c** (200 mg, 1.23 mmol), TosMIC (359 mg, 1.84 mmol), *N*-(tosylmethyl)formamide (784 mg, 3.68 mmol) and *t*BuNH_2 (543 mg, 7.35 mmol, 0.78 mL) in methanol (12.5 mL). Purification by FC (SiO_2, EtOAc/MeOH/NEt_3 93:5:2) afforded imidazole **14c**

Colorless solid (226 mg, 91 %); R_f = 0.28 (SiO_2, EtOAc/MeOH/NEt_3 93:5:2); m.p. 99 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (s, 1 H, NCHN), 6.89 (s, 1 H, CCHN), 4.35 (p, *J* = 2.7 Hz, 1 H, NC*H*(CH_2)$_2$), 2.37 (s, 1 H, CCHC), 1.74–1.63 (m, 6 H, NCH(CH_2^b)$_2$, CCH_2CH_2C), 1.46–1.38 (m, 2 H, NCH(CH_2^a)$_2$), 0.88 (s, 6 H, 2 × CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 130.3 (NCHN), 129.9 (*C*CHN), 124.4 (*C*CHN), 51.6 (*C*CHC), 49.4 (N*C*H(CH_2)$_2$), 46.1 (NCH(CH_2)$_2$), 43.6 (CCH_3), 39.5 (CCH_2CH_2C), 27.3 (CH_3); IR (KBr): $\tilde{\nu}$ = 3086, 2950, 2922, 2867, 1693, 1484, 1469, 1448, 1394, 1236, 1203, 1085, 942, 850, 803, 661 cm^{-1}; HRMS (ESI): *m/z* [M + H]$^+$ calcd. for $C_{13}H_{19}N_2$ 203.1543, found 203.1541.

3,6-Diphenyl-8(1,5)imidazolatricyclo[4.2.1.0^{3,7}]nonaphan 14d

Synthesis according to GP3 from imine **13d** (600 mg, 2.09 mmol), TosMIC (611 mg, 3.13 mmol), *N*-(tosylmethyl)formamide (1.34 g, 6.26 mmol) and *t*BuNH_2 (925 mg, 12.5 mmol, 1.32 mL) in methanol (21 mL). Purification by FC (SiO_2, EtOAc/MeOH/NEt_3 93:5:2) afforded imidazole **14d**.

Colorless solid (380 mg, 56 %); R_f = 0.32 (SiO_2, EtOAc/MeOH/NEt_3 93:5:2); m.p. 160 °C; ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.42 (s, 1 H, NCHN), 7.30–7.20 (m, 8 H, CC*H*CH, CCHC*H*), 7.18–7.10 (m, 2 H, CCHCHC*H*), 6.95 (t, *J* = 0.6 Hz, 1 H, CCHN), 4.62 (p, *J* = 2.7 Hz, 1 H, NC*H*(CH_2)$_2$), 3.94 (s, 1 H, CC*H*C), 2.39–2.32 (m, 2 H, NCH(CH_2^b)$_2$), 2.30–2.21 (m, 4 H, CCH_2CH_2C), 2.17–2.10 (m, 2 H, NCH(CH_2^a)$_2$); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 149.4 (*C*CHCH), 130.9 (NCHN), 130.4 (*C*CHN), 128.9 (CCH*C*H), 126.4 (CCHCH*C*H), 126.1 (*C*CHCH), 124.6 (*C*CHN), 50.8 (*C*CH_2), 49.9 (N*C*H(CH_2)$_2$), 48.3 (NCH(CH_2)$_2$), 45.9 (CCHC), 40.8 (CCH_2CH_2C); IR (KBr): $\tilde{\nu}$ = 3020, 2947, 2868, 1682, 1599, 1495, 1481, 1466, 1444, 1396, 1342, 1273, 1228, 1092, 1026, 945, 760, 729, 700, 656, 540 cm^{-1}; HRMS (ESI): *m/z* [M + H]$^+$ calcd. for $C_{23}H_{23}N_2$ 327.1856, found 327.1854.

3,7-Dimethyl-9(1,5-$^2H_2$)imidazolatricyclo[5.2.1.0^{3,8}]decaphan 14e

Synthesis according to GP3 from imine **13e** (22 mg, 0.12 mmol), TosMIC (36 mg, 0.18 mmol), *N*-(tosylmethyl)formamide (78 mg, 0.37 mmol) and *t*BuNH_2 (54 mg, 0.73 mmol, 78 µL) in ($^2H_4$)CH_3OH (1.25 mL). Purification by FC (SiO_2, EtOAc/MeOH/NEt_3 93:5:2) afforded imidazole **14e**.

Colorless oil (NMR-Yield 4 mg, 14 %); R_f = 0.18 (SiO_2, EtOAc/MeOH/NEt_3 93:5:2); ^{1}H NMR (500 MHz, CD_3OD): δ = 4.62–4.57 (m, 1 H, NC*H*(CH_2)$_2$) 2.19 (s, 1 H, CCHC), 1.79–1.55 (m, 6 H, 3 × CH_2), 1.32–1.21 (m, 4 H, 2 × CH_2), 0.69 (s, 6 H, 2 × CH_3); HRMS (ESI): *m/z* [M + H]$^+$ calcd. for $C_{14}H_{19}D_2N_2$ 219.1825, found 219.1824.

3,7-Diphenyl-9(1,5-$^2H_2$)imidazolatricyclo[5.2.1.0^{3,8}]decaphan 14f

Synthesis according to GP3 from imine **13f** (18 mg, 61 µmol), TosMIC (18 mg, 92 µmol), *N*-(tosylmethyl)formamide (39 mg, 0.18 mmol) and *t*BuNH_2 (27 mg, 0.37 mmol, 39 µL) in ($^2H_4$)CH_3OH (0.63 mL). Purification by FC (SiO_2, EtOAc/MeOH/NEt_3 93:5:2) afforded imidazole **14f**.

Colorless oil (NMR-Yield 2 mg, 12 %); R_f = 0.18 (SiO_2, EtOAc/MeOH/NEt_3 93:5:2); ^{1}H NMR (400 MHz, CD_3OD): δ = 7.31–7.25 (m, 4 H, C*C*HCHCH), 7.24–7.17 (m, 4 H, CCHC*H*CH), 7.07 (tt, *J* = 7.3/1.3 Hz, 2 H, CCHCHC*H*), 4.88–4.85 (m, 1 H, NC*H*(CH_2)$_2$), 3.88 (s, 1 H, CCHC), 2.47–2.37 (m, 2 H, CH_2), 2.35–2.27 (m, 2 H, CH_2), 2.16–2.02 (m, 1 H, CH_2^b), 1.93–1.86 (m, 2 H, CH_2), 1.86–1.78 (m, 1 H, CH_2^a), 1.77–1.66 (m, 2 H, CH_2); HRMS (ESI): *m/z* [M + H]$^+$ calcd. for $C_{24}H_{23}D_2N_2$ 343.2138, found 343.2138.

5,6,7,8-Tetrahydro(1,3-$^2H_2$)imidazo[1,5-a]pyridine 14g

Synthesis according to GP3 from imine **13g** (20 mg, 0.25 mmol), TosMIC (72 mg, 0.37 mmol), *N*-(tosylmethyl)formamide (157 mg, 0.736 mmol) and *t*BuNH_2 (109 mg, 1.47 mmol, 0.16 mL) in ($^2H_4$)CH_3OH (2.5 mL) at 25 °C. Purification by FC (SiO_2, EtOAc/MeOH/NEt_3 93:5:2) afforded imidazole **14g**.

Yellow oil (NMR-Yield 6 mg, 21 %); R_f = 0.24 (SiO_2, EtOAc/MeOH/NEt_3 93:5:2); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.96 (t, *J* = 6.1 Hz, 2 H, NCH_2), 2.75 (t, *J* = 6.4 Hz, 2 H, CCH_2), 1.96–1.89 (m, 2 H, CH_2), 1.84–1.77 (m, 2 H, CH_2); Due to rapid proton deuterium exchange of the starting imine **13g** in course of the imine enamine equilibrium unplanned deuterium incorporation into the tetrahydropyridine core occurred and led to a decreased signal intensity at 2.75 ppm. HRMS (ESI): *m/z* [M + H]$^+$ calcd. for $C_7H_9D_2N_2$ 125.1042, found 125.1043.

5,6-Dihydro(1,3-$^2H_2$)imidazo[5,1-a]isoquinoline 14h

Synthesis according to GP3 from imine **13h** (32 mg, 0.25 mmol), TosMIC (72 mg, 0.37 mmol), *N*-(tosylmethyl)formamide (157 mg, 0.736 mmol) and *t*BuNH_2 (109 mg, 1.47 mmol, 0.16 mL) in ($^2H_4$)CH_3OH (2.5 mL) at 25 °C. Purification by FC (SiO_2, EtOAc/MeOH/NEt_3 93:5:2) afforded imidazole **14h**.

Yellow oil (36 mg, 86 %); R_f = 0.21 (SiO_2, EtOAc/MeOH/NEt_3 93:5:2); ^{1}H NMR (400 MHz, CD_3OD): δ = 7.59–7.54 (m, 1 H, NCCC*H*), 7.29–7.22 (m, 2 H, CH_2CC*H*, NCCCHC*H*), 7.22–7.16 (m, 1 H, CH_2CCHC*H*), 4.19 (t, *J* = 6.6 Hz, 2 H, NCH_2), 3.06 (t, *J* = 6.6 Hz, 2 H, C*C*H_2); ^{13}C NMR (100 MHz, CD_3OD): δ = 137.2 (t, NCDN), 132.7 (CH_2C), 130.5 (NCC), 129.4 (NCCCH*C*H), 128.4 (CH_2C*C*H, CH_2CCH*C*H), 127.9 (NCC), 124.2 (NCCC*C*H), 123.2 (t, NCDC), 43.0 (NCH_2), 29.9 (CCH_2); IR (KBr): $\tilde{\nu}$ = 3375, 2971, 2893, 2630, 1692, 1608, 1547, 1482, 1458, 1426,

1322, 1212, 1025, 947, 816, 766, 737, 717 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $C_{11}H_9D_2N_2$ 173.1042, found 173.1042.

Dimer 18

Imine **13c** (30 mg, 0.18 mmol), *N*-(tosylmethyl)formamide (118 mg, 0.55 mmol) and Cs_2CO_3 (180 mg, 0.553 mmol) were dissolved in ($^2H_4$)CH_3OH (1.88 mL) and stirred for 20 min at 25 °C. Subsequent ^1H NMR analysis indicated the formation of dimer **18** to an extent of 65 % (determined by NMR ratio relative to the methyl group of Tos^-). Purification by twofold preparative TLC (SiO_2, CH_2Cl_2/MeOH 9:1) afforded dimer **18** (admixed with a substance (ratio 80:20) that is most likely a diastereomer of dimer **18**).

Colorless crystals (1.8 mg, 4 %); R_f = 0.70 (SiO_2, CH_2Cl_2/MeOH 9:1); m.p. 156 °C; ^1H NMR (500 MHz, CD_3OD): δ = 8.13 (s, 2 H, NC*H*O), 4.53 (d, *J* = 13.1 Hz, 2 H, 2 × $NCH_2{}^bN$), 4.31 (d, *J* = 2.9 Hz, 2 H, 2 × NC*H*CH), 3.99 (d, *J* = 13.1 Hz, 2 H, 2 × $NCH_2{}^aN$), 2.87 (p, *J* = 2.8 Hz, 2 H, 2 × NC*H*CH_2), 1.81 (dt, *J* = 12.7/2.8 Hz, 2 H, 2 × NCHC$H_2{}^d$), 1.74 (dt, *J* = 13.5/2.9 Hz, 2 H, 2 × NCHC$H_2{}^c$), 1.58–1.37 (m, 12 H, 2 × NCHC$H_2{}^b$, 4 × CH_3CCH_2, 2 × NCHC*H*), 1.28–1.19 (m, 8 H, 2 × CH_3, 2 × NCHC$H_2{}^a$), 1.09 (s, 6 H, 2 × CH_3); ^{13}C NMR (125 MHz, CD_3OD): δ = 164.3 (2 × NCHO), 92.8 (2 × NCHCH), 56.6 (2 × NCH_2N), 51.5 (2 × NCHCH_2), 50.8 (2 × NCHC*H*), 47.9 (2 × NCHCH_2), 42.4 (2 × CH_3CCH_2), 41.4 (2 × CH_3CCH_2), 41.3 (2 × *C*CH_3), 41.2 (2 × NCHCH_2), 39.8 (2 × *C*CH_3), 29.1 (2 × CH_3), 26.7 (2 × CH_3); IR (KBr): $\tilde{\nu}$ = 2941, 2924, 2866, 1657, 1365, 1313, 1261, 1238, 1174, 1146, 1120, 986, 970, 733 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $C_{26}H_{41}O_2N_4$ 441.3224, found 441.3222.

Keywords: Cyclic Imine · Cycloaddition · Nitrogen heterocycles · Organocatalysis · TosMIC

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