Nickel-catalyzed alkyne annulation by anilines: versatile indole synthesis by C–H/N–H functionalization†

Weifeng Song and Lutz Ackermann*

Versatile nickel catalysts enabled the step-economical synthesis of decorated indoles through alkyne annulations with anilines bearing removable directing groups. The C–H/N–H activation strategy efficiently occurred in the absence of any metal oxidants and with excellent selectivities.

Indoles are key structural motifs in bioorganic chemistry, drug discovery and medicinal chemistry. Therefore, there is a continuous strong demand for chemo- and site-selective syntheses of this heteroaromatic scaffold. While palladium-catalyzed C–C and C–N bond forming reactions have been particularly proven to be valuable for the preparation of indoles, these transformations largely relied on prefunctionalized starting materials. Significantly more step-economical strategies are represented by methods that capitalize upon unactivated C–H bonds as latent functional groups. As of yet, solely expensive second-row transition metal catalysts, such as rhodium, palladium, or ruthenium complexes, have been utilized for indole syntheses by oxidative alkyne annulation through C–H/N–H bond functionalizations. Furthermore, these methods relied on the use of copper(II) or silver(I) salts as the sacrificial oxidants—a notable advantage over previously developed protocols. Notably, there was accomplished by Chatani and coworkers with a versatile isoquinoline synthesis from arenes bearing electron-withdrawing amides. However, the atom-economic nature of this approach was compromised by the need for a specific, less atom-economical bidentate directing group. In consideration of the practical importance of modular indole syntheses, we became interested in developing unprecedented nickel-catalyzed alkyne annulations by electron-rich anilines, which we wish to report herein.

Notable features of our strategy are not limited to (a) the use of easily removable, monodentate directing groups, (b) a high catalytic efficacy with challenging electron-rich anilines, and (c) in contrast to previous indole syntheses, oxidative alkyne annulations devoid of copper(II) or silver(I) salts as the sacrificial oxidants (Scheme 1).

We commenced our studies by identifying the reaction conditions for the envisioned nickel-catalyzed indole synthesis with pyridyl-substituted aniline 1a (Table 1). Among a variety of ligands, bidentate dppf, in combination with Ni(cod)2, proved to be optimal (entries 1–9). We were pleased to find that stoichiometric amounts of copper(II) or silver(I) salts were not required as sacrificial oxidants—a notable advantage over previously developed protocols. Interestingly, the formation of indole 3aa occurred most efficiently in the absence of solvents (entries 10–14), thereby further improving the environmentally-benign nature of our approach. Control experiments verified that the formation of indole 3aa was neither achieved in the absence of Ni(cod)2 nor without the dppf ligand (entries 15 and 16). Moreover, our studies revealed that representative palladium or cobalt complexes in lieu of the nickel(0) catalyst were ineffective (entries 17 and 18).

With an optimized catalytic system in hand, we explored its versatility in the oxidative annulation of alkyne 2a (Scheme 2). Given that the N-2-pyrimidyl group is easily removed from the indole nucleus, we focused our studies on the use of N-pyrimidyl-substituted anilines 1. We were delighted to find that the challenging pyrimidyl-substituted substrate 1b was converted with a comparably high efficacy compared to reactions with the more electron-rich aniline 1a. The optimized...
Nickel(0) catalyst proved to be widely applicable, and allowed for the use of functionalized as well as sterically hindered ortho-substituted anilines, thereby furnishing the desired indoles. It is particularly notable that reactive electrophilic functional groups, such as the chloro, acetyl or cyano substituents, were well tolerated, which should prove instrumental for further derivatization of the thus obtained products.

Subsequently, we tested the scope of the nickel catalyst with a representative set of substituted alkynes (Scheme 3). We observed that tolane derivatives featuring either electron-donating or electron-withdrawing groups were efficiently converted by the optimized nickel complex. However, the catalytic system was not restricted to tolanes. Indeed, dialkylalkyne provided the desired product as well. Importantly, the C–H/N–H bond functionalization with the unsymmetrical alkyne yielded the corresponding indole with an excellent regioselectivity.

For future practical applications it is important to note that the 2-pyrimidyl group was easily removed from indole to deliver the corresponding NH-free indole (Scheme 4).

Considering the remarkable reactivity of the nickel(0) catalyst, we became interested in rationalizing its mode of action. To this end, we conducted intramolecular competition experiments with meta-substituted anilines. Here, the site-selectivity of the C–H bond functionalization was largely governed by steric interactions, while a fluoro-substituent led to significant amounts of product through C–H bond functionalization at the C-2 position (Scheme 5).

Furthermore, intermolecular competition experiments with differently substituted alkynes highlighted arylacetylenes to be preferentially converted (Scheme 6a), while electron-deficient arenes were found to be more reactive (Scheme 6b). These experimental

Table 1 Optimization of the nickel-catalyzed oxidative annulation

| Entry | [TM] | Ligand | Solvent | Yield (%) |
|-------|------|--------|---------|-----------|
| 1     | Ni(cod)_2 | TMEDA | PhMe  | —         |
| 2     | Ni(cod)_2 | Terpyridine | PhMe | —         |
| 3     | Ni(cod)_2 | PPh_3 | PhMe  | 40        |
| 4     | Ni(cod)_2 | dcpp | PhMe  | —         |
| 5     | Ni(cod)_2 | rac-BINAP | PhMe | 21        |
| 6     | Ni(cod)_2 | dppp | PhMe  | 30        |
| 7     | Ni(cod)_2 | DPEPhos | PhMe | 30        |
| 8     | Ni(cod)_2 | Xantphos | PhMe | 43        |
| 9     | Ni(cod)_2 | dppf | PhMe  | 48        |
| 10    | Ni(cod)_2 | dppf | PhMe  | 63        |
| 11    | Ni(cod)_2 | dppf | m-Xylene | 45    |
| 12    | Ni(cod)_2 | dppf | o-Xylene | 35    |
| 13    | Ni(cod)_2 | PPh_3 | —     | 65        |
| 14    | Ni(cod)_2 | dppf | —     | 82        |
| 15    | Ni(cod)_2 | dppf | PhMe  | —         |
| 16    | Ni(cod)_2 | dppf | m-Xylene | 45    |
| 17    | Ni(cod)_2 | dppf | o-Xylene | 35    |
| 18    | Ni(cod)_2 | dppf | PPh_3 | —         |
| 19    | Ni(cod)_2 | dppf | —     | 82        |
| 20    | Ni(cod)_2 | dppf | PhMe  | —         |

Scheme 2 Nickel-catalyzed oxidative annulation with anilines 1.
findings are in good agreement with a rate-determining migratory alkyne insertion.

Furthermore, we performed oxidative annihilations with isotopically labeled substrate [D]-1b (Scheme 7), revealing a considerable H/D exchange. Notably, scrambling with the free N–H functionality exclusively occurred at the ortho-positions of the arene. These results, thus, provide strong support for an initial reversible C–H/N–H bond activation event to be operative.

Based on our mechanistic studies we consequently propose the catalytic cycle to involve an initial reversible C–H/N–H bond activation of aniline 1. Subsequent migratory insertion and reductive elimination furnish the desired indole 3a and regenerate the catalytically active nickel complex.

In summary, we have reported an unprecedented nickel-catalyzed oxidative alkyne annihilation by electron-rich anilines with removable directing groups. The C–H/N–H bond functionalizations proceed with excellent chemoselectivity and site-selectivities in the absence of metal salts as oxidants, thereby furnishing substituted indoles with a broad scope. Experimental mechanistic studies provided support for reversible C–H/N–H bond activation, and are suggestive of a rate-limiting migratory alkyne insertion.

Support by the European Research Council under the European Community’s Seventh Framework Program (FP7 2007–2013)/ERC Grant agreement no. 307535 and the Chinese Scholarship Council (fellowship to W.S.) is gratefully acknowledged.

Notes and references

1. J. Alvarez-Builla, J. J. Vaquero and J. Barluenga, Modern Heterocyclic Chemistry, Wiley-VCH, Weinheim, 2011.
2. Select reviews on the preparation of indoles: (a) S. Cacchi, G. Fabrizi and A. Goggiamani, Org. React., 2012, 76, 281; (b) S. Cacchi, G. Fabrizi and A. Goggiamani, Org. Biomol. Chem., 2011, 9, 641; (c) K. Krüger, A. Tillack and M. Beller, Adv. Synth. Catal., 2008, 350, 2153; (d) L. Ackermann, Synlett, 2007, 507; (e) D. A. Horton, G. T. Bourne and M. L. Smythe, Chem. Rev., 2003, 103, 893 and references cited therein.
3. Selected reviews on C–H functionalizations: (a) N. Kuhl, M. N. Hopkinson, J. Wencel-Delord and F. Glorius, Angew. Chem., Int. Ed., 2012, 51, 10236; (b) J. Yamaguchi, A. D. Yamaguchi and K. Itami, Angew. Chem., Int. Ed., 2012, 51, 8960; (c) K. M. Engle, T.-S. Mei, M. Wasa and J.-Q. Yu, Acc. Chem. Res., 2012, 45, 788; (d) L. McMurray, F. O’Hara and F. Glorius, Chem. Soc. Rev., 2011, 40, 1885; (e) J. Wencel-Delord, T. Dröge, F. Liu and F. Glorius, Chem. Soc. Rev., 2011, 40, 4740; (f) L. Ackermann, Chem. Rev., 2011, 111, 1315; (g) M. Livendale and A. M. Echavarren, Isr. J. Chem., 2010, 50, 630; (h) P. Thansandote and M. Lautens, Chem.–Eur. J., 2009, 15, 5874.
4. [Rh]: (a) H. Wang, C. Grohmann, C. Nimphius and F. Glorius, J. Am. Chem. Soc., 2012, 134, 19592; (b) M. P. Huestis, L. N. Chan, D. R. Stuart and K. Fagnou, Angew. Chem., Int. Ed., 2011, 50, 1338; (c) J. Chen, G. Song, C.-L. Pan and X. Li, Org. Lett., 2012, 14, 5242; (d) D. R. Stuart, M. Bertrand-Laperle, K. M. Burgess and K. Fagnou, J. Am. Chem. Soc., 2008, 130, 16474; (e) D. R. Stuart, P. Alsabeh, M. Kuhn and K. Fagnou, J. Am. Chem. Soc., 2010, 132, 8326. Activated alkenes: (f) R. Bernini, G. Fabrizi, A. Sferrazza and S. Piacchi, Angew. Chem., Int. Ed., 2009, 48, 8078. [Pd]: (g) Z. Shi, C. Zhang, S. Li, D. Pan, S. Ding, Y. Cui and N. Jiao, Angew. Chem., Int. Ed., 2009, 48, 4572; (h) S. Würtz, S. Rakshit, J. J. Neumann, T. Dröge and F. Glorius, Angew. Chem., Int. Ed., 2008, 47, 7230. [Ru]: (i) L. Ackermann and A. V. Lygin, Org. Lett., 2012, 14, 764 and references cited therein.
5. Recent reviews: (a) L. Ackermann, Acc. Chem. Res., 2013, 46, DOI: 10.1021/ar300279b; (b) G. Song, F. Wang and X. Li, Chem. Soc. Rev., 2012, 41, 3651; (c) T. SATOH and M. Miura, Chem.–Eur. J., 2010, 16, 11212.
6. Reviews on the use of inexpensive first-row transition metal catalysts for C–H functionalization: (a) N. Yoshikai, Synlett, 2011, 1047; (b) Y. Nakao, Chem. Rev., 2011, 111, 242; (c) E. Nakamura and N. Yoshikai, J. Org. Chem., 2010, 75, 6061; (d) A. Uchikawa and O. Daugulis, Synthesis, 2009, 4087.
7. Nickel-catalyzed C–H functionalizations: (a) Y. Aihara and N. Chatani, J. Am. Chem. Soc., 2013, 135, 5308; (b) K. Muto, J. Yamaguchi and K. Itami, J. Am. Chem. Soc., 2012, 134, 169; (c) R. Tamura, Y. Yamada, Y. Nakao and T. Hiyama, Angew. Chem., Int. Ed., 2012, 51, 5679; (d) T. Yao, K. Hirano, T. Satoh and M. Miura, Angew. Chem., Int. Ed., 2012, 51, 775; (e) L. Ackermann, B. Punji and W. Song, Adv. Synth. Catal., 2011, 353, 3325; (f) O. Vechorkin, V. Proust and X. Hu, Angew. Chem., Int. Ed., 2010, 49, 3661; (g) H. Hachiya, K. Hirano, T. Satoh and M. Miura, Angew. Chem., Int. Ed., 2010, 49, 2202; (h) H. Hachiya, K. Hirano, T. SATOH and M. Miura, Org. Lett., 2009, 11, 1737; (i) J. Canivet, J. Yamaguchi, I. Ban and K. Itami, Org. Lett., 2009, 11, 1733.
8. H. Shiotani, Y. Ano, Y. Aihara, Y. Fukumoto and N. Chatani, J. Am. Chem. Soc., 2011, 133, 14952.
9. Careful analysis of the reaction mixtures revealed the alkyne to serve as the formal hydrogen acceptor.
10. The oxidative annihilation of 1-phenylpropyne by substrate 1a gave a low conversion of 25% as judged by GC analysis.
11. (a) D. Balc edition, E. Clot and O. Eisenstein, Chem. Rev., 2010, 110, 749; (b) E. Clot, C. Megret, O. Eisenstein and R. N. Perutz, J. Am. Chem. Soc., 2009, 131, 7817.
12. Catalytic annihilations of 1-ocytane or a TMS-substituted internal alkyne were thus far unsuccessful.