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COMMUNICATION

# Cu(OTf)$_2$-Catalyzed Access to 2,4,5-Trisubstituted Imidazoles from Acyclic Reissert Compounds

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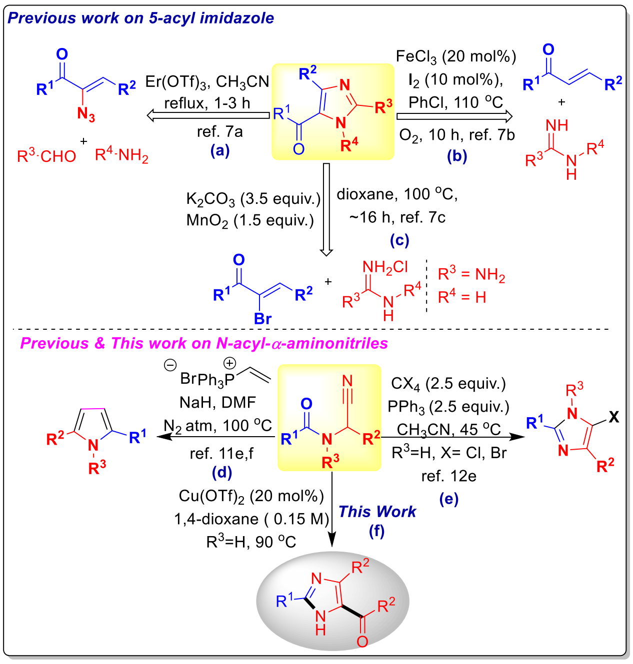
**A Cu(OTf)$_2$-catalyzed cascade self-coupling of *N*-acyl-α-aminonitriles (acyclic Reissert compounds) has been developed to afford 2,4,5-trisubstituted imidazoles in moderate to good yields. Single-crystal X-ray diffraction confirmed the structure of a representative 1*H*-2,4-disubstituted-5-acylimidazole, while NMR studies revealed N1/N3 tautomerism in selected cases. The synthetic utility of this protocol was further demonstrated by gram-scale synthesis and carbonyl reduction.**

Imidazole, a privileged core structure, finds diverse applications in medicinal chemistry,[1] natural products,[2] and drug discovery.[3] Substitution on the imidazole ring further extends its utility to functional materials,[4a,b] polymers,[4c,d] and coordination chemistry,[4e,f] spurring interest in 2,4,5-trisubstituted imidazoles.[5] Traditional syntheses rely on the Radziszewski multicomponent cyclocondensation of aldehydes, ammonia, and 1,2-diketones,[4] with numerous refinements enabling substituted analogues.[5] However, methods for 5(4)-acylimidazoles bearing ketones or esters remain underexplored.[6,7] For instance, Muthusubramanian and coworkers (2014) reported an Er(OTf)$_3$-catalyzed multicomponent reaction of α-azido chalcones, aryl aldehydes, and anilines (Scheme 1a).[7a] Li and coworkers (2015) developed an FeCl$_3$/I$_2$-catalyzed aerobic oxidative coupling of amidines and chalcones for regioselective acylimidazoles (Scheme 1b).[7b] Guchhait and coworkers (2017) devised a tandem aza-Michael addition/S$_N$2 redox-neutral process from α-bromo enones (Scheme 1c).[7c] With such limited precedents, substantial opportunities remain for new approaches to C-acylimidazoles.

More than 160 years after their discovery,[8] α-aminonitriles remain powerful synthetic linchpins, undergoing transformations[9] via deprotonation or decyanation to iminium ions, as demonstrated in our amide and 2,4-diarylquinoline syntheses.[10a-c] These findings prompted us to explore *N*-acyl-α-aminonitriles,[10d] an open-chain class of Reissert analogues. The 1,4- and 1,2-addition reactions of deprotonated Reissert compounds and their open-chain analogues have been widely exploited for the construction of diverse molecular frameworks.[11] The synergistic electrophilicity of the nitrile group and nucleophilicity of the amine functionality has enabled versatile access to *N*-heterocycles from these bifunctional scaffolds. In this context, cyclization reactions incorporating the nitrile moiety,[12a-c] as well as the use of electron-deficient arenes in place of classical electrophiles,[12d] further expanded the synthetic potential of *N*-acyl-α-aminonitriles.

**Scheme 1.** Prior art on acylimidazoles and N-acyl-α-aminonitriles, and this work



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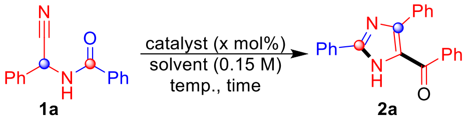
In a seminal contribution, Mcewen and co-workers developed a condensation of the conjugate base of *N*-acyl-α-aminonitriles with vinyltriphenylphosphonium bromide for the synthesis of substituted pyrroles (Scheme 1d).[11e,f] Later, Zhong et al reported the synthesis of 2,4-disubstituted 5-halo-1*H*-imidazoles from *N*-acyl-α-aminonitriles, which were subsequently converted into 2,4,5-trisubstituted imidazoles via Pd-catalyzed cross-coupling (Scheme 1e).[12e] Nearly two decades later, we describe a simple transformation of the same *N*-acyl-α-aminonitriles into C-acylimidazoles in a single step using catalytic $Cu(OTf)_2$ (Scheme 1f). Our initial hypothesis targeted the synthesis of 5-amino oxazole via a Lewis acid–promoted 5-*exo*-dig cyclization; however, the reaction selectively delivered imidazoles through a self-coupling cascade. Given the limited availability of efficient methods for synthesizing 5(4)-acyl-substituted imidazoles, this conversion provides a useful route and highlights a different reactivity pathway of *N*-acyl-α-aminonitriles.

**Table 1**. Reaction optimization studies[a,b,c]



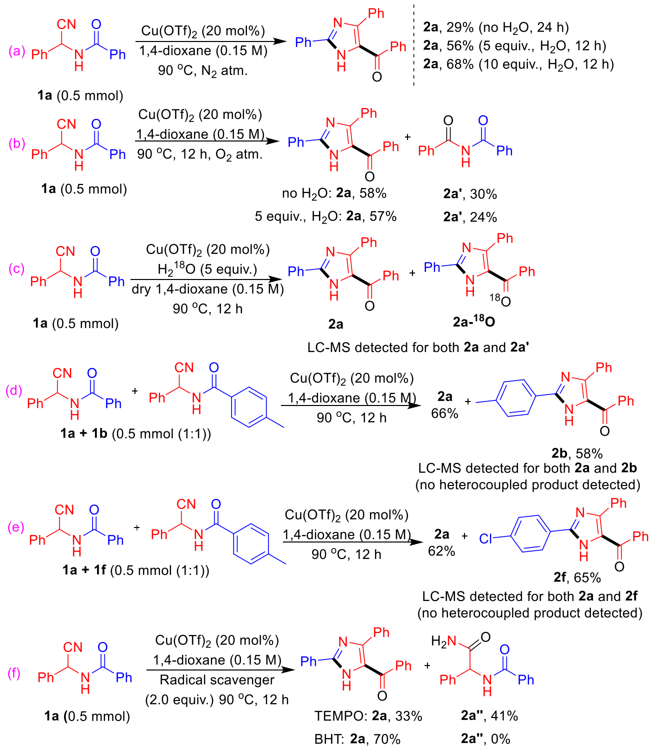
| s.no | catalyst (x mol%) | solvent | temp. (°C)/ time (h) | yield (%) |
|---|---|---|---|---|
| 1 | $FeCl_3$ (20) | 1,4-dioxane | 90/12 | 63 |
| 2 | $CoCl_2.6H_2O$ (20) | 1,4-dioxane | 90/24 | 17 |
| 3 | $CuCl_2$ (20) | 1,4-dioxane | 90/24 | 44 |
| 4 | $CuBr_2$ (20) | 1,4-dioxane | 90/16 | 56 |
| 5 | $ZnCl_2$ (20) | 1,4-dioxane | 90/24 | 31 |
| 6 | $Fe(OTf)_2$ (20) | 1,4-dioxane | 90/12 | 59 |
| **7** | **$Cu(OTf)_2$ (20)** | **1,4-dioxane** | **90/08** | **73** |
| 8 | $Sm(OTf)_3$ (20) | 1,4-dioxane | 90/24 | 48 |
| 9 | AgOTf (20) | 1,4-dioxane | 90/24 | 54 |
| 10 | Yb $(OTf)_3$ (20) | 1,4-dioxane | 90/24 | 51 |
| 11 | $Cu(OTf)_2$ (20) | ethanol | 80/24 | 42 |
| 12 | $Cu(OTf)_2$ (20) | IPA | 80/24 | 38 |
| 13 | $Cu(OTf)_2$ (20) | ethylene Glycol | 100/12 | 61 |
| 14 | $Cu(OTf)_2$ (20) | ethyl acetate | 80/24 | 34 |
| 15 | $Cu(OTf)_2$ (20) | acetonitrile | 80/24 | 19 |
| 16 | $Cu(OTf)_2$ (15) | 1,4-dioxane | 90/24 | 64 |
| 17 | $Cu(OTf)_2$ (25) | 1,4-dioxane | 90/8 | 72 |
| 18 | $Cu(OTf)_2$ (20) | 1,4-dioxane | 70/24 | 58 |
| 19 | $Cu(OTf)_2$ (20) | 1,4-dioxane | 110/8 | 74 |

[a]**Reaction conditions**: All reactions were carried out using **1a** (0.5 mmol), solvent (0.15 M) and catalyst (x mol%) in a sealed vial at indicated temperature and time unless otherwise noted. [b]Isolated yield. [c]See the ESI (Table S1-S4) for the detailed optimization studies.

The optimization began with *N*-(cyano(phenyl)methyl)benzamide **1a** as the model substrate. Screening of common metal halides in 1,4-dioxane at 90 °C (Table 1, entries 1-5) delivered the desired product **2a** in modest yields (17-63%). Subsequent evaluation of various metal triflates (Table 1, entries 6-10) identified $Cu(OTf)_2$ as the most effective catalyst, providing **2a in** 73% yield at 20 mol% loading (Table 1, entry 7). With copper triflate selected, solvent screening was carried out next. Replacing 1,4-dioxane with ethanol, isopropanol (IPA), ethylene glycol, ethyl acetate, or acetonitrile (Table 1, entries 11-15) failed to improve the reaction efficiency. Catalyst loading studies showed that reducing $Cu(OTf)_2$ to 15 mol% lowered the yield (Table 1, entry 16), while increasing it to 25 mol% offered no further enhancement (Table 1, entry 17). Temperature variation (Table 1, entries 18-19) confirmed that 90 °C was optimal for the formation of **2a**.

Control experiments under $N_2$ and $O_2$ were performed to probe the reaction pathway (ESI, Table S4). Under $N_2$, the reaction gave only 29% yield of **2a** without water, which increased to 56% and 68% upon addition of 5 and 10 equiv. of $H_2O$, respectively, indicating the role of water (Scheme 2a). Under $O_2$, the reaction afforded **2a** in 58% yield with 30% of decyanative product **2a'** in the absence of water, while similar yields of **2a** (57%) and reduced **2a'** (24%) were observed in the presence of water, indicating competing oxygen-mediated pathways (Scheme 2b). Next, the reaction was performed[13] in $H_2{}^{18}O$ using dry 1,4-dioxane, and LC–MS analysis showed a mixture of isotopic and non-isotopic mass peaks (ESI, Fig. S10). The non-isotopic mass suggests that oxygen may also arise from water generated *in situ* during the course of the reaction and from residual moisture (Scheme 2c). Further, cross-over experiments with **1a/1b** (electron-donating) and **1a/1f** (halogen-substituted) under standard conditions afforded only the corresponding products **2a/2b** and **2a/2f**, respectively (Scheme 2d & 2e). No heterocoupled products were detected, indicating exclusive homocoupling (ESI, Fig. S8 & Fig. S9). In the presence of TEMPO, the yield of **2a** decreased to 33%, along with formation of hydrolysed product **2''** in 41% yield likely due to the Cu/TEMPO

**Scheme 2.** Control experiments to study the reaction pathway



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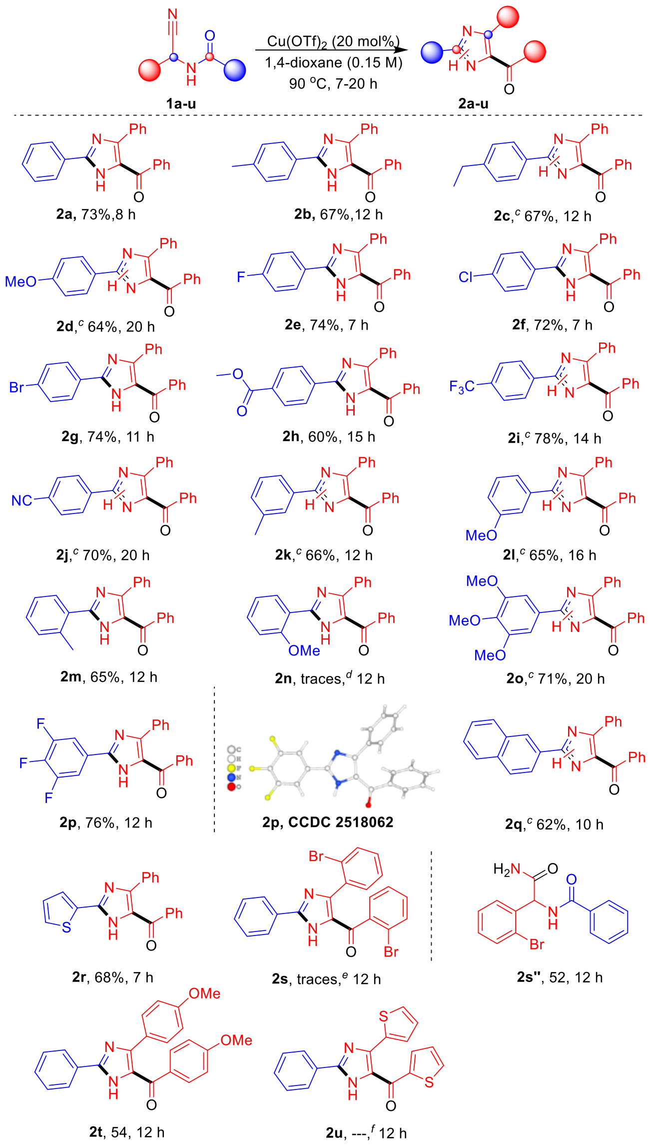
system. In contrast, BHT afforded **2a** in 70% yield (cf. 73% standard). These results suggest that the reaction does not proceed via a radical pathway (Scheme 2f).

With the optimized conditions and control studies, the substrate scope of *N*-acyl-α-aminonitriles was examined (Table 2). A range of *para*-substituted phenyl derivatives, including *p*-Me (**1b**), *p*-Et (**1c**), *p*-OMe (**1d**), *p*-F (**1e**), *p*-Cl (**1f**), *p*-Br (**1g**), *p*-COOMe (**1h**), *p*-$CF_3$ (**1i**), and *p*-CN (**1j**), were well tolerated, affording the corresponding products **2b**–**2j** in 60–78% yield. *Meta*- and *ortho*-substituted substrates such as *m*-Me (**1k**), *m*-OMe (**1l**), and *o*-Me (**1m**) also reacted smoothly, affording **2k**–**2n** in 65–66% yield. Whereas *o*-OMe (**1n**) was observed only in trace amounts and could not be isolated. Polysubstituted aromatics, including 3,4,5-tri-OMe (**1o**) and 3,4,5-trifluoro (**1p**), were compatible, producing **2o** and **2p** in 71% and 77% yield, respectively, with the structure of **2p** confirmed by single-crystal X-ray analysis.[14] Fused aromatics and heteroaryl **2q** and substrates, such as naphthyl (**1q**) and 2-thienyl (**1r**), furnished **2q** and **2r** in 62–68% yields. Substrates with aryl groups attached to the α-carbon, including *o*-Br (**1s**), *p*-OMe (**1t**), and 2-thienyl (**1u**), gave **2t** in 54% yield. For **1s**, only traces of **2s** were observed by TLC, and the major isolated product was the corresponding hydrolysed amide **2s''** in 52% yield. Similarly, **2u** was confirmed by HRMS analysis, while its isolation was unsuccessful. Overall, *para*-substituted substrates generally gave higher yields and shorter reaction times, *meta*-substituents gave moderate results, and *ortho*-substitution lowered yields and required longer reactions, likely due to steric effects.

**Table 2**. Scope and limitations of *N*-acyl-α-aminonitriles to 2,4,5-trisubstituted imidazoles[a,b]

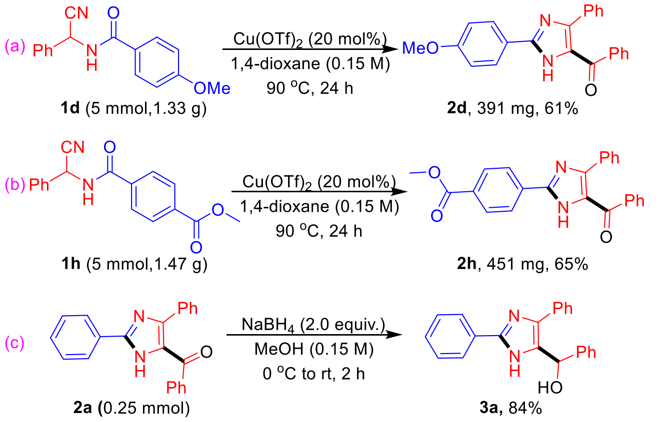


1a-u
2a-u
**2a**, 73%,8 h
**2b**, 67%,12 h
**2c**,[c] 67%, 12 h
**2d**,[c] 64%, 20 h
**2e**, 74%, 7 h
**2f**, 72%, 7 h
**2g**, 74%, 11 h
**2h**, 60%, 15 h
**2i**,[c] 78%, 14 h
**2j**,[c] 70%, 20 h
**2k**,[c] 66%, 12 h
**2l**,[c] 65%, 16 h
**2m**, 65%, 12 h
**2n**, traces,[d] 12 h
**2o**,[c] 71%, 20 h
**2p**, 76%, 12 h
**2p, CCDC 2518062**
**2q**,[c] 62%, 10 h
**2r**, 68%, 7 h
**2s**, traces,[e] 12 h
**2s''**, 52, 12 h
**2t**, 54, 12 h
**2u**, ---,[f] 12 h

[a] **Reaction conditions**: Compound **1a** (0.5 mmol), Cu(OTf)$_2$ (20 mol %), and 1,4-dioxane (0.15 M) were stirred at 90 °C for 7–20 h. [b] Isolated yields. [c] The presence of N1–N3 tautomeric forms was confirmed by NMR analysis. [d] Detected in trace amounts by TLC; not isolated due to multiple spots. [e] **2s** was detected in trace amounts and not isolated; the corresponding amide was obtained. [f] The mass was confirmed by HRMS analysis; however, isolation for pure NMR characterization was unsuccessful.

We further evaluated the scalability of the methodology on a gram-scale using the standard optimized conditions. Representative substrates bearing an electron-donating substituent (**1d**) and an electron-withdrawing substituent (**1h**) furnished the corresponding products **2d** and **2h** in moderate yields of 61% and 65%, respectively (Scheme 3a & b). In addition, reduction of carbonyl functional group in **2a** with $NaBH_4$ proceeded smoothly to afford the corresponding secondary alcohol **2a'** in **84%** yield (Scheme 3c).

**Scheme 3**. Synthetic applications and control Studies



A plausible mechanism, supported by control experiments and literature precedent,[11,12,15] is outlined in Scheme 4. Coordination of Cu(OTf)$_2$ to the nitrile group of α-aminonitrile **1** generates intermediate **A**, increasing the electrophilicity of the nitrile carbon and enabling intramolecular 5-*exo*-dig cyclization to form imino-oxazolone **B**. DFT calculations using UB3LYP/def2-TZVP with a 1,4-dioxane solvent model (see ESI for computational details) support preferential nitrogen coordination ($\Delta G = -8.04$ kcal/mol) over oxygen ($\Delta G = -3.35$ kcal/mol), with HOMO–LUMO overlap and a smaller band gap (2.13 eV) favouring the nitrile binding pathway (ESI, Fig. S13). Further, to assess the ring-closure mechanism and stability of cyclized intermediate **B**, transition state free energy calculations were performed (see ESI, Fig. S15). The process

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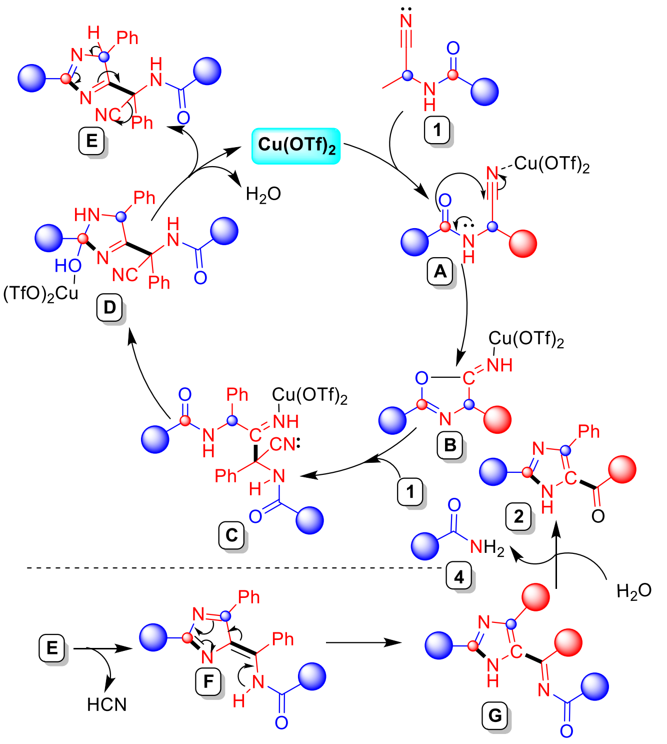
proceeds *via* transition state **A** with an activation free energy of $\Delta G^{\ddagger}$ = 23.4 kcal/mol, leading to intermediate **B**, which is thermodynamically stabilized by −4.46 kcal/mol relative to the initial reactant **1**.[16] Next, nucleophilic addition of a second molecule of **1** to **B**, followed by ring opening, affords intermediate **C**. Owing to the lability of Cu(II) coordination, intramolecular exchange between imine and amide carbonyl binding facilitates cyclization to imidazoline **D**. Dehydration of **D** regenerates $Cu(OTf)_2$ and furnishes intermediate **E**, which upon isomerization and HCN elimination gives **F**. Proton transfer affords aromatic intermediate **G**, and final hydrolysis yields the 2,4,5-trisubstituted imidazole **2** along with amide **4**, confirmed by $^1H$ NMR spectroscopy (ESI, Fig. S57).

**Scheme 4**. Plausible reaction mechanism



In conclusion, a copper-catalyzed synthesis of C-acylimidazoles from open-chain analogues of Reissert compound is disclosed. The reaction is proposed to proceed through an imino-oxazolone pathway, enabling access to 5-acylimidazole scaffolds. Broad aryl-substrate tolerance, gram-scale feasibility, and reduction of the carbonyl to the corresponding alcohol demonstrate the practicality of the method. A plausible mechanism was proposed based on control studies and DFT calculations. This work expands the synthetic toolbox for *N*-acyl-α-aminonitriles and provides a useful entry to acylimidazoles.

## Conflicts of interest

"There are no conflicts to declare".

## Data availability

The supporting data has been provided as part of the Supplementary information. Supplementary information: Tables S1-S4 and Figure S1-S2. NMR spectra and further experimental details, see DOI: [URL – format https://doi.org/DOI]. CCDC [2518062] contain the supplementary crystallographic data for this paper Ref.[14]

## Notes and references

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13 For detailed isotopic studies with $H_2{}^{18}O$ refer Supporting Information Fig. S10 to Fig. S12.

14 The CCDC number for compound **2p** is CCDC 2518062.

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## Data Availability Statement (DAS)

The supporting data has been provided as part of the Supplementary information. Supplementary information: Tables S1-S4 and Figure S1-S2. NMR spectra and further experimental details, see DOI: [URL – format https://doi.org/DOI]. CCDC [2518062] contain the supplementary crystallographic data for this paper Ref.[14]