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Application of a Sequential Multicomponent Assembly Process/ Huisgen Cycloaddition Strategy to the Preparation of Libraries of 1,2,3-Triazole-Fused 1,4-Benzodiazepines

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Abstract

A strategy featuring a multicomponent assembly process followed by an intramolecular azide–alkyne dipolar (Huisgen) cycloaddition was implemented for the facile synthesis of three different 1,2,3-triazolo-1,4-benzodiazepine scaffolds. A diverse library of 170 compounds derived from these scaffolds was then created through *N*-functionalizations, palladium-catalyzed cross-coupling reactions, and several applications of α-aminonitrile chemistry.

Keywords

Triazole; dipolar cycloaddition; azide–alkyne; benzodiazepine; multicomponent reaction; α-aminonitrile; diversity oriented synthesis

The identification of biologically active small molecules through high-throughput screening (HTS) is a common strategy in campaigns to discover both novel drug leads and molecular probes that may be used to study aberrant biological pathways leading to disease.[1] Because of their high hit rates in HTS and ‘drug-like’ pharmacological profiles, derivatives of privileged structures are uniquely well-suited as molecular scaffolds in drug discovery.[2] Straightforward variation of the substituents on privileged scaffolds often leads to potent and selective binders for multiple biological targets from a single library.

More than 20 years ago Evans identified the benzodiazepine ring system as the archetypal privileged structure, thereby introducing the term into medicinal chemistry.[3,4] Compounds derived from the 1,4-benzodiazepine ring system bind to a multitude of targets, including G protein-coupled receptors (GPCRs), ligand-gated ion channels, and enzymes.[2a] The propensity of compounds derived from the benzodiazepine nucleus to bind to GPCRs has been suggested to arise from the ability of the scaffold to act as a structural mimic of peptide β-turns[5] and α-helices.[6] Such secondary structural elements orient substituents in a manner that enhances protein binding. Indeed, virtually all GPCR-binding ligands adopt α-, β- or γ-turns.[7] It is therefore unsurprising that the 1,4-benzodiazepine substructure is a common structural subunit in numerous pharmaceutical agents, biological probes, and bioactive

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ASSOCIATED CONTENT:
Experimental procedures, full characterization data for representative compounds, LCMS data for representative compounds and tabulated Lipinski’s rule parameters for representative compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

natural products such as diazepam (**1**),[8] devazepide (**2**)[9] and anthramycin (**3**)[10] respectively (Figure 1).

A key consideration inherent in designing and preparing novel compound libraries for HTS is the efficient synthesis of core scaffolds that bear functionality to enable facile diversification. In this context, we have recently developed a Mannich-type multicomponent assembly process (MCAP) to construct aryl aminomethyl adducts that are suitably functionalized for use in subsequent cyclizations to afford a variety of nitrogen-containing heterocyclic structures.[11] This sequential MCAP/cyclization strategy has been successfully utilized to rapidly access natural products[11,12,13a] and unnatural heterocyclic frameworks.[13,14] We also applied this approach to the syntheses of diverse, medicinally-relevant scaffolds based upon the 1,2,3-triazolo-1,4-benzodiazepine core **6** (Scheme 1),[15,16] 2-aryl piperidines,[16,17] tetrahydroisoquinolines,[16,18] as well as isoindolinones, norbenzomorphans, benzazocines, and benzoxacines.[16,19] We now report the application of this general approach for diversity oriented synthesis (DOS) to the preparation of libraries of 1,2,3-triazolo-1,4-benzodiazepines, a subclass of the benzodiazepine privileged structure whose biological properties have not been widely explored.[20]

As described previously, the parent 1,2,3-triazolo-1,4-benzodiazepine **6** and brominated analog **7** were readily prepared on multi-gram scale by a reductive amination and azide–alkyne dipolar (Huisgen) cycloaddition sequence (Scheme 1).[15] This approach afforded scaffolds **6** and **7** in high purity after recrystallization and represents a considerably more expedient access to compound **6** than previously reported.[21]

The two heterocycles **6** and **7** were then subjected to various tactics for *N*-functionalization to diversify the scaffolds into libraries of amides **8** and **9**, sulfonamides **10** and **11**, ureas **12** and **13**, thioureas **14** and **15**, carbamate **16**, and amine derivatives **17–19** (Scheme 2, Figure 2, Table 1). Reagents were typically used in excess to mitigate for variations in the purity of reagents, which were used without purification, and reaction efficiency. Functionalizing agents were selected to contain a mixture of aliphatic and aromatic groups. Different aliphatic substituents were chosen to vary the nonpolar surface area, whereas aromatic groups were varied by selecting substituents that would modulate the electrostatic properties of the aromatic ring. In this manner, it would be possible to acquire preliminary structure activity relationship (SAR) data from a small set of compounds. *N*-Arylation procedures to access chemset **19** were explored for the formation of *p*-toluidine derivative **19**{*2*}. We discovered that conditions reported by Buchwald utilizing $Pd(OAc)_2$, (±)-BINAP and NaO*t*-Bu were superior to alternative protocols in which $Pd_2(dba)_3$ was employed as the Pd source.[22] Use of this method allowed the introduction of aryl halides onto the parent scaffold (B{*1*} and **19**{*3*}) without the intervention of observable side reactions involving secondary cross-couplings. The 2-amino pyridine derivative **19**{*6*} was also prepared using a procedure described by Buchwald, but a catalyst loading of 4 mol % Pd_2dba_3 was necessary for complete conversion.[23]

The aryl bromide functionality present within scaffold **7** was exploited as a handle for diversification through several palladium catalysed cross-couplings (Scheme 3, Figure 3, Table 2). In order to avoid homocoupling of **7** during Buchwald-Hartwig aminations, it was necessary to employ a 10-fold excess of amines **29** to afford the aniline derivatives **27** (Figure 3).[22] Suzuki cross-couplings of **7** with boronic acids **30** afforded biaryl products **28** bearing substituents having a broad range of electronic properties. The use of heteroaromatic boronic acid derivatives is exemplified by the synthesis of **28**{*7*}.

Five cross-coupled products (**27**{*1–2*}, **28**{*1–2*} and **28**{*5*}) were subjected to ten independent *N*-functionalizations to afford a 'two-dimensionally' functionalized collection of 50 compounds (chemsets **31–42**) in generally high yields (Scheme 4, Figure 4, Table 3).

Because compounds bearing the α-aminonitrile functionality are synthetically versatile intermediates, we envisioned that a scaffold containing this subunit might facilitate diversification through a number of strategies.[24] The Strecker MCAP employing benzaldehyde **4** and propargylamine furnished the α-aminonitrile **43** in 78% yield (Scheme 5). Upon mild heating, **43** underwent facile Huisgen cycloaddition to deliver the cyano-substituted scaffold **44** in 88% yield. It was necessary to perform this reaction under dilute conditions and at a temperature not exceeding 60 °C in order to avoid elimination of HCN from the product **44**. Interestingly, when **43** was *N*-acylated, the intermediate amide underwent facile cycloaddition at ambient temperature to yield the amide derivative of the scaffold **45**{*1*}. This observation led to the development of a convenient, 4-component process to afford **45**{*1*} directly from benzaldehyde **4** in 49% yield (Scheme 5). This MCAP approach is an expedient method to access amide derivatives of **44**. However, *N*-functionalization of this scaffold is a better strategy for the library synthesis outlined in Scheme 6, because this approach allows the use of a number of parallel diversification reactions to give products that may be easily purified.

N-Acylations and *N*-sulfonylations of scaffold **44** to produce chemsets **45** and **46** were conducted using pyridine as the base; when triethylamine was employed, elimination of HCN was a significant side-reaction (Scheme 6, Figure 5, Table 4). Reductive amination of **44**, which was achieved under the same conditions as those described for the preparation of **17** and **18** (Scheme 2), generally proceeded in good yields. However, the reaction of **44** with the electron poor aldehyde **25**{*5*} required the presence of trifluoroacetic acid and additional quantities of $NaBH(OAc)_3$ to consume the starting material **44** (Table 4, entry 19).

The acidic nature of the proton α to the cyano group in amide derivatives **45** was exploited to facilitate further elaboration of the scaffold (Scheme 7, Figure 6, Table 5). In the event, deprotonation of **45** with NaH, followed by trapping the intermediate carbanion with alkylating agents **50** delivered a small library of compounds bearing fully substituted carbon centers (chemset **48**). Following literature precedent, vinyltriphenylphosphonium bromide (Schweizer's reagent) (**51**) was utilized as an electrophile in order to prepare a novel collection of pyrrole-fused structures (chemset **49**) through an addition/intramolecular Wittig reaction/elimination sequence.[25] Notably, the Wittig reaction and aromatization steps were complete within 90 min at ambient temperature. With the sole exception of the pivalamide **45**{*4*}, *N*-alkyl substituted amides were good substrates for this sequence of reactions. Aryl-substituted amides such as **45**{*15*}, **45**{*16*} and **45**{*7*} also participated in this transformation, as did the nicotinamide **45**{*10*}, which represents the first example of the use of a heteroaryl-substituted amide in this reaction. On the other hand, treating the anion of 5-nitro-furanyl amide **45**{*17*} with the vinyl phosphonium salt **51** formed a complex mixture of products; no pyrrole was observed. It should be noted that the bromo-substituted benzaldehyde **5** might be used as a starting material to prepare the corresponding bromo derivatives of **44, 45, 48**, and **49**. These compounds could then be further derivatized by palladium catalyzed cross-coupling reactions to introduce aryl and amine substituents onto the benzodiazepine rings of **44, 45, 48**, and **49**.

We were also interested in exploiting the Bruylants reaction to generate substituted benzylamine derivatives **52** by displacing cyanide ion from α-aminonitriles **47** with organometallic reagents (Scheme 8, Figure 7, Table 6).[26] After conducting a brief series of exploratory studies, we discovered that transmetallation of Grignard reagents to their corresponding organo-zinc species was necessary to avoid competitive deprotonation of the

acidic proton α to the cyano group.[27] Displacement of cyanide ion under 'Reformatsky-type' conditions with the enolate of ethyl acetate afforded chemset **53**; these compounds bear an ethyl ester group that might serve as a further point of diversification.[28]

In summary, a diverse collection of 170 1,2,3-triazolo-1,4-benzodiazepines was prepared. A sequential MCAP/Huisgen cycloaddition strategy was instrumental for the rapid construction of the parent scaffolds. *N*-Functionalization and cross-coupling reactions were then applied to these scaffolds to enable the rapid production of derivatives through a combinatorial style approach, whereas exploitation of α-aminonitrile chemistry facilitated the introduction of significant structural diversity via a DOS approach. A complete Lipinski analysis of a representative selection of 80 compounds containing at least two examples of each structural subtype and having a maximal diversity of substituents was performed, and no compound was found that violated the Lipinski rule of five.[29] Hence, the library members have physiochemical properties that are likely to be associated with good solubility, membrane permeability, and bioavailability. All compounds have been submitted to the National Institutes of Health (NIH) Molecular Libraries Small Molecule Repository (MLSMR) and are being distributed to the Molecular Libraries Probe Production Centers Network (MLPCN) for HTS in a wide range of biological assays. Selected compounds have also been sent to the National Institute of Mental Health, Psychoactive Drug Screening Program (NIMH PDSP). The further development and application of our sequential MCAP/cyclization strategy to the synthesis of medicinally relevant small molecules is ongoing and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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27. Treatment of α-aminonitrile **47**{14} with **54**{2} followed by quenching with d_4-AcOD gave the desired Bruylants reaction product in 56% yield along with starting material in 20% yield which exhibited >95% D incorporation, as determined by ^{1}H NMR spectroscopy.

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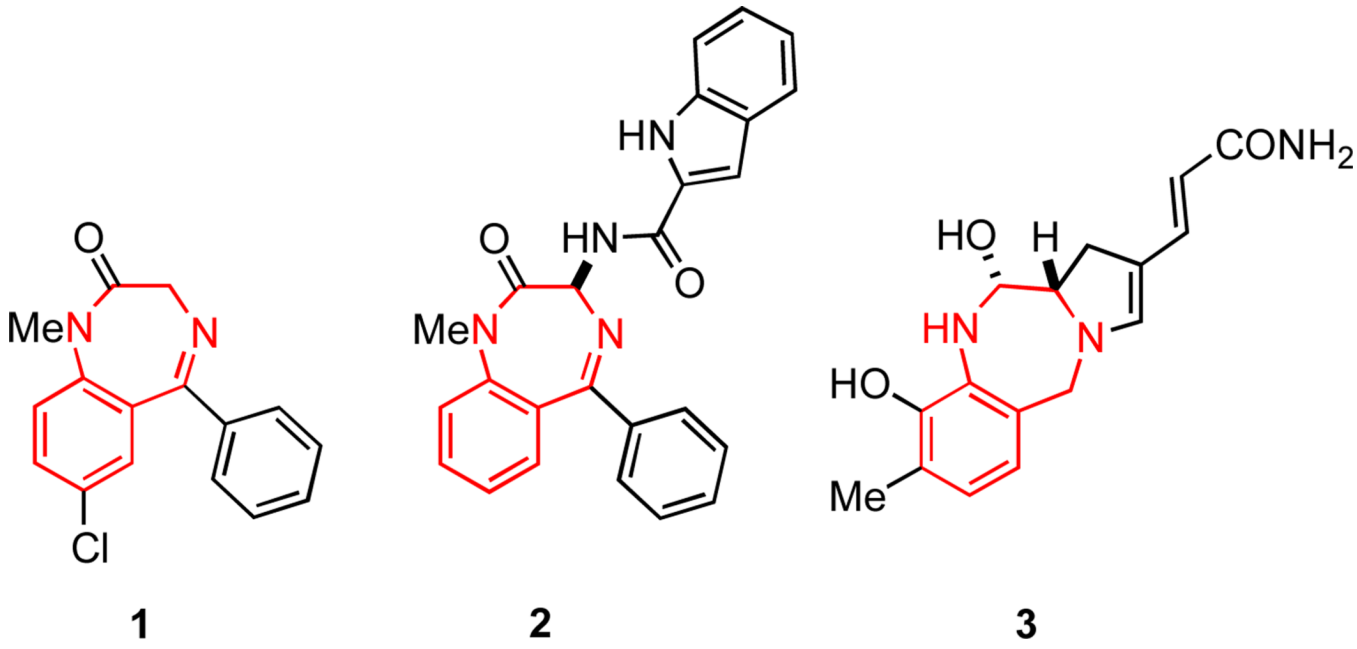


1 2 3

Figure 1.
Derivatives of the 1,4-benzodiazepine ring system.

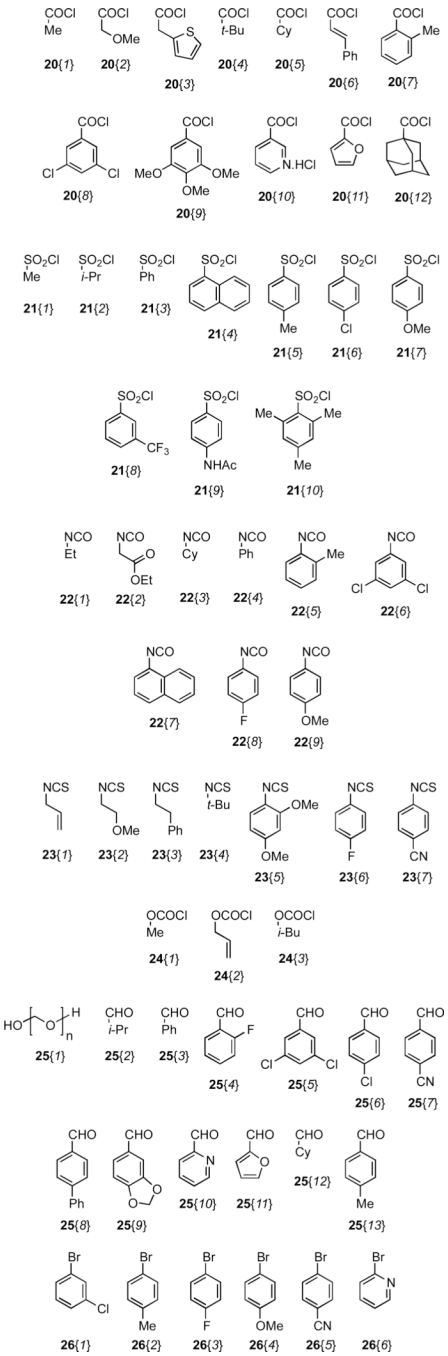


Figure 2.
Nitrogen-functionalizing agents used to derivatize scaffolds **6** and **7**.

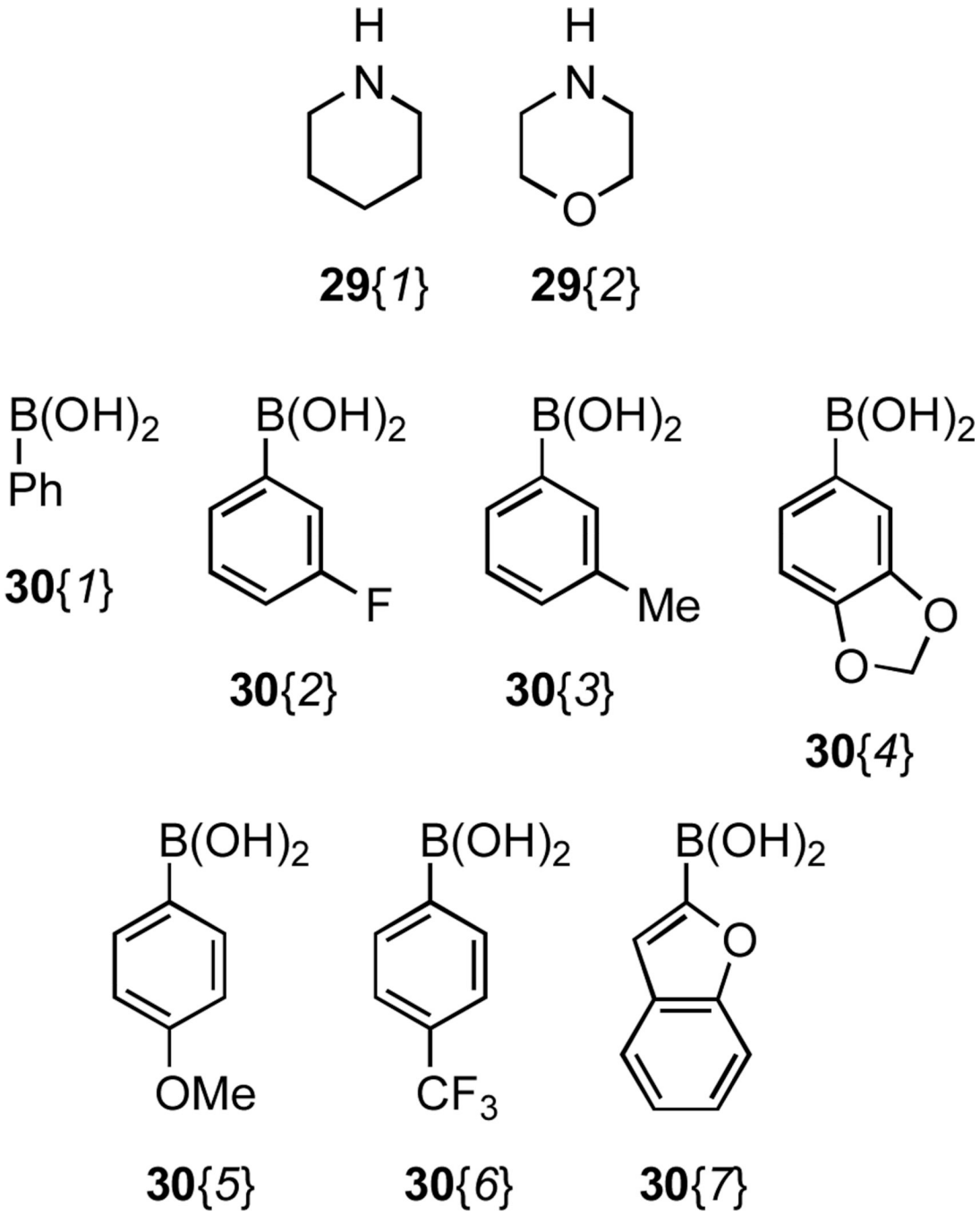


Figure 3.
Cross-coupling partners employed with scaffold **7**.

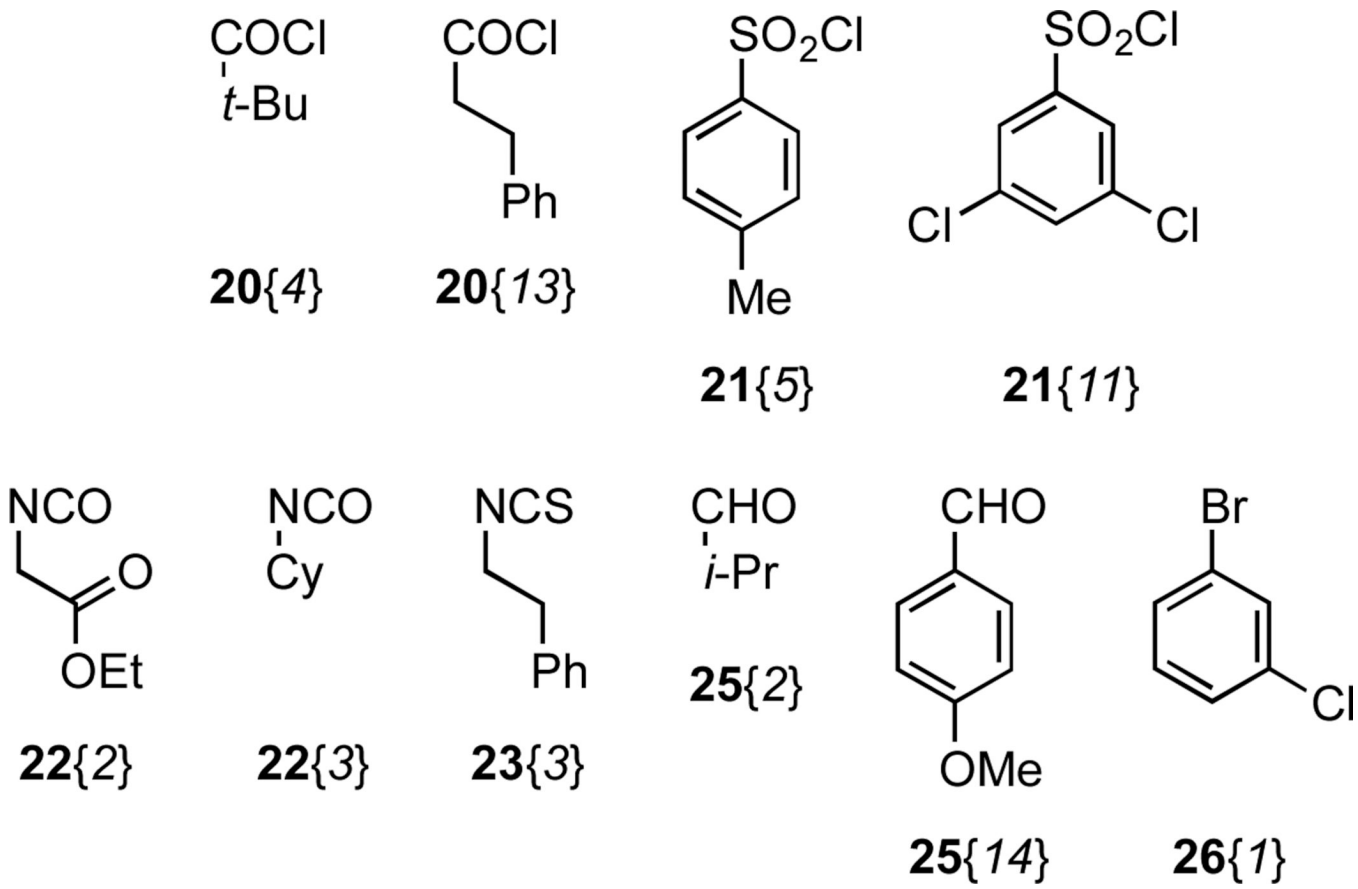


Figure 4.
Nitrogen-functionalizing agents used in the two-dimensional library derived from scaffold **7**.

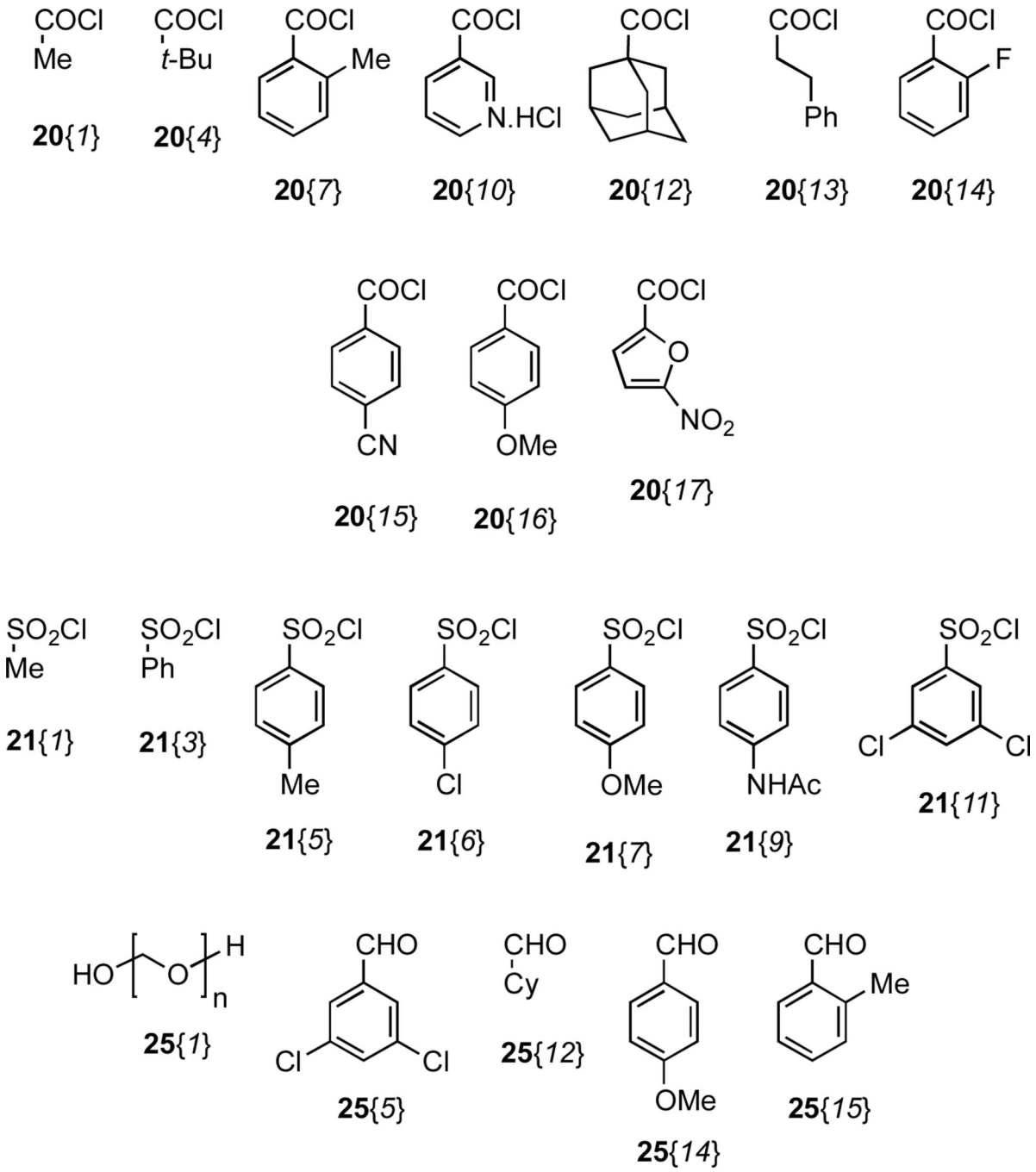


Figure 5.
Nitrogen functionalizing agents used with scaffold **44**.

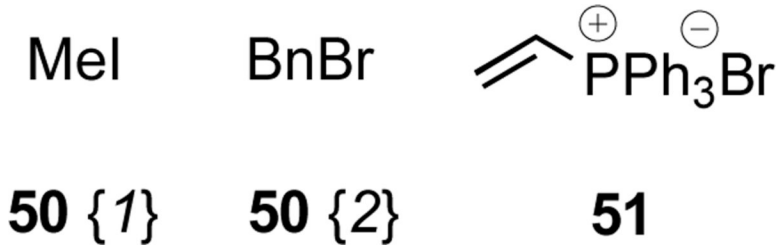


Figure 6.
Electrophiles employed to trap anions derived from amides **45**.

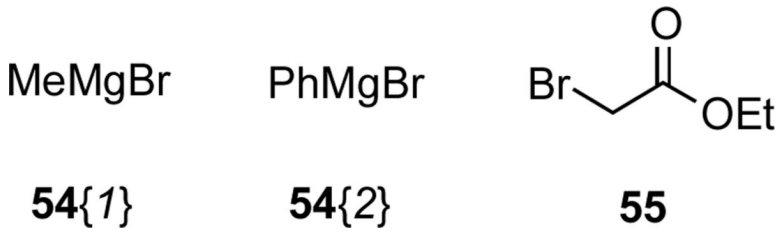
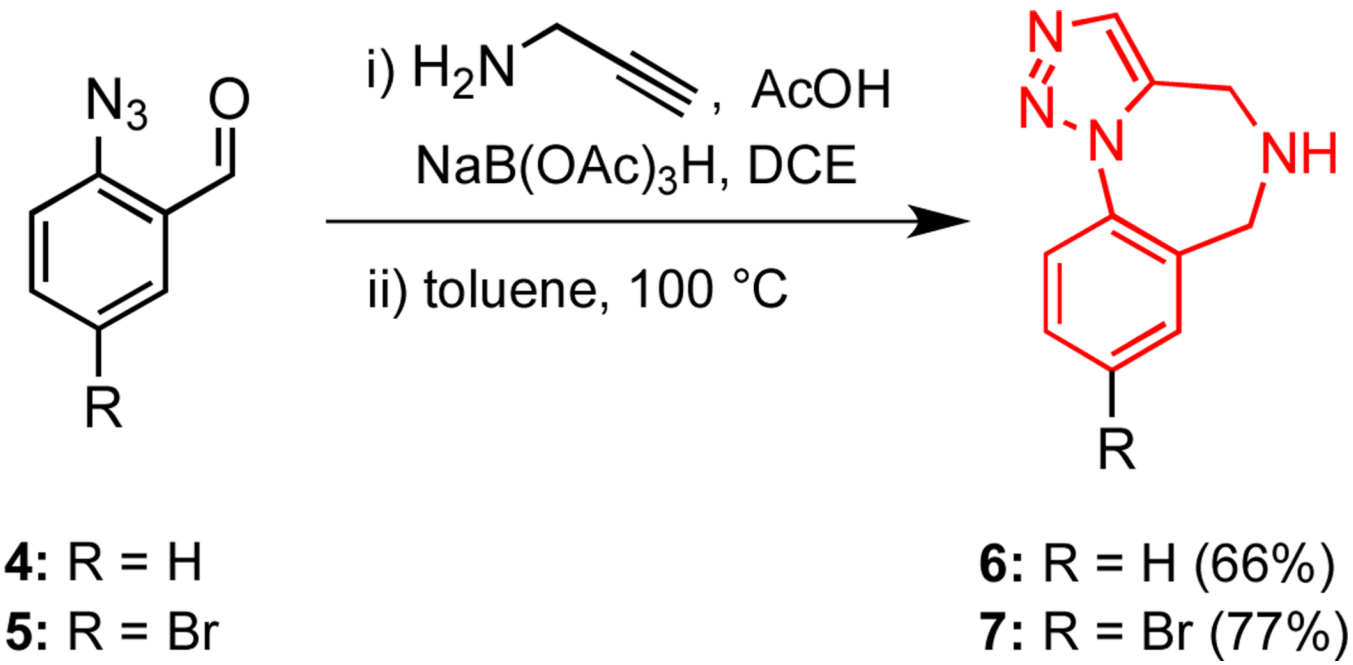


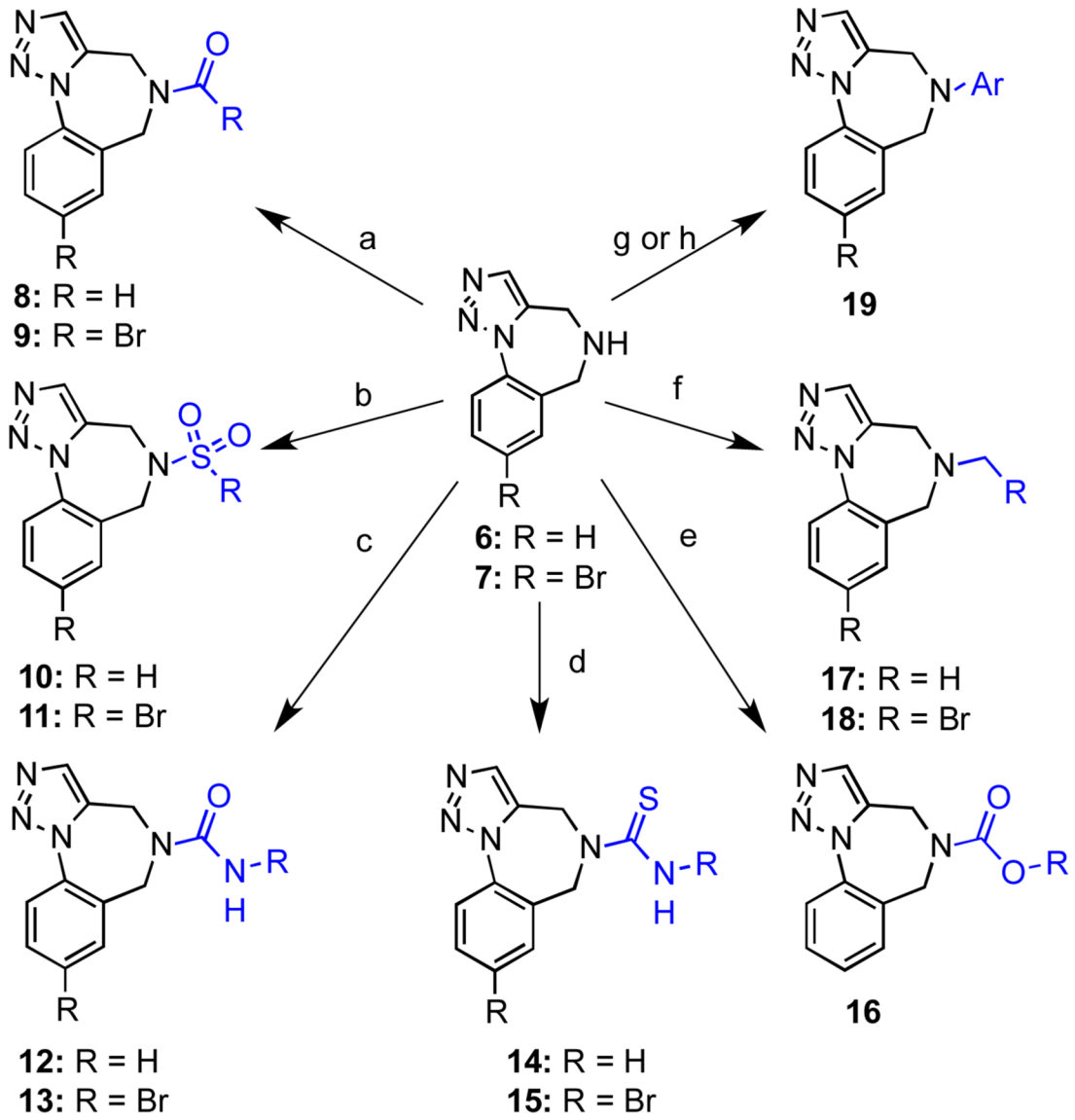
Figure 7.
Precursors to organo-zinc reagents used in the Bruylants reaction.



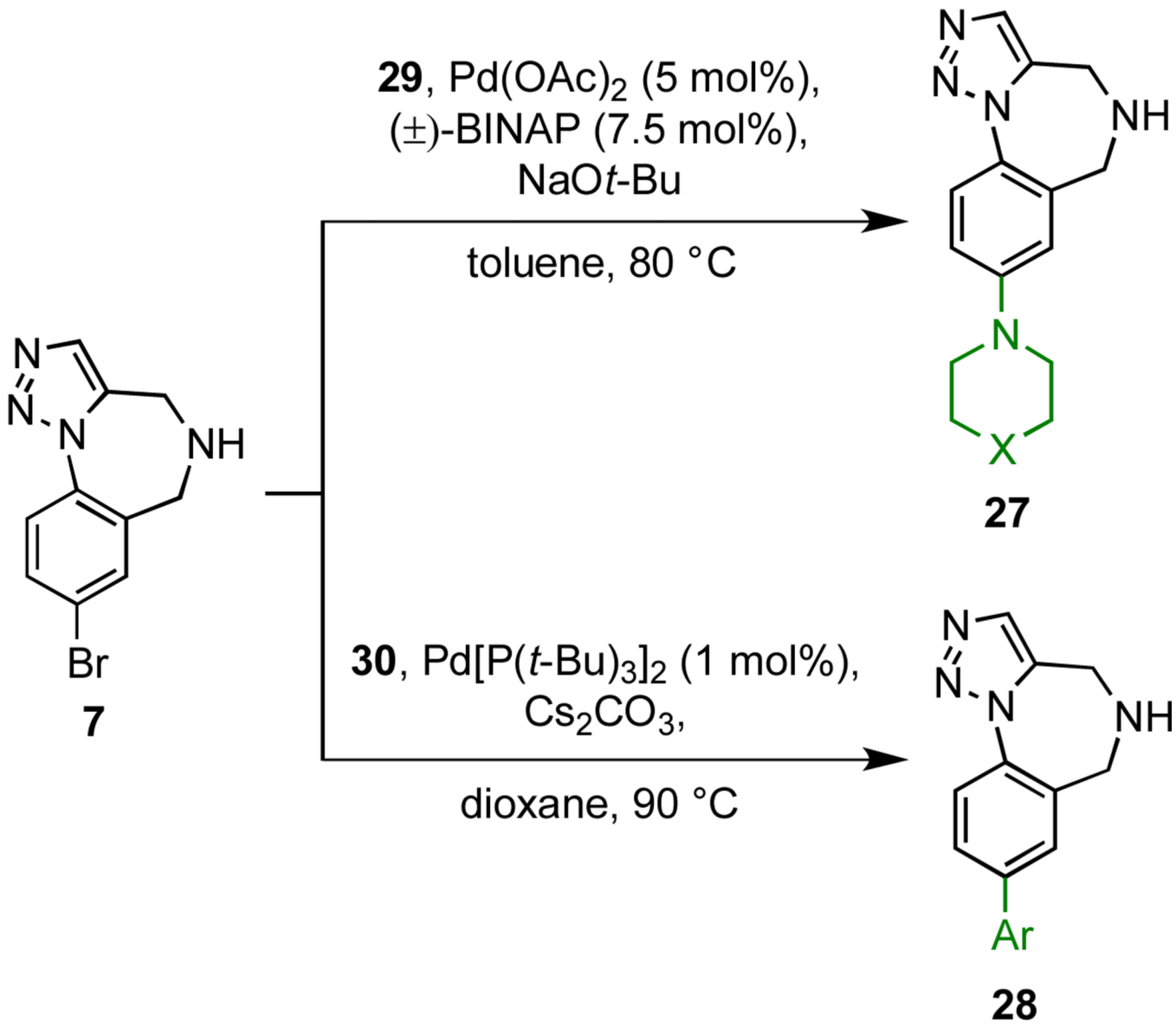
4: R = H
5: R = Br

6: R = H (66%)
7: R = Br (77%)

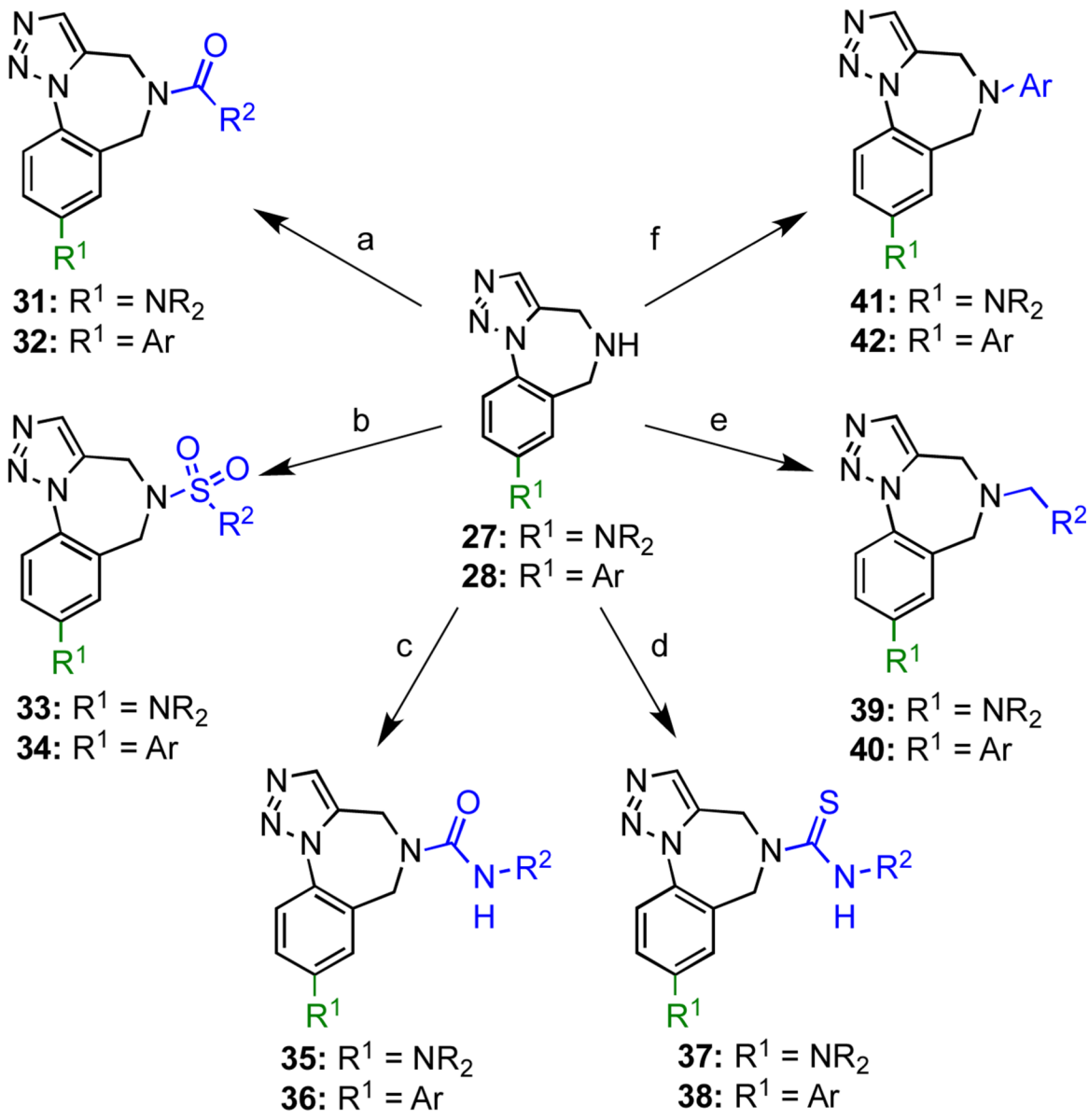
Scheme 1.
Synthesis of Scaffolds **6** and **7**.



Scheme 2.
Nitrogen functionalization of scaffolds **6** and **7**.

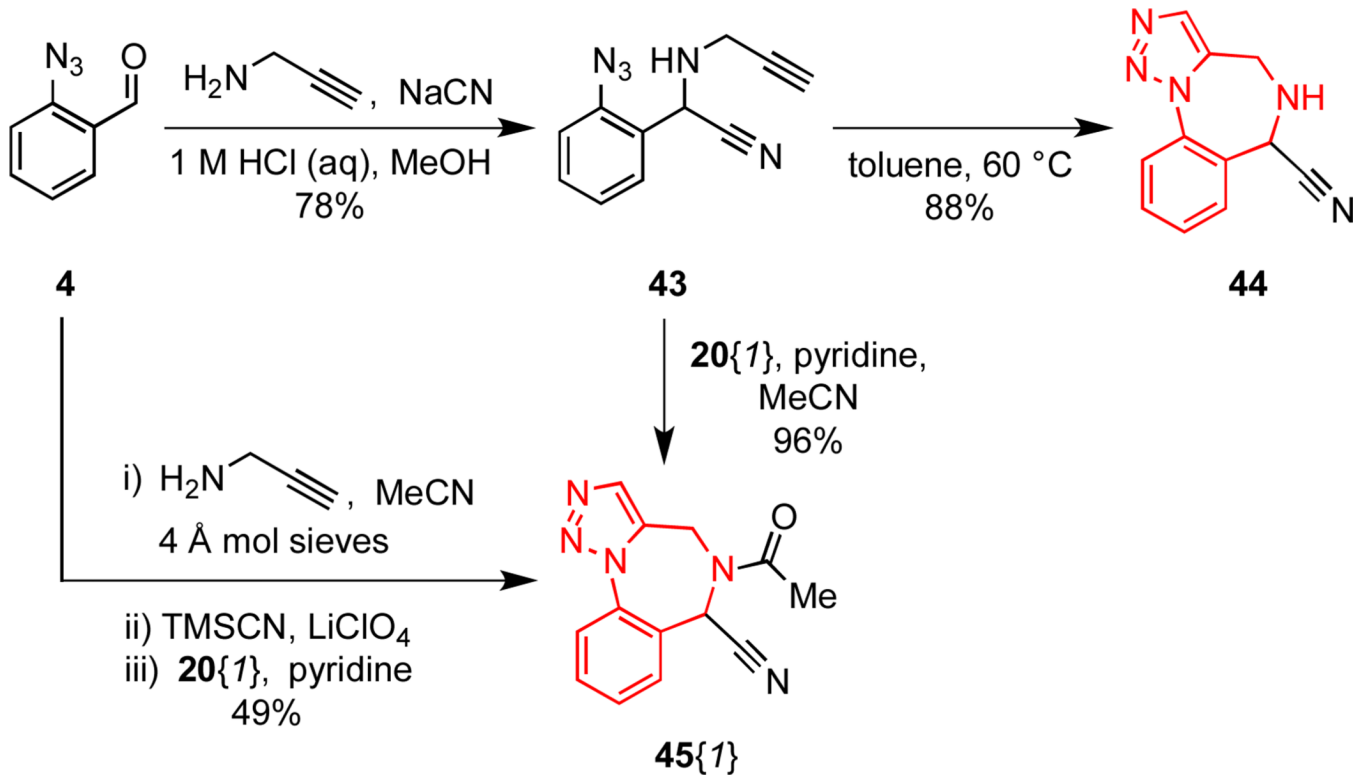


Scheme 3.
Cross-coupling reactions with scaffold **7**.

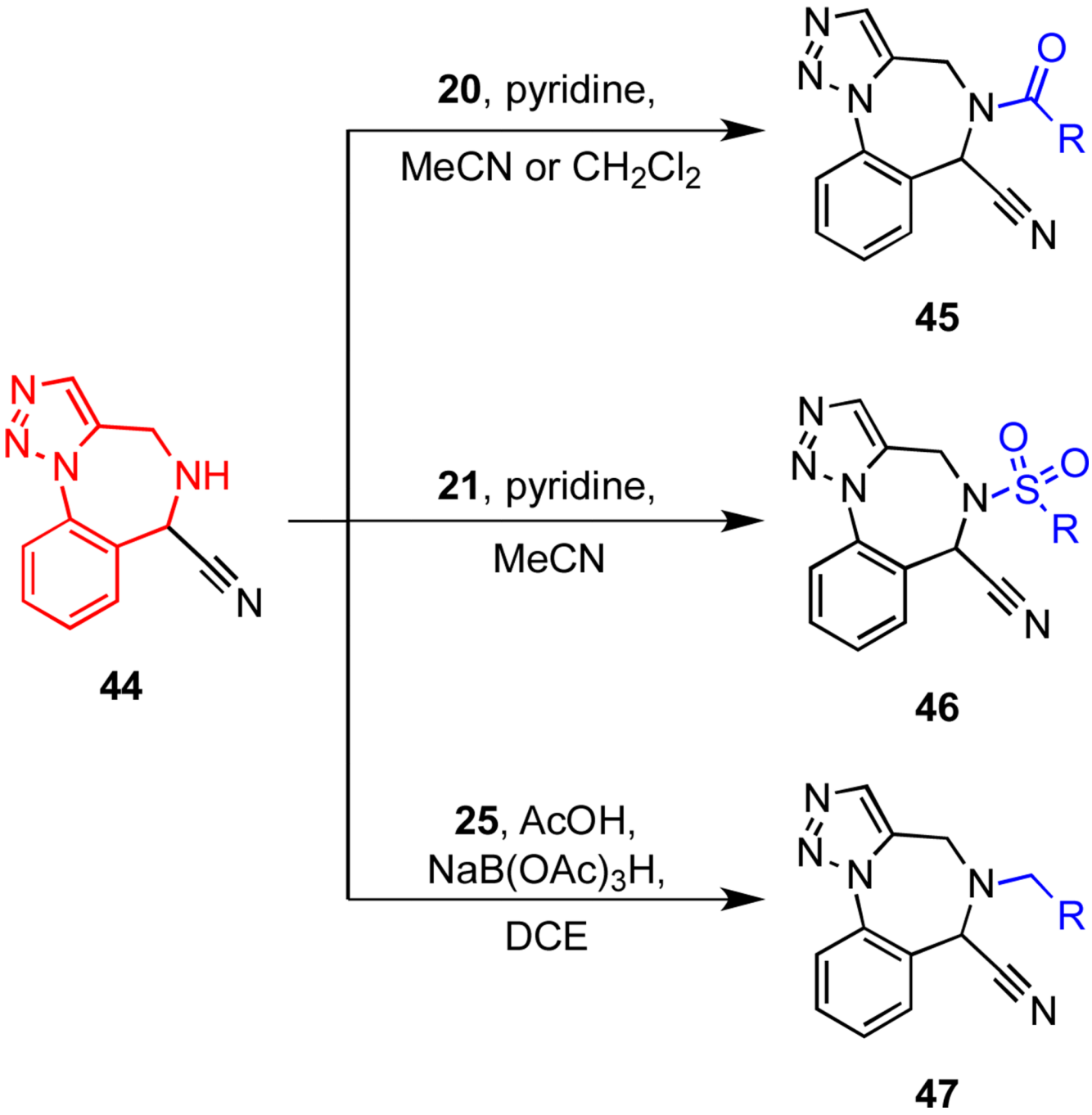


a) **20**, Et_3N, CH_2Cl_2. b) **21**, Et_3N, CH_2Cl_2. c) **22**, CH_2Cl_2. d) **23**{*3*}, CH_2Cl_2. e) **25**, RCHO, $NaB(OAc)_3H$, AcOH, DCE. f) **26**{*1*}, $Pd(OAc)_2$ (5 mol%), (±)-BINAP (7.5 mol%), NaO*t*-Bu, toluene, 80 °C.

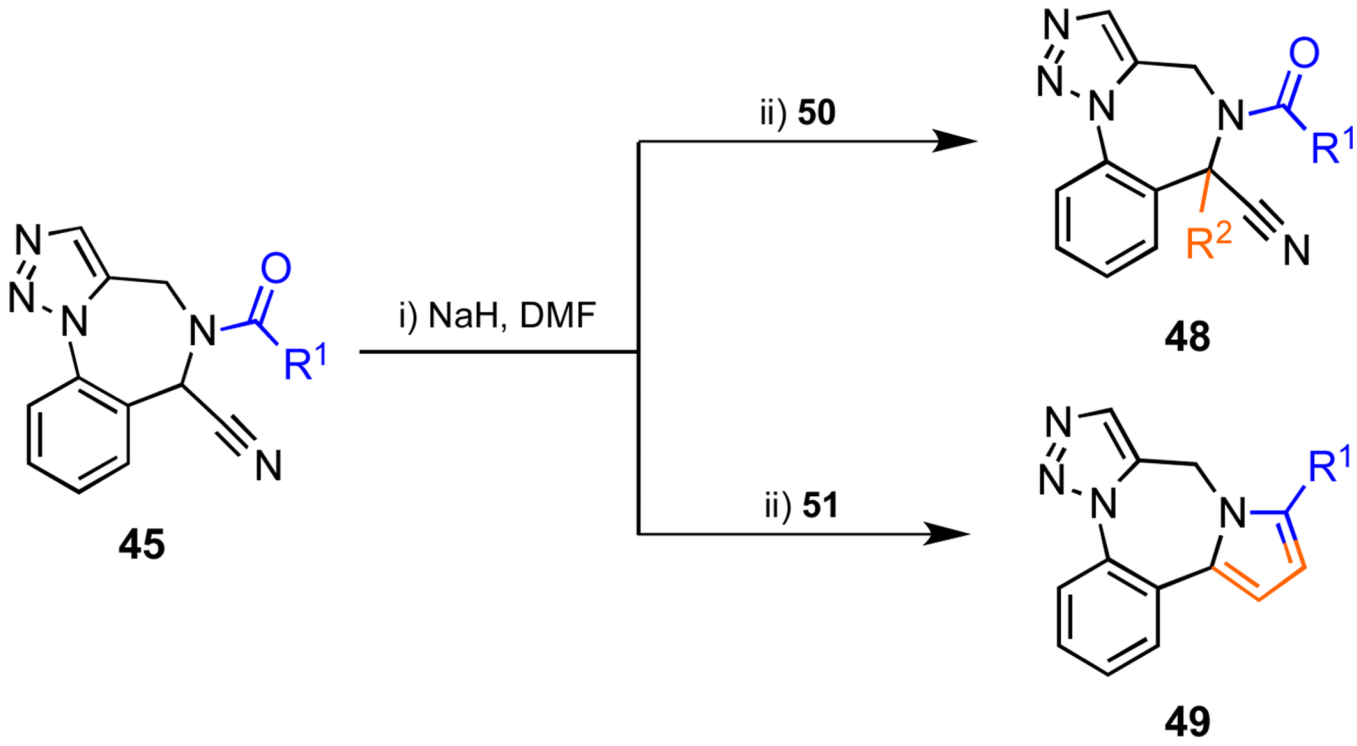
Scheme 4.
Two-dimensional library derived from scaffold **7**.



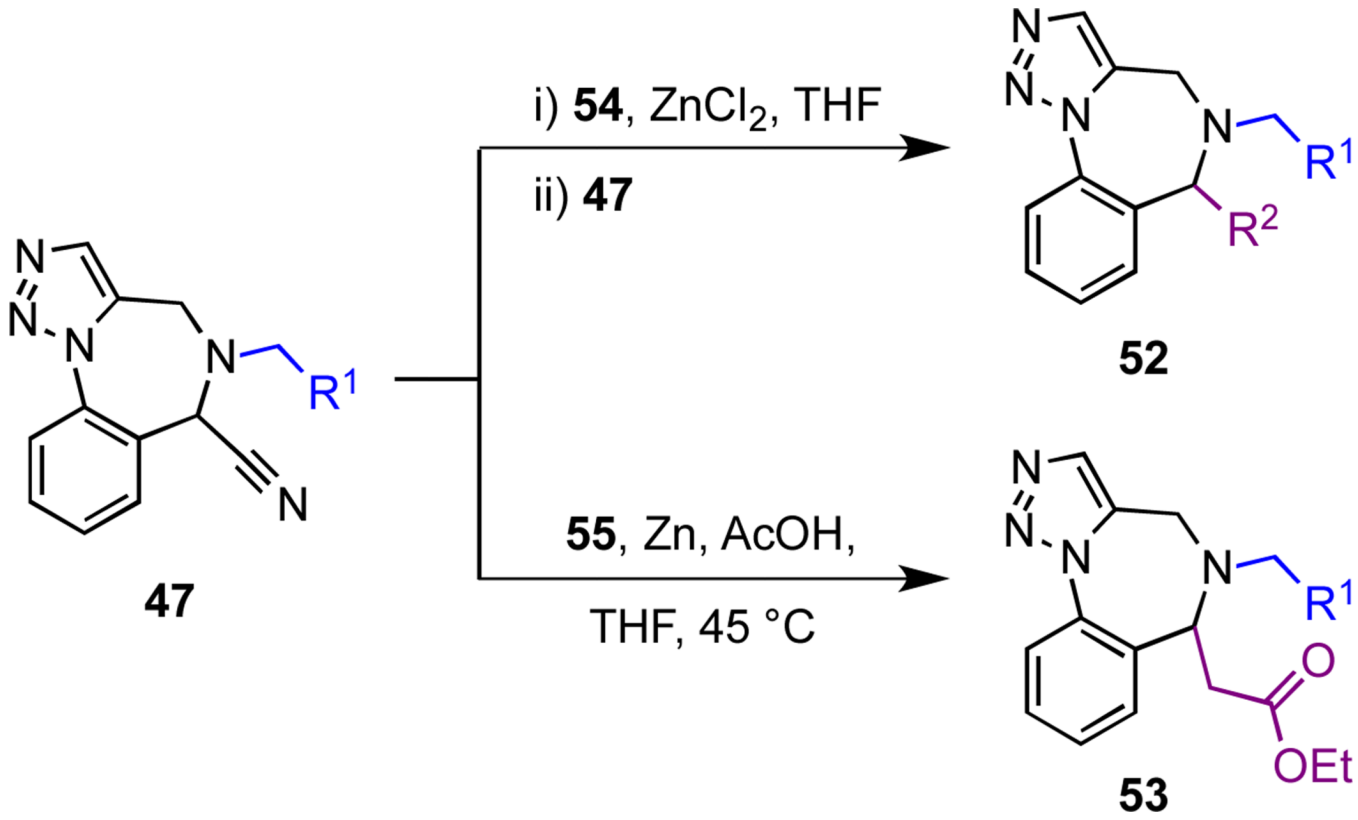
Scheme 5.
Synthesis of nitrile substituted scaffold **44**.



Scheme 6.
Nitrogen functionalization of scaffold **44**.



Scheme 7.
Anion derived diversification of amides **45**.



Scheme 8.
Diversification of aminonitriles **47** using the Bruylants reaction.

Table 1

Nitrogen functionalization of scaffolds **6** and **7**.

Entry	Scaffold	Functionalizing agent	Product	Yield (%)
1	**6**	**20**{*1*}	**8**{*1*}	95
2	**6**	**20**{*2*}	**8**{*2*}	96
3	**6**	**20**{*3*}	**8**{*3*}	Quant.
4	**6**	**20**{*4*}	**8**{*4*}	93
5	**6**	**20**{*5*}	**8**{*5*}	98
6	**6**	**20**{*6*}	**8**{*6*}	96
7	**6**	**20**{*7*}	**8**{*7*}	98
8	**6**	**20**{*8*}	**8**{*8*}	98
9	**6**	**20**{*9*}	**8**{*9*}	98
10	**6**	**20**{*10*}	**8**{*10*}	82[a,b]
11	**6**	**20**{*11*}	**8**{*11*}	95
12	**7**	**20**{*9*}	**9**{*9*}	90
13	**7**	**20**{*12*}	**9**{*12*}	67
14	**6**	**21**{*1*}	**10**{*1*}	97
15	**6**	**21**{*2*}	**10**{*2*}	64
16	**6**	**21**{*3*}	**10**{*3*}	91
17	**6**	**21**{*4*}	**10**{*4*}	98
18	**6**	**21**{*5*}	**10**{*5*}	98
19	**6**	**21**{*6*}	**10**{*6*}	89
20	**6**	**21**{*7*}	**10**{*7*}	94
21	**6**	**21**{*8*}	**10**{*8*}	88
22	**6**	**21**{*9*}	**10**{*9*}	81
23	**6**	**21**{*10*}	**10**{*10*}	84
24	**7**	**21**{*1*}	**11**{*1*}	85
25	**7**	**21**{*4*}	**11**{*4*}	53
26	**7**	**21**{*6*}	**11**{*6*}	55
27	**6**	**22**{*1*}	**12**{*1*}	99
28	**6**	**22**{*2*}	**12**{*2*}	79
29	**6**	**22**{*3*}	**12**{*3*}	96
30	**6**	**22**{*4*}	**12**{*4*}	99
31	**6**	**22**{*5*}	**12**{*5*}	99
32	**6**	**22**{*6*}	**12**{*6*}	86
33	**6**	**22**{*7*}	**12**{*7*}	91
34	**6**	**22**{*8*}	**12**{*8*}	Quant.
35	**6**	**22**{*9*}	**12**{*9*}	Quant.
36	**7**	**22**{*2*}	**13**{*2*}	58
37	**7**	**22**{*3*}	**13**{*3*}	55
38	**7**	**22**{*4*}	**13**{*4*}	Quant.
39	**6**	**23**{*1*}	**14**{*1*}	99

Entry	Scaffold	Functionalizing agent	Product	Yield (%)
40	**6**	**23**{*2*}	**14**{*2*}	98
41	**6**	**23**{*3*}	**14**{*3*}	98
42	**6**	**23**{*4*}	**14**{*4*}	83
43	**6**	**23**{*5*}	**14**{*5*}	94
44	**6**	**23**{*6*}	**14**{*6*}	95
45	**6**	**23**{*7*}	**14**{*7*}	90
46	**7**	**23**{*1*}	**15**{*1*}	79
47	**7**	**23**{*3*}	**15**{*3*}	83
48	**7**	**23**{*7*}	**15**{*7*}	Quant.
49	**6**	**24**{*1*}	**16**{*1*}	88
50	**6**	**24**{*2*}	**16**{*2*}	77
51	**6**	**24**{*3*}	**16**{*3*}	98
52	**6**	**25**{*1*}	**17**{*1*}	71
53	**6**	**25**{*2*}	**17**{*2*}	Quant.
54	**6**	**25**{*3*}	**17**{*3*}	98
55	**6**	**25**{*4*}	**17**{*4*}	83
56	**6**	**25**{*5*}	**17**{*5*}	Quant.
57	**6**	**25**{*6*}	**17**{*6*}	82
58	**6**	**25**{*7*}	**17**{*7*}	65
59	**6**	**25**{*8*}	**17**{*8*}	60
60	**6**	**25**{*9*}	**17**{*9*}	96
61	**6**	**25**{*10*}	**17**{*10*}	96
62	**6**	**25**{*11*}	**17**{*11*}	56[c]
63	**7**	**25**{*5*}	**18**{*5*}	98
64	**7**	**25**{*12*}	**18**{*12*}	55
65	**7**	**25**{*13*}	**18**{*13*}	70
66	**6**	**26**{*1*}	**19**{*1*}	96
67	**6**	**26**{*2*}	**19**{*2*}	83
68	**6**	**26**{*3*}	**19**{*3*}	73
69	**6**	**26**{*4*}	**19**{*4*}	48
70	**6**	**26**{*5*}	**19**{*5*}	0
71	**6**	**26**{*6*}	**19**{*6*}	85[c]

[a] An additional 3.0 equivalents of Et_3N were employed.

[b] Isolated as the free-base.

[c] No AcOH added.

Table 2

Cross-coupling reactions with scaffold **7**.

Entry	Coupling Partner	Product	Yield (%)
1	**29**{*1*}	**27**{*1*}	75
2	**29**{*2*}	**27**{*2*}	69
3	**30**{*1*}	**28**{*1*}	84
4	**30**{*2*}	**28**{*2*}	73
5	**30**{*3*}	**28**{*3*}	74
6	**30**{*4*}	**28**{*4*}	78
7	**30**{*5*}	**28**{*5*}	78
8	**30**{*6*}	**28**{*6*}	76
9	**30**{*7*}	**28**{*7*}	92

Table 3

Two-dimensional library derived from scaffold **7**.

Entry	Amine input	Functionalizing agent	Product	Yield (%)
1	**27**{*1*}	**20**{*4*}	**31**{*1,4*}	Quant.
2	**27**{*1*}	**20**{*13*}	**31**{*1,13*}	86
3	**27**{*1*}	**21**{*5*}	**33**{*1,5*}	86
4	**27**{*1*}	**21**{*11*}	**33**{*1,11*}	87
5	**27**{*1*}	**22**{*2*}	**35**{*1,2*}	92
6	**27**{*1*}	**22**{*3*}	**35**{*1,3*}	7
7	**27**{*1*}	**23**{*3*}	**37**{*1,3*}	91
8	**27**{*1*}	**25**{*2*}	**39**{*1,2*}	78
9	**27**{*1*}	**25**{*14*}	**39**{*1,14*}	88
10	**27**{*1*}	**26**{*1*}	**41**{*1,1*}	83
11	**27**{*2*}	**20**{*4*}	**31**{*2,4*}	94
12	**27**{*2*}	**20**{*13*}	**31**{*2,13*}	73
13	**27**{*2*}	**21**{*5*}	**33**{*2,5*}	87
14	**27**{*2*}	**21**{*11*}	**33**{*2,11*}	88
15	**27**{*2*}	**22**{*2*}	**35**{*2,2*}	76
16	**27**{*2*}	**22**{*3*}	**35**{*2,3*}	90
17	**27**{*2*}	**23**{*3*}	**37**{*2,3*}	94
18	**27**{*2*}	**25**{*2*}	**39**{*2,2*}	88
19	**27**{*2*}	**25**{*14*}	**39**{*2,14*}	79
20	**27**{*2*}	**26**{*1*}	**41**{*2,1*}	90
21	**28**{*1*}	**20**{*4*}	**32**{*1,4*}	Quant.
22	**28**{*1*}	**20**{*13*}	**32**{*1,13*}	88
23	**28**{*1*}	**21**{*5*}	**34**{*1,5*}	91
24	**28**{*1*}	**21**{*11*}	**34**{*1,11*}	Quant.
25	**28**{*1*}	**22**{*2*}	**36**{*1,2*}	86
26	**28**{*1*}	**22**{*3*}	**36**{*1,3*}	97
27	**28**{*1*}	**23**{*3*}	**38**{*1,3*}	98
28	**28**{*1*}	**25**{*2*}	**40**{*1,2*}	85
29	**28**{*1*}	**25**{*14*}	**40**{*1,14*}	39
30	**28**{*1*}	**26**{*1*}	**42**{*1,1*}	94
31	**28**{*2*}	**20**{*4*}	**32**{*2,4*}	Quant.
32	**28**{*2*}	**20**{*13*}	**32**{*2,13*}	73
33	**28**{*2*}	**21**{*5*}	**34**{*2,5*}	Quant.
34	**28**{*2*}	**21**{*11*}	**34**{*2,11*}	Quant.
35	**28**{*2*}	**22**{*2*}	**36**{*2,2*}	90
36	**28**{*2*}	**22**{*3*}	**36**{*2,3*}	Quant.
37	**28**{*2*}	**23**{*3*}	**38**{*2,3*}	Quant.
38	**28**{*2*}	**25**{*2*}	**40**{*2,2*}	94
39	**28**{*2*}	**25**{*14*}	**40**{*2,14*}	35

Entry	Amine input	Functionalizing agent	Product	Yield (%)
40	**28**{*2*}	**26**{*1*}	**42**{*2,1*}	96
41	**28**{*5*}	**20**{*4*}	**32**{*5,4*}	Quant.
42	**28**{*5*}	**20**{*13*}	**32**{*5,13*}	85
43	**28**{*5*}	**21**{*5*}	**34**{*5,5*}	97
44	**28**{*5*}	**21**{*11*}	**34**{*5,11*}	Quant.
45	**28**{*5*}	**22**{*2*}	**36**{*5,2*}	94
46	**28**{*5*}	**22**{*3*}	**36**{*5,3*}	98
47	**28**{*5*}	**23**{*3*}	**38**{*5,3*}	99
48	**28**{*5*}	**25**{*2*}	**40**{*5,2*}	94
49	**28**{*5*}	**25**{*14*}	**40**{*5,14*}	40
50	**28**{*5*}	**26**{*1*}	**42**{*5,1*}	99

Table 4

Nitrogen functionalization of scaffold **44**.

Entry	Functionalizing Agent	Product	Yield (%)
1	**20**{*1*}	**45**{*1*}	92
2	**20**{*4*}	**45**{*4*}	92
3	**20**{*7*}	**45**{*7*}	93
4	**20**{*10*}	**45**{*10*}	92[a]
5	**20**{*12*}	**45**{*12*}	49[b]
6	**20**{*13*}	**45**{*13*}	95
7	**20**{*14*}	**45**{*14*}	98
8	**20**{*15*}	**45**{*15*}	66[c]
9	**20**{*16*}	**45**{*16*}	Quant.
10	**20**{*17*}	**45**{*17*}	Quant.
11	**21**{*1*}	**46**{*1*}	97
12	**21**{*3*}	**46**{*3*}	91
13	**21**{*5*}	**46**{*5*}	86
14	**21**{*6*}	**46**{*6*}	90
15	**21**{*7*}	**46**{*7*}	91
16	**21**{*9*}	**46**{*9*}	85
17	**21**{*11*}	**46**{*11*}	80
18	**25**{*1*}	**47**{*1*}	63
19	**25**{*5*}	**47**{*5*}	41[d]
20	**25**{*12*}	**47**{*12*}	84
21	**25**{*14*}	**47**{*14*}	74
22	**25**{*15*}	**47**{*15*}	87

[a] Isolated as the free-base

[b] Yield after recrystallization from toluene (following chromatography).

[c] Yield after the product was washed with hexanes (3 × 5 mL) following chromatography.

[d] The addition of TFA (1.0 eq.) and extra $NaBH(OAc)_3$ (4.0 eq.) was required to fully consume **44**.

Table 5

Libraries derived from amides **45**.

Entry	Amide	Electrophile	Product	Yield(%)
1	**45**{*1*}	**50**{*1*}	**48**{*1,1*}	80
2	**45**{*1*}	**50**{*2*}	**48**{*1,2*}	86
3	**45**{*15*}	**50**{*1*}	**48**{*15,1*}	80
4	**45**{*15*}	**50**{*2*}	**48**{*15,2*}	76
5	**45**{*1*}	**51**	**49**{*1*}	72
6	**45**{*13*}	**51**	**49**{*13*}	66
7	**45**{*4*}	**51**	**49**{*4*}	Trace[a]
8	**45**{*15*}	**51**	**49**{*15*}	95
9	**45**{*16*}	**51**	**49**{*16*}	85
10	**45**{*7*}	**51**	**49**{*7*}	44
11	**45**{*10*}	**51**	**49**{*10*}	91
12	**45**{*17*}	**51**	**49**{*17*}	0

[a]Trace formation of the pyrrole product **49**{*4*} was observed in the ^{1}H NMR spectrum of the crude reaction mixture.

Table 6

Amines derived from the Bruylants reaction.

Entry	Aminonitrile	Organo-zinc precursor	Product	Yield (%)
1	**47**{*1*}	**54**{*1*}	**52**{*1,1*}	73
2	**47**{*1*}	**54**{*2*}	**52**{*1,2*}	86
3	**47**{*12*}	**54**{*1*}	**52**{*12,1*}	75
4	**47**{*12*}	**54**{*2*}	**52**{*12,2*}	73
5	**47**{*14*}	**54**{*1*}	**52**{*14,1*}	80
6	**47**{*14*}	**54**{*2*}	**52**{*14,2*}	81
7	**47**{*1*}	**55**	**53**{*1*}	74
8	**47**{*12*}	**55**	**53**{*12*}	77
9	**47**{*14*}	**55**	**53**{*14*}	75