Graphical abstract

Rapid access to diverse indoles by addition/SNAr with grignard reagents and 2-fluorophenyl acetonitriles

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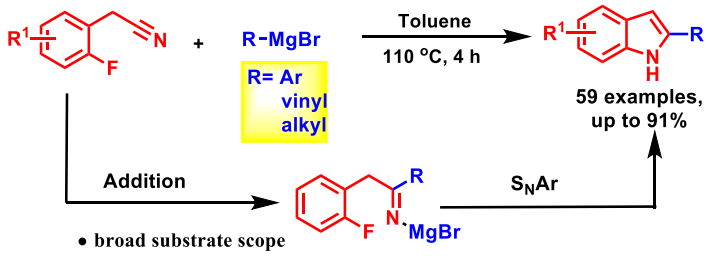

Indoles made easy! A simple method for the rapid synthesis of diversly substituted indoles (69 examples) is advanced. Using 2-fluorophenyl acetonitrile derivatives and aryl, heteroaryl, alkyl or vinyl Grignard reagents furnishes indoles in 45%–95% yields. The reactions involve the addition of the Grignard reagent to the nitrile followed by SNAr. Piggybacking on the indole synthesis with alkyl electrophiles affords 2,3-disubstituted derivatives in one-pot.

Article

Rapid Access to Diverse Indoles by Addition/S_NAr with Grignard Reagents and 2-Fluorophenyl Acetonitriles

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ABSTRACT

Indoles are essential heterocycles in natural products, biological chemistry, and medicinal chemistry. Efficient approaches to their synthesis, therefore, remain in demand. Herein is reported a novel and scalable method to produce a wide variety of indoles by combining Grignard reagents and 2-fluorobenzyl cyanides (59 examples, 45–95% yields). The Grignard reagent adds to the nitrile to give a metalated imine that undergoes S_NAr with unactivated C–F bonds. This strategy installs the R group of RMgX at the indole 2-position, and it is noteworthy that a diverse array of Grignard reagents (aryl, alkyl, vinyl, and cyclopropyl) provide the desired heterocyclic products. The resulting *N*-magnesiated indole can be in situ functionalized at the 3-position with alkyl halides or functionalized on the nitrogen with silyl chlorides. This method enables the synthesis of indoles with functional groups at each position of the indole backbone (C4–C7), providing handles for further functionalization.

1. Introduction

The unique heterocyclic structure and documented biological activity of indoles contribute to their vital role in medicinal chemistry [1,2] and their great value as building-blocks in the pharmaceutical industry [3-5]. Indole-based drugs are known to have antioxidant [6-11], anti-tumor [12-14], antifungal and anti-bacterial properties [15-17]. Due to their broad applications, many selective and economical syntheses have been introduced [18].

Classic routes for the synthesis of indoles include the Bischler-Möhlau indole synthesis [19,20] and Fischer indole synthesis [21]. Transition metal-catalyzed syntheses of indoles have greatly improved the flexibility and efficiency of their preparations [22-29]. The use of transition metals, however, often leads to undesirable trace metal contaminants that can be difficult and expensive to remove [30]. To address these issues, considerable progress has been made toward the synthesis of indoles under transition metal-free conditions. For example, Barluenga and co-workers were inspired by the Larock indole synthesis [31,32] and used IPy_2BF_4 in place of palladium to mediate the intramolecular cyclization of 2-ethynylaniline derivatives (Scheme 1a) [33]. This is an excellent method to access *N*-protected 3-iodoindoles. Drawing from the Hegedus indole synthesis [34-36], Muniz and co-workers employed PhIO to replace palladium to facilitate the oxidative isomerization of vinyl aniline derivatives (Scheme 1b) [37]. Schiedt's *N*-heterocyclic carbene-catalyzed methods of aza-ortho-azaquinone methide precursors and aldehydes for the synthesis of 2-aryl indoles are a valuable alternative [38].

Among the named indole syntheses, organometallic reagents, such as Grignard reagents and organolithium reagents, are often employed. For example, Bartoli and co-workers reported a method for the low-temperature synthesis of 7-substituted indole derivatives by employing nitrobenzene and alkenyl Grignard reagents (Scheme 1c) [39,40]. Smith and co-workers synthesized indoles at –78 °C with *N*-silylated anilines and esters in the presence of *n*-BuLi (Scheme 1d) [41]. Similarly, O'Shea and co-workers generated carbanions through the addition of organolithium reagents to styrenes followed by condensation with nitriles at –78 °C to obtain indole derivatives (Scheme 1e) [42]. Knochel and co-workers described an elegant organometallic variation of the Fischer indole synthesis using readily prepared aryldiazonium tetrafluoroborates and functionalized alkylzinc halides (Scheme 1f) [43,44]. Knochel's team also reported a method to prepare various functionalized indoles through intramolecular copper-mediated carbomagnesization of ynamides [45].

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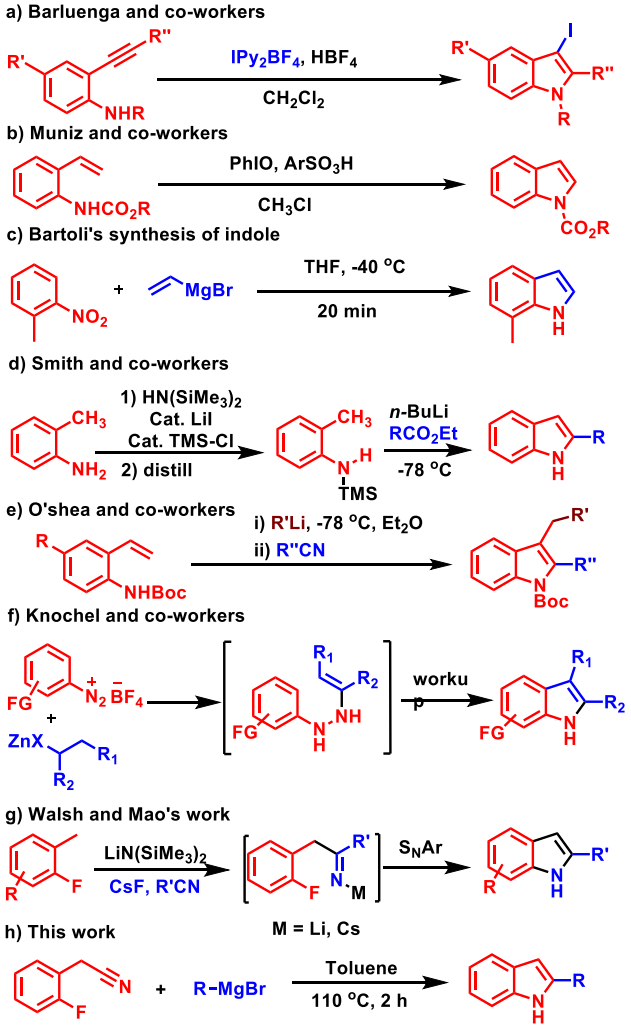
More recently, we developed an alternative route to access indoles from 2-fluorotoluenes and nitriles (Scheme 1g) [46] Many of the coupling partners of this synthesis are commercially available, increasing its appeal. The key findings in this work include: 1) the weakly acidic benzylic C–H bonds ($pK_a \approx 43$ in DMSO) could be reversibly deprotonated with commercially available bases [$MN(SiMe_3)_2$, M = Li, Na, K, $pK_a \approx 26$ for $HN(SiMe_3)_2$ in THF] [46-50] in the presence of Cs^+ sources and 2) this mild base exhibited excellent benzylic selectivity [50, 51], without reaction at the aromatic $C(sp^2)$–H bonds. A shortcoming of our indole synthesis is that only nitriles devoid of acidic α-C–H's were suitable [52]. Deprotonation of the cyano α-C–H's is a long-standing challenge in the reactions between organometallic reagents and aliphatic nitriles [53,54]. Herein we address some of the shortcomings of our prior work and report a general method to synthesize indoles from simple 2-(2-fluorophenyl)acetonitriles and a diverse array of Grignard reagents (Scheme 1h). Of particular note, this procedure does not require added transition metals nor does it need cryogenic temperatures that can be challenging to access on scale. Although such conditions are easily accessible on a small scale, as would be employed in many academic and medicinal chemistry laboratories, cryogenic temperatures can be a significant shortcoming in large-scale applications. Thus, we restricted our optimization studies to reactions at or above room temperature.



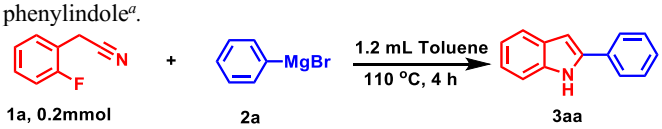
Scheme 1. Transition-metal-free synthesis of indoles.

2. Results and discussion

2.1 Reaction design.

We began our study using 2-fluorophenylacetonitrile (**1a**) and phenylmagnesium bromide (**2a**) as model substrates (Table 1). Toluene was used as the solvent with heating to 100 °C for 4 h to investigate the ratio of the nitrile and Grignard reagents (Table 1, entries 1–4). The AY of the target product reached 86% when 3 equiv of phenylmagnesium bromide was used (Table 1, entry 3, AY = assay yield determined by GC integration of the unpurified reaction mixture against an internal standard). Next, we screened the effect of reaction temperature on the efficiency of this transformation (Table 1, entries 5–8). The results showed that the yield reached 94% at 110 °C (Table 1, entry 7). A solvent evaluation (di*iso*propyl ether, 1,4-dioxane, cyclopentyl methyl ether, 2-methyltetrahydrofuran, *tert*-butyl methyl ether, and cyclohexane) under the conditions of entry 7 did not improve upon the results with toluene (Table 1, entries 9–13 *vs.* entry 7).

Table 1
Optimization of reaction conditions for the synthesis of 2-phenylindole[a].

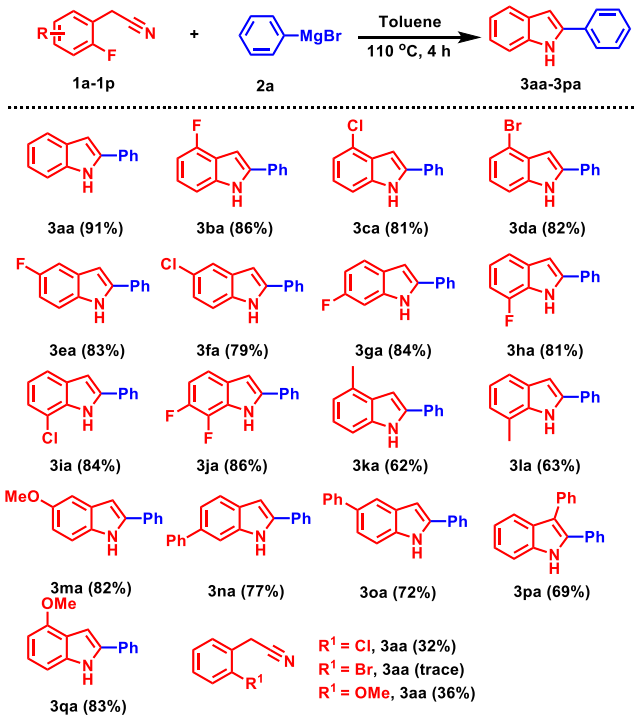


Entry[a]	PhMgBr (equiv.)	T (°C)	Time (h)	AY[b]
1	1	100	4	28
2	2	100	4	78
3	3	100	4	86
4	3.5	100	4	82
5	3	70	4	18
6	3	90	4	61
7	3	110	4	94
8	3	120	4	88
9[c]	3	110	4	70
10[d]	3	110	4	54
11[e]	3	110	4	62
12[f]	3	110	4	46
13[g]	3	110	4	< 70
14	3	110	8	92
15	3	110	12	88

[a] Reactions conducted under argon on a 0.2 mmol scale.
[b] Assay yield determined by GC integration with *n*-tetradecane as an internal standard.
[c] THF as solvent.
[d] DME as solvent.
[e] Diisopropyl ether as solvent.
[f] 1,4-Dioxane as solvent.
[g] Other solvents (CPME, 2-MeTHF, TBME and cyclohexane).

Further studies showed that longer reaction times decreased the yield of the indole product (Table 1, entries 14–15). Ultimately, the optimized conditions employed 1 equiv of 2-fluorophenylacetonitrile (**1a**), 3 equiv. of phenylmagnesium bromide (**2a**) and 1.2 mL toluene at 110 °C for 4 h (entry 7).

With the optimized reaction conditions in hand (Table 1, entry 7), we evaluated the scope of 2-fluorophenylacetonitrile derivatives with phenylmagnesium bromide (Scheme 2). In general, under our optimized conditions, various 2-fluorophenylacetonitrile derivatives with different substituents on the aryl ring were compatible with this method. The parent 2-fluorophenylacetonitrile was converted to **3aa** in a 91% isolated yield. 2-Fluorophenylacetonitriles containing halogen substituents at the C6 position, such as -F, -Cl and -Br, showed excellent reactivity. After isolation, indoles substituted at the C4 position (**3ba**–**3da**) were produced in 81%–86% yields. Likewise, 2-fluorophenylacetonitrile derivatives containing halogens in other positions furnished the corresponding target products **3ea**–**3ja** in 79%–86% yields. Thus, this method can enable the introduction of halogen substituents at each position of the indole backbone (C4–C7). It should be noted that these halogenated derivatives could be further elaborated by a variety of cross-coupling procedures.

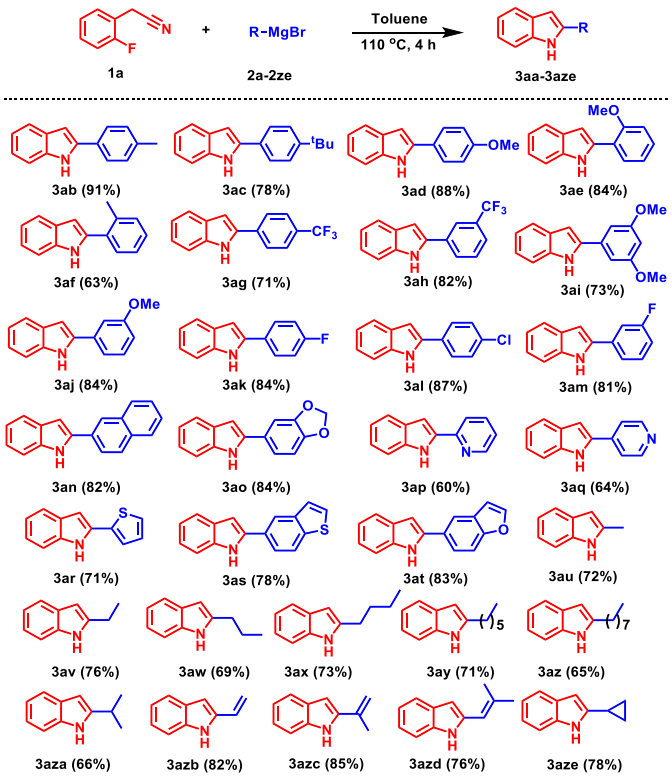


Scheme 2. The substrate scope of 2-fluorophenylacetonitrile.

2-Fluorophenylacetonitriles containing electron-donating substituents, such as 6-Me, 3-Me and 3-OMe, gave the indole products **3ka**–**3ma** in 62%–82% yields. 2-Fluorophenylacetonitriles containing 4-Ph or 5-Ph reacted smoothly with phenylmagnesium bromide to afford the desired products in 77% and 72% yields (**3ma**–**3oa**), respectively. We were concerned that a diaryl acetonitrile derivative, with its acidic benzylic C–H (pK_a = 17 in DMSO) [55], would undergo rapid deprotonation by the Grignard reagent. Surprisingly, the 2,3-diphenyl indole target product **3pa** was generated in 69% yield under standard conditions. It is worth noting that 2,3-disubstituted indoles could be obtained by cyclization of disubstituted alkynes with aniline derivatives. This cyclization approach often encounters chemoselectivity issues when unsymmetrical alkynes are employed [56,57]. 2-(2-Fluoro-6-methoxyphenyl) acetonitrile was also useful substrate, affording the desired product **3qa** in 83% yield. We were curious how the S_NAr would work if a methoxy group was substituted for the 2-fluoro leaving group. Despite the known leaving group ability of methoxy groups in S_NAr reactions [58-61], a 2-methoxy phenylacetonitrile substrate gave only a 36% yield of indole product. The 2-chloro derivative reacted similarly, affording only 32% yield of the indole product while the 2-bromo analogue gave trace conversion to the indole.

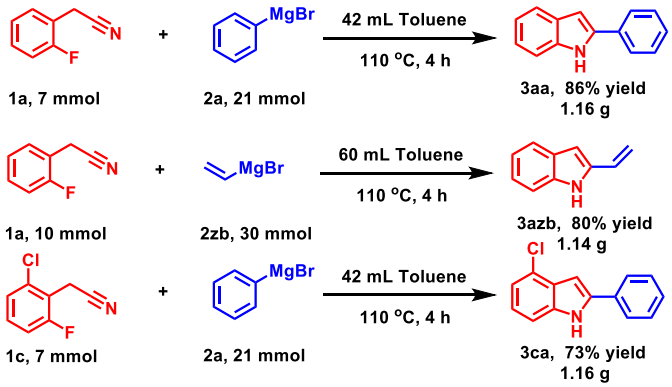
Next, we explored the substrate scope with various aryl Grignard reagents. We were pleased to find that a wide range of aryl and heteroaryl magnesium bromide derivatives could be easily converted into the desired indole products. As shown in Scheme 3, aryl magnesium bromides containing electron-donating functional groups, including 4-^{t}Bu, 4-OMe, 2-OMe and 2-Me, exhibited good to excellent reactivity, producing 2-arylindoles in 63%–91% yields (**3ab**–**3af**). The more sterically hindered 2-tolyl Grignard reagent reacted to give the indole in 63% yield. Aryl magnesium bromides bearing electron-withdrawing groups, such as 4-CF_3, 3-CF_3, 3,5-$(OMe)_2$ and 3-OMe were also suitable reagents, furnishing the products in 71%, 82%, 73% and 84% yields (**3ag**, **3ah**, **3ai** and **3aj**), respectively. Likewise, Grignard reagents containing halogen substituents (4-F, 4-Cl, 3-F) were also compatible, and the corresponding products **3ak**–**3am** were obtained in 81–87% yields. Among them, **3ak** and **3al** have known antioxidant properties [62]. π-Extended 2-naphthylmagnesium bromide gave the target product **3an** in 82% yield. Heterocyclic substrates are often found in bioactive compounds [2]. To our delight, pyridine, thiophene, benzothiophene, benzofuran and other heterocyclic Grignard reagents exhibited very good reactivity, furnishing the products **3ao**–**3at** in 60%–83% yield.

Alkyl Grignard reagents are more basic than their aryl analogues, with a greater likelihood of deprotonating the nitrile α-C–H's [54]. We next investigated if alkyl Grignard reagents were tolerated under our conditions. Fortunately, various alkyl Grignard reagents, such as methyl-, ethyl-, *n*-propyl-, *n*-butyl, *n*-hexyl- and *n*-octyl- were compatible, generating the desired products **3au–3az** in 65–76% yields. Our method was also suitable for sterically hindered isopropyl magnesium bromide and vinyl magnesium bromide. The corresponding products **3aza–3azd** were obtained in 66%–85% yields. Cyclopropyl magnesium bromide was found to be a viable reagent, furnishing the target product **3aze** in 78% yield. In medicinal chemistry, alkylation of substituted drug analogues is occasionally found to improve biological activity with the "magic methyl" effect being most well-recognized [63-65]. Thus, our tandem alkylation/cyclization process is potentially beneficial in medicinal chemistry.



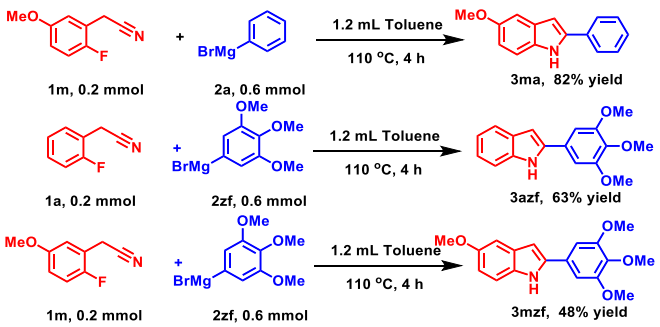
Scheme 3. Substrate scope of Grignard reagents.

To demonstrate the scalability of this transformation, we performed the synthesis of **3aa**, **3azb** and **3ca** on a gram scale and found that the desired products could be isolated in 86%, 80% and 73% yields, respectively (Scheme 4). We note that **3azb**, containing an exocyclic carbon-carbon double bond is primed for further functionalization, increasing its potential utility in medicinal chemistry. Additionally, the product **3ca** would be expected to undergo a series of derivatizations, such as Suzuki–Miyaura cross-coupling, cyanation, Buchwald–Hartwig amination, and alkynylation [46].



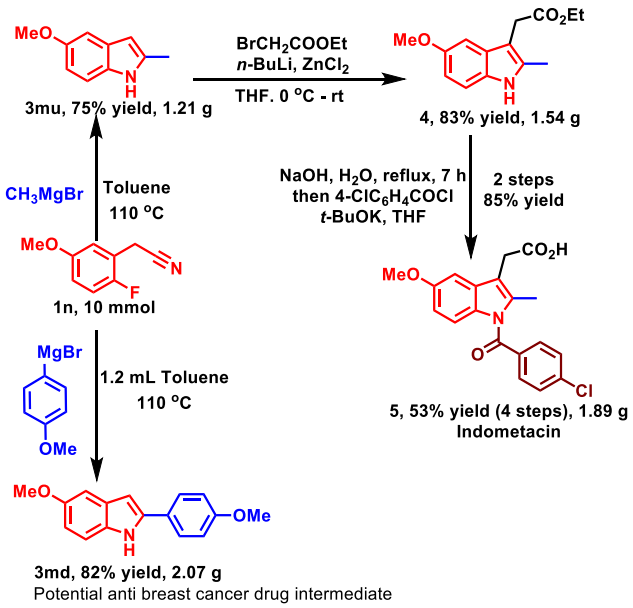
Scheme 4. Gram scale synthesis of **3aa**, **3azb** and **3ca**

Some 2-aryl indole derivatives are biologically active and are effective at inhibiting fungal and bacterial infections. For example, 5-methoxy-2-phenyl-1H-indole displays significant activity against the gram-positive pathogen *Bacillus cereus*. In addition, 2-(3,4,5-trimethoxyphenyl)-1*H*-indole and 5-methoxy-2-(3,4,5-trimethoxyphenyl)-1*H*-indole have antifungal activity against *Cryptococcus neoformans*[66]. By using 2-(2-fluoro-5-methoxyphenyl)acetonitrile (**1m**) and phenylmagnesium bromide (**2a**), we successfully obtained the target product 5-methoxy-2-phenyl-1*H*-indole (**3ma**) in 82% yield under the standard conditions (Scheme 5). Similarly, 2-(3,4,5-trimethoxyphenyl)-1*H* indole (**3azf**) and 5-methoxy-2-(3,4,5-trimethoxyphenyl)-1*H* indole (**3mzf**) were obtained in 63% and 48% yield, respectively .



Scheme 5. Synthesis of antibacterial and antifungal 2-arylindole

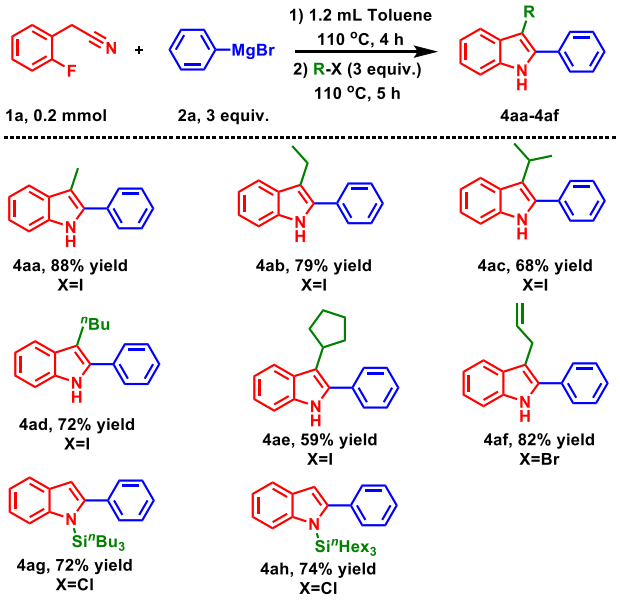
As an anti-inflammatory drug, Indomethacin relieves fever and inflammatory pain. It is often used in acute and chronic rheumatoid arthritis, gout and pain related to cancer [67]. Using our method, 1.23 g of **3mu**, which is the important intermediate for the synthesis of indomethacin, was obtained in 75% yield. Following the literature route to complete the synthesis, [67,68], 1.89 g of indomethacin was synthesized with a total yield of 53% using an additional three steps (Scheme 6, top). Compared to the previous methods, our method reduces the number of synthetic steps and increases the yield. Compound **3md** is an intermediate en route to a candidate to fight breast cancer [67]. In Scheme 6 (bottom) it was prepared using our standard conditions in 82% yield.



Scheme 6. Gram-scale synthesis of pharmaceuticals.

We expected that the first-formed products of our indole synthesis, before workup, would be deprotonated indoles. We envisioned that such intermediates might be more synthetically valuable if they could be trapped by the addition of a second electrophile. Thus, after refluxing the nitrile and Grignard reagent,

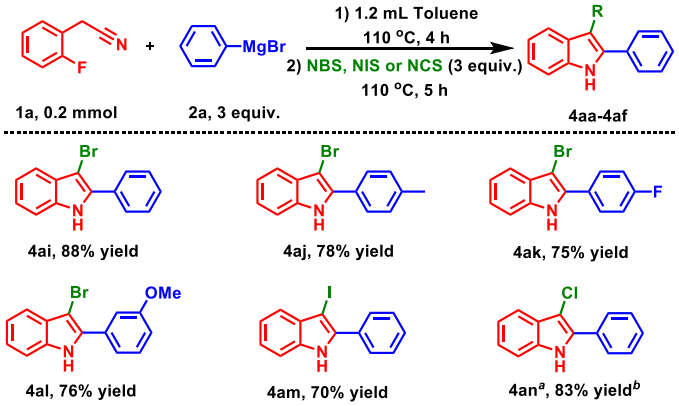
a variety of alkyl halide electrophiles were added to the reaction mixture with heating at 110 °C for 5 h. We were pleased to isolate a series of C3-substituted indoles (Scheme 7, **4aa**–**4af**, 59%–88% one-pot yields). Compared with the previous methods to synthesize 3-substituted indoles, this method omits the *N*-protection and -deprotection steps [69, 70]. When the electrophiles were changed from *C*-based to *Si*-based, the *N*-silylated indoles were obtained in 72%–74% yields (**4ag**–**4ah**). TMSCl and TESCl were also suitable electrophiles, but the corresponding *N*-silyl indole products were unstable and we could not isolate and purify them. Other electrophiles, such as phosphorus (Ph_2PCl) and boron reagents (Cl-Bpin and $B(OMe)_2Cl$) did not furnish the corresponding target products.



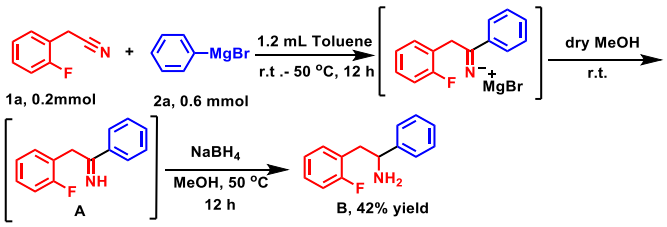
Scheme 7. One-pot synthesis of C3-substituted and *N*-substituted 2-aryl indoles.

The successful synthesis of C3-alkyl substituted indoles above made us wonder whether there were suitable electrophiles to capture the metallated indole intermediates that would lead to C3-halogenated indoles. C3-halogenated indoles are excellent partners for cross-coupling reactions and their synthesis would greatly increase the utility of this method. The results showed that NBS (*N*-bromosuccinimide), NIS (*N*-iodosuccinimide) and NCS (*N*-chlorosuccinimide) were suitable electrophiles. Thus, after refluxing the nitrile and Grignard reagent, NBS and NIS were added to the reaction mixture with heating at 110 °C for 5 h. We were pleased to isolate a series of C3-halogenated indoles (Scheme 8, **4ai**–**4am**) in 70–88% one-pot yields. When we use NCS as the electrophiles, the C3-chlorinated indoles (**4an**, 76-83% ^{1}H NMR yield) contained nearly half of the C3-brominated indole. If we reduce the amount of NCS to 2 equiv or less, the ratio of Br to Cl is about 3:1. The bromine originates from the Grignard reagents.

To gain insight into the mechanism and relative rates of these tandem processes, experiments were performed to isolate intermediates. We anticipated that the Grignard reagents react by addition to the nitrile to generate metalated imine intermediates **A**. Intermediate **A** then undergoes intramolecular nucleophilic aromatic substitution to afford the indole products. One of our goals was to determine if Grignard addition or S_NAr was faster. Despite extensive effort, we were not able to isolate intermediate **A**. When we conducted the reactions at a lower temperature (50 °C) for 12 h followed by quenching with dry MeOH and rapid addition of $NaBH_4$, the corresponding amine product **B** obtained in 42% yield (Scheme 9). These results demonstrated that the metalated imine intermediate is formed faster and undergoes slower S_NAr.



Scheme 8. One-pot synthesis of C3-halogenated 2-aryl indoles. [a] 3 equiv. or more NCS, Br: Cl = 1:1; 2 equiv or less NCS, Br: Cl = 3:1. [b] ^{1}H NMR yield using CH_2Br_2 as internal standard.



Scheme 9. Examination of intermediates.

We performed density functional theory (DFT) calculations to gain insight into the reaction mechanisms. The computed Gibbs free energy profile of the reaction pathway is shown in Figure 1. The nucleophilic addition of PhMgBr to 2-fluorophenyl acetonitrile (**1a**) via the transition state TS1 produces a metalated imine intermediate **A**, which is 10.2 kcal/mol lower in Gibbs free energy relative to **1a** and PhMgBr. This step requires a 19.2 kcal/mol free energy of activation. In TS1, the breaking C6–Mg bond is 2.21 Å and the forming C2–C6 and N1–Mg bonds are 2.12 Å and 2.04 Å, respectively. Intermediate **A** undergoes a concerted S_NAr process via a four-membered ring transition state TS2 to give the intermediate **B1** in which the fluorine atom is transferring from C5 to Mg with simultaneous C5–N1 bond formation. This step requires an activation-free energy of 26.6 kcal/mol. Attempts to locate transition states for a stepwise S_NAr process via a tetrahedral intermediate were unsuccessful. We speculate that this is due to the aromaticity loss cost that would be incurred in a stepwise S_NAr pathway. It is noteworthy that the C–N bond formation takes place on unactivated aryl fluorides and an anionic pentadienyl intermediate in the stepwise pathway is not stabilized by an electron withdrawing group.

Next, the N1–Mg bond cleavage occurs to release MgBrF and afford the intermediate **B2**. This process requires Gibbs free

energy of 15.6 kcal/mol. Subsequently, a second equiv of PhMgBr coordinates to the N1 center of **B2** to form **B3**. Intermediate **B3** undergoes deprotonation via the transition state **TS3,** leading to the generation of intermediate **C** and the release of a molecule of benzene. The deprotonation step requires an activation-free energy of 24.7 kcal/mol. Finally, intermediate **C** undergoes protonation via a four-membered ring transition state **TS4**. Here, one hydrogen atom in a water molecule is transferred to the nitrogen atom of intermediate **C**, leading to the formation of the product **3aa** together with the release of the formed MgBr(OH). The energy barrier of this step (**TS3**) is only 2.9 kcal/mol. Overall, the reaction of substrate **1a** with PhMgBr involves sequential nucleophilic addition, concerted S_NAr, deprotonation with the aid of a second equivalent of PhMgBr, and protonation upon workup to generate the product **3aa**. The concerted S_NAr has the highest activation-free energy (26.6 kcal/mol) and is suggested to be the rate-determining step. The activation free energy of 26.6 kcal/mol is too high for the overall reaction to take place at r.t., which is consistent with the experimental observation that heat is needed (110 °C).

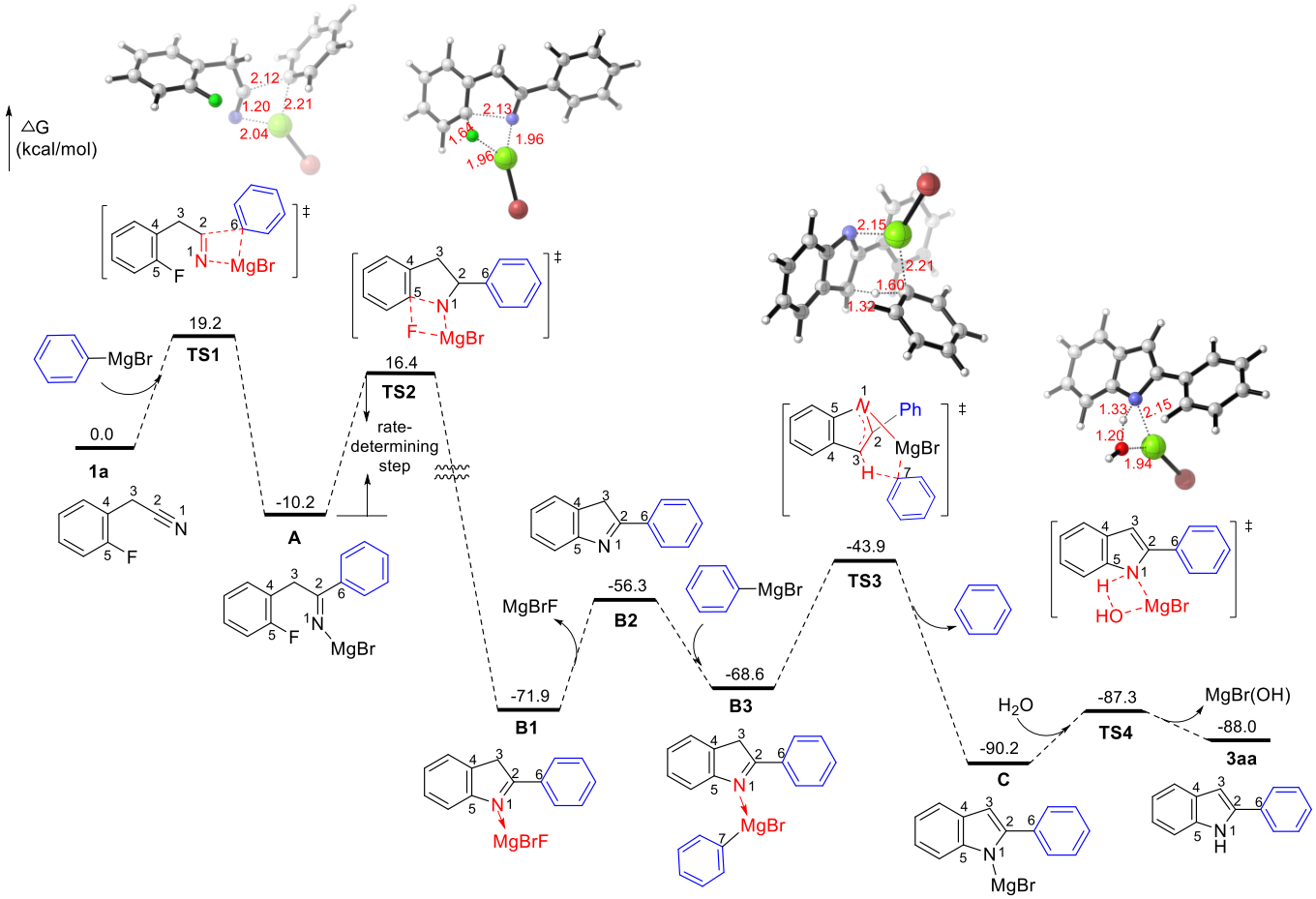


Figure 1. Gibbs free energy profile for the reaction of PhMgBr and 2-fluorophenyl acetonitrile (**1a**) to form indole **3aa**. Energies are calculated using M06-D3/def2-TZVP/SMD(toluene)//B3LYP-D3/ def2-SVP method.

To explore the origin of the site-selectivity of *C3*-alkylation and *N*-silylation of intermediate **C**, the model electrophiles CH_3–I and Me_3Si–Cl were employed. We calculated the nucleophilic attack with intermediate **C** on each of the two electrophiles (see Figure S1 for the Gibbs free energy profiles for the pathways). As shown in Figure 2a, the DFT calculations indicate that the attack of the metalated indole C3-position on CH_3–I via the transition state $\mathbf{TS_{C–C}}$ requires an activation-free energy of 31.5 kcal/mol. This cost is much lower than that calculated for an attack of N1 on CH_3–I via the transition state $\mathbf{TS_{C–N}}$ ($\Delta G^{\neq}$ = 45.8 kcal/mol). This result suggests that *C3*-alkylation is favored when using *C*-based electrophiles. In contrast, calculations with Me_3Si–Cl indicate an attack by N1 has a lower activation free energy ($\Delta G^{\neq}$ ($\mathbf{TS_{Si–N}}$) =26.3 kcal/mol compared to C3 on the $\Delta G^{\neq}$ ($\mathbf{TS_{Si–C}}$) = 32.1 kcal/mol, Figure 2b). Therefore, *N*-silylation is predicted when using *Si*-based electrophiles. These calculations are consistent with experimental observations. We further calculated the NPA charges on atoms of the reaction sites in CH_3–I, Me_3Si–Cl and intermediate **C** to explain the site-selectivity. Figure 2c shows that the C atom of CH_3–I has a partial negative charge (–0.411 e) while the Si atom of Me_3Si–Cl has a partial positive charge (0.533 e). Intermediate **C** has a more negative charge on N1 (–0.540) than on C3 (–0.349 e), indicating N1 is more basic than the C3 center. According to the "hard and soft acids and bases theory" (HSAB), the positively charged Si atom (strong acid) of Me_3Si–Cl prefers to react at the more negatively charged N1 (strong base) in intermediate **C**, while the partially negatively charged C atom (weak base) of CH_3–I is more likely to react at C3.

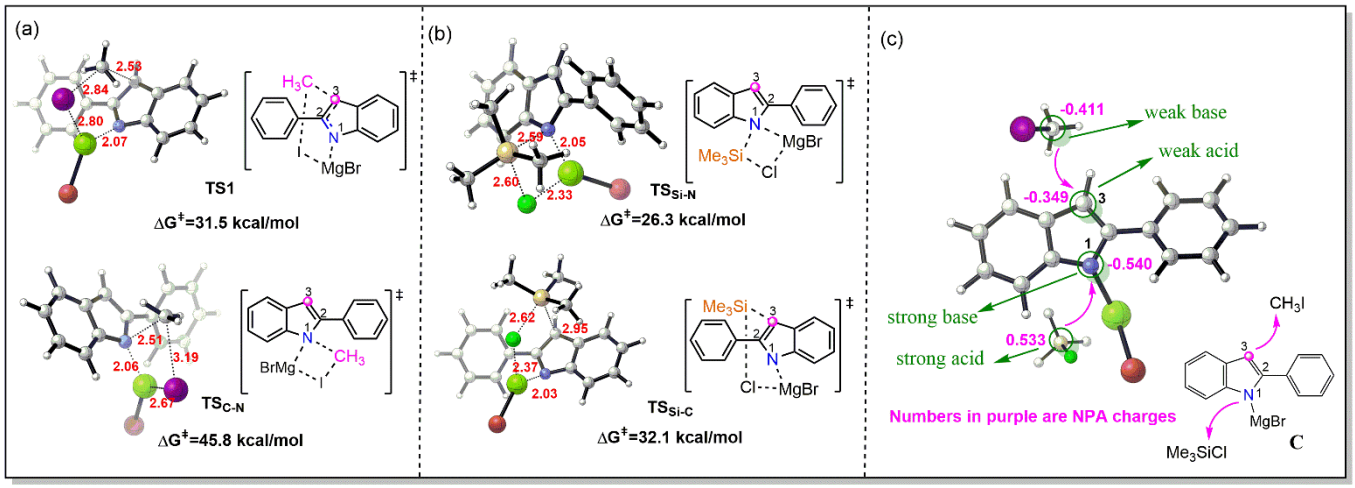
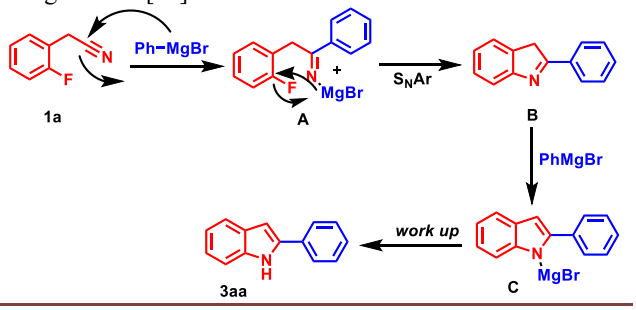


Figure 2. (a) Geometries and activation free energies of transition states $\mathbf{TS_{C\text{-}C}}$ and $\mathbf{TS_{C\text{-}N}}$ for the two pathways of intermediate **C** attacking CH_3–I and (b) Geometries and activation free energies of transition states $\mathbf{TS_{Si\text{-}N}}$ and $\mathbf{TS_{Si\text{-}C}}$ for the two pathways of intermediate **C** attacking Me_3Si–Cl. Numbers in red are bond distances in Å. (c) NPA charges on atoms of reaction sites in CH_3–I, Me_3Si–Cl, and intermediate **C** and the selectivity for the attack on CH_3–I and Me_3Si–Cl. For clarity, the hydrogen atoms on Me_3Si–Cl are not shown.

Thus, *C*-based electrophiles favor C3-alkylation of intermediate **C** and *Si*-based electrophiles favor *N*-silylation of intermediate **C**. Based on these observations, we propose a plausible mechanism (Scheme 10). First, the nucleophilic addition of phenylmagnesium bromide to 2-fluorophenyl acetonitrile produces a metalated imine intermediate. This intermediate undergoes rate-determining S_NAr to generate the 3*H*-indole **B**. Intermediate **B** is then deprotonated by the Grignard reagent to give metallated **C**. As shown in Scheme 10, the deprotonated indole can be trapped by C3-alkylation. Workup ultimately affords the product **3aa**. It is likely that the Lewis acidic Mg^{2+} interacts with the fluorine during the S_NAr process, as we have seen computationally in other C–F bond cleavage events [71].



Scheme 10. Possible mechanism.

3. Conclusions

In summary, indoles are common building-blocks in the pharmaceutical industry. We have presented a simple, convenient, and economical method to synthesize a wide range of indole derivatives (66 examples, 45%–95% yields) by using easily accessible and often commercially available Grignard reagents and commercially available 2-fluorophenylacetonitrile derivatives. Compared with the traditional approach, this method is easy to employ, does not involve cryogenic temperatures, and can install a variety of substituents at most sites on the indole skeleton. In addition, a diverse array of aryl-, alkyl-, vinyl-, and cyclopropyl Grignard reagents were incorporated, which greatly increased the potential utility of this method. Further transformations achieved a gram-scale synthesis of indomethacin and an intermediate towards an anti-breast cancer drug candidate, demonstrating the application of this approach. Given the utility of this approach to generate bioactive indoles from readily accessible starting materials, we anticipate that it will find numerous applications in medicinal chemistry.

4. Experimental

4.1. General procedure for the synthesis of C2-substituted indoles

To an oven-dried microwave vial equipped with a stir bar under an argon atmosphere inside a glove box was added the corresponding 2-fluorophenylacetonitrile (0.2 mmol) and dry toluene (1.2 mL). The microwave vial was sealed with a cap containing a rubber septum in its center, removed from the glove box, and 0.6 mL corresponding Grignard reagent (0.6 mmol, 3.0 equiv, 1 M in THF) were added dropwise with a 1 mL syringe at room temperature, and the reaction was stirred for 2 h at room temperature. Next, the reaction was heated for 4 h in an oil bath at 110 °C. The sealed vial was removed from the oil bath, cooled to room temperature, opened to air, and then 3 drops of water were added. The reaction mixture was passed through a short pad of silica, which was then washed with an additional 6 mL of ethyl acetate (3 × 2 mL). The combined solutions were concentrated in *vacuo*. The crude material was loaded onto a column of silica gel for purification.

4.2. General procedure for the synthesis of C3-alkyl substituted 2-phenyl indoles

To an oven-dried microwave vial equipped with a stir bar under an argon atmosphere inside a glove box was added 2-fluorophenylacetonitrile (0.2 mmol) and dry toluene (1.2 mL). The microwave vial was sealed with a cap that contained a septum in its center, removed from the glove box, and 0.6 mL

phenylmagnesium bromide (0.6 mmol, 3.0 equiv, 1 M in THF) were added dropwise with a 1 mL syringe at room temperature, and the reaction was stirred for 2 h at room temperature. Next, the vial was heated for 4 h in an oil bath at 110 °C. After the initial 4 h, the corresponding alkyl halides (3 equiv, 0.6 mmol) was injected into the microwave vial at 110 °C and stirring was continued for an additional 5 h. The sealed vial was removed from the oil bath, cooled to room temperature, opened to air, and then 3 drops of water were added. The reaction mixture was passed through a short pad of silica, which was then washed with an additional 6 mL of ethyl acetate (3 × 2 mL). The combined solutions were concentrated in *vacuo*. The crude material was loaded onto a column of silica gel for purification.

4.3. General procedure for the synthesis of N-substituted 2-phenyl indoles

To an oven-dried microwave vial equipped with a stir bar under an argon atmosphere inside a glove box was added 2-fluorophenylacetonitrile (0.2 mmol) and dry toluene (1.2 mL). The microwave vial was sealed with a cap containing a rubber septum in its center, removed from the glove box, and 0.6 mL phenylmagnesium bromide (0.6 mmol, 3.0 equiv, 1 M in THF) were added dropwise with a 1 mL syringe at room temperature, and the reaction was stirred for 2 h at room temperature. Next, the reaction was heated for 4 h in an oil bath at 110 °C. Afterwards, the corresponding chlorosilanes (3 equiv, 0.6 mmol) was directly injected into the microwave vial at 110 °C and stirring was continued for 5 h. The sealed vial was removed from the oil bath, cooled to room temperature, opened to air, and then 3 drops of water were added. The reaction mixture was passed through a short pad of silica, which was then washed with an additional 6 mL of ethyl acetate (3 × 2 mL). The combined solutions were concentrated in *vacuo*. The crude material was loaded onto a column of silica gel for purification.

4.4. General procedure for the synthesis of C3-halogenated 2-aryl indoles

To an oven-dried microwave vial equipped with a stir bar under an argon atmosphere inside a glove box was added 2-fluorophenylacetonitrile (0.2 mmol) and dry toluene (1.2 mL). The microwave vial was sealed with a cap containing a rubber septum in its center, removed from the glove box, and 0.6 mL phenylmagnesium bromide (0.6 mmol, 3.0 equiv, 1 M in THF) were added dropwise with a 1 mL syringe at room temperature, and the reaction was stirred for 2 h at room temperature. Next, the reaction was heated for 4 h in an oil bath at 110 °C. Afterwards, NBS (N-bromosuccinimide), NIS (N-Iodosuccinimide) or NCS (N-chlorosuccinimide) (3 equiv, 0.6 mmol) was directly injected into the microwave vial at 110 °C and stirring was continued for 5 h, respectively. The sealed vial was removed from the oil bath, cooled to room temperature, opened to air, and then 3 drops of water were added. The reaction mixture was passed through a short pad of silica, which was then washed with an additional 6 mL of ethyl acetate (3 × 2 mL). The combined solutions were concentrated in *vacuo*. The crude material was loaded onto a column of silica gel for purification.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://XXXXXXXXXXXXX

References

[1] S.A. Patil, R. Patil, D.D. Miller, Future Med. Chem. 4, (2012), 2085-2115.
[2] E. Vitaku, D.T. Smith, J.T. Njardarson, J. Med. Chem. 57, (2014), 10257-10274.
[3] T. Kawasaki, K. Higuchi, Nat. Prod. Rep. 22, (2005), 761-793.
[4] G.R. Humphrey, J. T. Kuethe, Chem. Rev. 106, (2006), 2875-2911.
[5] Y.K. Zou, A.B. Smith, J. Antibiot. 71, (2018), 185-204.
[6] D.X. Tan, R.J. Reiter, L.C. Manchester, M.T. Yan, M. El-Sawi, R.M. Sainz, J.C. Mayo, R. Kohen, M. Allegra, R. Hardeland, Curr. Top. Med. Chem. 2, (2002), 181-197.
[7] S. Suzen, Comb. Chem. High Throughput Screening 9, (2006), 409-419.
[8] A. Brancale, R. Silvestri, Med. Res. Rev. 27, (2007), 209-238.
[9] G. Gurkok, T. Coban, S. Suzen, J. Enzyme Inhib. Med. Chem. 24, (2009), 506-515.
[10] P. Lemoine, N. Zisapel, Expert Opin Pharmacother 13, (2012), 895-905.
[11] S. Suzen, S.S. Cihaner, T. Coban, Chem. Biol. Drug Des. 79, (2012), 76-83.
[12] I. Hutchinson, S.A. Jennings, B.R. Vishnuvajjala, A.D. Westwell, M.F.G. Stevens, J. Med. Chem. 45, (2002), 744-747.
[13] C.G. Mortimer, G. Wells, J.P. Crochard, E.L. Stone, T.D. Bradshaw, M.F.G. Stevens, A.D. Westwell, J. Med. Chem. 49, (2006), 179-185.
[14] V.T. Abaev, A.T. Plieva, P.N. Chalikidi, M.G. Uchuskin, I.V. Trushkov, A.V. Butin, Org. Lett. 16, (2014), 4150-4153.
[15] S. Samosorn, J.B. Bremner, A. Ball, K. Lewis, Bioorg. Med. Chem. 14, (2006), 857-865.
[16] J.I. Ambrus, M.J. Kelso, J.B. Bremner, A.R. Ball, G. Casadei, K. Lewis, Bioorg. Med. Chem. Lett. 18, (2008), 4294-4297.
[17] T.C. Leboho, J.P. Michael, W.A.L. van Otterlo, S.F. van Vuuren, C.B. de Koning, Bioorg. Med. Chem. Lett. 19, (2009), 4948-4951.
[18] B.S. Mathada, N.G. Yernale, J.N. Basha, J. Badiger, Tetrahedron Lett. 85, (2021), 153458.
[19] R. Moehlau, Ber. Dtsch. Chem. Ges. 14, (1881), 171-175.

[20] Y. Vara, E. Aldaba, A. Arrieta, J.L. Pizarro, M.I. Arriortua, F.P. Cossio, Org. Biomol. Chem. 6, (2008), 1763-1772.
[21] E. Fischer, O. Hess, Ber. Dtsch. Chem. Ges. 17, (1884), 559-568.
[22] G. Zeni, R.C. Larock, Chem. Rev. 104, (2004), 2285-2309.
[23] R.J. Phipps, N.P. Grimster, M.J. Gaunt, J. Am. Chem. Soc. 130, (2008), 8172-8174.
[24] R. Bernini, G. Fabrizi, A. Sferrazza, S. Cacchi, Angew. Chem., Int. Ed. 48, (2009), 8078-8081.
[25] S. Cacchi, G. Fabrizi, Chem. Rev. 111, (2011), PR215-PR283.
[26] B. Yao, Q. Wang, J.P. Zhu, Angew. Chem., Int. Ed. 51, (2012), 12311-12315.
[27] J. Zoller, D.C. Fabry, M.A. Ronge, M. Rueping, Angew. Chem., Int. Ed. 53, (2014), 13264-13268.
[28] G.N. Hermann, C.L. Jung, C. Bolm, Green Chem. 19, (2017), 2520-2523.
[29] Y.Q. Yang, Z.Z. Shi, Chem. Commun. 54, (2018), 1676-1685.
[30] I. Thome, A. Nijs, C. Bolm, Chem. Soc. Rev. 41, (2012), 979-987.
[31] R.C. Larock, E.K. Yum, J. Am. Chem. Soc. 113, (1991), 6689-6690.
[32] R.C. Larock, E.K. Yum, M.D. Refvik, J. Org. Chem. 63, (1998), 7652-7662.
[33] J. Barluenga, M. Trincado, E. Rubio, J.M. Gonzalez, Angew. Chem., Int. Ed. 42, (2003), 2406-2409.
[34] L.S. Hegedus, G.F. Allen, J.J. Bozell, E.L. Waterman, J. Am. Chem. Soc. 100, (1978), 5800-5807.
[35] P.J. Harrington, L.S. Hegedus, J. Org. Chem. 49, (1984), 2657-2662.
[36] P.J. Harrington, L.S. Hegedus, K.F. McDaniel, J. Am. Chem. Soc. 109, (1987), 4335-4338.
[37] L. Fra, A. Millan, J. A. Souto and K. Muniz, Angew. Chem., Int. Ed. 53, (2014), 7349-7353.
[38] M.T. Hovey, C.T. Check, A.F. Sipher, K.A. Scheidt, Angew. Chem., Int. Ed. 53, (2014), 9603-9607.
[39] G. Bartoli, G. Palmieri, M. Bosco, R. Dalpozzo, Tetrahedron Lett. 30, (1989), 2129-2132.
[40] A. Dobbs, J. Org. Chem. 66, (2001), 638-641.
[41] A.B. Smith, III, M. Visnick, J.N. Haseltine, P.A. Sprengeler, Tetrahedron 42, (1986), 2957-2969.
[42] C.M. Coleman, D.F. O'Shea, J. Am. Chem. Soc. 125, (2003), 4054-4055.
[43] B.A. Haag, Z.G. Zhang, J.S. Li, P. Knochel, Angew. Chem., Int. Ed. 49, (2010), 9513-9516.
[44] Z.G. Zhang, B.A. Haag, J.S. Li, P. Knochel, Synthesis, (2011), 23-29.
[45] A. Frischmuth, P. Knochel, Angew. Chem., Int. Ed. 52, (2013), 10084-10088.
[46] J.Y. Mao, Z.T. Wang, X.Y. Xu, G.Q. Liu, R. Jiang, H.X. Guan, Z.P. Zheng, P. J. Walsh, Angew. Chem., Int. Ed. 58, (2019), 11033-11038.
[47] S.C. Sha, S. Tcyrulnikov, M.Y. Li, B.W. Hu, Y. Fu, M.C. Kozlowski, P.J. Walsh, J. Am. Chem. Soc. 140, (2018), 12415-12423.
[48] Z.T. Wang, Z.P. Zheng, X.Y. Xu, J.Y. Mao, P.J. Walsh, Nat. Commun. 9, (2018), 1-8.
[49] H. Jiang, S.C. Sha, S.A. Jeong, B.C. Manor, P.J. Walsh, Org. Lett. 21, (2019), 1735-1739.
[50] G.Q. Liu, P.J. Walsh, J.Y. Mao, Org. Lett. 21, (2019), 8514-8518.
[51] Y.Y. Gu, Z. Zhang, Y.E. Wang, Z.T. Dai, Y.Q. Yuan, D. Xiong, J. Li, P.J. Walsh, J.Y. Mao, J. Org. Chem. 87, (2022), 406-418.
[52] L.R. Mills, R.K. Edjoc, S.A.L. Rousseaux, J. Am. Chem. Soc. 143, (2021), 10422-10428.
[53] F.F. Fleming, B.C. Shook, Tetrahedron 58, (2002), 1-23.
[54] M. Purzycki, W.Liu, G. Hilmersson, F.F. Fleming, Chem. Commun. 49, (2013), 4700-4702.
[55] F.G. Bordwell, J.E. Bares, J.E. Bartmess, G.J. McCollum, M. Van der Puy, N.R. Vanier, W.S. Matthews, J. Org. Chem. 42, (1977), 321-325.
[56] D.R. Stuart, P. Alsabeh, M. Kuhn, K. Fagnou, J. Am. Chem. Soc. 132, (2010), 18326-18339.
[57] Y. Liang and N. Jiao, Angew. Chem., Int. Ed. 55, (2016), 4035-4039.
[58] S. Kou, J.Q. Huo, Y. Wang, S.S. Sun, F. Xue, J.Y. Mao, J.L. Zhang, L. Chen, P. J. Walsh, J. Org. Chem., 88, (2023), 5147–5152
[59] A.I. Meyers, M.Reuman, R.A. Gabel, J. Org. Chem. 46, (1981), 783-788.
[60] W. ten Hoeve, C.G. Kruse, J.M. Luteyn, J.R.G. Thiecke, H. Wynberg, J. Org. Chem. 58, (1993), 5101-5106.
[61] A. Kaga, H. Hayashi, H. Hakamata, M. Oi, M. Uchiyama, R. Takita, S. Chiba, Angew. Chem., Int. Ed. 56, (2017), 11807-11811.
[62] S. Suzen, P. Bozkaya, T. Coban and D. Nebioglu, J. Enzyme Inhib. Med. Chem. 21, (2006), 405-411.
[63] E.J. Barreiro, A. E. Kummerle and C. A. M. Fraga, Chem. Rev. 111, (2011), 5215-5246.
[64] H. Schoenherr and T. Cernak, Angew. Chem., Int. Ed. 52, (2013), 12256-12267.
[65] S. Sun and J. Fu, Bioorg. Med. Chem. Lett. 28, (2018), 3283-3289.
[66] S. Lal and T. J. Snape, Curr. Med. Chem. 19, (2012), 4828-4837.
[67] X.S. Ning, X. Liang, K.F. Hu, C.Z. Yao, J.P. Qu and Y.B. Kang, Adv. Synth. Catal. 360, (2018), 1590-1594.
[68] X.S. Ning, M.M. Wang, J.P Qu and Y.B. Kang, J. Org. Chem. 83, (2018), 13523-13529.
[69] M. Amat, S. Hadida, S. Sathyanarayana and J. Bosch, J. Org. Chem. 59, (1994), 10-11.
[70] M. Amat, S. Sathyanarayana, S. Hadida and J. Bosch, Heterocycles 43, (1996), 1713-1718.
[71] C. Wu, S.P. McCollom, Z.P. Zheng, J. Zhang, S.C. Sha, M. Li, P.J. Walsh, N.C. Tomson, ACS Catal. 10, (2020), 7934-7944.