



CrossMark
click for updates

Cite this: *Chem. Sci.*, 2015, 6, 6792

C–H arylation and alkenylation of imidazoles by nickel catalysis: solvent-accelerated imidazole C–H activation†

Kei Muto,^a Taito Hatakeyama,^b Junichiro Yamaguchi*^a and Kenichiro Itami*^{a,c}

The first nickel-catalyzed C–H arylations and alkenylations of imidazoles with phenol and enol derivatives are described. Under the influence of Ni(OTf)₂/dcype/K₃PO₄ (dcype: 1,2-bis(dicyclohexylphosphino)ethane) in *t*-amyl alcohol, imidazoles can undergo C–H arylation with phenol derivatives. The C–H arylation of imidazoles with chloroarenes as well as that of thiazoles and oxazoles with phenol derivatives can also be achieved with this catalytic system. By changing the ligand to dcyp^t (3,4-bis(dicyclohexylphosphino)thiophene), enol derivatives could also be employed as coupling partners achieving the C–H alkenylation of imidazoles as well as thiazoles and oxazoles. Thus, a range of C2-arylated and alkenylated azoles can be synthesized using this newly developed nickel-based catalytic system. The key to the success of the C–H coupling of imidazoles is the use of a tertiary alcohol as solvent. This also allows the use of an air-stable nickel(II) salt as the catalyst precursor.

Received 10th August 2015
Accepted 7th September 2015

DOI: 10.1039/c5sc02942b

www.rsc.org/chemicalscience

Introduction

Imidazoles, including benzimidazoles, are recognized as important chemical motifs since they are frequently found in a range of natural products, and are exploited as core structures in pharmaceuticals, agrochemicals, and organic materials. Because of the high versatility of imidazole-containing compounds (particularly C2-arylated and alkenylated imidazoles; Fig. 1),¹ functionalization and derivatization thereof are of significant importance in synthetic organic chemistry. Numerous synthetic methods to construct C2-aryl and alkenyl imidazoles have been reported thus far. Although cyclization and annulation reactions have found wide use, these methods often suffer from multi-step reaction sequences.² Transition metal-catalyzed cross-coupling reactions of arylmetal compounds and aryl halides have also been employed, albeit requiring the pre-functionalization of metalated or halogenated imidazoles prior to the coupling reactions.³

In recent years, the transition metal-catalyzed C–H functionalization approach has attracted attention as it enables rapid and straightforward synthesis of various functional heteroarenes.⁴ Within this class of reactions, C–H arylations and

alkenylations of imidazoles using transition-metal catalysts have been reported, mainly involving palladium⁵ and rhodium.⁶ In 2009, Daugulis and coworkers discovered the Cu-catalyzed C–H arylation of imidazoles, which allowed the use of an inexpensive transition metal catalyst.⁷

In our studies of catalytic C–H functionalization,⁸ we have developed several unique nickel catalysts⁹ that facilitate the C–H arylation of 1,3-azoles, such as oxazoles and thiazoles, with haloarenes (C–H/C–X coupling),¹⁰ phenol derivatives (C–H/C–O coupling),¹¹ and arenecarboxylates (decarboxylative C–H coupling).¹² The advantages of our recent nickel-based catalytic systems¹¹ are not only their low cost, but also their ability to activate and couple phenol derivatives (C–O electrophiles).^{13,14}

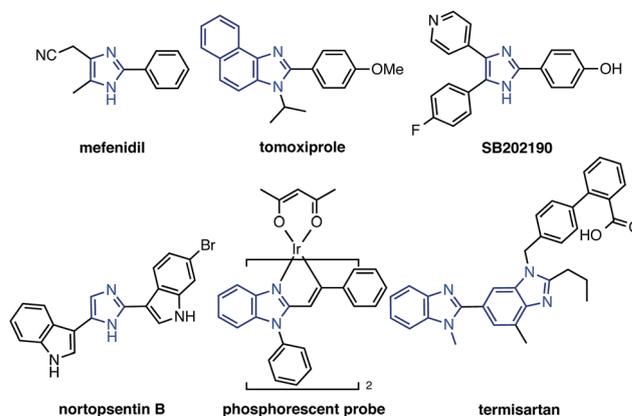


Fig. 1 C2-arylated and alkenylated imidazoles and benzimidazoles in natural products, pharmaceuticals, and organic materials.

^aInstitute of Transformative Bio-Molecules (WPI-ITbM) and Graduate School of Science, Nagoya University, Chikusa, Nagoya 464-8602, Japan. E-mail: itami@chem.nagoya-u.ac.jp; junichiro@chem.nagoya-u.ac.jp

^bCentral Research Laboratory Technology and Development Division, Kanto Chemicals Co. Inc., Saitama 340-0003, Japan

^cJST, ERATO, Itami Molecular Nanocarbon Project, Nagoya University, Chikusa, Nagoya 464-8602, Japan

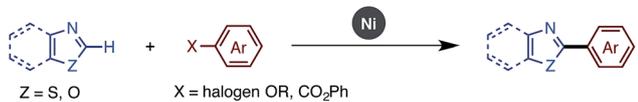
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c5sc02942b



Previous Metal-catalyzed C–H Coupling of Imidazoles



Previous Ni-Catalyzed C–H Coupling of Oxazoles and Thiazoles



This Work: The first Ni-Catalyzed C–H Coupling of Imidazoles



Fig. 2 Transition metal-catalyzed C–H arylation of imidazoles and benzimidazoles.

However, imidazoles and benzimidazoles still remained challenging substrates for our nickel-catalyzed C–H coupling campaign. Herein, we report the first general protocol for Ni-catalyzed C–H arylation as well as alkenylation of imidazoles (Fig. 2).

Results and discussion

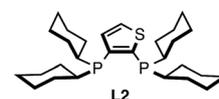
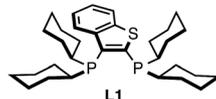
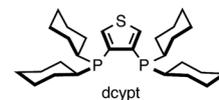
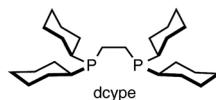
C–H arylation of imidazoles with phenol derivatives

Among the myriad of nickel catalysts for C–H arylation reported over the past decade from our group,^{10–12} Miura,¹⁵ and Chatani,¹⁶ our Ni(cod)₂/dcype (cod = 1,5-cyclooctadiene; dcype = 1,2-bis(dicyclohexylphosphino)ethane) catalyst with Cs₂CO₃ as the base in 1,4-dioxane as the solvent is well suited for the direct coupling of 1,3-azoles and phenol derivatives (C–H/C–O coupling). The selection of an appropriate ligand is crucial, as this reaction proceeds only when dcype is used. In contrast, this catalytic system was not affected by the choice of base and solvent since C2-functionalized azoles could be formed in the absence of base. Through several mechanistic investigations including the isolation of a catalytic intermediate, kinetic studies,^{11c} and theoretical calculations,^{11d} we have previously identified the ligand effect and a plausible catalytic cycle for the reaction. In particular, DFT calculations provided significant insight regarding the mechanism of the C–H nickelation steps: the formation of a Cs–Ni cluster was found to play a key role in accelerating C–H nickelation. However, experimentally and computationally, it has also been revealed that new catalytic conditions need to be developed for the C–H coupling of imidazoles.

With these considerations in mind, we focused on the investigation of base and solvent effects by using *N*-methylbenzimidazole (**1A**) and phenyl carbamate **2a** as model substrates (Table 1). Our previous Ni(cod)₂/dcype-based catalytic conditions, employing Cs₂CO₃ and 1,4-dioxane, afforded no coupling products (entry 1). An intensive and thorough investigation led to the discovery that the combination of K₃PO₄ and *t*-amyl alcohol (*t*-amylOH) could facilitate the C–H arylation

Table 1 Screening of the reaction conditions^a

Entry	Ligand	Base	Solvent	3Aa ^b (%)
1	dcype	Cs ₂ CO ₃	1,4-Dioxane	0
2	dcype	K ₃ PO ₄	<i>t</i> -AmylOH	83
3	dcype	K ₃ PO ₄	<i>t</i> -BuOH	70
4	dcype	K ₃ PO ₄	1,4-Dioxane	0
5	dcype	K ₃ PO ₄	DMF	0
6	dcype	K ₃ PO ₄	<i>i</i> -PrOH	0
7	dcype	Cs ₂ CO ₃	<i>t</i> -AmylOH	44
8	dcype	LiOt-Bu	<i>t</i> -AmylOH	59
9	dcype	KOt-Bu	<i>t</i> -AmylOH	0
10	PCy ₃	K ₃ PO ₄	<i>t</i> -AmylOH	0
11	IPr·HCl	K ₃ PO ₄	<i>t</i> -AmylOH	0
12	dcypt	K ₃ PO ₄	<i>t</i> -AmylOH	55
13	L1	K ₃ PO ₄	<i>t</i> -AmylOH	53
14	L2	K ₃ PO ₄	<i>t</i> -AmylOH	64
15 ^c	dcype	K ₃ PO ₄	<i>t</i> -AmylOH	82



^a Unless otherwise noted, the reaction conditions were as follows: **1A** (0.40 mmol), **2a** (1.5 equiv.), Ni(cod)₂ (10 mol%), ligand (bidentate: 12 mol%, monodentate: 24 mol%), base (3.0 equiv.), solvent (1.6 mL), 110 °C, and 12 h. ^b GC yield. ^c Ni(OTf)₂ (10 mol%) was used.

of **1A** to afford **3Aa** in 83% yield (entry 2). The replacement of *t*-amylOH with *t*-BuOH gave **3Aa** in slightly lower yield (entry 3). When the base and/or the solvent were changed, the reaction efficiency diminished. For example, the use of aprotic solvents and secondary alcohol solvents was completely ineffective for this reaction (entries 4–6). Additionally, the reaction in the presence of Cs₂CO₃ or LiOt-Bu resulted in lower yields than with K₃PO₄ (entries 7 and 8). While we initially thought that *in situ*-generated potassium tertiary alkoxides might be the reactive species, this seems not to be the case; the use of KOt-Bu completely shut down the catalytic activity (entry 9). Regarding the ligand effect, PCy₃ and an *N*-heterocyclic carbene ligand were inactive for the present reaction (entries 10 and 11). Our thiophene-based diphosphine ligand, dcypt (3,4-bis(dicyclohexylphosphino)thiophene),¹⁷ as well as other dcype derivatives such as L1 and L2 furnished **3Aa** in moderate yields (entries 12–14). To our delight, the replacement of Ni(cod)₂ with Ni(OTf)₂ as the pre-catalyst maintained the catalytic activity (entry 15). Considering the significant advantage of using air-stable Ni(OTf)₂, we decided to use the Ni(OTf)₂/dcype catalyst and K₃PO₄ in *t*-amylOH for further studies.

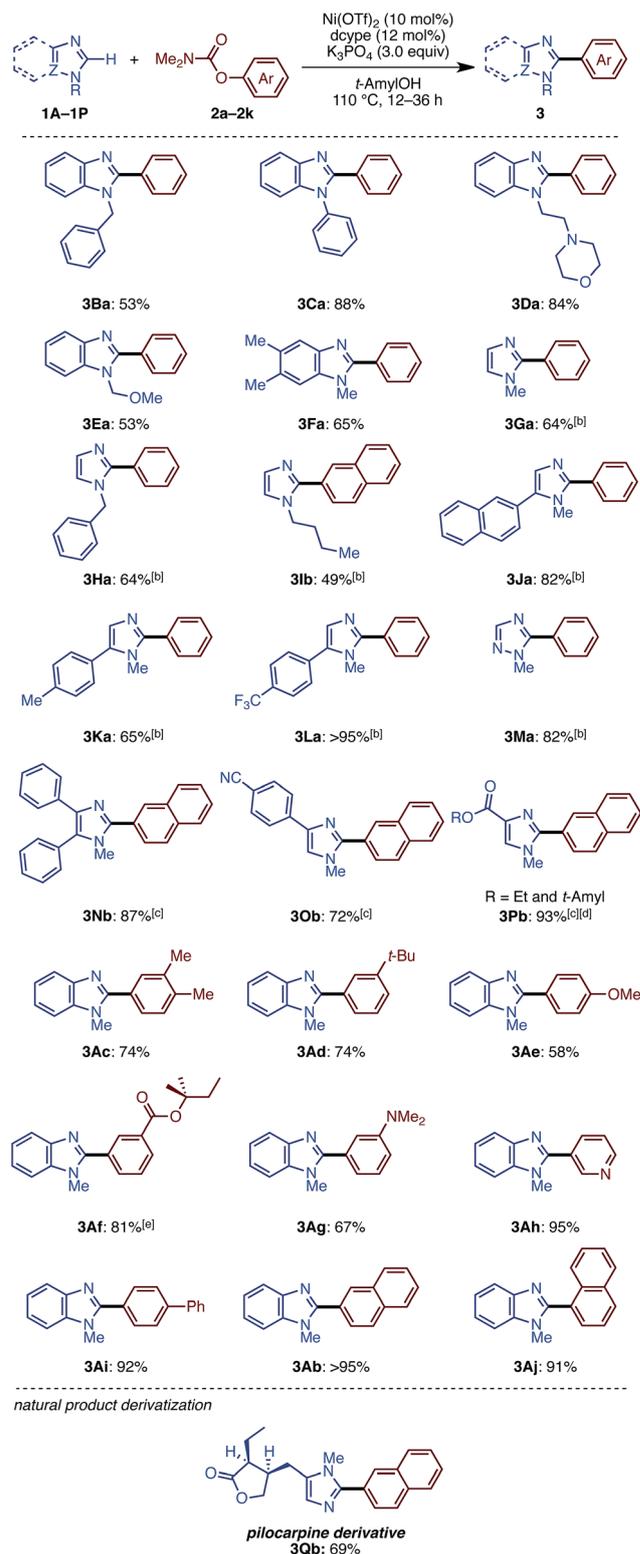


We then examined the substrate scope of the Ni(OTf)₂/dcypt-catalyzed C–H arylation (C–H/C–O coupling) of imidazoles **1** with carbamates of phenol derivatives **2** (Scheme 1). Several *N*-substituted benzimidazoles such as *N*-benzyl (**1B**), phenyl (**1C**), morpholinoethyl (**1D**), and methoxymethyl benzimidazoles (**1E**) underwent C–H/C–O coupling to afford the corresponding products in moderate to excellent yields. In addition to benzimidazoles, imidazoles were also successfully coupled with phenol derivatives **2**, although it was necessary to use Ni(cod)₂ as the catalyst precursor as well as a longer reaction time. In general, the coupling proceeded smoothly with the substrates having electron-withdrawing groups on the phenyl rings at the C5 position of the imidazole ring. For example, the reaction of trifluoromethyl-substituted 5-arylimidazole furnished triaryl **3La** in a superior yield (>95%) than that for the methyl-substituted triaryl **3Ka** (65%). Although the reason remains unclear at this stage, the dcypt ligand gave better results for the coupling of C4-substituted imidazoles (**1N**, **1O**, and **1P**). Notably, triazole **1M** also underwent C–H/C–O coupling with **2a** to afford 5-phenyl *N*-methyl-1,2,4-triazole (**3Ma**) in 82% yield. Regarding aryl electrophiles, a broad functional group tolerance was observed. An amino group or nitrogen heterocycle, which often behaves as a catalyst-deactivating group, did not inhibit the reaction; **3Da**, **3Ag**, and **3Ah** were obtained in good to excellent yields. Although transesterification took place with *t*-amylOH when the ethoxycarbonyl-substituted phenol electrophile **2f** was used, the product **3Af** was generated in good yield. Delightfully, we could directly functionalize pilocarpine (**1Q**), which is a drug for the treatment of a dry mouth,¹⁸ in 69% yield without any lactone opening or epimerization at the α -position of the carbonyl group. It should be emphasized that this coupling reaction proceeds with high regioselectivity at the C2 position of the imidazole rings.

C–H alkenylation of imidazoles with enol derivatives

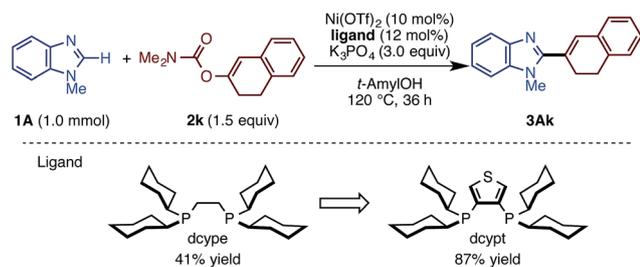
Following our previous success of the Ni-catalyzed C–H alkenylation of oxazoles with enol derivatives,^{11b,19} we envisioned that alkenylation of imidazoles would be feasible under a Ni(OTf)₂/diphosphine/K₃PO₄/*t*-amylOH system. The use of C–O alkenyl electrophiles for coupling reactions is advantageous because they can be easily prepared from the corresponding ketones and aldehydes. Motivated by the fact that the alkenyl group is a versatile platform in organic synthesis, we next embarked on the development of the C–H/C–O alkenylation of imidazoles (Scheme 2). Although the coupling reaction of **1A** and **2k** under Ni(OTf)₂/dcypt catalysis is feasible, it provided the alkenylated product **3Ak** in only 41% yield. While changes in base and solvent did not lead to the improvement of the reaction yield, the Ni(OTf)₂/dcypt catalyst dramatically boosted the reaction efficiency, providing the coupling product **3Ak** in 87% yield.

It turns out that this newly discovered Ni(OTf)₂/dcypt catalytic system can effectively facilitate the imidazole C–H alkenylation with broad scope (Scheme 3). As with the case of biaryl couplings, several *N*-alkylated benzimidazoles (such as **1D** and **1R**) could couple with enol carbamates. Both of the enol carbamates synthesized from α - and β -tetralones were reactive with

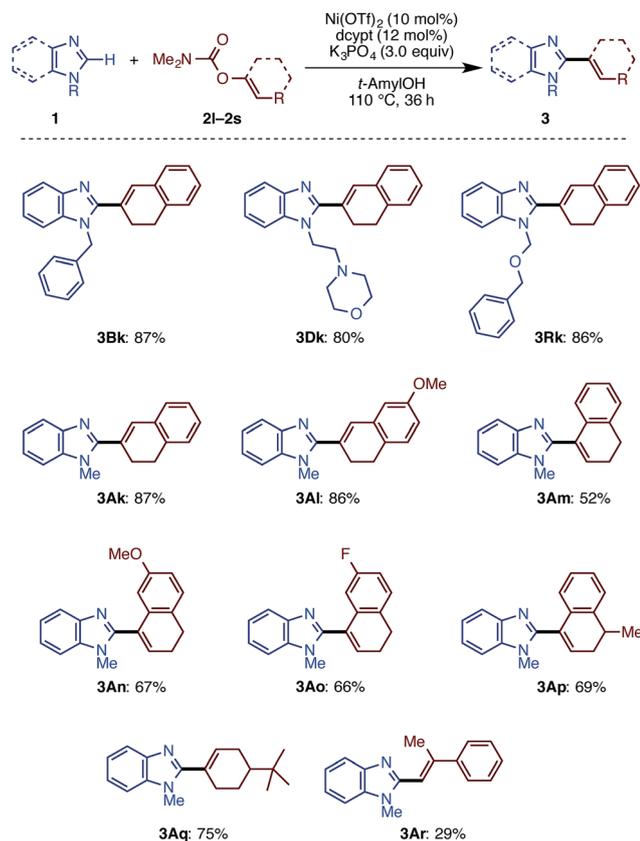


Scheme 1 Substrate scope of imidazole C–H arylation with phenol derivatives. ^a Unless otherwise noted, the reaction conditions were as follows: **1** (0.40 mmol), **2** (1.5 equiv.), Ni(OTf)₂ (10 mol%), dcypt (12 mol%), K₃PO₄ (3.0 equiv.), *t*-amylOH (1.6 mL), 110 °C, and 12–36 h. ^b Ni(cod)₂ (10 mol%) was used. ^c Ni(cod)₂ (10 mol%) and dcypt (12 mol%) were used. ^d Starting from ethyl 4-imidazolecarboxylate **1P**. (R = Et: 33%; *t*-amyl: 60%). ^e Starting from methyl 3-((dimethylcarbamoyl)oxy)benzoate (**2f**).





Scheme 2 Dramatic effect of dcypt ligand in the C–H alkenylation of imidazoles.

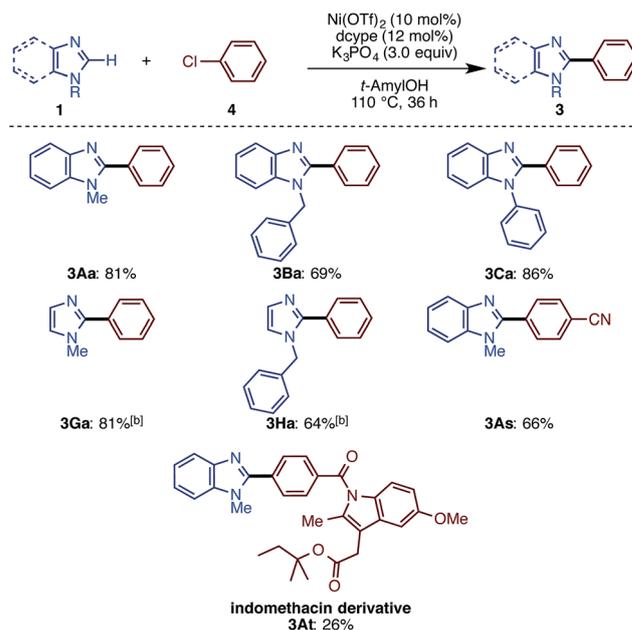


Scheme 3 Scope of imidazole C–H alkenylation with $\text{Ni}(\text{OTf})_2/\text{dcypt}$.^a Unless otherwise noted, the reaction conditions were as follows: **1** (1.0 mmol), **2** (1.5 equiv.), $\text{Ni}(\text{OTf})_2$ (10 mol%), dcypt (12 mol%), K_3PO_4 (3.0 equiv.), *t*-AmylOH (4.0 mL), 120 °C, and 36 h.

the $\text{Ni}(\text{OTf})_2/\text{dcypt}$ catalyst to afford the coupling products **3Al–3Ap**. Cyclohexenyl benzimidazoles could be synthesized from cyclohexanone derived electrophiles. The aldehyde-derived enol derivative **2r** also coupled with **1A**, but its rather fast decomposition under the reaction conditions turned out to be somewhat problematic. It is known that C–OMe^{14a,e} and C–F bonds²⁰ can be cleaved with nickel complexes, but these groups were completely tolerated in the present Ni-catalyzed coupling reaction.

C–H arylation of imidazoles with chloroarenes

While we mainly focused on the use of C–O electrophiles in this study, it was found that the newly developed $\text{Ni}(\text{OTf})_2/\text{dcypt}/$



Scheme 4 C–H arylation of imidazoles with chloroarenes with $\text{Ni}(\text{OTf})_2/\text{dcypt}$.^a Unless otherwise noted, the reaction conditions were as follows: **1** (0.40 mmol), **4** (1.5 equiv.), $\text{Ni}(\text{OTf})_2$ (10 mol%), dcypt (12 mol%), K_3PO_4 (3.0 equiv.), *t*-AmylOH (1.6 mL), 110 °C, and 36 h. ^b $\text{Ni}(\text{cod})_2$ (10 mol%) was used.

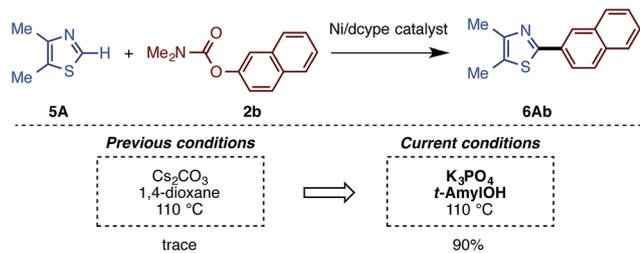
$\text{K}_3\text{PO}_4/t$ -AmylOH system is also effective for imidazole arylation with chloroarenes. As shown in Scheme 4, a range of imidazoles and benzimidazoles cross-coupled with chlorobenzene derivatives under the standard conditions. *N*-Methyl, -phenyl, and -benzyl benzimidazoles underwent C–H arylation with chlorobenzene (**4a**) to deliver phenylated imidazoles in good yield. *N*-Methyl and -benzyl imidazoles also reacted as well. Nitrile-substituted aryl chloride **4s** furnished the corresponding product **3As** in good yield. Although the reaction yield was low (26%), we could apply the indomethacin derivative **4t** to the reaction to give **3At**, but with significant amounts of a homo-dimerization by-product. Very interestingly, the reactions of aryl iodides and bromides in turn resulted in poor or zero yields of product.

C–H arylation and alkenylation of other 1,3-azoles

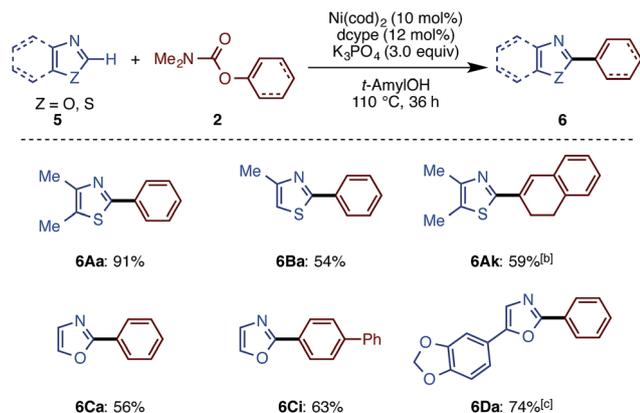
The present catalytic protocols were found to be applicable not only for imidazoles, but also for thiazoles and oxazoles. While our previous catalyst, employing $\text{Ni}(\text{cod})_2/\text{dcypt}/\text{Cs}_2\text{CO}_3$ in 1,4-dioxane, was effective for oxazoles and thiazoles (in particular for benzo-fused substrates),¹¹ coupling was not efficient for relatively electron-rich azoles. For example, the reaction of 4,5-dimethylthiazole (**5A**) with naphthyl carbamate **2b** under the previous conditions furnished no coupling product. Thus, we applied our new protocol with K_3PO_4 and *t*-AmylOH to the reaction of the previously unreactive azole **5A**. Gratifyingly, **5A** and **2b** cross-coupled very smoothly under the present conditions to furnish **6Ab** in 90% yield (Scheme 5).

Depicted in Scheme 6 are the results of the Ni-catalyzed reactions of the other 1,3-azoles. In addition to thiazoles,





Scheme 5 Comparison of the previous and current conditions for the reaction of thiazole 5A.



Scheme 6 C–H arylation and alkenylation of oxazoles and thiazoles with $\text{Ni}(\text{OTf})_2/\text{dcype}/\text{K}_3\text{PO}_4$ in *t*-amyOH. ^a Unless otherwise noted, the reaction conditions were as follows: 5 (0.40 mmol), 2 (1.5 equiv.), $\text{Ni}(\text{OTf})_2$ (10 mol%), dcype (12 mol%), K_3PO_4 (3.0 equiv.), *t*-amyOH (1.6 mL), 110 °C, and 36 h. ^b $\text{Ni}(\text{OTf})_2$ (10 mol%) and dcype (12 mol%) were used. ^c $\text{Ni}(\text{OTf})_2$ (10 mol%) and dcype (12 mol%) were used.

oxazoles were also found to be good substrates, generating the corresponding coupling products in good yields. Although previous alkenylation reactions with C–O electrophiles were limited to the reaction of oxazoles, the present Ni-catalyzed reaction in *t*-amyOH was also applicable to thiazoles.

Plausible mechanism

We succeeded in developing new catalytic systems to significantly expand the C–H/C–O coupling of 1,3-azoles with phenol/enol-based electrophiles, but we feel that the basic catalytic cycle with $\text{Ni}(\text{OTf})_2/\text{diphosphine}/\text{K}_3\text{PO}_4/\text{t}$ -amyOH should be similar to those operating under the previous conditions. First, $\text{Ni}(\text{OTf})_2$ should be reduced to a nickel(0) species by the action of diphosphine (dcype or dcyp) and/or an imidazole substrate to initiate a Ni(0)/Ni(II) redox cycle as shown in Fig. 3. Oxidative addition of the C–O or C–Cl bond of the electrophile to Ni(0) **A** affords intermediate **B**. Then, base-promoted C–H nickelation of imidazoles, followed by reductive elimination would furnish the coupling products with regeneration of the active Ni(0) species. Previously, we successfully isolated and characterized intermediate **B** by using naphthalen-2-yl-pivalate as a C–O electrophile,^{11c} which supports our hypothesized catalytic cycle. The remaining question is how the new conditions (particularly

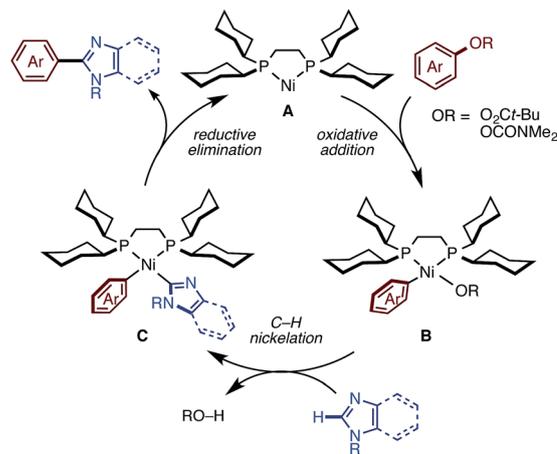


Fig. 3 A plausible catalytic cycle.

the activation modes of K_3PO_4 and *t*-amyOH) allow imidazoles to participate in this catalytic cycle. We are currently focusing on uncovering these phenomena experimentally and theoretically.

Conclusions

In summary, we have established a general protocol for the nickel-catalyzed C–H coupling of imidazoles. The newly discovered conditions, employing a catalytic amount of $\text{Ni}(\text{OTf})_2/\text{dcype}$ or $\text{Ni}(\text{OTf})_2/\text{dcyp}$ and K_3PO_4 in *t*-amyOH, enable direct C–C bond-forming reactions of imidazoles including C–H/C–O arylations and alkenylations. The C–H arylation of imidazoles with chloroarenes as well as that of thiazoles and oxazoles with phenol/enol derivatives can also be achieved with this catalytic system. The key to the success of the new nickel-catalyzed system is the choice of a tertiary alcohol as solvent, as neither aprotic solvents nor secondary alcohols were effective. We believe that the present method provides significant opportunities to synthesize and derivatize valuable functionalized imidazoles.

Acknowledgements

This work was supported by the ERATO program from JST (K. I.), KAKENHI (25708005 to J. Y.) from MEXT, and a JSPS research fellowship for young scientists (to K. M.). We thank Ryosuke Takise (Nagoya University) for providing phosphine ligands. ITbM is supported by the World Premier International Research Center (WPI) Initiative, Japan.

Notes and references

- 1 L. D. Luca, *Curr. Med. Chem.*, 2006, **13**, 1.
- 2 M. R. Grimmett, *Imidazole and Benzimidazole Synthesis*, Academic Press, London, 1997.
- 3 (a) M. Kosugi, M. Koshiba, A. Atoh, H. Sano and T. Migita, *Bull. Chem. Soc. Jpn.*, 1986, **59**, 677; (b) A. S. Bhanu Prasad,



- T. M. Stevenson, J. R. Citineni, V. Nyzam and P. Knochel, *Tetrahedron*, 1997, **53**, 7237.
- 4 For reviews, see: (a) L. Ackermann, R. N. Vicente and A. R. Kapdi, *Angew. Chem., Int. Ed.*, **48**, 9792; (b) X. Chen, K. M. Engle, D.-H. Wang and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2009, **48**, 5094; (c) D. Alberico, M. E. Scott and M. Lautens, *Chem. Rev.*, 2007, **107**, 174; (d) J. Wencel-Delord and F. Glorius, *Nat. Chem.*, 2013, **5**, 369; (e) J. Yamaguchi, A. D. Yamaguchi and K. Itami, *Angew. Chem., Int. Ed.*, 2012, **51**, 8960; (f) Y. Segawa, T. Maekawa and K. Itami, *Angew. Chem., Int. Ed.*, 2014, **54**, 66.
- 5 For Pd-catalyzed C–H coupling of imidazoles, see: (a) J. M. Joo, B. B. Touré and D. Sames, *J. Org. Chem.*, 2010, **75**, 4911; (b) L.-C. Campeau, D. R. Stuart, J.-P. Leclerc, M. Bertrand-Laperle, E. Villemure, H.-Y. Sun, S. Lasserre, N. Guimond, M. Lecavallier and K. Fagnou, *J. Am. Chem. Soc.*, 2009, **131**, 3291; (c) D. Zhao, W. Wang, S. Lian, F. Yang, J. Lan and J. You, *Chem.–Eur. J.*, 2009, **15**, 13370.
- 6 For Rh-catalyzed C–H coupling of imidazoles, see: (a) J. C. Lewis, S. H. Wiedemann, R. G. Bergman and J. A. Ellman, *Org. Lett.*, 2003, **6**, 35; (b) J. C. Lewis, J. Y. Wu, R. G. Bergman and J. A. Ellman, *Angew. Chem., Int. Ed.*, 2006, **45**, 1589; (c) J. C. Lewis, A. M. Berman, R. G. Bergman and J. A. Ellman, *J. Am. Chem. Soc.*, 2008, **130**, 2493; (d) J. C. Lewis, R. G. Bergman and J. A. Ellman, *Acc. Chem. Res.*, 2008, **41**, 1013.
- 7 For Cu-catalyzed C–H coupling of imidazoles, see: (a) H.-Q. Do and O. Daugulis, *J. Am. Chem. Soc.*, 2007, **129**, 12404; (b) H.-Q. Do, R. M. K. Khan and O. Daugulis, *J. Am. Chem. Soc.*, 2008, **130**, 15185; (c) D. Zhao, W. Wang, F. Yang, J. Lan, L. Yang, G. Gao and J. You, *Angew. Chem., Int. Ed.*, 2009, **48**, 3296; (d) O. Daugulis, H.-Q. Do and D. Shabashov, *Acc. Chem. Res.*, 2009, **42**, 1074.
- 8 (a) S. Yanagisawa, T. Sudo, R. Noyori and K. Itami, *J. Am. Chem. Soc.*, 2006, **128**, 11748; (b) B. Join, T. Yamamoto and K. Itami, *Angew. Chem., Int. Ed.*, 2009, **48**, 3644; (c) S. Yanagisawa, K. Ueda, H. Sekizawa and K. Itami, *J. Am. Chem. Soc.*, 2009, **131**, 14622; (d) K. Ueda, S. Yanagisawa, J. Yamaguchi and K. Itami, *Angew. Chem., Int. Ed.*, 2010, **49**, 8946; (e) S. Kirchberg, S. Tani, K. Ueda, J. Yamaguchi, A. Studer and K. Itami, *Angew. Chem., Int. Ed.*, 2011, **50**, 2387; (f) K. Mochida, K. Kawasumi, Y. Segawa and K. Itami, *J. Am. Chem. Soc.*, 2011, **133**, 10716; (g) D. Mandal, A. D. Yamaguchi, J. Yamaguchi and K. Itami, *J. Am. Chem. Soc.*, 2011, **133**, 19660; (h) K. Kawasumi, Q. Zhang, Y. Segawa, L. T. Scott and K. Itami, *Nat. Chem.*, 2013, **5**, 739; (i) S. Tani, T. N. Uehara, J. Yamaguchi and K. Itami, *Chem. Sci.*, 2014, **5**, 123; (j) K. Ueda, K. Amaike, R. M. Maceiczky, K. Itami and J. Yamaguchi, *J. Am. Chem. Soc.*, 2014, **136**, 13226; (k) A. D. Yamaguchi, K. M. Chepiga, J. Yamaguchi, K. Itami and H. M. L. Davies, *J. Am. Chem. Soc.*, 2015, **137**, 644; (l) T. Kawakami, K. Murakami and K. Itami, *J. Am. Chem. Soc.*, 2015, **137**, 2460; (m) Y. Saito, Y. Segawa and K. Itami, *J. Am. Chem. Soc.*, 2015, **137**, 5193; (n) S. Suzuki, Y. Segawa, K. Itami and J. Yamaguchi, *Nat. Chem.*, 2015, **7**, 227; (o) K. Ozaki, K. Kawasumi, M. Shibata, H. Ito and K. Itami, *Nat. Commun.*, 2015, **6**, 6251.
- 9 For recent reviews on nickel-catalyzed reactions, see: (a) S. Z. Tasker, E. A. Standley and T. F. Jamison, *Nature*, 2014, **509**, 299; (b) J. Yamaguchi, K. Muto and K. Itami, *Eur. J. Org. Chem.*, 2013, 19.
- 10 (a) J. Canivet, J. Yamaguchi, I. Ban and K. Itami, *Org. Lett.*, 2009, **11**, 1733; (b) T. Yamamoto, K. Muto, M. Komiyama, J. Canivet, J. Yamaguchi and K. Itami, *Chem.–Eur. J.*, 2011, **17**, 10113.
- 11 (a) K. Muto, J. Yamaguchi and K. Itami, *J. Am. Chem. Soc.*, 2012, **134**, 169; (b) L. Meng, Y. Kamada, K. Muto, J. Yamaguchi and K. Itami, *Angew. Chem., Int. Ed.*, 2013, **52**, 10048; (c) K. Muto, J. Yamaguchi, A. Lei and K. Itami, *J. Am. Chem. Soc.*, 2013, **135**, 16384; (d) H. Xu, K. Muto, J. Yamaguchi, C. Zhao, K. Itami and D. G. Musaev, *J. Am. Chem. Soc.*, 2014, **136**, 14834.
- 12 K. Amaike, K. Muto, J. Yamaguchi and K. Itami, *J. Am. Chem. Soc.*, 2012, **134**, 13573.
- 13 Reviews on C–O activation: (a) B.-J. Li, D.-G. Yu, C.-L. Sun and Z.-J. Shi, *Chem.–Eur. J.*, 2011, **17**, 1728; (b) B. M. Rosen, K. W. Quasdorf, D. A. Wilson, N. Zhang, A.-M. Resmerita, N. K. Garg and V. Percec, *Chem. Rev.*, 2011, **111**, 1346; (c) D.-G. Yu, B.-J. Li and Z.-J. Shi, *Acc. Chem. Res.*, 2010, **43**, 1486; (d) T. Mesganaw and N. K. Garg, *Org. Process Res. Dev.*, 2013, **17**, 29; (e) S. I. Kozhushkov, H. K. Potukuchi and L. Ackermann, *Catal. Sci. Technol.*, 2013, **3**, 562; (f) M. Tobisu and N. Chatani, *Acc. Chem. Res.*, 2015, **48**, 1717.
- 14 For representative examples of C–O activation, see: (a) M. Tobisu, T. Shimasaki and N. Chatani, *Angew. Chem., Int. Ed.*, 2008, **47**, 4866; (b) B.-T. Guan, Y. Wang, B.-J. Li, D.-G. Yu and Z.-J. Shi, *J. Am. Chem. Soc.*, 2008, **130**, 14468; (c) K. W. Quasdorf, X. Tian and N. K. Garg, *J. Am. Chem. Soc.*, 2008, **130**, 14422; (d) K. W. Quasdorf, A. Antoft-Finch, P. Liu, A. L. Silberstein, A. Komaromi, T. Blackburn, S. D. Ramgren, K. N. Houk, V. Snieckus and N. K. Garg, *J. Am. Chem. Soc.*, 2011, **133**, 6352; (e) C. Zarate and R. Martin, *J. Am. Chem. Soc.*, 2014, **136**, 2236; (f) C. Zarate, R. Manzano and R. Martin, *J. Am. Chem. Soc.*, 2015, **137**, 6754.
- 15 (a) H. Hachiya, K. Hirano, T. Satoh and M. Miura, *Org. Lett.*, 2009, **11**, 1737; (b) H. Hachiya, K. Hirano, T. Satoh and M. Miura, *Angew. Chem., Int. Ed.*, 2010, **49**, 2202; (c) H. Hachiya, K. Hirano, T. Satoh and M. Miura, *ChemCatChem*, 2010, **2**, 1403.
- 16 For review, see: (a) L. C. M. Castro and N. Chatani, *Chem. Lett.*, 2015, **44**, 410 For representative examples, see: (b) M. Tobisu, I. Hyodo and N. Chatani, *J. Am. Chem. Soc.*, 2009, **131**, 12070; (c) Y. Aihara and N. Chatani, *J. Am. Chem. Soc.*, 2013, **135**, 5308; (d) Y. Aihara and N. Chatani, *J. Am. Chem. Soc.*, 2014, **136**, 898; (e) Y. Aihara, M. Tobisu, Y. Fukumoto and N. Chatani, *J. Am. Chem. Soc.*, 2014, **136**, 15509.
- 17 (a) R. Takise, K. Muto, J. Yamaguchi and K. Itami, *Angew. Chem., Int. Ed.*, 2014, **53**, 6791; (b) E. Koch, R. Takise, A. Studer, J. Yamaguchi and K. Itami, *Chem. Commun.*, 2015, **51**, 855; (c) K. Muto, J. Yamaguchi, D. G. Musaev and K. Itami, *Nat. Commun.*, 2015, **6**, 7508.
- 18 P. C. Fox, *Arch. Intern. Med.*, 1991, **151**, 1149.



- 19 (a) Y. Nakao, K. S. Kanyiva, S. Oda and T. Hiyama, *J. Am. Chem. Soc.*, 2006, **128**, 8146; (b) K. S. Kanyiva, F. Löbermann, Y. Nakao and T. Hiyama, *Tetrahedron Lett.*, 2009, **50**, 3463; (c) Y. Nakao, K. S. Kanyiva and T. Hiyama, *J. Am. Chem. Soc.*, 2008, **130**, 2448; (d) C.-C. Tsai, W.-C. Shih, C.-H. Fang, C.-Y. Li, T.-G. Ong and G. P. A. Yap, *J. Am. Chem. Soc.*, 2010, **132**, 11887.
- 20 For representative examples of C–F activation by Ni catalysts, see: (a) N. Yoshikai, H. Matsuda and E. Nakamura, *J. Am. Chem. Soc.*, 2009, **131**, 9590; (b) M. Tobisu, T. Xu, T. Shimasaki and N. Chatani, *J. Am. Chem. Soc.*, 2011, **133**, 19505.

