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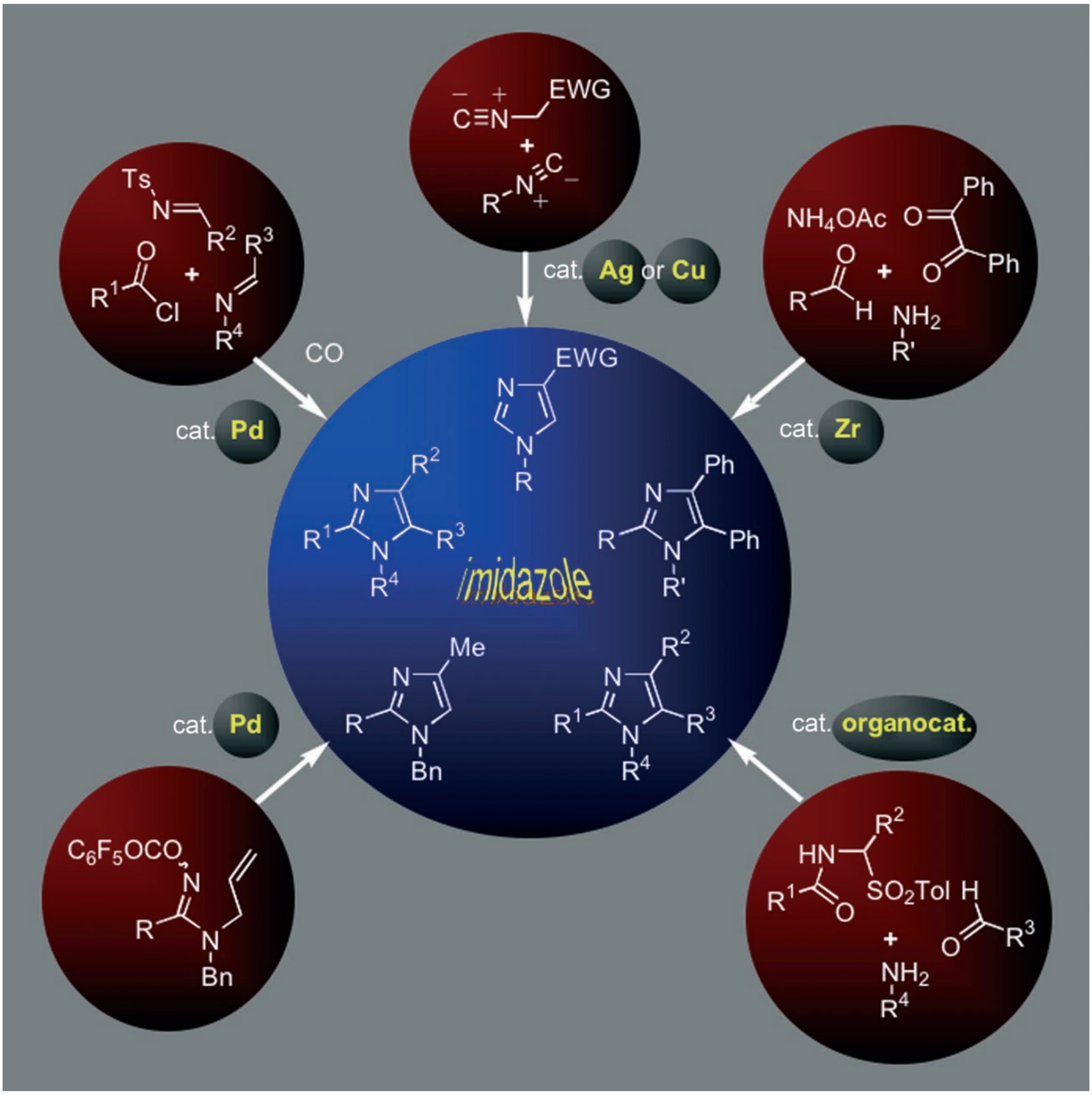
Recent Progress in the Catalytic Synthesis of Imidazoles

Shin Kamijo*[a] and Yoshinori Yamamoto[b]



Abstract: Imidazole is one of the important heteroaromatic compounds that have found a broad range of uses in, for example, pharmaceutical and industrial applications. Several conventional methodologies for the synthesis of imidazole rings are known; however, they are limited in terms of substrate generality and are not always efficient. Recent studies toward the development of catalytic reactions have brought significant improvements to the preparation of imidazoles. This Focus Review highlights the very recent progress in the catalytic synthesis of imidazoles, particularly those involving the formation of five-membered ring cores.

Keywords: catalysis · cyclization · cycloaddition · imidazoles · multicomponent reactions

1. Introduction

Imidazole is a five-membered heteroaromatic ring with two nitrogen atoms at the 1- and 3-positions.[1] This type of compound is known to exhibit a broad range of uses in, for example, pharmaceutical and industrial applications. For instance, imidazole rings are found in many drug cores, such as angiotensin II inhibitors,[2] anti-inflammatory[3] and anticancer agents,[4] as well as building blocks of naturally occurring products.[5] They also play an important role as ligands in metalloenzymes,[6] and it is well-known that imidazolium salts can serve as excellent precursors of stable carbene ligands in various metal complexes.[7] The application of imidazolium salts to environmentally friendly ionic solvents is another example.[8]

Owing to the wide applicability of imidazoles, preparative methodologies for this class of compounds have been intensively developed.[1] Conventional methods for imidazole-core synthesis usually consist of cyclocondensation reactions. Representative methods are 1) the reaction of α-diketones and α-haloketones with formamide (Bredereck synthesis) and 2) the base-promoted reaction of tosylmethyl isocyanides and aldimines or imidoyl chlorides (van Lausen's TosMIC chemistry[9]). These traditional procedures work well in certain cases; however, we often encounter limitations in terms of substrate generality and diversity. Under such reaction conditions, compatibility with a variety of functional groups, efficiency of the transformations, and regioselectivity of imidazole products could be problematic due to the relatively harsh reaction conditions (e.g., basic conditions, high temperature).

Recent investigations toward the development of catalytic reactions have brought significant improvements for the preparation of imidazoles. Many catalysts were examined and employed for the synthesis of imidazole derivatives. These processes can be categorized into the following two types: I) catalytic derivatization of imidazole rings[10–14] and II) catalytic formation of imidazole cores.[15–20] The former method is based on stepwise functionalization of imidazole rings, such as C–H activations,[10,11] metal-catalyzed N-arylations,[12,13] and cross-coupling reactions.[14] The major drawback of this type of methodology exists in the use of corresponding imidazoles as a starting material. On the other hand, the latter method is based on newly developed transformations that enable one to use a variety of starting compounds other than imidazole rings; these reactions are especially effective for the preparation of densely functionalized imidazoles such as trisubstituted and tetrasubstituted imidazoles. Intensive investigations into the catalytic derivatization of imidazole rings (type I) have been carryied out and many advanced approaches have been reported, but in this Focus Review we would like to focus on the most-recent progress in the formation of five-membered ring cores of imidazole by utilizing a variety of catalysts (type II).

2. Palladium-Catalyzed Intramolecular Cyclization Reaction

Imidazoles that bear a functional group at the 2-position are usually prepared by the metallation of imidazole cores followed by trapping with various electrophiles such as alde-

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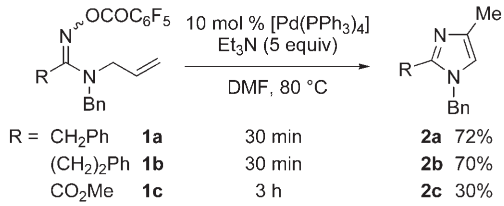
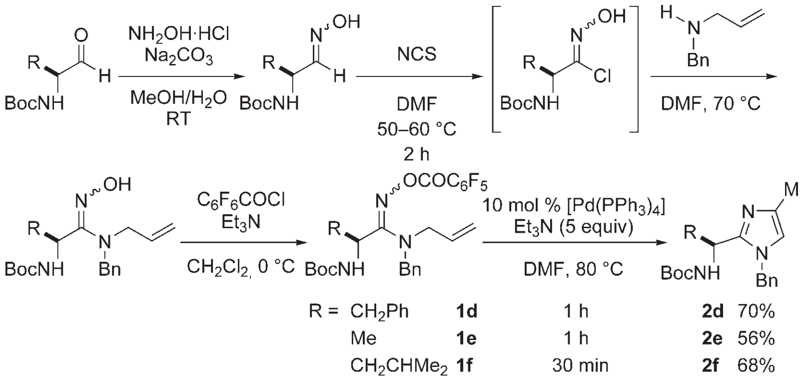
hydes and isocyanates.[21] More recently, a similar type of reaction between imidazole-derived azolium ylides and reactive carbonyl compounds was reported for the preparation of 2-substituted imidazoles.[22] These procedures, however, generally require a stoichiometric amount of strong base to activate the imidazole core; moreover, the corresponding imidazoles themselves have to be used as the starting compound.

Abell and co-workers recently developed a new synthetic method for trisubstituted imidazoles, 2-substituted 1-benzyl-4-methylimidazoles **2**, based on the palladium-catalyzed intramolecular amino-Heck reaction of amidoximes **1** (Scheme 1).[15] The corresponding imidazoles **2a** and **2b** were obtained in good yields from *N,O*-pentafluorobenzoyloximes **1a** and **1b**, respectively, in the presence of [Pd(PPh$_3$)$_4$] (10 mol %) and Et$_3$N (5 equiv) in *N,N*-dimethylformamide (DMF) at 80 °C for 30 min. In the case of the amidoxime **1c**, which was derived from methyl glyoxylate, **2c** was formed only in modest yield.



Scheme 1. Pd-catalyzed intramolecular amino-Heck reaction of amidoximes.

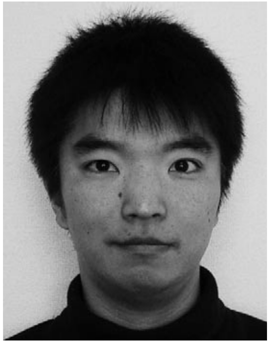
With the success of the catalytic imidazole synthesis by the Pd-catalyzed intramolecular cyclization reaction, which employed relatively simple amidoximes, Abell and co-workers applied this transformation to the substrates prepared from amino acids to introduce an imidazole moiety as a stable ester isostere at the C terminus of peptidomimetics[23] (Scheme 2). The aldehydes were prepared by DIBALH reduction of (*S*)-*N*-BocPheOMe, (*S*)-*N*-BocAlaOMe, and (*S*)-*N*-BocLeuOMe, respectively (Boc = *tert*-butoxycarbonyl, DIBALH = diisobutylaluminum hydride). Dehydrative condensation with hydroxylamine hydrochloride in the presence of Na$_2$CO$_3$ furnished an *E/Z* mixture of α-amino aldoximes. Chlorination with *N*-chlorosuccinimide (NCS) gave the hy-



Scheme 2. Pd-catalyzed intramolecular amino-Heck reaction of amidoximes derived from amino acids.[15]

Abstract in Japanese:

イミダゾールは、医薬品化学や化学工業を含む様々な分野で幅広い用途が知られる重要なヘテロ環化合物の一つである。イミダゾール環骨格を構築するための手法は古くから幾つか知られているが、基質一般性に乏しく必ずしも効率的とは言えない。触媒反応開発を目指した最近の研究のなかで、イミダゾール合成に関して大きな進展が見られた。本稿では特に、イミダゾール五員環の構築に焦点をあて最新の触媒的イミダゾール合成法を紹介する。



__Shin Kamijo__ was born in 1973 in Hofu, Japan and received his MS (1999) and PhD (2002) degrees from Tohoku Univ. under the supervision of Prof. Yoshinori Yamamoto. From 2002 to 2004 he was appointed as a Research Associate at Tohoku Univ. From 2004 to 2006 he worked with Prof. Gregory B. Dudley at Florida State Univ. as a JSPS Postdoctoral Fellow. He is currently a Postdoctoral Associate in Prof. Masakatsu Shibasaki's group at The Univ. of Tokyo. His research interests focus on transition-metal-catalyzed reactions and their applications to organic synthesis.

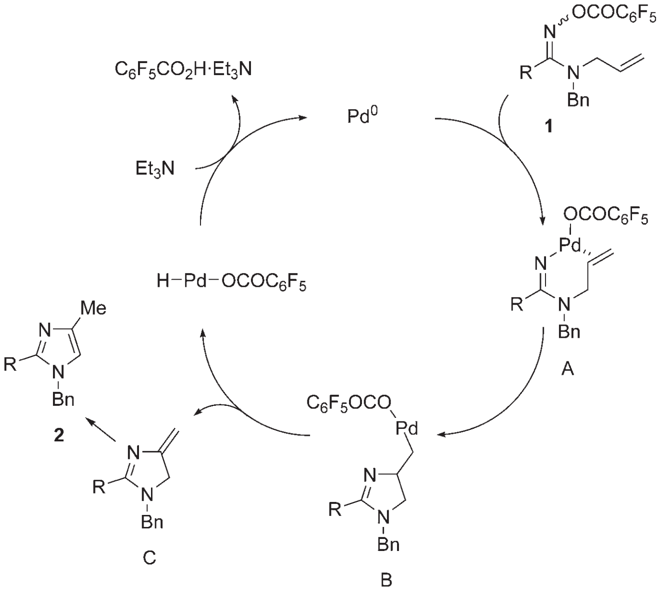
__Yoshinori Yamamoto__ was born in Kobe, Japan and received his MS and PhD degrees from Osaka Univ. In 1970 he became Instructor at Osaka Univ., after which he joined Prof. H. C. Brown's group at Purdue Univ. as a Postdoctoral Associate (1970–1972). In 1977 he was appointed Assoc. Prof. at Kyoto Univ., and in 1986 he moved to Tohoku Univ. to take up his present position as Prof. of Chemistry. As of 2006 he is Vice President of Tohoku Univ. He has won many awards, including the Humboldt Research Award (2002). His research interests range from the use of transition-metal and Lewis acid catalysts in organic synthesis to the synthesis of complex natural products.

droxyamoyl chlorides, and treatment in situ with allyl benzylamine afforded the amidoximes as a mixture of *E/Z* isomers. Subsequent reaction with pentafluorobenzoyl chloride in the presence of Et_3N gave the starting materials **1d–f**. The Pd-catalyzed intramolecular amino-Heck reaction proceeded smoothly to produce the corresponding imidazoles **2d–f** in good to moderate yields. After Boc deprotection of **2d** and coupling of the resulting free amine with (*S*)-BocAla, the corresponding amide was obtained with over 95% de, which indicates that little or no racemization of the chiral center in the original amino acid took place. This is one of the advantages of the present transformation, as the problem of racemization often arises in conventional methods during the preparation of imidazole rings.[24]

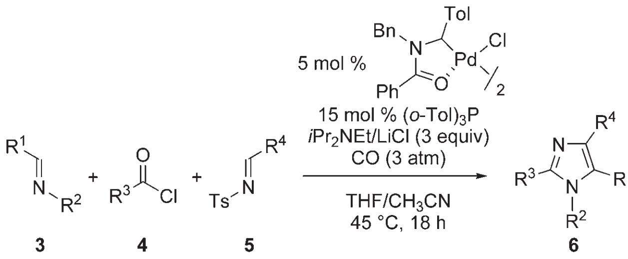
The mechanism for the Pd-catalyzed intramolecular amino-Heck reaction of amidoximes is proposed in Scheme 3. The catalytic cycle starts with oxidative addition of a Pd^0 species to the N−O bond of amidoxime **1** to form alkylideneaminopalladium(II) intermediate A.[25] Olefin insertion then takes place at the Pd−N bond of A to afford the intermediate B. Subsequent β elimination affords a palladium hydride species and the dihydroimidazole C, which eventually isomerizes under the reaction conditions to form imidazole **2**. Regeneration of the active Pd^0 species is achieved in the presence of Et_3N, which makes the catalytic cycle feasible.

3. Palladium-Catalyzed Multicomponent Coupling Reaction

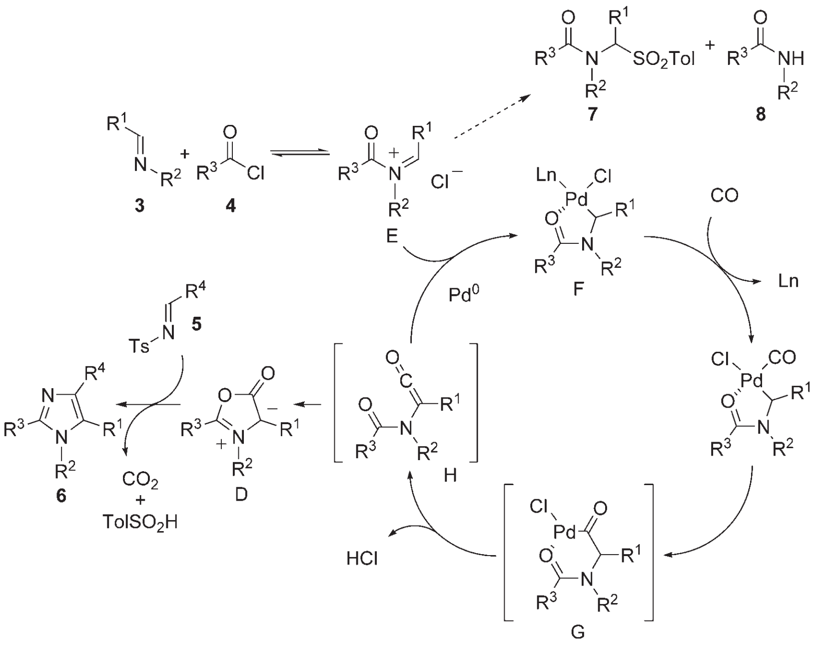
Imidazole synthesis by the palladium-catalyzed intramolecular amino-Heck reaction in the previous section works very well, though the strategy has severe disadvantages in terms of diversity and generality of starting compounds. This limitation is inherent in its reaction pattern: intramolecular cyclization. A key to expanding substrate diversity and generality, and hence the variety of imidazole products, is to create a convergent strategy involving multiple starting building blocks.[26] Siamaki and Arndtsen succeeded in developing a direct synthesis of imidazoles by the palladium-catalyzed multicomponent coupling reaction (MCR) starting from two imines **3** and **5** and acid chlorides **4** under CO atmosphere (Scheme 4).[16] This reaction provides tetrasubstituted imidazoles **6** in a single step.



Scheme 3. Proposed reaction mechanism for the Pd-catalyzed intramolecular amino-Heck reaction of amidoximes.



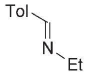
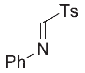
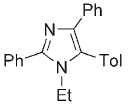
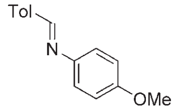
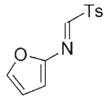
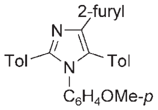
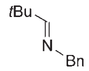
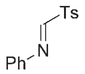
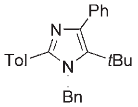
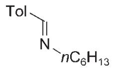
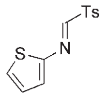
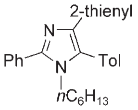
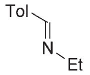
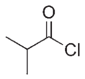
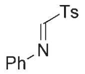
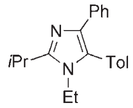
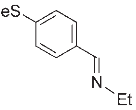
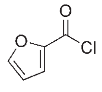
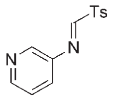
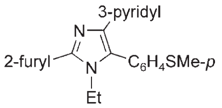
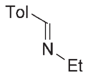
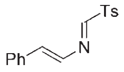
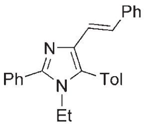
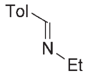
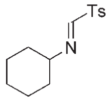
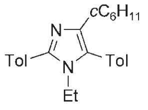
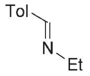
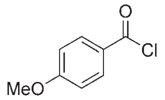
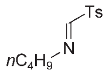
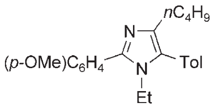
Scheme 4. Pd-catalyzed MCR of imines and acid chlorides under CO.



Scheme 5. Plausible reaction mechanism for the Pd-catalyzed MCR leading to tetrasubstituted imidazoles.

A plausible mechanism for this Pd-catalyzed MCR, which leads to fully substituted imidazoles, is illustrated in Scheme 5. The approach is based on the 1,3-dipolar cycloaddition reaction of 1,3-oxazolium-5-olates (Münchnones; D) with *N*-tosylimine **5**. The formation of D through the palladium-catalyzed three-component coupling reaction of imines, acid chlorides, and CO gas had already been reported by the same group.[27] Before entering the catalytic cycle, the reaction starts with selective nucleophilic attack of imine **3** on acid chloride **4** to form iminium salt E. Under the influence of a Pd^0 catalyst, E is converted into the intermediate F, which acts as the active catalytic species. Subsequent insertion of CO gas into the Pd−C bond of F produces the intermediate G. β Elimination affords the ketene intermediate H along with regeneration of the Pd^0 species in the presence of $i\mathrm{Pr_2NEt}$. Intramolecular cyclization of H provides D, and selective 1,3-dipolar cycloaddition with electron-deficient **5** affords imidazole **6** with concomitant extrusion of CO_2 gas and toluenesulfinic acid.[28]

Table 1. Imidazole synthesis by the Pd-catalyzed MCR with a variety of starting compounds.[a]

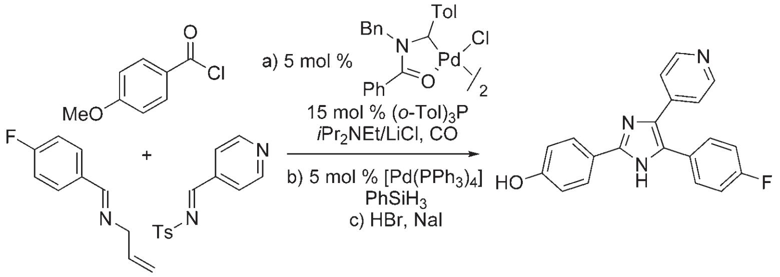
Entry	**3**	**4**	**5**	**6**	Yield [%]
1		PhCOCl			76
2		*p*-TolCOCl			71
3		*p*-TolCOCl			67
4		PhCOCl			70
5					60
6					70
7		PhCOCl			74
8		*p*-TolCOCl			68
9					69

[a] Conditions: **3** (1 equiv), **4** (1.4 equiv), **5** (1.2 equiv), palladium catalyst (5 mol%) (Scheme 4), (*o*-Tol)$_3$P (15 mol%), $i\mathrm{Pr_2NEt}$/LiCl (3 equiv), CO (4 atm), THF/CH_3CN, 45 °C, 18 h. Tol = tolyl, Ts = tosyl.

In the early stages of the investigation, Siamaki and Arndtsen suffered low yields of the desired imidazole due to the formation of undesired α-sulfonylamide **7** and amide **8** (Scheme 5). The reaction between iminium salt E generated in situ and sulfinic acid released by the 1,3-cycloaddition reaction was responsible for the formation of **7**, and thermal decomposition of E accounted for the formation of **8**. On the basis of the postulates, the reaction conditions were optimized to avoid these competing processes; the best reaction conditions are shown in Scheme 4. Addition of the bulky (*o*-Tol)$_3$P ligand and increasing the CO pressure accelerated the reaction progress; as a result, the reaction temperature could be reduced to 45 °C. Addition of LiCl suppressed the formation of **7** completely by shifting the equilibrium in favor of E.

Table 1 summarizes the results of the synthesis of tetrasubstituted imidazoles by the Pd-catalyzed MCR with a range of building blocks. Imines derived from alkyl- and arylamines as well as from aryl and nonenolizable alkyl aldehydes could be utilized as substrate. Various acid chlorides, such as aryl, heteroaryl, and alkyl, could be applied. Even greater diversity was possible for *N*-tosylimines, which included aryl, heterocyclic, alkyl, and α,β-unsaturated substituents. Although enolizable aldehydes were not suitable for *N*-alkylimines, they could be used as a component of *N*-tosylimines. This transformation displays good compatibility with a wide variety of functional groups and provides complete regiochemical control of all the substituents on the imidazole ring, in which they can be independently varied by proper choice and combination of starting compounds.

To demonstrate the utility of this reaction, the synthesis of a potent p38 MAP kinase inhibitor (MAP = mitogen-activated protein) was carried out (Scheme 6), which led to the design of new anti-inflammatory agents.[3] The desired compound was obtained in a regioselective manner from the readily available imines and acid chloride, after deprotection.

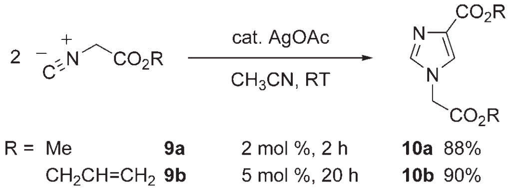


Scheme 6. Synthesis of a potent p38 MAP kinase inhibitor.

4. d^{10}-Metal-Catalyzed Cycloaddition Reaction

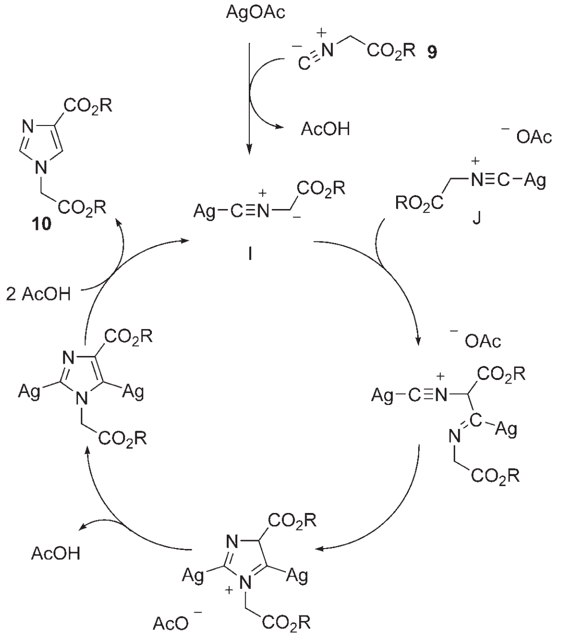
The MCR strategy can increase dramatically the variety of substituents in the products; however, the palladium-catalyzed MCR presented in the previous section is not ideal in terms of atom economy.[29] The generation of a stoichiometric amount of waste such as toluenesulfinic acid and CO_2 cannot be ruled out even though the whole reaction sequence is well-planned to proceed without the desired pathways being interfered with. To develop atom-economical processes, new catalytic reactions need to be devised, especially those with raw starting materials.[30] Such transformations eliminate prior activation of reagents, for instance, base treatment or formation of silyl enol ethers to increase nucleophilicity, in a separate step; thus, side-products can theoretically be minimized.

Grigg et al. reported a catalytic imidazole synthesis by silver-catalyzed homodimerization of isocyanoacetates.[17] They mainly focused on the catalytic synthesis of pyrrolines derived from the coupling reaction between isocyanoacetates and olefins that bear an electron-withdrawing group (Michael acceptors), and it seems that they happened to observe the homodimerization of isocyanoacetates to give imidazoles in some cases. As shown in Scheme 7, only two examples were reported. The reaction of isocyanides **9a** and **9b** afforded the corresponding imidazoles **10a** and **10b** in excellent yields.



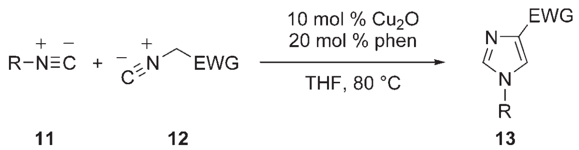
Scheme 7. Ag-catalyzed homodimerization of isocyanides.

Further experiments were carried out to elucidate a possible reaction mechanism for the Ag-catalyzed formation of imidazole relevant to that of pyrroline. The reaction of methyl isocyanoacetate with methyl acrylate in the presence of a catalytic amount of AgOAc resulted in the formation of pyrroline, whereas the reaction in the presence of a stoichiometric amount of AgOAc predominantly produced the corresponding imidazole through homodimerization of the isocyanide. Accordingly, these results suggest that both of the isocyanides involved in homodimerization were coordinated to the silver catalyst (Scheme 8). Such coordination would activate one isocyanide as a nucleophile by increasing the acidity of the methylene proton (I), while at the same time activating the other isocyanide as an electrophile at the isocyano moiety (J).



Scheme 8. Possible reaction mechanism for the Ag-catalyzed homodimerization of isocyanides.

We later discovered independently the formation of imidazole rings by the copper-catalyzed cross-cycloaddition of two different isocyanides.[18] During the course of our research on the copper-catalyzed synthesis of pyrroles starting from isocyanides and acetylenes conjugated with an electron-withdrawing group (EWG),[31] we encountered homodimerization of ethyl isocyanoacetate (**12a**, EWG = CO_2Et; Scheme 9) with a catalytic amount of Cu_2O and 1,10-phenanthroline (phen) to produce 1-(ethoxycarbonylmethyl)-4-(ethoxycarbonyl)imidazole (**10c**, R = Et; Scheme 7) in 49% yield. Encouraged by this finding, we envisioned that cross-

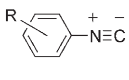
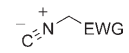
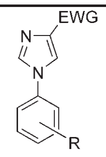
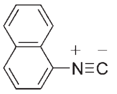
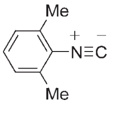


Scheme 9. Cu-catalyzed cross-cycloaddition of isocyanides.

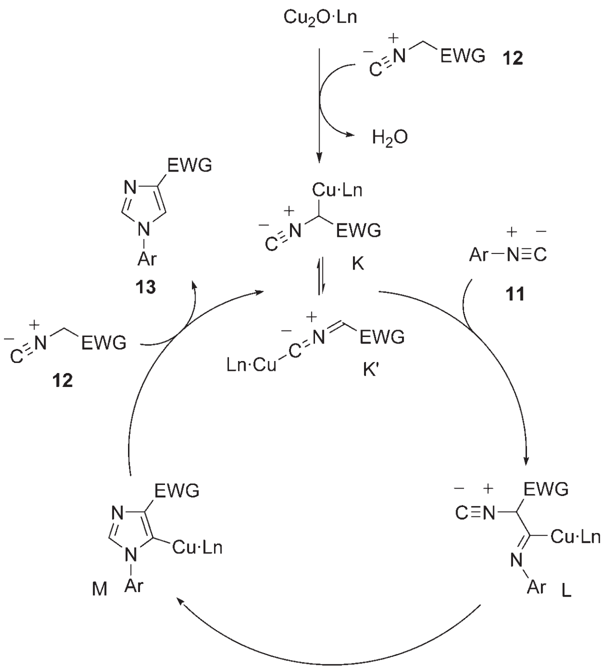
cycloaddition could be possible if a different isocyanide was utilized as a coupling partner (Scheme 9). As expected, the reaction of 4-methoxy-1-isocyanobenzene (**11a**, R=*p*-$\mathrm{MeOC_6H_4}$) with **12a** in the presence of $\mathrm{Cu_2O}$ catalyst and phen ligand furnished the corresponding product, 4-ethoxycarbonyl-1-(4-methoxyphenyl)imidazole (**13a**, R=*p*-$\mathrm{MeOC_6H_4}$, EWG=$\mathrm{CO_2Et}$), in excellent yield. As for metal sources, CuCl or $\mathrm{CuCl_2}$ resulted in the formation of trace amounts of cycloadduct or no reaction. Interestingly, copper powder also furnished the target product in good yield. In this cross-cycloaddition, the catalytic activity of AgOAc[17] was low and $\mathrm{[RhH(PPh_3)_4]}$[32] did not catalyze the reaction at all, although these catalysts are known to activate the C–H bond of isocyanides. The best yield was attained when aryl isocyanide **11** was treated with 1.4 equivalents of isocyanoacetate **12** under the reaction conditions shown in Scheme 9.

Reactions between a range of aryl isocyanides **11** and **12a** were carried out to clarify the scope and limitations of the present imidazole synthesis by Cu-catalyzed cross-cycloaddition. The results are summarized in Table 2. Imidazole formation starting from *para*-, *meta*-, and *ortho*-substituted isocyanobenzenes **11a–c** took place to give the corresponding products **13a–c** in excellent yields. The substrates **11d–g** with an electron-withdrawing group on the aromatic ring also produced the imidazoles **13d–g** in high yields. These results indicate that the present transformation proceeds irrespective of the electronic nature of the aryl isocyanides and is highly compatible with various functionalities, such as ester, cyano, nitro, and chloro groups. The reaction also proceeded with aryl isocyanide **11h**, which is conjugated with an alkynyl group. Not only did nonsubstituted isocyanobenzene (**11i**) undergo the reaction, so did sterically hindered 1-naphthyl isocyanide (**11j**) and 2,6-dimethylphenyl isocyanide (**11k**), although slightly longer reaction times were required. When aliphatic isocyanides, such as *n*-butyl and cyclohexyl isocyanides, were employed as starting material, the corresponding imidazoles were obtained only in low yields (12 and 10%, respectively), and the homodimerized product **10c** was formed as the major product. These results indicate that the order of electrophilicity of isocyanides is as follows: Ar–NC>EWG–$\mathrm{CH_2}$–NC>R–NC (R=alkyl).

Table 2. Imidazole synthesis by Cu-catalyzed cross-cycloaddition with a variety of starting compounds.[a]

Entry	Aryl isocyanide R	11	Isocyanide EWG	12	*t* [h]	13	Yield [%]
							
1	*p*-MeO	**11a**	$\mathrm{CO_2Et}$	**12a**	3	**13a**	93
2	*m*-MeO	**11b**	$\mathrm{CO_2Et}$	**12a**	2	**13b**	98
3	*o*-MeO	**11c**	$\mathrm{CO_2Et}$	**12a**	2	**13c**	88
4	*p*-$\mathrm{CO_2Me}$	**11d**	$\mathrm{CO_2Et}$	**12a**	2	**13d**	98
5	*p*-CN	**11e**	$\mathrm{CO_2Et}$	**12a**	1.5	**13e**	97
6	*p*-$\mathrm{NO_2}$	**11f**	$\mathrm{CO_2Et}$	**12a**	1	**13f**	88
7	*p*-Cl	**11g**	$\mathrm{CO_2Et}$	**12a**	5	**13g**	93
8	*p*-TMSC≡C	**11h**	$\mathrm{CO_2Et}$	**12a**	2	**13h**	91
9	H	**11i**	$\mathrm{CO_2Et}$	**12a**	2.5	**13i**	93
10		**11j**	$\mathrm{CO_2Et}$	**12a**	4	**13j**	95
11		**11k**	$\mathrm{CO_2Et}$	**12a**	4	**13k**	92
12	*p*-$\mathrm{CO_2Me}$	**11d**	$\mathrm{CO_2}t\mathrm{Bu}$	**12b**	3	**13l**	97
13	*p*-$\mathrm{CO_2Me}$	**11d**	$\mathrm{P(O)(OEt)_2}$	**12c**	24	**13m**	62
14	*p*-$\mathrm{CO_2Me}$	**11d**	$\mathrm{CONEt_2}$	**12d**	20	**13n**	71
15	*p*-$\mathrm{CO_2Me}$	**11d**	Ph	**12e**	24	**13o**	trace[b]

[a] Conditions: **11** (1 equiv), **12** (1.4 equiv), $\mathrm{Cu_2O}$ (10 mol%), phen (20 mol%), THF, 80°C. [b] Significant amounts of **11d** and **12e** were recovered. TMS=trimethylsilyl.

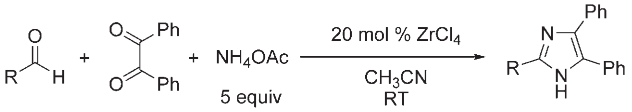


Scheme 10. Plausible reaction mechanism for the Cu-catalyzed cross-cycloaddition of two different isocyanides.

We next examined the reaction between isocyanobenzene **11d** (R=*p*-$\mathrm{MeO_2CC_6H_4}$) and various isocyanides **12** to investigate the effect of the electron-withdrawing group in this transformation. The size of the ester moiety did not exert a significant effect on the reactivity of isocyanoacetates. Installation of the phosphonate (**12c**) and amide (**12d**) moieties instead of the ester group did not disturb the formation of imidazoles **13m** and **13n**, despite elongation of the reaction times. On the contrary, benzyl isocyanide (**12e**) afforded only a trace amount of the desired imidazole **13o**, and most of the starting compounds (**11d** and **12e**) were recovered, presumably due to the low acidity of **12e**.

A plausible mechanism for the present Cu-catalyzed cross-cycloaddition of two different isocyanides is depicted in Scheme 10. The reaction is initiated by C–H bond activation of the isocyanide **12** with $\mathrm{Cu_2O}$ catalyst to form the active species K, α-cuprioisocyanide, or its tautomer K′

along with extrusion of H_2O.[33] Subsequent nucleophilic addition of the intermediate K and/or K′ to isocyanobenzene **11** occurs to form the intermediate L. Intramolecular cyclization between the imine moiety generated from the isocyanobenzene and the carbon atom of the isocyano moiety ($C^{-}\equiv N^{+}-$) followed by 1,3-hydrogen shift produces the cyclized intermediate M; this step can be considered as a formal [3+2] cycloaddition process. The C−Cu bond in M is then protonated by the existing excess of **12** in the reaction mixture to furnish 1,4-disubstituted imidazole **13** with regeneration of the active catalytic species K and/or K′.



14 **15**

Scheme 11. $ZrCl_4$-catalyzed TCR for the synthesis of trisubstituted imidazoles.

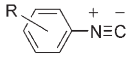
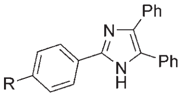
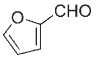
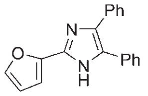
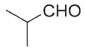
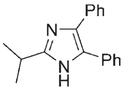
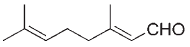
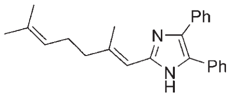
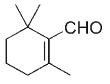
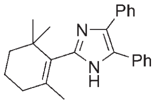
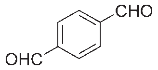
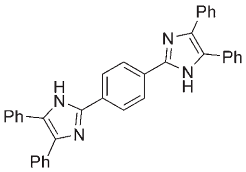
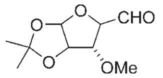
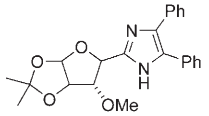
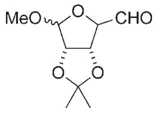
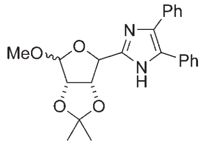
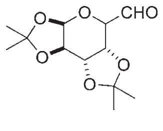
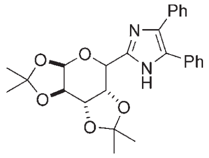
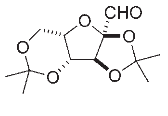
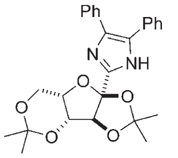
5. Lewis Acid Catalyzed Multicomponent Coupling Reaction

Another important feature of the MCR is its potent applicability in the construction of a library of compounds that bear a wide array of substitutions while keeping a common structural scaffold. The power of the MCR is often seen in combinatorial chemistry in the field of medicinal science for finding leads for drug candidates and optimizing the structures of these leads.[34,35] In this context, Sharma et al. investigated a Lewis acid catalyzed synthesis of imidazoles. They surveyed the three-component coupling reaction (TCR) of benzil, aldehydes **14**, and NH_4OAc in the presence of a catalytic amount of $ZrCl_4$ and observed a dramatic acceleration in imidazole formation (Scheme 11).[19] The combination of these compounds is well-known as a classical preparative method of trisubstituted imidazoles;[1] however, the reaction often produces a mixture of compounds in rather low yields owing to the harsh reaction conditions.[36] This $ZrCl_4$-catalyzed formation of imidazoles took place at room temperature and was completed within 6 h in most cases to give product yields of over 84 %, although the role of $ZrCl_4$ was not mentioned at all.

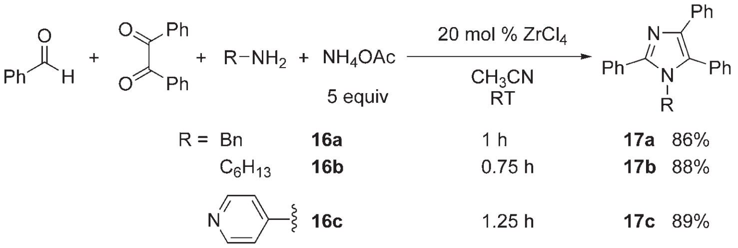
The strategy is based on condensation of benzil with aldehydes **14** in the presence of an excess amount of NH_4OAc to afford trisubstituted imidazoles **15** under the influence of $ZrCl_4$ (20 mol %). The reaction proceeded with a range of aldehydes, and the results are summarized in Table 3. Both aromatic and heteroaromatic aldehydes gave the corresponding imidazoles. The reactions with benzaldehydes with an electron-withdrawing group such as Cl, F, and NO_2 furnished the target imidazoles in high yields, whereas the reaction with *p*-anisaldehyde did not go to completion. Aliphatic and terpenoidal aldehydes also produced the products in high yields. Terephthalaldehyde, which has two reaction sites on the aromatic ring, gave the bis(imidazoyl)benzene. The reaction with aldehydes derived from sugars provided the corresponding glycoconjugated imidazoles without difficulty.[37]

The $ZrCl_4$-catalyzed four-component coupling reaction (FCR) was further examined with benzil, benzaldehyde, primary amine **16**, and NH_4OAc to synthesize the fully substituted imidazoles **17** (Scheme 12). As expected, the FCR proceeded smoothly to furnish the corresponding tetrasubstituted imidazoles starting from both aliphatic and aromatic amines.

Table 3. Imidazole synthesis by the $ZrCl_4$-catalyzed TCR with a variety of starting compounds.[a]

Entry	**14**	*t* [h]	**15**	Yield [%]
1		0.75		95
2		10		93
3		5		96
4		7		89
5		6		95
6		2		91
7		4		84
8		4.5		84
9		6		84
10		1.25		88
11		1.5		87
12		1.5		85
13		2		87

[a] Conditions: **14** (1 equiv), benzil (1 equiv), NH_4OAc (5 equiv), $ZrCl_4$ (20 mol %), CH_3CN, room temperature.

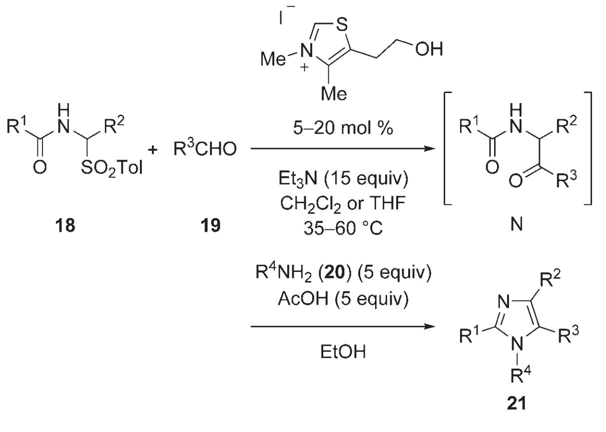


Scheme 12. $ZrCl_4$-catalyzed FCR for the synthesis of tetrasubstituted imidazoles.

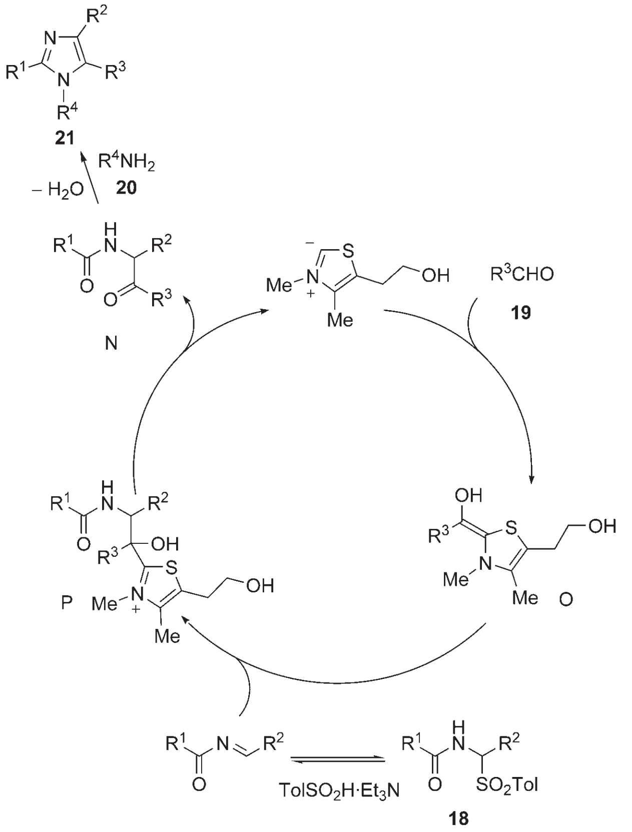
6. Thiazolium-Catalyzed Three-Component Coupling Reaction

In recent years, considerable effort has been made to develop reactions catalyzed by small organic molecules.[38] Such catalysts are often referred to as organocatalysts, and they can be attractive alternatives to metal-based catalysts. These reactions often proceed even in the presence of water under air, and in many cases, the starting compounds can be employed without any preactivation in a separate step.

Frantz et al. developed the one-pot synthesis of imidazoles through the synthesis of α-ketoamides (N) via the thiazolium-catalyzed addition of aldehydes **19** to acylimines generated from α-sulfonylamides **18**[39] and subsequent treatment with amines **20** (Scheme 13).[20] A possible reaction mechanism with emphasis on some key intermediates is illustrated in Scheme 14. Sulfonylamide **18** exists in equilibrium with acylimine and triethylammonium sulfinate in the reaction mixture.[40] Aldehyde **19** is converted into the thiazole-enamine O by addition of the stabilized ylide derived from thiazolium salt. Carbon–carbon bond formation takes place to form the intermediate P, and subsequent release of the catalytic thiazolium ylide species furnishes the α-ketoamide N. Treatment of N with amine **20** and acetic acid in refluxing EtOH produces imidazole **21**.



Scheme 13. Thiazolium-catalyzed TCR for imidazole synthesis.



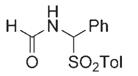
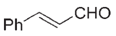
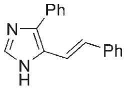
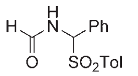
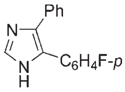
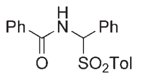
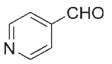
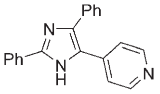
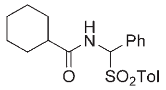
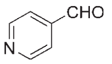
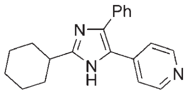
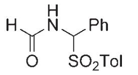
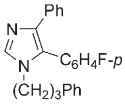
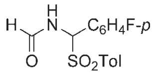
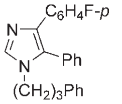
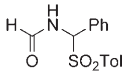
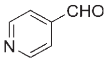
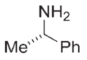
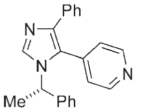
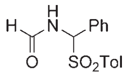
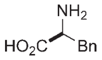
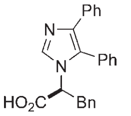
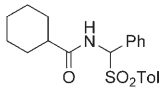
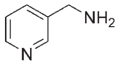
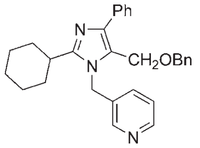
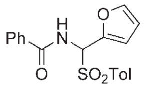
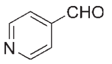
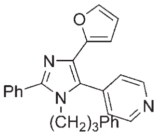
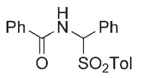
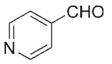
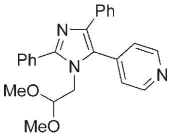
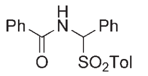
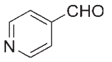
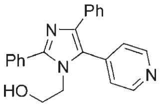
Scheme 14. Possible reaction mechanism for the thiazolium-catalyzed imidazole synthesis.

The results of the thiazolium-catalyzed one-pot synthesis of densely functionalized imidazoles are summarized in Table 4. The present transformation allows for regiospecific introduction of various substituents onto the imidazole ring just by choosing the proper combination of starting compounds; aldehyde **19** is installed in the 5-position, and sulfonylamide **18** in the 2- and 4-positions. When a primary amine is employed instead of NH_4OAc, the functional group on the nitrogen atom is introduced onto the 1-position of the imidazole core. Besides simple amines, chiral amines and amino acids can also be employed. The reaction progress was conveniently monitored by HPLC, and some of the imidazole products could be isolated by direct recrystallization from the crude reaction mixture. This methodology is also applicable to the synthesis of tetrasubstituted imidazoles. Again, the choice of starting compounds regulates the positions of substituents on the imidazole ring. The derived imidazole in Table 4, entry 8 is especially interesting as 2-imidazol-1-yl alkanoic acids have been implicated as angiotensin II receptor antagonists.[2]

7. Conclusions

This Focus Review describes the most recent progress on the catalytic synthesis of five-membered ring cores of imidazole. The utilization of palladium catalysts realized imidazole formation either through the intramolecular amino-Heck reaction of amidoximes or the multicomponent cou-

Table 4. Imidazole synthesis by the thiazolium-catalyzed TCR with a variety of starting compounds.[a]

Entry	18	19	20	21	Yield [%][b]
1			NH_4OAc		68 (47)
2		p-FC_6H_4CHO	NH_4OAc		82
3			NH_4OAc		78
4			NH_4OAc		82 (55)
5		p-FC_6H_4CHO	$Ph(CH_2)_3NH_2$		58 (35)
6		PhCHO	$Ph(CH_2)_3NH_2$		61 (42)
7					83[c]
8		PhCHO			73 (48)[c]
9		$BnOCH_2CHO$			22
10			$Ph(CH_2)_3NH_2$		76
11			$(MeO)_2CHCH_2NH_2$		80
12			$HO(CH_2)_2NH_2$		75

[a] Conditions: **18** (1 equiv), **19** (1.1 equiv), Et_3N (15 equiv), 2–5 mol% of thiazolium catalyst, in CH_2Cl_2 or THF, 35–60°C, then **20** (5 equiv), acetic acid (5 equiv), in EtOH, reflux. [b] Reaction yields and isolations were not optimized and represent the result of a single experiment. Product yields were determined by isolation on SiO_2 chromatography. Yields of products isolated by crystallization are shown in parentheses. [c] >98% *ee*.

pling reaction of two imines and acid chloride. The silver and copper catalysts promoted the cycloaddition of two isocyanides to form 1,4-disubstituted imidazoles. The Lewis acid $ZrCl_4$ was applied in the three-component coupling reaction to afford trisubstituted and tetrasubstituted imidazoles. An organocatalyst derived from thiazolium salt was also successfully employed for the construction of densely functionalized imidazoles. Nonetheless, there is still room to improve the efficiency of these catalytic transformations. The development of more practical, atom-economical, and general routes for the preparation of imidazole cores remains a challenge for the future.

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