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Recent advances in the C(1)-functionalization of tetrahydroisoquinolines *via* multicomponent reactions

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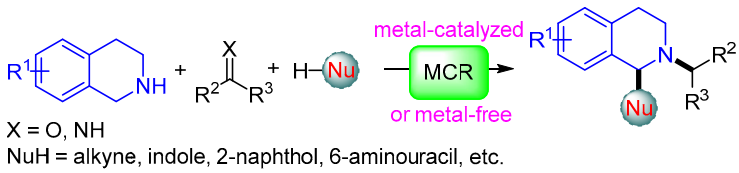


1,2,3,4-Tetrahydroisoquinoline is an important structural motif of various natural products and therapeutic lead compounds. In recent years, considerable research interest has been witnessed toward synthesis of its C(1)-substituted derivatives, since they can act as precursors for various alkaloids displaying multifarious biological activities. This minireview offers short and non-exhaustive epitome of various multicomponent reactions for the C(1)-functionalization of 1,2,3,4-tetrahydroisoquinolines. In particular, reactions involving isomerization of iminium intermediate (*exo*/*endo* isomerization) are highlighted for the period of 2013–2019.

Keywords: heterocyclic compounds, iminium ion, tetrahydroisoquinoline, C(1)-functionalization, multicomponent reactions.

Over the past several years, considerable interest in organic and medicinal chemistry has been directed toward the synthesis of various biologically important nitrogen heterocycles.[1] Among these compounds, 1,2,3,4-tetrahydroisoquinoline (THIQ) has garnered significant attention, as it is the most "privileged scaffold"[1f] present in various natural and non-natural compounds with intriguing biological properties. THIQs with stereogenic center at position C(1) are the key fragments of diverse range of alkaloids and bioactive molecules (Fig. 1).[2] Also, *N*-benzyl THIQs are known to function as antineuroinflammatory agents.[3] Apart from this, THIQ derivatives have broad applications in asymmetric catalysis as chiral scaffolds.[4] Due to their broad range of applications, various new and environmental friendly methods for the synthesis of THIQ derivatives are on rise.

Traditional approaches to the synthesis of C(1)-substituted THIQs include the use of harsh conditions or preassembled substrates. Recently, transition metal-catalyzed cross-dehydrogenative coupling (CDC) strategies involving direct coupling of C(sp^3)–H bond of THIQ with various nucleophiles (two-component coupling) have been explored in the presence of cooxidants like H_2O_2, TBHP, etc.[5] Despite the success of CDC approach, sometimes the use of stoichiometric amount of oxidant limits its versatility. Also, the use of prefunctionalized *N*-arylated/protected THIQ is indispensable for better reaction

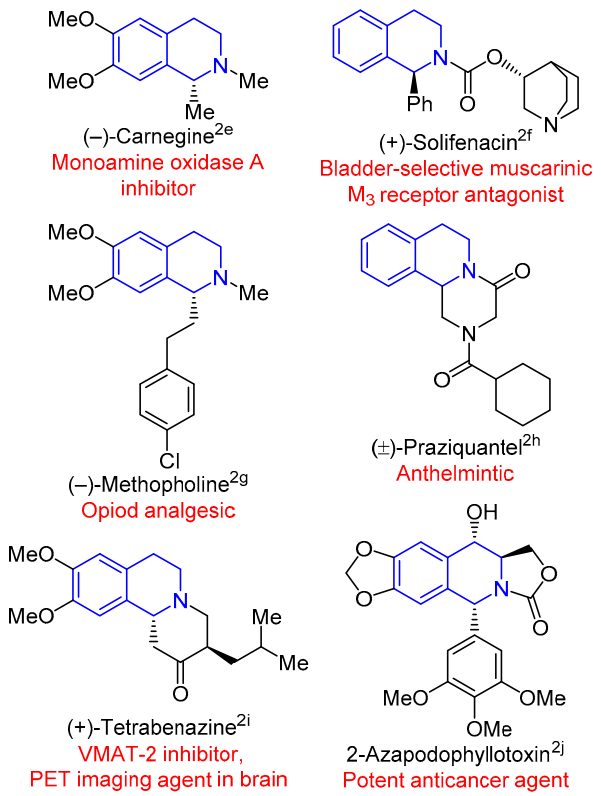
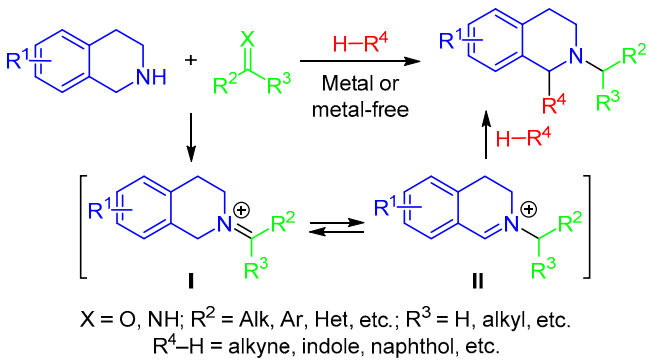


Figure 1. Biologically active molecules containing THIQ motif.

performance as otherwise nitrogen of unprotected THIQ can undergo oxidation. Nowadays, multicomponent reactions (MCRs) are considered as powerful strategies in organic synthesis for the generation of molecular diversity and complexity. MCRs improve the atom economy, selectivity, and yield of the product and thus occupy a central place in the toolbox of sustainable synthetic methodologies.[6]

Recently, a number of transition metal-catalyzed or metal-free coupling methodologies resulting in the decoration of THIQ core *via* MCRs have appeared. The reaction of THIQ with aldehydes, ketones, or imines can generate *exo*-iminium ion **I** (C=N bond outside the THIQ ring) which can isomerize to more stable *endo*-iminium ion **II** (C=N bond within the THIQ ring). The coupling of *in situ* generated *endo*-iminium ion with a nucleophile, such as alkyne, indole, naphthol, can provide C(1)-substituted THIQs *via* a one-pot multicomponent strategy (Scheme 1). However, in general, the *exo*/*endo* selectivity of iminium ion and hence the final product depends on the nature of catalyst, ligand, time of the reaction, and temperature.

Scheme 1. General multicomponent strategy for C(1)-functionalization of THIQ *via exo*/*endo*-iminium isomerization



X = O, NH; R^2 = Alk, Ar, Het, etc.; R^3 = H, alkyl, etc.
R^4–H = alkyne, indole, naphthol, etc.

This minireview exemplifies the recent developments from the years 2013–2019 that has been made toward C(1)-functionalization of THIQ by MCRs involving tunable iminium ions as intermediates.

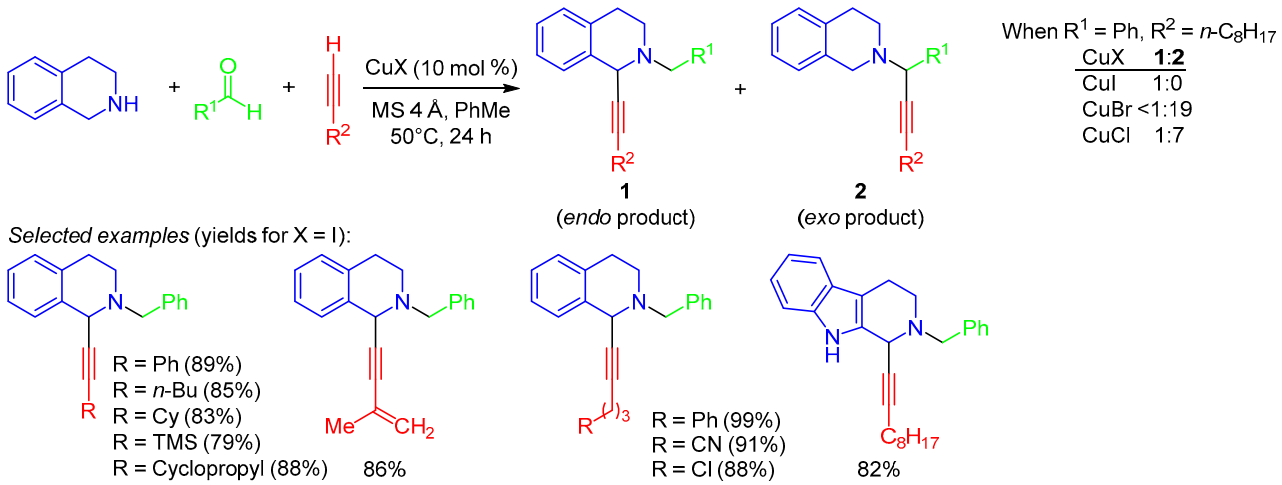
C(1)-Functionalization of THIQ with alkynes

In 2013, the research group of Yu[7] reported a CuI-catalyzed three-component coupling of THIQs with aldehydes and alkynes (A^3-type coupling, Scheme 2). As discussed earlier, the initially formed *exo*-iminium ion isomerizes to a more stable *endo*-iminium ion which is then attacked by terminal alkyne (activated by Cu catalyst) providing C(1)-alkynylated THIQs **1**. Surprisingly, use of CuBr or CuCl, in place of CuI, competitively changed the selectivity toward *exo*-alkynylated products **2**. The presence of inert atmosphere and molecular sieves (MS) was found to be crucial for this reaction. The developed reaction conditions proved futile in case of electron-rich THIQ and α,β-unsaturated aldehyde such as cinnamaldehyde. However, on using tryptoline (β-carboline), a common motif in natural products, as the secondary amine, exclusive formation of *endo*-alkynylated product was observed.

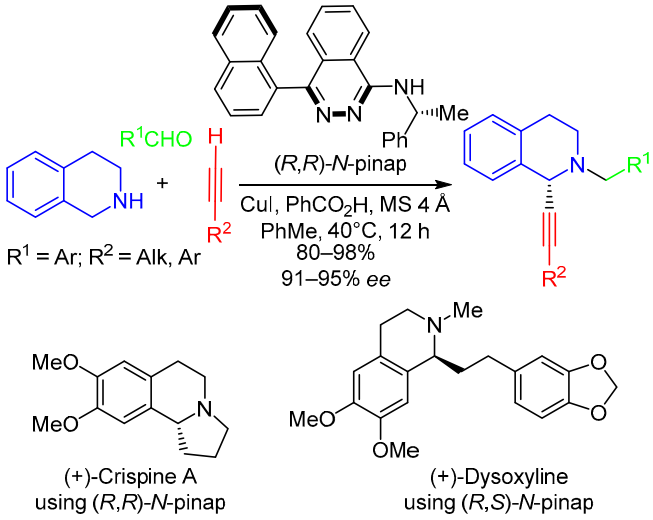
In 2014, Ma and coworkers[8] have shown that on using CuBr along with PPh_3 as a ligand, the selectivity of the above reaction can be changed toward *endo*-alkynylated products **1**. Also, low loading of CuBr favored the formation of *endo* product **1** over *exo* product **2**, as A^3-coupling reaction slowed down, which provided more time for the isomerization of iminium ion. Various C(1)-substituted THIQs could be easily accessed at 80°C for 12 h in PhMe using a combination of CuBr (2.5 mol %) and PPh_3 (2.75 mol %). Furthermore, use of chiral ligands permitted to explore the enantioselective version of this reaction. Diverse range of alkyl- and arylalkynes provided the corresponding C(1)-alkynylated products in high enantioselectivity on using (*R*,*R*)-*N*-pinap (2.2 mol %) along with CuI catalyst (proved superior to CuBr in terms of *ee*). In another research article,[9] the same research group further demonstrated the utility of their methodology by asymmetric synthesis of natural products (+)-dysoxyline and (+)-crispine A, each with up to 98% *ee* (Scheme 3).

Apart from use of Cu-based catalysts, an Ag-based catalyst has also been used for alkynylation reaction. The research group of Shao,[10] evaluated the role of AgOAc as

Scheme 2. CuI-catalyzed multicomponent coupling for synthesis of C(1)-alkynylated THIQ derivatives



Scheme 3. CuI-catalyzed asymmetric synthesis of C(1)-alkynylated THIQ derivatives



catalyst to facilitate C(1)-alkynylation of THIQs in air. No formation of competitive *exo* product was reported. It was speculated that the soft nature of AgOAc (as compared to copper) might be promoting the isomerization toward thermodynamically more stable *endo*-iminium ion. CH_2Cl_2 was found to be the solvent of choice, and no product formation occured in PhMe or MeOH. Excellent yields of C(1)-substituted THIQs were obtained even at room temperature using a variety of phenylacetylenes substituted with electron-donating groups (EDGs) and electron-withdrawing groups (EWGs). Also, aliphatic alkynes (possessing ester groups and C=C bonds) could be used in this reaction. However, on using an aliphatic aldehyde as coupling partner, only *exo*-alkynylated product was obtained. Synthesis of polycyclic compound **3**, a structural component of naturally occurring alkaloid tetrahydroberberine was achieved in two steps (Scheme 4).

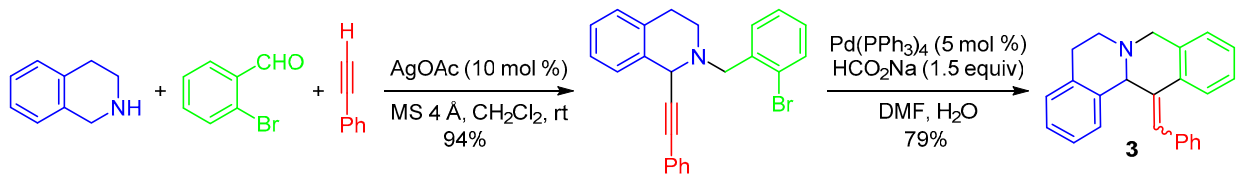
Liu and coworkers[11] reported the multicomponent coupling of indole-2-carboxaldehyde and terminal alkynes with THIQs (and other secondary amines). Using $AuBr_3$ as a catalyst for this reaction, the exclusive formation of *endo* products in good to excellent yields was observed (Scheme 5). Various aromatic alkynes containing halo and methoxy groups were well tolerated. However, only *N*-protected indole-2-carbaldehydes (e. g., Me-, Bn-, or Boc-protected) could be employed. It was observed that steric hindrance of aldehyde plays a major role in determining the *exo*/*endo* selectivity. On using formaldehyde as coupling partner, only *exo* product was formed. In coupling reaction with benzaldehyde, a mixture of *exo*/*endo*-alkynylated products was obtained in ratio 4.8:1. Overall, this $AuBr_3$-based strategy provided an efficient entry to the assembly of complex indole derivatives.

Using A^3-coupling between THIQ, 2-bromobenzaldehyde, and trimethylsilylacetylene as the key step, Zhou and Tong[12] achieved the total synthesis of 22 natural 13-methylprotoberberines (13-MeTHPBs), a class of pharmaceutically active isoquinoline alkaloids. For this purpose, A^3-coupling products (i. e., C(1)-alkynylated THIQs) after desilylation with K_2CO_3 were subjected to a Pd-catalyzed carbocyclization and PtO_2-mediated hydrogenation. In particular, the yield of A^3-step could be dramatically enhanced from <5 to 81% by using catalytic amount of benzoic acid (0.1 equiv) along with CuI (Scheme 6). The utility of this method was further demonstrated for the total synthesis, *via* the versatile intermediate **4**, of more than 30 natural protoberberines (lacking C-13 methyl group) and 5 aporhoeadane alkaloids.

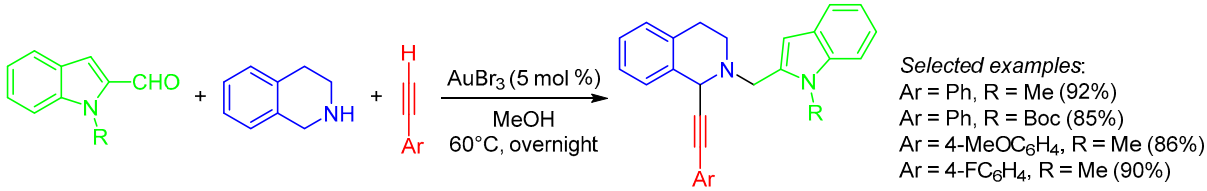
The same research group[13] further explored the asymmetric total synthesis of 13-MeTHPBs (Scheme 7). The conditions developed by Ma and coworkers,[8] i. e., CuI along with (*R*,*R*)-*N*-pinap, provided low *ee* (50% *ee*) of A^3-product with sterically hindered benzaldehyde and electron-rich THIQ as coupling partners. Further screening of other chiral ligands and controlled experiments revealed (*S*,*R*)-*N*-pinap as the best ligand for sterically hindered aldehydes, whereas (*R*,*R*)-*N*-pinap proved optimal in the case of benzaldehyde without neighboring substituents. Chiral PyBOX ligand could not provide complete conversion of the starting materials and also resulted in poor enantioselectivity (0–40% *ee*). Finally, the reductive carbocyclization and hydrogenation were achieved using $Pd(PPh_3)_4$ and PtO_2 catalysts, respectively.

Recyclability of the catalyst is an important consideration from the industrial point of view. In particular, leaching of metal catalyst to the final product can limit its

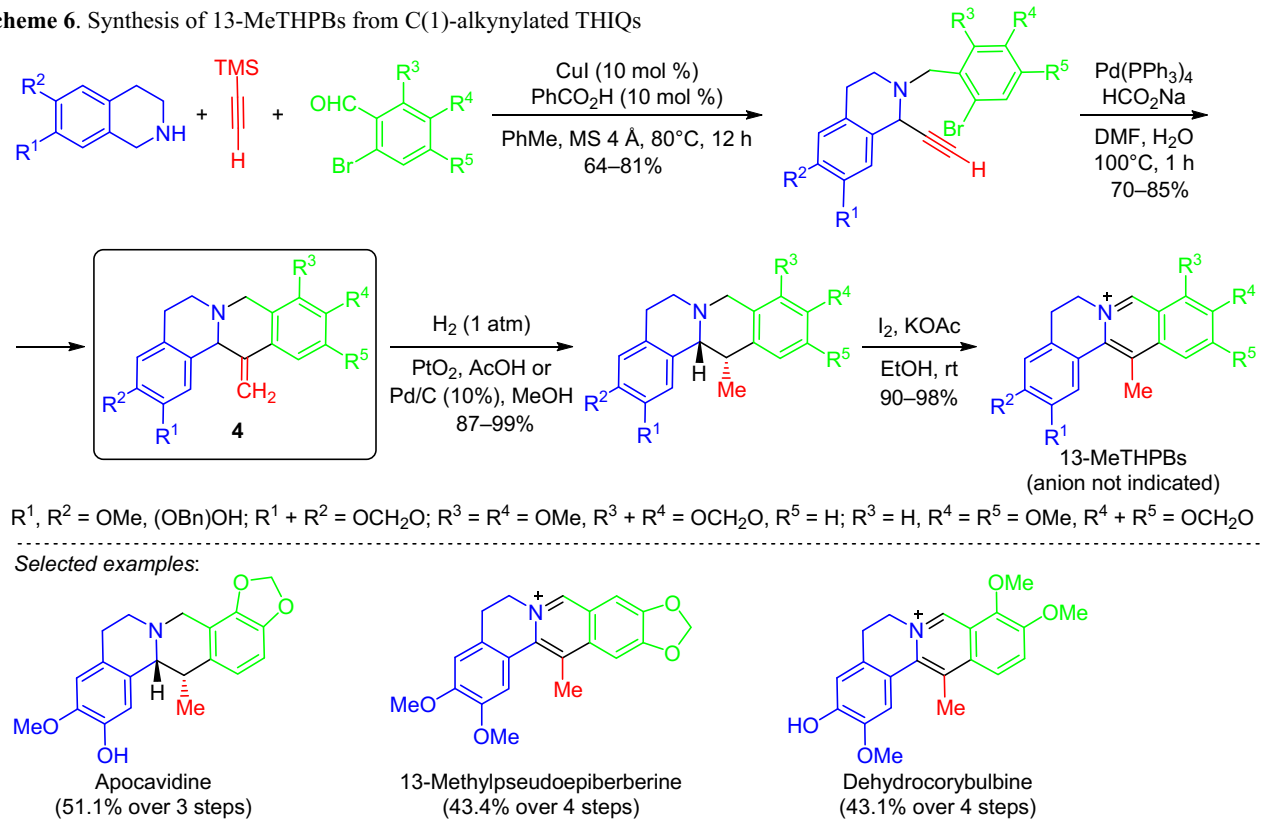
Scheme 4. AgOAc-catalyzed multicomponent coupling for C(1)-alkynylation of THIQ



Scheme 5. $AuBr_3$-catalyzed multicomponent coupling of indole-2-carboxaldehydes and terminal alkynes with THIQs



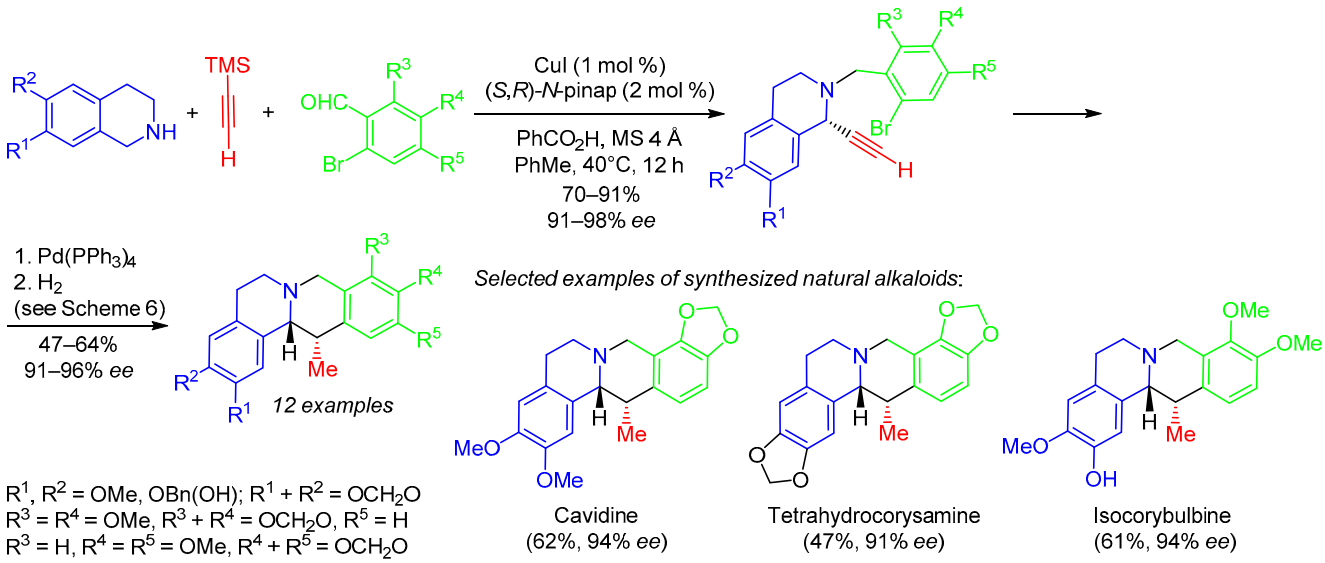
Scheme 6. Synthesis of 13-MeTHPBs from C(1)-alkynylated THIQs



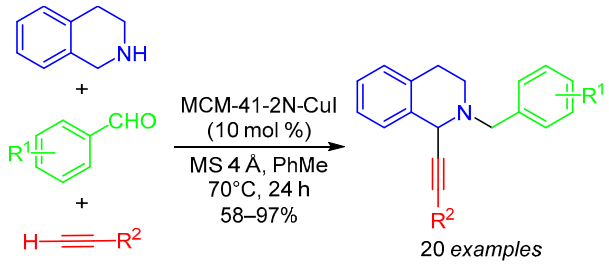
use in various pharmaceutical applications.[14] Thus, keeping the concept of green and sustainable chemistry in mind, use of efficient and recyclable catalysts in MCRs is highly desired.

Various heterogeneous catalysts have been explored for the C(1)-functionalization of THIQs with alkynes. Cai and coworkers[15] synthesized 3-(2-aminoethylamino)-propyl-functionalized MCM-41-supported CuI complex (MCM-41-2N-CuI) and explored it as a heterogeneous catalyst for A^3-coupling of THIQ, aldehyde, and alkynes Scheme 8). Exclusive formation of C(1)-alkynylated THIQs (*endo* products) was observed in good to excellent yields. However, when the catalytic system was switched from MCM-41-2N-CuI to MCM-41-2N-CuBr, the selectivity of product changed toward *exo*-alkynylated product (*exo*:*endo* = 18:1). Increasing the amount of Cu catalyst enhanced the rate of the reaction, though at the expense of regioselectivity. The aliphatic alkynes (substituted with CN, Cl, ester group), sterically hindered aromatic aldehydes, and heterocyclic aldehydes were well tolerated. However, poor regioselectivity was observed when 4-(trifluoromethyl)benzaldehyde was used as

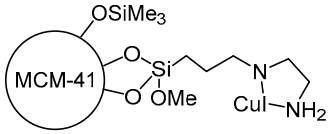
Scheme 7. Total asymmetric synthesis of 13-MeTHPBs



Scheme 8. Recyclable supported CuI catalyst for synthesis of C(1)-alkynylated THIQs



R^1 = H, *p*-Me, *p*-Br, *p*-OMe, *p*-CF_3, etc.
R^2 = *n*-C_6H_{13}, CH_2OAc, $SiMe_3$, etc.



MCM-41-2N-CuI

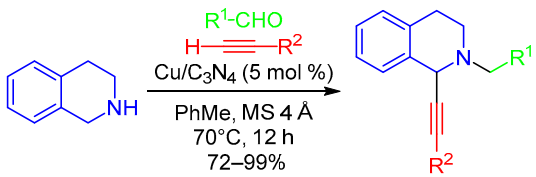
Recyclability study of the catalyst for A^3-coupling
R^1 = H, R^2 = $(CH_2)_3Ph$

Cycle No.	1	2	3	4	5	6	7	8	9	10
Time, h	24	24	24	24	24	24	26	28	28	30
Isolated yield, %	97	96	96	97	96	95	95	96	95	95

substrate and corresponding *exo*-ynyl-THIQ was obtained in 11% yield only. This might be because of the slow isomerization of the iminium ion generated *in situ*. Importantly, the catalyst could be recovered by simple filtration and recycled up to ten times without any change in catalytic activity. Also, no leaching of Cu from the solid surface of catalyst was observed during the reaction.

Similarly, Cu/C_3N_4 composite as a recyclable heterogeneous catalyst was reported for the C(1)-functionalization of THIQ with alkynes (Scheme 9).[16] The optimized reaction conditions (5 mol % Cu/C_3N_4 in PhMe with 4 Å MS at 70°C for 12 h under N_2 atmosphere) were found compatible with a variety of aromatic aldehydes including thiophene-2-carbaldehyde and alkynes substituted with EDGs and EWGs. The use of 20% Cu/Cu_3N_4 or Cu nanoparticles provided lower yields. The catalyst was recyclable upto five cycles without any significant loss in catalytic activity.

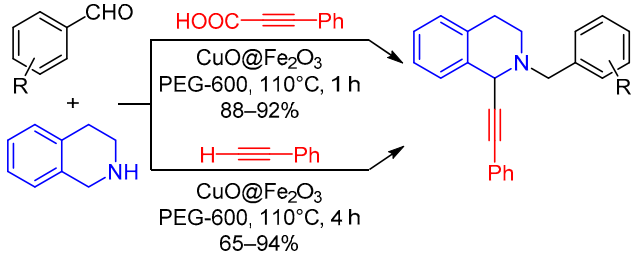
Scheme 9. MCR between THIQ, aldehyde, and alkyne using recyclable Cu/Cu_3N_4 composite



R^1 = Ar, 2-thienyl, *n*-C_7H_{15}; R^2 = Ar, *n*-Bu, Cy

In 2017, Rawat and coworkers[17] reported the utility of recyclable $CuO@Fe_2O_3$ nanocatalyst in green solvent PEG-600 for the regioselective synthesis of C(1)-alkynylated THIQs (Scheme 10). The catalyst was magnetically recovered and recyclable for up to five cycles without any

Scheme 10. Recyclable $CuO@Fe_2O_3$ nanocatalyst for synthesis of C(1)-alkynylated THIQs



R = *p*-Me, H, *p*-CN, *p*-F, 2,3-Cl, *p*-OMe, etc.

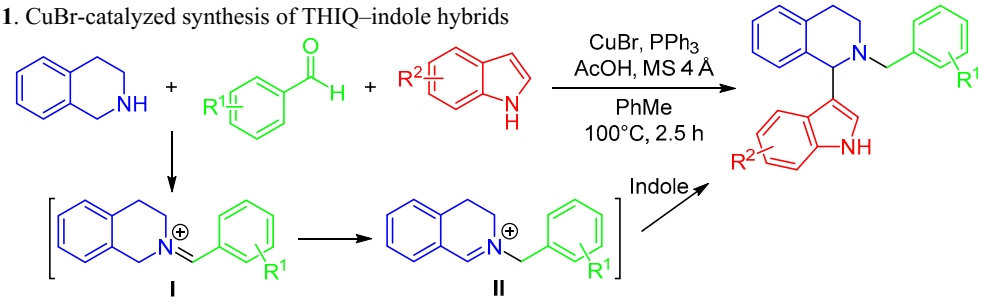
significant loss in the catalytic activity. The reaction was compatible with various substituted aldehydes and aromatic or aliphatic alkynes (such as cyclopropylacetylene, octyne). In general, alkynes are prone to polymerization and require delicate reaction conditions. The authors successfully explored phenylpropiolic acids as stable surrogates for alkynes in this coupling reaction *via* decarboxylative coupling. The reactions were carried out using $CuO@Fe_2O_3$ (10 mg), PEG-600 (2 ml) at 110°C. The rate of decarboxylative A^3-coupling was found to be higher than that of A^3-coupling with terminal alkynes.

C(1)-Functionalization of THIQ with indoles

Similar to THIQ, indole is a privileged structural motif for target-based drug design.[1f,18] Various efforts have been made toward assembling both moieties in a single complex structure. In this regard, Zhang and coworkers[19] carried out MCR between THIQ, aldehyde, and indole. The use of CuBr along with AcOH and PPh_3 provided C(1)-substituted THIQ–indole hybrids in good yields (Scheme 11). The role of PPh_3 was found to be crucial, as its absence led to the formation of a byproduct bisindolylmethane. Various other copper catalysts such as CuCl, CuI, $CuNO_3$, $CuBr_2$, $Cu(OAc)_2$ proved inferior to CuBr. Similarly, iron catalysts ($FeCl_3·4H_2O$, $Fe_2(SO_4)_3$, $Fe(NO_3)_3·9H_2O$) could not provide satisfactory yield of the desired product. AcOH might be assisting the reaction of THIQ with aldehyde for the formation of iminium ion **I** (isomerized into ion **II**). The reaction was also performed on gram scale.

Recently, Haldar and Jana[20] reported a metal-free synthesis of THIQ–indole hybrids *via* MCR between THIQs, indoles, and 9-fluorenone imine (in place of aldehyde) at 100°C under neat conditions (Scheme 12). A variety of halogen-substituted indoles and heteroatom-containing indoles (7-azaindoles) reacted well under the studied conditions. Surprisingly, 1-methyl- and 3-methyl-substituted indoles could not provide the desired product. However, when pyrrole was used as the nucleophile instead of indole the coupling product was obtained in 53% yield. Mechanistically, the reaction between THIQ and 9-fluorenone imine generates the corresponding iminium ion **I** which isomerizes to *endo* isomer **II**. The electrophilic aromatic substitution of indole by ion **II** provides the desired THIQ–indole hybrid under metal-free conditions. *N*-fluorenyl group could be removed easily under Pd/C-mediated hydrogenolysis to provide unprotected THIQ–indole hybrids (Scheme 12).

Scheme 11. CuBr-catalyzed synthesis of THIQ–indole hybrids



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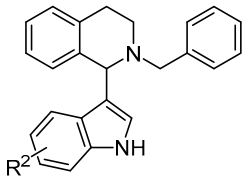
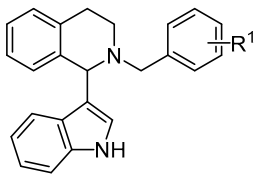
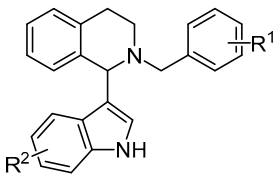


R^2 = 2-Me (83%), R^2 = H (90%)
R^2 = 5-OMe (67%), R^2 = 5-NO_2 (85%)

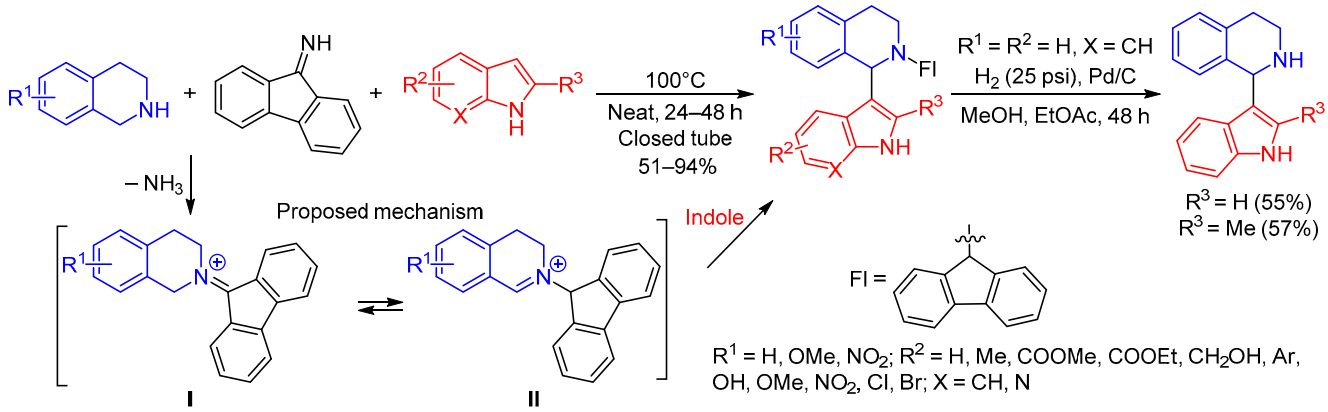


R^1 = 3-OMe (94%), R^1 = 3-NO_2 (96%)
R^1 = 2,4-Cl (95%), R^1 = 2-OMe (78%)



R^1 = 2-Cl, R^2 = 2-CH_3 (95%)
R^1 = 2-OMe, R^2 = 5-OMe (68%)
R^1 = 2-Cl, R^2 = 5-OMe (90%)
R^1 = 2-Cl, R^2 = 5-NO_2 (73%)

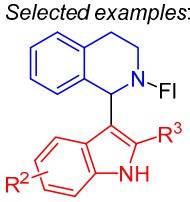
Scheme 12. Metal-free synthesis of THIQ–indole hybrid *via* MCR between THIQ, indole, and 9-fluorenone imine



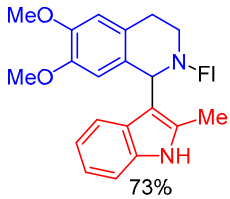
R^3 = H (55%)
R^3 = Me (57%)

R^1 = H, OMe, NO_2; R^2 = H, Me, COOMe, COOEt, CH_2OH, Ar, OH, OMe, NO_2, Cl, Br; X = CH, N

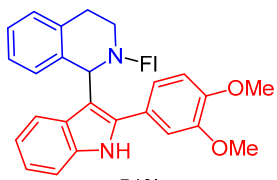
Selected examples:



R^3 = COOEt (60%)
R^3 = Me (60%)
R^3 = CH_2OH (72%)
R^2 = 5-OH (94%)
R^2 = 5-COOMe (65%)



73%



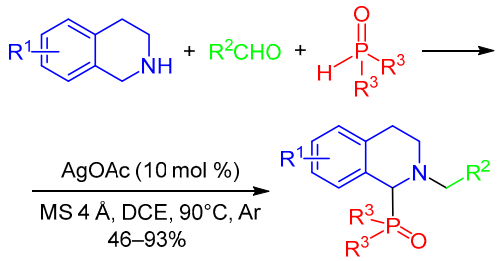
51%

C(1)-Functionalization of THIQ with phosphorus-containing compounds

α-Aminophosphonates are versatile functional surrogates for both natural and unnatural α-amino acids and possess various applications in agrochemical (e. g., glyphosate) and medicinal chemistry (e. g., alafosfalin).[21] The combination of α-aminophosphonates and THIQ moieties has grabbed significant attention of organic and medicinal chemists. Various CDC approaches for the synthesis of C(1)-phosphonylated THIQs have emerged in recent years.

Gao and coworkers[22] reported the synthesis of C(1)-phosphonylated THIQs *via* MCR of THIQs, aldehydes, and dialkyl phosphonates. The reaction proceeds in the presence of AgOAc catalyst, 4 Å MS in DCE under inert atmosphere (Scheme 13). Satisfactory yield of the product was not obtained in the absence of AgOAc. Various aromatic and heteroaromatic aldehydes (e. g., picolinaldehyde, furan-2-carbaldehyde, thiophene-2-carbaldehyde) responded well. Also, a variety of dialkyl phosphonates such as diisopropyl, methyl, benzyl, or ethyl phosphonates as coupling partners successfully furnished the corresponding C(1)-phosphonylated products. However, with diphenylphosphine oxide, only *exo* product was obtained in 64% yield. Also, on using an aliphatic aldehyde, 3-methylbutanal, a mixture of *endo*- and *exo*-phosphonylated products was obtained in 9:1 ratio (72% combined yield).

Scheme 13. AgOAc-catalyzed synthesis of C(1)-phosphonylated THIQs



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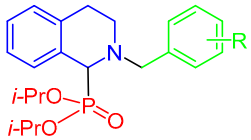
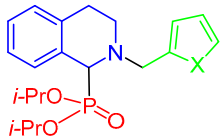
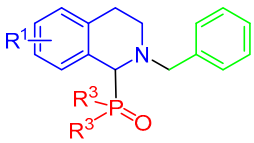


R = H (93%), R = 3-Me (77%)
R = 4-OMe (61%), R = 4-SMe (74%)
R = 4-Cl (82%), R = 4-CF_3 (74%)
R = 4-COOMe (81%)



X = O (83%)
X = S (79%)



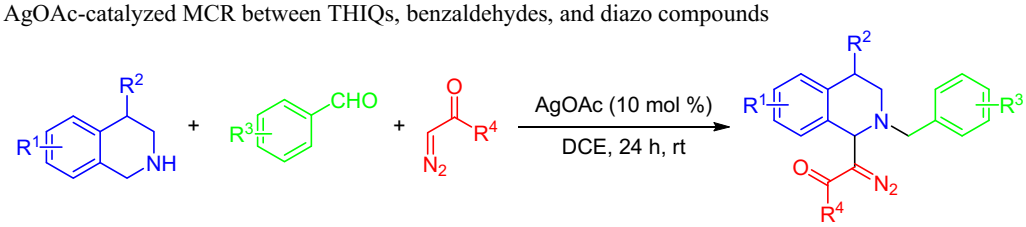
R^1 = H, R^3 = OMe (82%)
R^1 = H, R^3 = OEt (84%)
R^1 = H, R^3 = OBn (75%)
R^1 = 6,7-OMe, R^3 = O*i*-Pr (66%)
R^1 = 7-Br, R^3 = O*i*-Pr (77%)

Recently, Yi and coworkers[23] achieved the synthesis of C(1)-phosphonylated THIQs using low-cost trimethyl phosphite. In this AgOAc-mediated reaction, 1,4-dioxane was the solvent of choice at 120°C. However, the optimized reaction conditions proved futile in case of triethyl and triphenyl phosphite.

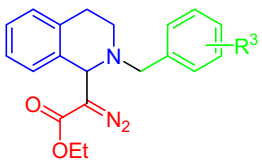
C(1)-Functionalization of THIQ with diazo carbonyl compounds

β-Amino-α-diazo compounds are known to function as versatile building blocks for the synthesis of many valuable products. In 2014, the research group of Zhou[24] reported a CDC of *N*-arylated THIQ with diazo compounds in visible light. The same group further explored a three-component coupling of THIQs, benzaldehydes, and diazo compounds (Scheme 14).[25] Using AgOAc in 1,2-dichloroethane at room temperature various C(1)-functionalized THIQs with diazo motifs were obtained in good yield *via exo*/*endo*-iminium isomerization route. However, no product formation occurred with CuI and $InCl_3$. Various diazo compounds such as diazoamides and acyl diazo compounds underwent smooth reaction. However, regioselectivity of the product was found to be highly dependent on the steric hindrance and electronic nature of aldehydes. For example, on using 2,6-dimethylbenzaldehyde or 2,6-dichlorobenzaldehyde *endo* products were formed as the major isomers. However, with 2-methylbenzaldehyde or 4-methylbenzaldehyde *exo* products dominated wherein *endo:exo* ratio was found to be 1:1.2 and 1:1.5, respectively. Similarly, the use of unsubstituted benzaldehyde led to *exo* product as the major one (*endo*:*exo* = 1:3.6). The reaction between piperidine (in place of THIQ), 2,6-dimethylbenzaldehyde, and ethyl diazoacetate led to only *exo* product. The *endo*-selectivity issues could be significantly improved by switching the catalyst from AgOAc to PhCOOH (1 equiv) in PhMe at room temperature. However, the decreased yield of the product was a drawback in such a case (Scheme 14). Furthermore, the resulting β-amino-α-diazo compounds were converted into benzazepines *via* 1,2-aryl

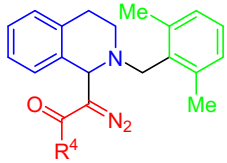
Scheme 14. AgOAc-catalyzed MCR between THIQs, benzaldehydes, and diazo compounds



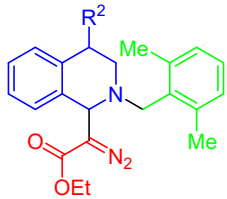
Selected examples:



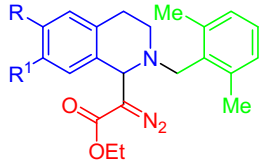
R^3 = 2-Me (72%) *endo*:*exo* = 1:1.2
R^3 = 4-Me (69%) *endo*:*exo* = 1:1.5
R^3 = H (78%) *endo*:*exo* = 1:3.6
R^3 = 2,6-Cl (80%) *endo*:*exo* = >20:1



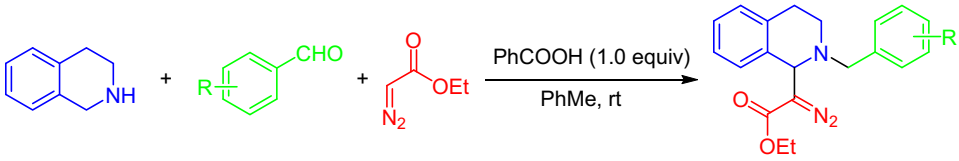
R^4 = Ph (53%), R^4 = *t*-Bu (54%)
R^4 = $OCHEt_2$ (73%)
R^4 = OCH_2CH_2Cl (62%)
R^4 = NEt_2 (66%)



R^2 = Me (72%), *dr* 1:2
R^2 = Ph (75%), *dr* 1:1.2



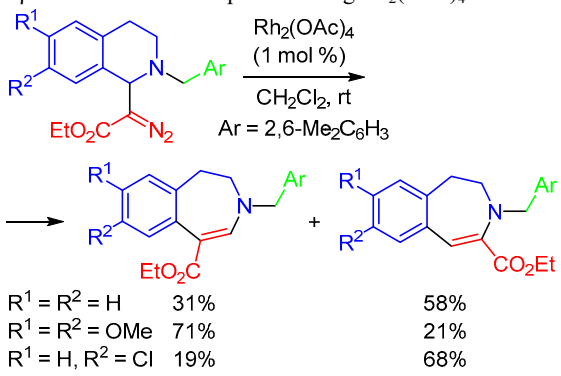
R = R^1 = H (79%)
R = R^1 = OMe (82%)
R = OMe, R^1 = H (70%)
R = H, R^1 = Cl (77%)



R = H (43%), R = 4-Me (45%)
R = 2-Me (46%), R = 2,6-Cl (70%)

shift/ring expansion in the presence of $Rh_2(OAc)_4$ at room temperature (Scheme 15).[25]

Scheme 15. Synthesis of benzazepines from β-amino-α-diazo compounds using $Rh_2(OAc)_4$

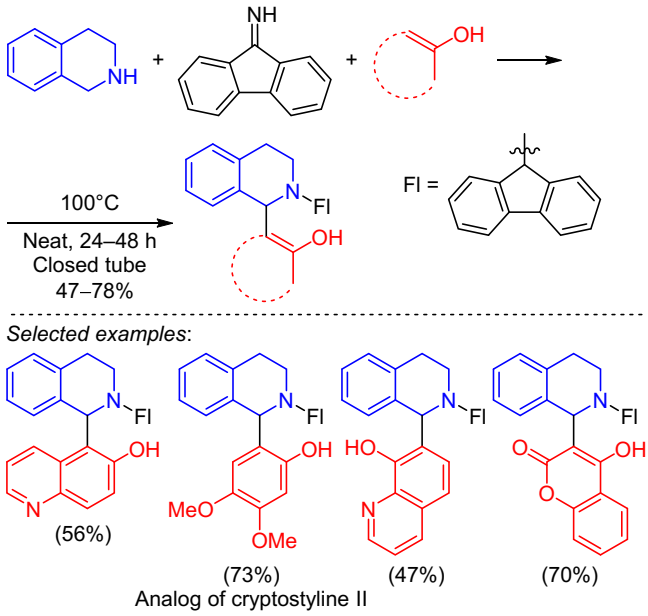


C(1)-Functionalization of THIQ with naphthols and related hydroxy compounds

C(1)-arylated THIQs are important part of natural compounds and bioactive molecules. Haldar and Jana[20] reported a metal-free coupling between THIQs, 9-fluorenone imine, and 2-naphthols to provide the corresponding C(1)-arylated THIQs (Scheme 16). Using 1-naphthol the corresponding product was obtained in moderate yield (55%). Other phenols like catechol, 3,4-dimethoxyphenol, and sesamol, as well as various related heterocyclic nucleophiles, such as 6-hydroxyquinoline, 8-hydroxyquinoline, and 4-hydroxycoumarin were found to be efficient coupling partners leading to the corresponding C(1)-arylated products. However, when benzaldehyde was used as the coupling partner in place of 9-fluorenone imine an inseparable mixture of *exo*- and *endo*-arylated THIQ was obtained.

Chandrasekharam and coworkers[26] discovered that CuI-catalyzed three-component coupling of THIQ, benzaldehydes, and 2-naphthol can furnish naphthoxazine **5** (7a,12,13,15-tetrahydronaphtho[1',2':5,6][1,3]oxazino[2,3-*a*]-isoquinoline) derivatives without using any external oxidant (Scheme 17). Various other catalysts screened for this reaction such as CuCN, $Cu(OTf)_2$, FeF_3, $FeBr_3$, $Pd(dba)_2$, $Pd(OAc)_2$, provided lower yield as compared to CuI. Reaction temperature of 65°C proved optimal and further increase or decrease in temperature led to a

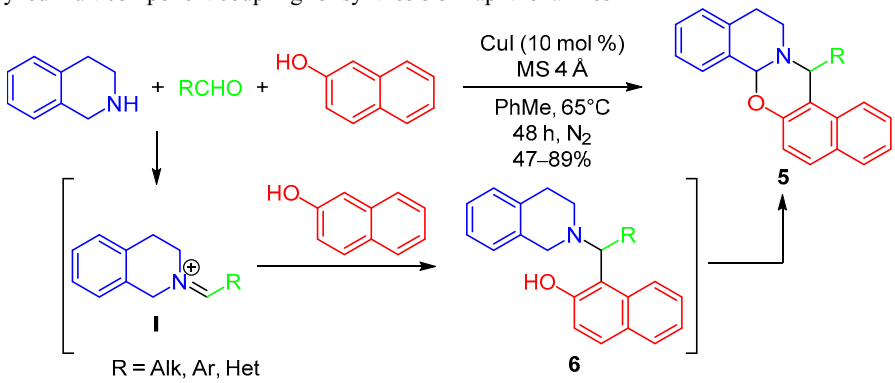
Scheme 16. Synthesis of C(1)-functionalized THIQs by metal-free coupling between THIQs, 9-fluorenone imine, and aromatic hydroxy compounds



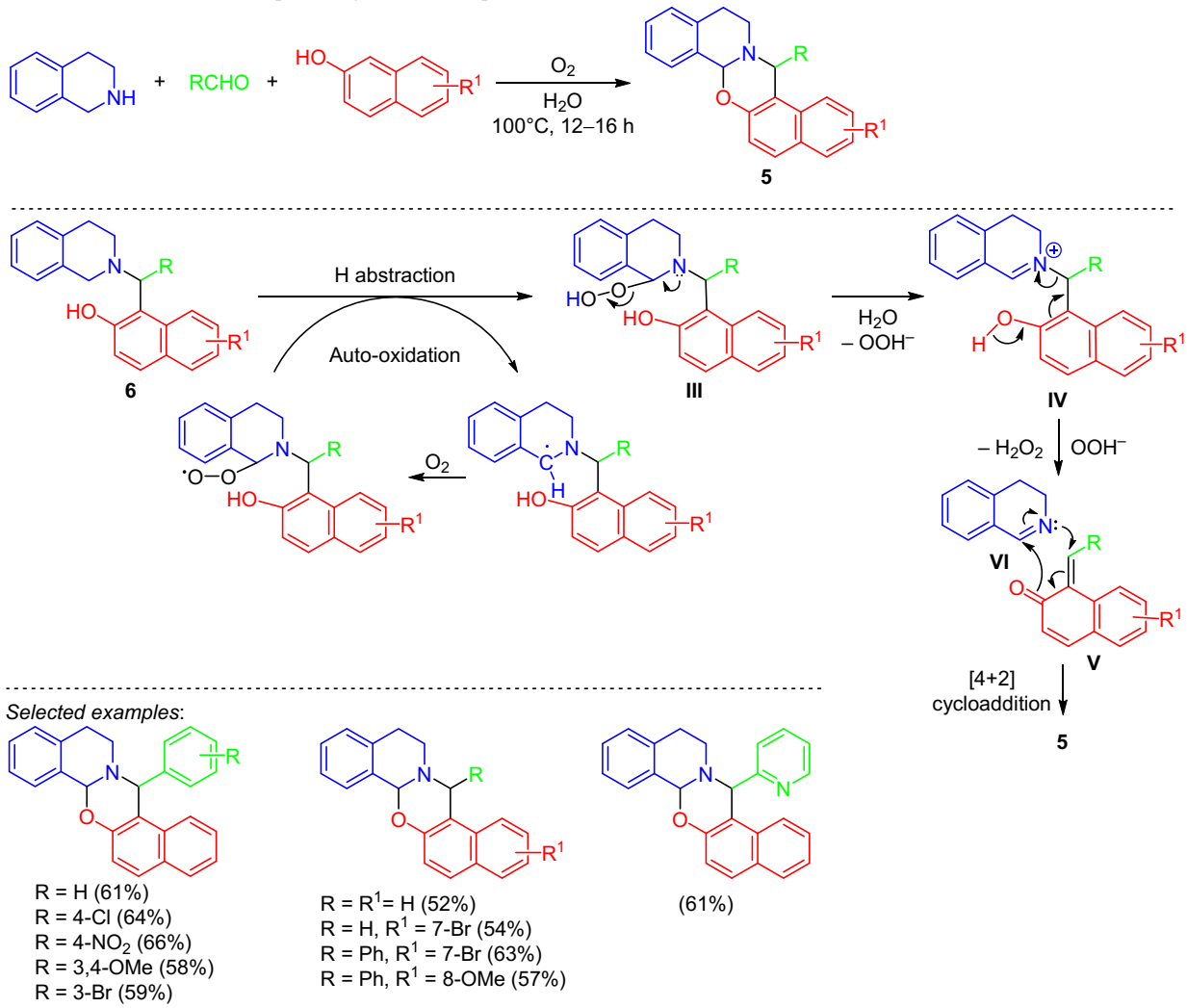
significant reduction in the yield of the product. The reaction conditions worked efficiently with aliphatic and aromatic aldehydes and heteroaldehydes. Detailed mechanistic studies have not been carried out for this reaction. However, it is proposed that the initial generation of iminium ion **I** followed by nucleophilic attack of napthol results into the respective 1-(aminoalkyl)-2-naphthol **6** as *exo* adduct which undergoes cyclization to naphthoxazine **5**. Importantly, the resulting naphthoxazines are biologically active scaffolds possessing antidepressant activity and are potential candidates for the treatment of Parkinson's disease.

A metal-free three-component coupling of THIQ, benzaldehydes, and 2-naphthols for the synthesis of naphthoxazines **5** has also been demonstrated in green solvent H_2O (Scheme 18).[27] In the developed metal-free approach, molecular O_2 as oxidant at 100°C was found to play a crucial role for *in situ* cyclization of 1-(aminoalkyl)-2-naphthols **6**. Interestingly, other oxidants such as TBHP, DTBP, and H_2O_2 under anaerobic conditions could not provide the product. Instead, in each case a mixture of *endo*

Scheme 17. CuI-catalyzed multicomponent coupling for synthesis of naphthoxazines



Scheme 18. Metal-free multicomponent synthesis of naphthoxazines



product and uncyclized adduct **6** was obtained. Better yields of products were obtained in the case of aldehydes possessing EWGs. When 2-naphthol was replaced with 2-thionaphthol, the desired product was not observed and disulfide of 2-thionaphthol was isolated. After several control experiments, a free-radical pathway was proposed in which an initial three-component reaction gives *exo* intermediate **6** as the major isomer which undergoes oxidation in the presence of O_2 to provide iminium ion **IV**. Probably, the polar solvent used in the reaction helps in the elimination of OOH group from hydroperoxide **III** through solvation. The iminium ion **IV** further undergoes fragmentation to quinone methide species **V** and 3,4-dihydroisoquinoline **VI**. The coupling of these two fragments through [4+2] cycloaddition results in the formation of the desired naphthoxazine **5**.

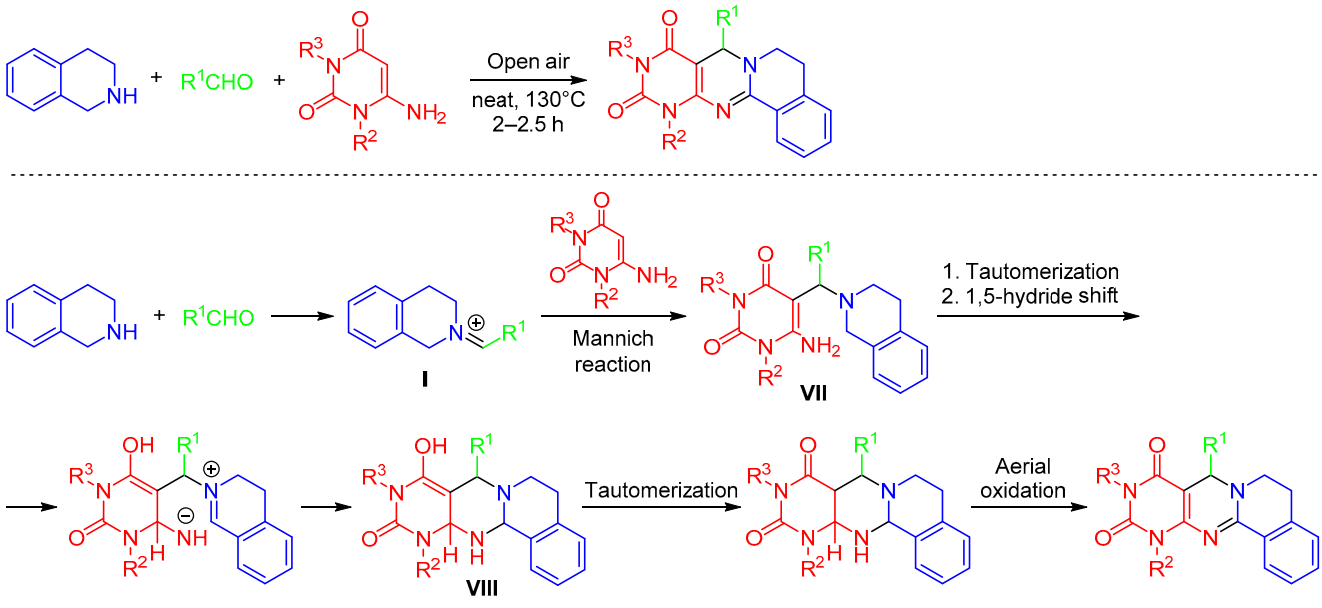
C(1)-Functionalization of THIQ with 6-aminouracil derivatives

The metal-free conditions developed by Baruah and coworkers[27] (i. e., H_2O, O_2, 100°C) completely failed when applied for the construction of pyrimidine nucleus *via* multicomponent coupling of THIQ with aldehyde and 6-aminouracil. The same research group further optimized the reaction conditions and found that reaction occurred efficiently at 130°C in open air without any solvent.[28] Mechanistically the Mannich-type product (intermediate **VII**, formed from *exo*-iminium ion **I**) undergoes tautomerization followed by 1,5-hydride shift, and cyclization to intermediate **VIII**. Finally, the oxidation of the latter leads to the desired tetracyclic product. In overall, the developed methodology provided a metal-free access to various pyrimido[4,5-*d*]pyrimidines which are valuable scaffolds from biological perspective (Scheme 19).

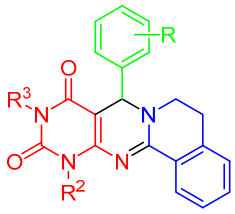
C(1)-Functionalization of THIQ by Ugi reaction

Feng and coworkers[29] reported the Ugi coupling between THIQs, aldehydes, isonitriles, and carboxylic acids using molecular sieves in PhMe as solvent at 80°C for the synthesis of *endo*-substituted product **7** (Scheme 20). Surprisingly, replacement of PhMe with MeCN led to the *exo*-substituted product **8** at room temperature. However, at 80°C using MeCN provided a mixture of products **7** and **8**. Various Ugi *endo* products **7** were obtained in good yields using a broad range of carboxylic acids and aromatic as well as heteroaldehydes.

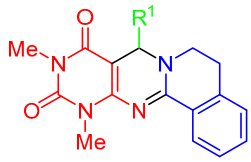
Scheme 19. Metal-free C(1)-functionalization of THIQ with 6-aminouracil and aldehyde



Selected examples:

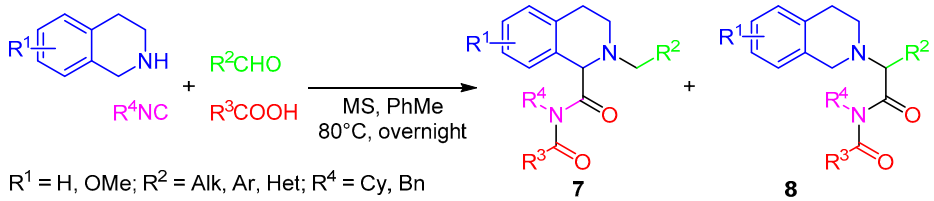


$R^2 = R^3$ = Me, R = H (92%)
$R^2 = R^3$ = Me, R = 4-Cl (94%)
$R^2 = R^3$ = Me, R = 3,4,5-OMe (90%)
$R^2 = R^3$ = Me, R = 4-NO_2 (98%)
$R^2 = R^3$ = Pr, R = H (82%)
$R^2 = R^3$ = Pr, R = 4-Br (84%)
$R^2 = R^3$ = R = H (90%)
R^2 = Me, R^3 = H, R = OMe (87%)



R^1 = 2-pyridyl (91%)
R^1 = 2-thienyl (95%)
R^1 = *i*-Pr (72%)

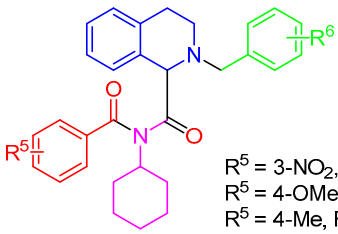
Scheme 20. MCR between THIQ, aldehyde, carboxylic acid, and isonitrile for the synthesis of C(1)-functionalized THIQ



R^1 = H, OMe; R^2 = Alk, Ar, Het; R^4 = Cy, Bn

Additive	Tempe-rature, °C	Solvent	Time, h	Yield, % **7/8**
–	rt	MeCN	48	0/84
–	rt	PhMe	18	5/0
MS	80	PhMe	18	87/0
MS	80 (MW)	PhMe	1	64/0
MS	80	MeCN	18	32/27
MS	80	THF	18	28/0

Selected examples of product **7**:



R^5 = 3-NO_2, R^6 = 4-Me (57%)
R^5 = 4-OMe, R^6 = 4-Me (44%)
R^5 = 4-Me, R^6 = 3-NO_2 (90%)

In this review, we have highlighted the recent progress of the multicomponent functionalization of THIQs *via exo*/*endo* isomerization of iminium intermediate. Various nucleophiles such as alkynes, indoles, 2-naphthols, and 6-aminouracils have been explored for the C(1)-functionalization of THIQs. These MCRs have proved powerful tools delivering molecular complexity including synthesis of diverse heterocycles and natural products. There still remains a huge opportunity to design and develop various recyclable heterogeneous catalytic systems to carry out the reaction under mild conditions besides improving the overall efficiency and selectivity of these transformations.

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