C–H Activation

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Iron-Catalyzed C(sp^2)–H and C(sp^3)–H Arylation by Triazole Assistance**

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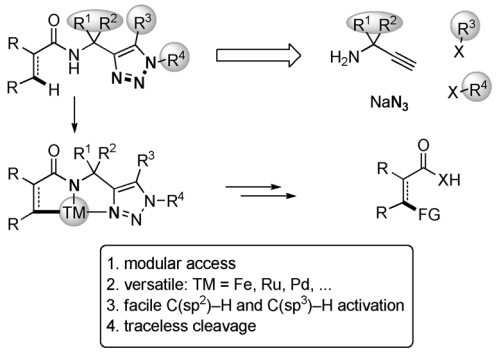
Abstract: *Modular 1,2,3-triazoles enabled iron-catalyzed C–H arylations with broad scope. The novel triazole-based bidentate auxiliary is easily accessible in a highly modular fashion and allowed for user-friendly iron-catalyzed C(sp^2)–H functionalizations of arenes and alkenes with excellent chemo- and diastereoselectivities. The versatile iron catalyst also proved applicable for challenging C(sp^3)–H functionalizations, and proceeds by an organometallic mode of action. The triazole-assisted C–H activation strategy occurred under remarkably mild reaction conditions, and the auxiliary was easily removed in a traceless fashion. Intriguingly, the triazole group proved superior to previously used auxiliaries.*

The use of nonprecious metal catalysts for C–C bond-forming reactions is highly attractive, because of the cost-effective nature of these naturally abundant compounds.[1–3] Considerable advances have been accomplished, in particular, with inexpensive iron complexes. Methods for the functionalization of otherwise unreactive C–H bonds have received considerable recent attention,[4,5] because they avoid the synthesis and use of prefunctionalized starting materials.[6] The organic substrates of interest usually display a multitude of C–H bonds with comparable dissociation energies. Therefore, controlling site selectivity is of central importance for the development of synthetically useful C–H activation procedures. One of the most powerful strategies exploits chelation assistance.[7] Monodentate Lewis-basic functionalities embedded in the substrate have thus proven instrumental for advancing the field of C–H activation.[4] The studies by Daugulis and co-workers indicated the power of bidentate directing groups derived from 8-aminoquinoline,[8,9] which set the stage for novel approaches for bond disconnection.[10] The practical importance of the 8-aminoquinoline directing group was particularly highlighted by a very recent elegant iron-catalyzed direct functionalization devised by Nakamura and co-workers.[11] Despite remarkable advances achieved with bidentate directing groups, this approach continues to be restricted largely to the 8-aminoisoquinoline auxiliary, and structural modifications thereof are challenging to realize in a modular fashion.[9] In consideration of these severe limitations, we became intrigued in establishing a novel family of highly modular bidentate directing groups for C–H activation. At the outset, we identified the following key criteria as our prime guidelines for the molecular design. First, the bidentate scaffold should be easily accessible under mild reaction conditions. Second, the auxiliary would need to be available in a highly modular fashion so as to guarantee the prerequisite flexibility for C–H functionalizations with different transition-metal catalysts. Third, the electronic nature of the bidentate auxiliary should ensure high catalytic efficacy in the elementary step of the C–H activation. Fourth, the bidentate directing group would need to be removable in a traceless manner.

Herein, we report on a novel concept that successfully addresses all of these key challenges by exploiting easily accessible 1,2,3-triazoles, which are available in a modular fashion through copper(I)-catalyzed 1,3-dipolar Huisgen cycloadditions[12] between diversely substituted alkynes and azides (Scheme 1). It is noteworthy that our strategy was widely applicable, as illustrated by the effective iron-catalyzed direct functionalizations of arenes, alkenes, and even unactivated alkanes through C(sp^2)–H and C(sp^3)–H activation with excellent chemo-, site-, and diastereoselectivities.



Scheme 1. Triazole-assisted C–H activation strategy.

We initiated our studies by preparing a representative set of novel benzamides **1** containing 1,2,3-triazoles through Huisgen cycloadditions under mild reaction conditions (see the Supporting Information). We then probed various reaction conditions for the iron-catalyzed C–H bond arylation[13] of triazolyldimethylmethyl (TAM) amide **1a**. Detailed optimization studies revealed C–H functionalizations to be viable

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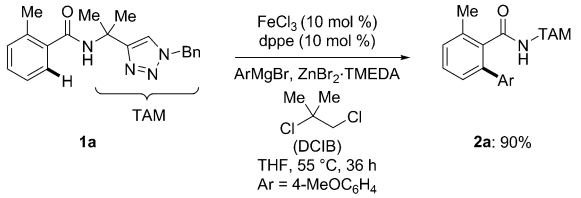
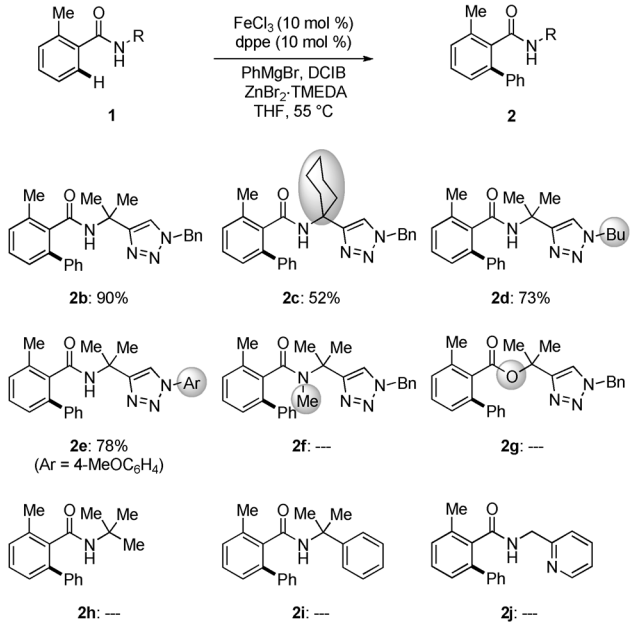
with a catalyst system consisting of $FeCl_3$ as the metal source and dppe as the ligand (see Tables S1 and S2 in the Supporting Information). With this system, direct arylations proceeded efficiently on the benzamides **1a** under considerably mild[14] reaction conditions (Scheme 2). It is noteworthy that an iron catalyst derived from the dppe ligand previously only provided an unsatisfactory low yield (9%) when using the 8-aminoquinoline auxiliary.[11]



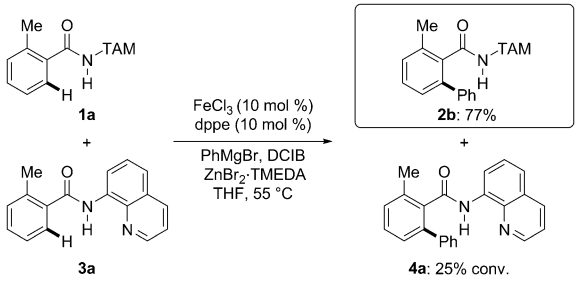
Scheme 2. Optimized reaction conditions for iron-catalyzed C–H arylation. dppe = 1,2-bis(diphenyphosphanyl)ethane, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, Bn = benzyl.

The optimized iron catalyst also proved amenable to substrate **1c** with a spiro substitution pattern in the amide backbone (Scheme 3). Likewise, the *N*-alkyl- and *N*-aryl-substituted triazole **1d**,**e** were converted efficiently into the desired products. However, in line with the proposed bidentate mode of action, tertiary amide **1f** failed to undergo the C–H activation, thus highlighting the importance of the acidic, free NH functional group. In accordance with this hypothesis, the corresponding ester **1g** was not a viable substrate for the iron-catalyzed direct arylation. Simple secondary amides **1h**,**i**, being devoid of the second Lewis basic nitrogen atom, were not converted by the iron catalyst. Interestingly, a similar observation was made when using the pyridyl-substituted amide **1j**.



Scheme 3. Influence of the substitution pattern.

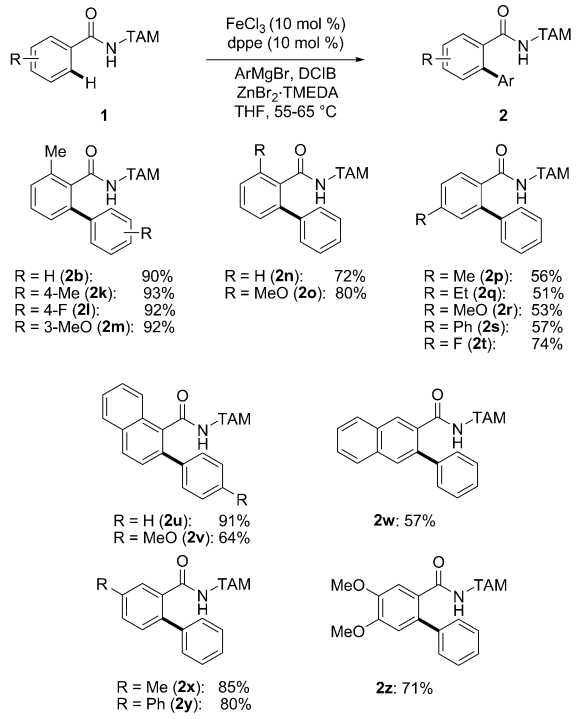
Intermolecular competition experiments between the triazole- and the quinolinyl-derived benzamides **1a** and **3a** clearly revealed the TAM group to display a significantly more powerful directing group ability (Scheme 4).



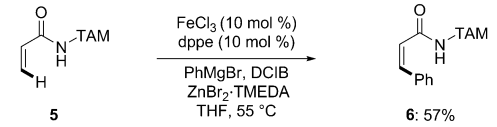
Scheme 4. Competition experiment.

Having identified the TAM group as the ideal substituent, we probed the scope of the optimized iron catalyst in C–H arylations of various substrates **1** (Scheme 5). Benzamides **1** with an *ortho*- or *para*-substitution pattern were efficiently converted into the corresponding products **2b–v**.[15] Substrates **1w–z** bearing two chemically inequivalent *ortho*-C–H bonds were site-selectively functionalized at the sterically less congested site within intramolecular competition experiments.

The user-friendly iron catalyst was not limited to C–H arylations of arenes, but also enabled alkenylic functionalizations (Scheme 6). It is noteworthy, that the formation of alkene **6** occurred with excellent diastereoselectivity, thereby delivering the thermodynamically less-stable *Z*-olefin as the sole product.

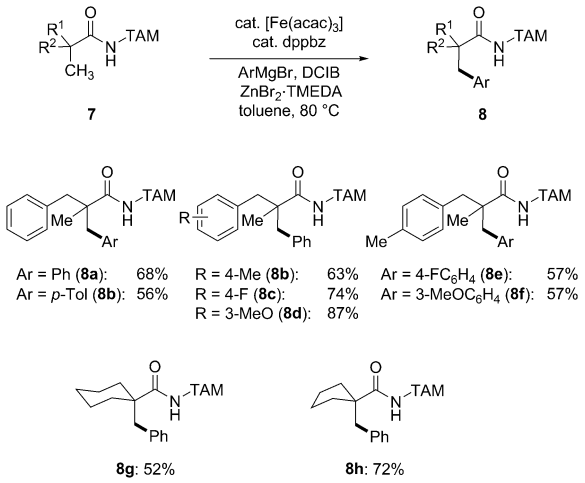


Scheme 5. Scope of the iron-catalyzed C–H arylation.



Scheme 6. Iron-catalyzed C–H arylation of alkene **5**.

Transformations of C(sp^2)–H bonds are favored by precoordination of the arene π system, and the resulting aryl–metal bonds are typically stronger than the corresponding alkyl–metal bonds. Hence, for both kinetic and thermodynamic reasons, metal-catalyzed functionalizations of unactivated C(sp^3)–H bonds are considered to be particularly challenging.[16] Therefore, we were pleased to find that iron catalysis in the presence of our modular triazole-based TAM auxiliary also resulted in the direct arylation of otherwise inert C(sp^3)–H bonds (Scheme 7).

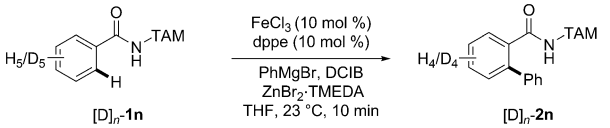


Scheme 7. Iron-catalyzed C(sp^3)–H arylations.

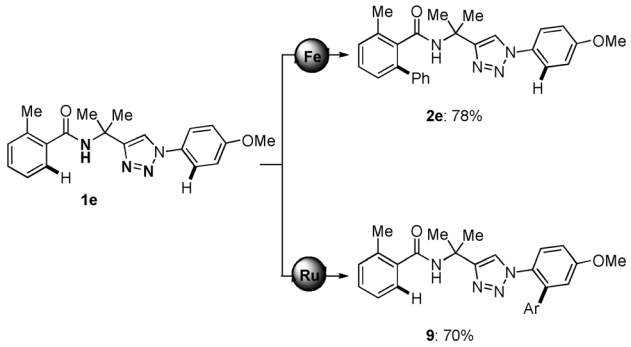
The selective functionalization of the primary over the secondary benzylic C–H bond in substrates **7a–f** renders an organometallic C–H activation mechanism likely to be operative. Further support for this hypothesis was gathered through experiments with the isotopically labeled substrate [D]$_5$-**1n**, which led to a considerable kinetic isotope effect (KIE) of $k_H/k_D \approx 1.8$ (Scheme 8).

Controlling site selectivity is not only crucial for the development of synthetically meaningful C–H functionalizations,[4,5] but is also mandatory for the late-stage diversification of functional molecules in medicinal chemistry, drug discovery, and material sciences.[17] Hence, it is noteworthy that we observed a complementary selectivity with *N*-aryl-substituted substrates **1e** (Scheme 9). Indeed, the judicious choice of a ruthenium(II) biscarboxylate complex[18] or the optimized iron catalyst allowed for direct arylations at either of the two aromatic moieties.

Finally, we were delighted to observe that the TAM directing group could be easily removed in a traceless fashion,



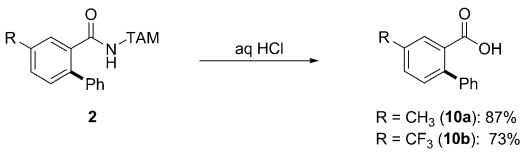
Scheme 8. Kinetic isotope effect studies.



Scheme 9. Complementary site selectivity of iron- versus ruthenium(II)-catalyzed C–H activation. Reaction conditions: [Fe]: $FeCl_3$ (10 mol%), dppe (10 mol%), PhMgBr, DCIB, $ZnBr_2$·TMEDA, THF, 55 °C, 36 h. [Ru]: [{$RuCl_2$(*p*-cymene)}$_2$] (2.5 mol%), $MesCO_2H$ (30 mol%), ArBr, K_2CO_3, toluene, 120 °C, 22 h. Ar = 4-MeC(O)C_6H_4.

thereby furnishing the desired products **10** in high yields (Scheme 10).

In summary, we have reported the development of a novel family of powerful auxiliaries for the catalyzed activation of



Scheme 10. Removal of the TAM group.

otherwise inert C(sp^2)–H and C(sp^3)–H bonds. The triazole-derived amides were easily accessible in a highly modular fashion through copper(I)-catalyzed 1,3-dipolar cycloadditions. The triazole auxiliary proved to be superior to the hitherto employed bidentate directing groups. Indeed, direct arylations with inexpensive iron catalysts efficiently proceeded on arenes and alkenes through chemo-, site-, and diastereoselective C(sp^2)–H bond arylations under mild reaction conditions. Interestingly, the iron catalysts displayed a complementary site selectivity compared to a ruthenium(II) biscarboxylate complex. The versatile iron catalyst also enabled high-yielding arylations of unactivated C(sp^3)–H bonds. Mechanistic studies provided strong support for an organometallic C–H activation by the versatile iron catalyst.

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