Tetrahedron Letters xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Preparation of highly functionalized 1,5-disubstituted tetrazoles via palladium-catalyzed Suzuki coupling

Edward J. Hennessy *, Mark Cornebise, Lakshmaiah Gingipalli, Tyler Grebe, Sudhir Hande, Valerie Hoesch, Hoan Huynh, Scott Throner, Jeffrey Varnes, Ye Wu

IMED Oncology, Innovative Medicines & Early Development, AstraZeneca, 35 Gatehouse Drive, Waltham, MA 02451, United States

ARTICLE INFO

Article history:
Received 2 March 2017
Accepted 17 March 2017
Available online xxxx

Keywords:
Tetrazoles
Heterocycles
Suzuki coupling
Biologically-active Molecules

ABSTRACT

The preparation of a range of 1,5-disubstituted tetrazoles has been achieved through palladium-catalyzed Suzuki coupling. Using appropriately substituted 5-*p*-toluenesulfonyltetrazoles as substrates (obtained by cycloaddition of a substituted azide with *p*-toluenesulfonyl cyanide), this methodology provides access to a variety of highly substituted tetrazoles that would be difficult to access otherwise. The procedure is compatible with functional groups commonly found in drug-like molecules, and has been used to generate a number of compounds of potential biological interest.

Aromatic heterocycles are ubiquitous in synthetic compounds designed to have biological activity, in large part due to the ability of the heteroatoms within these ring systems to interact favorably with functional groups in the biological target of interest. In addition, the ability to modulate the properties (such as lipophilicity, aqueous solubility, etc.) of a scaffold through the inclusion of heterocyclic rings is commonly exploited in the drug discovery process. For example, the replacement of carbocyclic rings with heterocyclic moieties in general results in quantifiably improved physical properties, lowered risk of drug-drug interactions, and improved overall developability.[1]

Amongst the heterocycles commonly encountered in medicinal chemistry programs, tetrazoles are often used to modulate binding affinity or physical properties of a series.[2] N—H tetrazoles, by virtue of the electron-deficient nature of the heterocyclic ring, are ionized at physiological pH and are thus often employed as non-classical carboxylic acid isosteres in the design of biologically active compounds.[3] Indeed, this ring system can be found in various approved medicines, such as in a number of angiotensin II receptor blockers (sartans).[4]

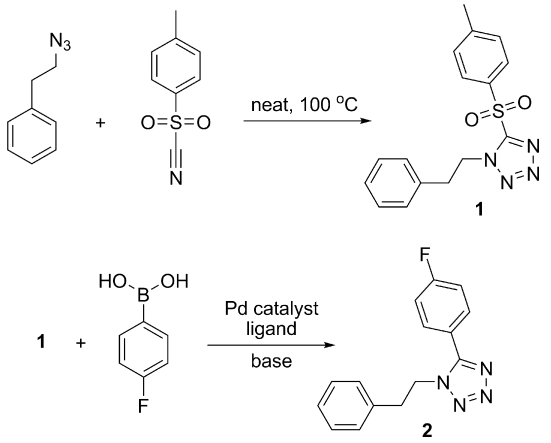
Tetrazoles in which the carbon atom as well as one of the nitrogen atoms are substituted have also found applications in the construction of biologically-active motifs. For example, 1,5-disubstituted tetrazoles have been successfully employed as an isosteric replacement for *cis*-amide bonds in peptidomimetics.[5] 2,5-Disubstituted tetrazoles have similarly been utilized as components of synthetic nucleotides and oligonucleotides.[6]

As part of a drug discovery program aimed at identifying compounds with activity against a biological target of interest, we postulated that an *ortho*-disubstituted phenyl ring common to compounds within the lead series could be replaced with a 1,5-disubstituted tetrazole ring, thus largely maintaining the overall shape of the scaffold but with a substantial beneficial reduction in lipophilicity. To test this hypothesis, we designed a series of compounds containing such a disubstituted tetrazole ring to assess whether this change would be compatible with the desired biological activity. Synthetic access to many of these compounds proved troublesome, however, as it has been established repeatedly throughout the literature that the alkylation of N—H tetrazoles proceeds to give mixtures of the 1,5- and 2,5-disubstituted isomers, with product ratios largely dependent upon the nature of the 5-substitutent.[7] Thus, we sought a synthetic methodology that would provide a reliable route to a variety of tetrazoles with the desired substitution pattern.[8]

In devising a strategy to address this problem, we were inspired by a publication from the Sharpless group describing the regiospecific preparation of 1-substituted 5-sulfonyltetrazoles through the cycloaddition of an organic azide with commercially available *p*-toluenesulfonyl cyanide.[9] This operationally-simple reaction was shown to be high-yielding, providing access to a relatively broad scope of substituted tetrazoles. Moreover, the 5-*p*-toluenesulfonyl group of these adducts can be readily displaced by heteroatom-based nucleophiles, thus offering the

* Corresponding author.
E-mail address: edward.hennessy@astrazeneca.com (E.J. Hennessy).

http://dx.doi.org/10.1016/j.tetlet.2017.03.056
0040-4039/

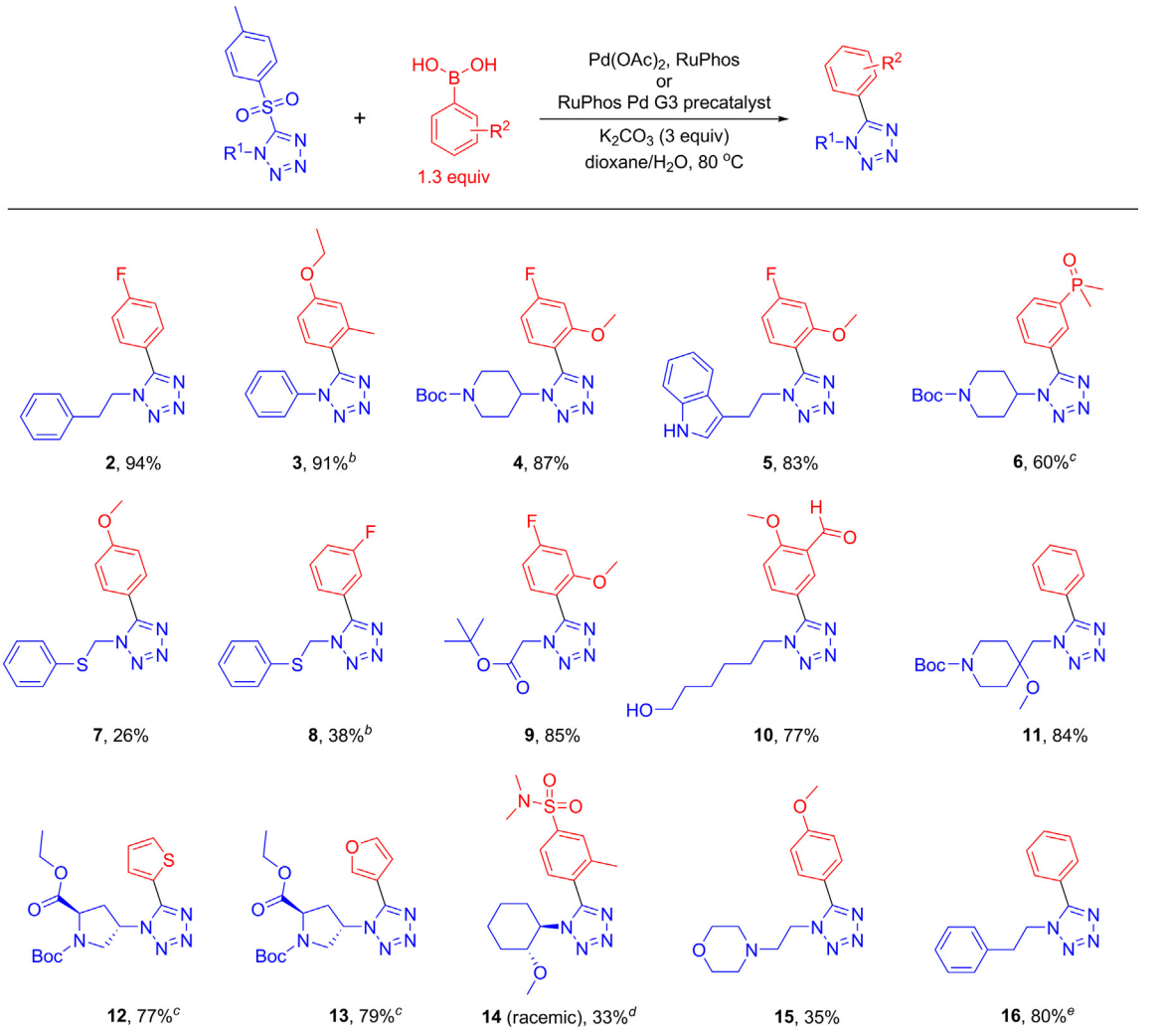


Scheme 1. Preparation of 1-phenethyl-5-*p*-toluenesulfonyltetrazole (**1**) and coupling with 4-fluorophenylboronic acid to yield tetrazole **2**.

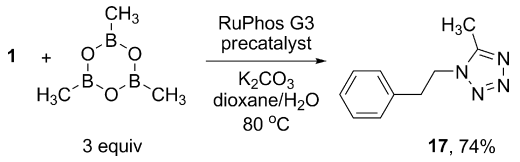
opportunity to prepare a diverse array of 1,5-disubstituted tetrazoles. While this methodology was useful for the construction of some of our designed targets, we also desired compounds in which a carbon atom was bound to the 5-position of the tetrazole ring, which would be derived from reaction with carbon-based nucleophiles. At the time of our studies, however, there were only a few reports of the use of activated carbon nucleophiles (such as ethyl cyanoacetate) to displace a 5-sulfonyl group from a tetrazole.[10] In addition, an aryl Grignard reagent has similarly been shown to undergo this reaction.[11] Given the modest reported yield of this transformation, however, along with limited functional group compatibility expected with the use of organomagnesium reagents, we sought an alternative method to construct carbon–carbon bonds within this scaffold that would be more generally applicable to a range of functionalized substrates.

While palladium-catalyzed Suzuki couplings employing 5-chloro or 5-bromotetrazole substrates have been described in the literature,[12] preparation of these substrates typically requires multiple synthetic steps, often using reagents incompatible with

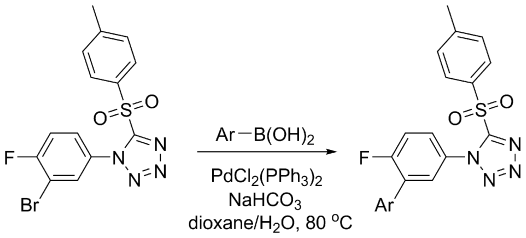
Table 1
Pd-catalyzed synthesis of 1,5-disubstituted tetrazoles.



[a]Reported yields are for analytically pure material isolated following the reaction, and unless otherwise indicated are the average of two independent runs. [b]$NaHCO_3$ used as base. [c]Aryl or heteroarylpinacolboronate ester used instead of boronic acid. [d]Isolated yield from single run. [e]Aryl potassium trifluoroborate used instead of arylboronic acid.



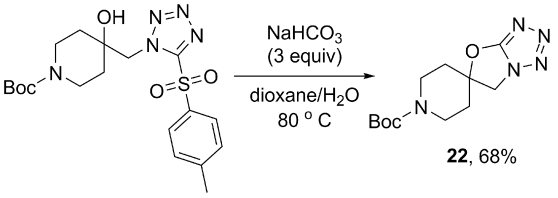
Scheme 2. Preparation of a 5-methyltetrazole derivative.



Scheme 3. Preferential Suzuki coupling at an aryl bromide.

functionality commonly present in compounds designed to be biologically active. A direct arylation of 1-substituted-5-H tetrazoles has been reported that offers an alternative approach to the desired substitution pattern, however the scope of this methodology appears limited to aryl iodides.[13] Given the ease of preparation of a diverse array of 5-*p*-toluenesulfonyl tetrazoles, and recognizing that the *p*-toluenesulfonyl group appended to the 5-position is an activated leaving group, we envisioned the possibility of conducting palladium-catalyzed carbon–carbon bond formation at this center. While alkyl or arylsulfonyl groups appended to activated positions of heterocycles have found widespread use as leaving groups in nucleophilic aromatic substitution reactions,[14] there are only a few reports in the patent literature of their use in palladium-catalyzed cross coupling reactions.[15] To assess whether or not our approach was feasible, we conducted exploratory studies on the Suzuki-Miyaura type coupling of 1-phenethyl-5-*p*-toluenesulfonyltetrazole (**1**, prepared by cycloaddition of phenethyl azide and *p*-toluenesulfonyl cyanide, Scheme 1) and 4-fluorophenylboronic acid as a model system.

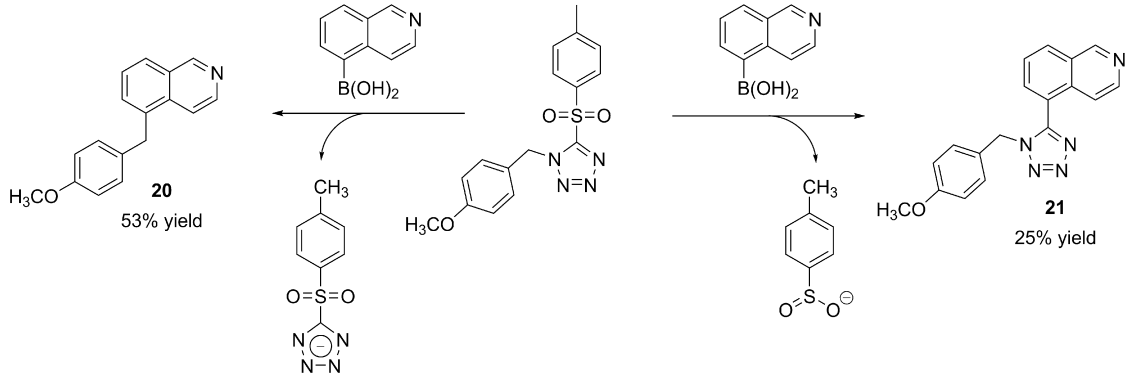
Early in our explorations, we quickly found that a number of biaryl phosphine ligands popularized for a range of palladium chemistry over recent years were highly effective at promoting the desired transformation.[16] For example, ligands such as S-Phos, BrettPhos, and RuPhos provided high conversions of the starting sulfonyltetrazole to afford the desired product, while traditionally



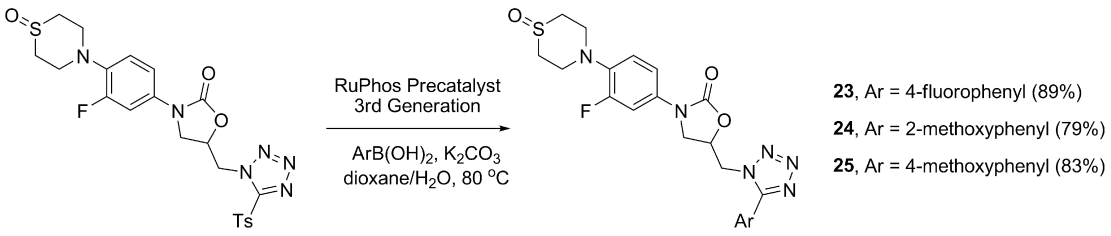
Scheme 5. Intramolecular displacement of *p*-toluenesulfonyl group under typical coupling reaction conditions.

less active phosphine ligands (such as triphenylphosphine) did not afford any observable product. Since Suzuki-Miyaura couplings are often conducted with heating under biphasic conditions in the presence of a stoichiometric excess of base, and the aforementioned precedent for facile nucleophilic displacement of the 5-sulfonyl group from the tetrazole ring, we were mindful of the possibility of hydrolysis of the substrate competing with the desired transformation. Indeed, hydrolysis products were commonly observed in our initial studies and were expected to accompany the desired coupling in all cases. We therefore opted to use RuPhos (2-dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl) in our continued work, since the use of this ligand seemed to give the cleanest reaction mixtures, suggestive of the most rapid cross-coupling. Thus, heating a mixture of 5-*p*-toluenesulfonyl tetrazole substrate **1**, 4-fluorophenylboronic acid, potassium carbonate, RuPhos, and palladium (II) acetate in a mixture of 1,4-dioxane and water provided a high isolated yield of the desired coupling product **2**. While we did not conduct exhaustive screening to identify the most optimal ligand for this reaction in a more general sense, the conditions we developed for this particular coupling were amenable to effecting the desired transformation across a range of substrates (Table 1). Interestingly, the commercially-available RuPhos Pd G3 precatalyst[17] was similarly effective, further simplifying the experimental setup for conducting this transformation (see Supplementary content for experimental details).

Using this methodology, a range of functionalized tetrazoles can be prepared from the appropriate choice of starting material and boronic acid (Table 1). Isolated yields are generally high, particularly for substrates lacking highly polar moieties or suitably protected functional groups. Thioethers, which are known to often result in inhibition of palladium-catalyzed chemistry,[18] are tolerated albeit with significantly reduced yields (examples **7** and **8**). Similarly, sterically-encumbered tetrazoles (such as **14**) or tetrazoles containing polar functional groups (such as **15**) are accessible in more modest yields; in some cases these diminished yields result from low recoveries following reverse-phase HPLC purification rather than incomplete conversion of substrate during the reaction.



Scheme 4. Coupling of 1-benzylic tetrazole substrates results in two major products.



Scheme 6. Preparation of 5-aryltetrazole-containing oxazolidinone analogs.

Both the desired transformation and the competing hydrolysis reaction result in the release of *p*-toluenesulfinate anion; this material can be observed when monitoring reaction progress by HPLC, and is readily removed by aqueous workup following completion of the reaction. In couplings employing more electron-deficient substrates (such a 1-phenyl-substituted tetrazole **3**), we found that the competing hydrolysis reaction seemed to occur more quickly, resulting in greater amounts of undesired side products. Gratifyingly, when a weaker base was used (such as $NaHCO_3$) in the reaction mixture, we found that while the desired coupling proceeded more slowly, the hydrolysis of the substrate occurs to a negligible extent thus resulting in higher yields of the desired product.

In order to broaden the utility of this reaction, we surveyed whether nucleophiles other than boronic acids could employed in this transformation. We were pleased to find that the use of pinacolboronate esters (examples **6**, **12**, and **13**) and potassium trifluoroborate salts (example **16**) was well-tolerated under these conditions, providing access to moderate to high yields of the desired products. While we didn't exhaustively optimize the reaction parameters for non-aromatic nucleophiles, we found that the use of trimethylboroxine under the standard reaction conditions allowed for the introduction of a methyl group at the 5-position in reasonable yield (Scheme 2).

Given the failure of less active catalyst systems to activate the 5-*p*-toluenesulfonyl group observed in our initial studies, we considered whether the judicious choice of reaction conditions would allow for palladium-catalyzed chemistry to be conducted on other functional groups that may be present within a substrate, while leaving the 5-sulfonyltetrazole moiety intact. For example, Suzuki coupling occurs exclusively at an aryl bromide moiety when $PdCl_2(PPh_3)_2$ is used as catalyst, with no reaction derived from activation of the sulfonyl group observed (Scheme 3). This selectivity could theoretically allow for the preparation of a diverse array of compounds based on this scaffold, with the Suzuki reaction as the penultimate step prior to displacement of the sulfonyl group with a suitable nucleophile.

While were able to utilize the procedure described in this paper to prepare a variety of interesting compounds, the methodology is not without notable limitations. In particular, presumably because of the electron-deficient nature of 5-*p*-toluenesulfonyltetrazole ring common to all substrates, this group itself can behave as a leaving group under certain situations at the expense of the desired chemistry occurring at the tetrazole 5-position. For example, in attempted couplings of 5-*p*-toluenesulfonyltetrazoles containing benzyl or substituted benzyl groups at the 1-position, Suzuki products derived from oxidative addition at both the tetrazole 5-position (with *p*-toluenesulfinic acid as leaving group) as well as at the benzylic position (with the entire 5-*p*-toluenesulfonyltetrazole as leaving group) were observed (Scheme 4). Similar observations were seen in the reaction of tetrazoles bearing an α-keto substituent at the 1-position. Other limitations are largely the result of the labile *p*-toluenesulfonyl group and its proclivity to be displaced by nucleophiles. For example, slower couplings are often plagued by higher amounts of competing hydrolysis, resulting in lower isolated yields. Moreover, substrates bearing nucleophilic heteroatoms capable of addition into the tetrazole ring may require suitable protection to avoid intramolecular cyclization that can occur under the reaction conditions. For example, while no cyclization byproduct was observed in the coupling reaction to generate compound **10**, complicated reaction mixtures were obtained in the attempted couplings of substrates poised to undergo more geometrically-favorable cyclization to generate 5- or 6-membered rings. Indeed, such cyclizations readily occur under the milder reaction conditions developed for hydrolytically-sensitive substrates (Scheme 5).

In line with our original motivations to develop this chemistry, we have been able to successfully use this reaction to prepare compounds of potential interest to our drug discovery programs. For example, a series of analogs based on the oxazolidinone scaffold common to a number of antibacterial agents[19] were prepared in high yield using this methodology (Scheme 6).

In conclusion, we have developed a novel synthetic protocol to access a range of 1,5-disubstituted tetrazoles through palladium-catalyzed coupling of readily-prepared 5-*p*-toluenesulfonyltetrazole substrates with boron-based nucleophiles. This methodology is compatible with a variety of functional groups commonly found in medicinal chemistry programs, and has been successfully applied to the preparation of a number of compounds of potential interest to ongoing drug discovery programs.

A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2017.03.056.

References

1. Ritchie TJ, Macdonald SJF, Young RJ, Pickett SD. *Drug Discovery Today*. 2011;16:164.
2. (a) Myznikov LV, Hrabalek A, Koldobskii GI. *Chem Heterocycl Compd*. 2007;43:1;
   (b) Ostrovskii VA, Trifonov RE, Popova EA. *Russ Chem Bull Int Ed*. 2012;61:768.
3. Herr RJ. *Bioorg Med Chem*. 2002;10:3379.
4. Michel MC, Foster C, Brunner HR, Liu L. *Pharmacol Rev*. 2013;65:809.
5. Zabrocki J, Smith GD, Dunbar Jr JB, Iijima H, Marshall GR. *J Am Chem Soc*. 1988;110:5875.
6. (a) Filichev VV, Jasko MV, Malin AA, Zubarev VY, Ostrovskii VA. *Tetrahedron Lett*. 2002;43:1901;
   (b) Filichev VV, Malin AA, Ostrovskii VA, Pedersen EB. *Helv Chim Acta*. 2002;85:2847.
7. (a) Henry RA. *J Am Chem Soc*. 1951;73:4470;
   (b) Henry RA, Finnegan WG. *J Am Chem Soc*. 1954;76:923;
   (c) Huff L, Henray RA. *J Med Chem*. 1970;13:777;
   (d) Koyama M, Ohtani N, Kai F, Moriguchi I, Inouye S. *J Med Chem*. 1987;30:552;
   (e) Couri MR, Luduvico I, Santos L, Alves R, Prado MA, Gil RF. *Carbohydr Res*. 2007;342:1096;
   (f) Kang SY, Lee S-H, Seo HJ, et al. *Bioorg Med Chem Lett*. 2008;18:2385.
8. For a recent review on the synthesis of 1,5-disubstituted tetrazoles, see: Sarvary A, Maleki A. *Mol Divers*. 2015;19:189.
9. Demko ZP, Sharpless KB. *Angew Chem Int Ed Engl*. 2002;41:2110.
10. Gol'tsberg MA, Koldobskii GI. *Chem Heterocycl Compd*. 1996;32:1300.

11. Nören-Müller A, Reis-Corrêa Jr I, Prinz H, et al. *Proc Natl Acad Sci USA*. 2006;103:10606.
12. For representative examples, see: (a) Yi KY, Yoo S. *Tetrahedron Lett*. 1995;36:1679;
(b) Walker SD, Barder TE, Martinelli JR, Buchwald SL. *Angew Chem Int Ed Engl*. 2004;43:1871;
(c) Tang Q, Giantassio R. *Tetrahedron Lett*. 2010;51:3473;
(d) El Kaim L, Grimaud L, Patil P. *Org Lett*. 2011;13:1261.
13. Špulák M, Lubojacky R, Šenel P, Kuneš J, Pour M. *J Org Chem*. 2010;75:241.
14. (a) Brown DJ, Ford PW. *J Chem Soc C*. 1967;568;
(b) Chisari A, Maccarone E, Parisi G, Perrini G. *J Chem Soc Perkin Trans 2*. 1982;957;
(c) Smith MB, March J*March's Advanced Organic Chemistry*. 5th ed. New York: Wiley; 2001:860–861;
(d) Joule JA, Mills K*Heterocyclic Chemistry*. 5th ed. West Sussex, UK: Wiley; 2010:24–26.
15. For representative examples, see: (a) Aldous SC, Fennie MW, Jian JZ, et al. WO 2008121670.
(b) Lynch R, Cansfield AD, Niblock HS, Hardy DP, Taylor J. WO 2011107585.
(c) Chen KX, Dong L, Estrada A, et al. WO 2014177060.
16. (a) Martin R, Buchwald SL. *Acc Chem Res*. 2008;41:1461;
(b) Surry DD, Buchwald SL. *Angew Chem Int Ed Engl*. 2008;47:6338.
17. (a) Bruno NC, Tudge MT, Buchwald SL. *Chem Sci*. 2013;4:916;
(b) Bruno NC, Niljianskul N, Buchwald SL. *J Org Chem*. 2014;79:4161.
18. Kondo T, Mitsudo T. *Chem Rev*. 2000;100:3205.
19. (a) Leach KL, Swaney SM, Colca JR, et al. *Mol Cell*. 2007;26:393;
(b) Shaw KJ, Barbachyn MR. *Ann. NY. Acad. Sci*. 2011;1241:48.