Synthesis of 2-oxindoles via ‘transition-metal-free’ intramolecular dehydrogenative coupling (IDC) of \( sp^2 \) C–H and \( sp^3 \) C–H bonds

Nivesh Kumar‡, Santanu Ghosh‡, Subhajit Bhunia and Alakesh Bisai*

Full Research Paper

Address:
Department of Chemistry, Indian Institute of Science Education and Research Bhopal, Bhopal Bypass Road, Bhauri, Bhopal – 462 066, Madhya Pradesh, India

Email: Alakesh Bisai* - alakesh@iiserb.ac.in

* Corresponding author ‡ Equal contributors

Keywords:
C–H functionalization; intramolecular dehydrogenative coupling (IDC); iodine; N-iodosuccinimide; oxidants; 2-oxindoles

Abstract

The synthesis of a variety of 2-oxindoles bearing an all-carbon quaternary center at the pseudo benzylic position has been achieved via a ‘transition-metal-free’ intramolecular dehydrogenative coupling (IDC). The construction of 2-oxindole moieties was carried out through formation of carbon–carbon bonds using KO\( \text{t-Bu} \)-catalyzed one pot C-alkylation of \( \beta \)-N-arylamido esters with alkyl halides followed by a dehydrogenative coupling. Experimental evidences indicated toward a radical-mediated path for this reaction.

Introduction

The C–H functionalization is an attractive synthetic strategy used in organic synthesis for the development of atom- and step-economical routes [1-10]. In recent years it was witnessed a mushrooming growth in the number of reports in the literature owing to the efficiency of the oxidative coupling of two C–H bonds [also termed as cross-dehydrogenative-coupling (CDC)] in the formation of C–C bonds [11-16]. This was facilitated by the introduction of transition metals in organic synthesis providing an amazing tool to explore these oxidative coupling reactions in an efficient manner. However, despite the associated advantages, these methodologies require one or two metal catalysts for efficient reactions, which are sometimes undesirable [17-21]. Therefore, an alternate strategy to carry out these transformations under ‘transition-metal-free’ conditions has recently gained immense importance.

2-Oxindoles having all carbon quaternary centres at the pseudobenzylic position are common structural scaffolds in many naturally occurring alkaloids of biological relevance [22-25]. These heterocyclic motifs especially exist in indole alkaloids with a wide spectrum of biological and pharmacological properties and hence are very attractive as well as challenging
Scheme 1: Synthesis of 2-oxindoles via oxidative processes.

Results and Discussion

We decided to use iodine as an oxidant for the synthesis of 2-oxindoles [48-53], starting from \( \beta-N \)-arylamido ester 3a and methyl iodide as the substrates (Table 1). An elaborate optimization study suggested that the methylation can be done in the presence of Cu(OAc)\(_2\)-H\(_2\)O as oxidant (Scheme 1) [40-44]. Experimental evidence suggests involvement of a free-radical process in the addition of \( \alpha \)-carbonylalkyl radicals to the phenyl ring. The \( \alpha \)-carbonylalkyl radicals were formed by Cu(II)-mediated oxidation of the respective enolate precursors. In 2010, Yu and co-workers have reported the synthesis of 3-acetyloxindoles via Ag\(_2\)O-mediated intramolecular oxidative coupling [45]. For the past few years, our group is engaged in the development of efficient methodologies for the synthesis of 2-oxindoles with intriguing ring systems. To this end, recently, we have reported a transition-metal-free 'intramolecular-dehydrogenative-coupling' (IDC) strategy to access such 2-oxindole moieties through a C-alkylation followed by an oxidative construction of the C–C bond (Scheme 1) [46]. Applying the aforementioned strategy, we were able to synthesize several 3-alkyl-2-oxindoles bearing ester functionalities at the pseudobenzylic position from \( \beta-N \)-arylamido allyl, methallyl, dimethylallyl, and geranyl esters. Here, in this article, we disclose the scope and limitations of 'transition-metal-free' IDC of Csp\(^2\)-H and Csp\(^3\)-H using iodine and N-iodosuccinimide (NIS) as oxidants. In addition, we have also demonstrated the synthetic utility of oxidative coupling products in the syntheses of 3-substituted-2-oxindoles, via a decarboxylative protonation on 2-oxindoles bearing an benzylester or \( \alpha \)-methoxybenzyl ester at the 3-position in presence of a catalytic amount of Pd on activated charcoal. We have also shown the direct installation of allyl, prenyl, reverse-prenyl, or geranyl groups at the 3-position of 2-oxindole using Pd-catalyzed decarboxylative strategies [47].

In the same year, Taylor and co-workers independently reported synthesis of 2-oxindoles in the presence of Cu(OAc)\(_2\)-H\(_2\)O as oxidant (Scheme 1) [40-44]. Experimental evidence suggests involvement of a free-radical process in the addition of \( \alpha \)-carbonylalkyl radicals to the phenyl ring. The \( \alpha \)-carbonylalkyl radicals were formed by Cu(II)-mediated oxidation of the respective enolate precursors. In 2010, Yu and co-workers have reported the synthesis of 3-acetyloxindoles via Ag\(_2\)O-mediated intramolecular oxidative coupling [45]. For the past few years, our group is engaged in the development of efficient methodologies for the synthesis of 2-oxindoles with intriguing ring systems. To this end, recently, we have reported a transition-metal-free 'intramolecular-dehydrogenative-coupling' (IDC) strategy to access such 2-oxindole moieties through a C-alkylation followed by an oxidative construction of the C–C bond (Scheme 1) [46]. Applying the aforementioned strategy, we were able to synthesize several 3-alkyl-2-oxindoles bearing ester functionalities at the pseudobenzylic position from \( \beta-N \)-arylamido allyl, methallyl, dimethylallyl, and geranyl esters. Here, in this article, we disclose the scope and limitations of 'transition-metal-free' IDC of Csp\(^2\)-H and Csp\(^3\)-H using iodine and N-iodosuccinimide (NIS) as oxidants. In addition, we have also demonstrated the synthetic utility of oxidative coupling products in the syntheses of 3-substituted-2-oxindoles, via a decarboxylative protonation on 2-oxindoles bearing an benzylester or \( \alpha \)-methoxybenzyl ester at the 3-position in presence of a catalytic amount of Pd on activated charcoal. We have also shown the direct installation of allyl, prenyl, reverse-prenyl, or geranyl groups at the 3-position of 2-oxindole using Pd-catalyzed decarboxylative strategies [47].
NaH, NaOMe, K₂CO₃, Cs₂CO₃, and NaOt-Bu (Table 1, entries 9–13). Among other metal-free oxidants, iodosobenzeneacetate (PIDA), DBDMH (1,3-dibromo-5,5-dimethylhydantoin), and ICl afforded 2-oxindole 4a in 82%, 16%, and 69%, respectively (Table 1, entries 14 and 20). Next, the substrate scope of the reaction was explored as shown in Figure 1. A variety of substrates were prepared by a coupling reaction of N-methyl arylamines and monoalkyl malonates/cyanoacetic acids. Under optimized conditions A and B, various β-N-arylamido esters and nitriles (3) were subjected to a one-pot alkylations using 1.2 equivalents of KOt-Bu to produce C-alkylated intermediate 5 followed by oxidative cou-

![Table 1: Optimization of intramolecular-dehydrogenative-coupling (IDC)](null)

| entry | solvent | base     | Alkylations at 25 °C | oxidants   | time      | % 4a   |
|-------|---------|----------|----------------------|------------|-----------|--------|
| 1.    | DMF     | t-BuOK   | 20 min               | 1.5 equiv I₂ | 6 h       | 65%    |
| 2.    | DMF     | t-BuOK   | 20 min               | 1.2 equiv I₂ | 3 h       | 62%    |
| 3.    | THF     | t-BuOK   | 30 min               | 1.2 equiv I₂ | 3 h       | 85%    |
| 4.    | xylene  | t-BuOK   | 45 min               | 1.2 equiv I₂ | 1 h       | 49%    |
| 5.    | dioxane | t-BuOK   | 20 min               | 1.2 equiv I₂ | 2 h       | 88%    |
| 6.    | benzene | t-BuOK   | 45 min               | 1.2 equiv I₂ | 1 h       | 45%    |
| 7.    | toluene | t-BuOK   | 20 min               | 1.2 equiv I₂ | 30 min    | 90%    |
| 8.    | DMSO    | NaH      | 20 min               | 1.2 equiv I₂ | 30 min    | 33%    |
| 9.    | DMSO    | NaOMe    | 2 h                  | 1.2 equiv I₂ | 30 min    | –      |
| 10.   | DMSO    | K₂CO₃    | 1 h¹                 | –          | –        | –      |
| 11.   | DMSO    | Cs₂CO₃   | 2 h                  | 1.5 equiv I₂ | 30 min    | 26%²   |
| 12.   | DMSO    | t-BuONa  | 30 min               | 1.5 equiv I₂ | 30 min    | –      |
| 13.   | DMSO    | t-BuOK   | 15 min               | 1.2 equiv I₂ | 30 min    | 90%    |
| 14.   | DMSO    | t-BuOK   | 15 min               | 0.6 equiv I₂ | 1 h       | 54%    |
| 15.   | DMSO    | t-BuOK   | 15 min               | 0.3 equiv I₂ | 1 h       | 29%    |
| 16.   | DMSO    | t-BuOK   | 15 min               | 1.2 equiv PIDA | 30 min | 82%    |
| 17.   | DMSO    | t-BuOK   | 15 min               | 1.2 equiv DBDMH² | 30 min | 16%²   |
| 18.   | DMSO    | t-BuOK   | 15 min               | 1.2 equiv ICl | 30 min | 69%    |
| 19.   | DMSO    | t-BuOK   | 15 min               | 1.2 equiv NIS | 30 min | 84%    |
| 20.   | DMSO    | t-BuOK   | 15 min               | 1.2 equiv NBS | 30 min | 75%    |
| 21.   | DMSO    | t-BuOK   | 15 min               | 1.2 equiv NCS | 30 min | 58%    |
| 22.   | DMSO    | t-BuOK   | 15 min               | 1.0 equiv TCICA³ | 30 min | 62%    |
| 23.   | DMSO    | t-BuOK   | 15 min               | 0.5 equiv TCICA³ | 30 min | 56%    |

²Isolated yields of 4a after column chromatography. ³Mixture of products were observed for rest of the mass balance. ⁴C-methylation as major product. ⁵Starting material was recovered (92%). ⁶Decomposition of starting materials. ⁷DBDMH (1,3-dibromo-5,5-dimethylhydantoin) as oxidant. ⁸TCICA (trichloroisocyanuric acid).

---

*Beilstein J. Org. Chem.* **2016**, **12**, 1153–1169.

---
Figure 1: Substrates scope of one-pot ‘transition-metal-free’ IDC. The syntheses of compounds 4a–s according to method A have been reproduced from reference [46]. Conditions A: KOT-Bu, iodine; conditions B: KOT-Bu, NIS.
pling using 1.2 equivalents iodine or NIS. Gratifyingly, it was found that a range of \( \beta \)-N-arylamido esters (3a–s) and \( \beta \)-N-arylamido ketones (3t–x) underwent intramolecular dehydrogenative coupling (IDC) under both conditions A and B to afford a wide range of 2-oxindoles (4a–x) having an all-carbon quaternary center in high yields. However, we observed that in case of 2-oxindoles 4v and 4k, a two-step protocol is necessary, where in first step C-alkylation of \( \beta \)-N-arylamido ketone was carried out using 1.2 equivalents of KO\(_t\)-Bu to afford products 5v and 5k, respectively (Figure 1), followed by a second oxidative coupling reaction in the presence of iodine or NIS.

We envisioned that the oxidative coupling products containing benzyl or \( p \)-methoxybenzyl ester could be effective intermediates for the synthesis of 3-monosubstituted 2-oxindoles via deprotection of the benzyl group followed by decarboxylative protonation in presence of a catalytic amount of Pd on activated charcoal under hydrogenolysis. Thus, we explored the substrate scope using \( \beta \)-N-arylamido benzyl ester or \( \beta \)-N-arylamido \( p \)-methoxybenzyl ester as starting materials for the oxidative coupling reaction shown in Figure 2. Towards this end, \( \beta \)-N-aryl amido benzyester or \( \beta \)-N-arylamido \( p \)-methoxybenzyl ester 3 were subjected to an one pot alkylation to generate the intermediate 7 followed by oxidative coupling reaction using our optimized conditions A and B to furnish products of type (±)-6 in good yields (Figure 2). For the synthesis of compound (±)-6g, we followed a two-step protocol: In first step a C-alkylation of \( \beta \)-N-arylamido benzyester in presence of 1.2 equivalents of NaH and alkylating agent afford compound (±)-7g in good yields (74%), followed by an oxidative coupling in presence of 1.2 equivalents of KOt-Bu and iodine or NIS as oxidant.

Next, we focussed our attention to prenylated, reverse-prenylated, and geranylated hexahydropyrrolo[2,3-b]indole alkaloids showing broad biological activities [55-61]. For the synthesis of these compounds, we thought of utilizing the Pd-catalyzed decarboxylative strategy to install the prenyl, reverse-prenyl, or

---

**Figure 2:** Further substrates scope of one-pot ‘transition metal-free’ IDC. Conditions A: KO\(_t\)-Bu, iodine; conditions B: KO\(_t\)-Bu, NIS.
geranyl group at the 3-position of 2-oxindole starting from the corresponding β-amido esters such as 8\(^{[47]}\). This further extended the methodology to a variety of β-N-arylamido esters containing allyl, methallyl, dimethylallyl, and geranyl ester groups (9). It is noteworthy that, the substrate of type 9 could undergo smooth IDC in the presence of iodine (conditions A) to provide an access to compounds 8 in synthetically useful yields (Figure 3).

Noticeably, we could directly construct the 2-oxindoles with a geranyl group at the 3-position using geranyl bromide as an alkylating agent. Upon a subsequent oxidative coupling step, products in good yields (8q–s, Figure 3) were formed using conditions A. Later, the IDC was extended to substrates having β-N-arylamido geranyl esters to afford compounds 8t–v (Figure 3). These compounds could be excellent substrates for carrying out Tsuji–Trost decarboxylative geranylations/reverse-

![Figure 3: Substrates scope of 'transition-metal-free' IDC using KOt-Bu/I₂. Reproduced from [46].](image-url)
geranylations [62,63]. However, conditions B (NIS) were found unsuccessful in case of β-N-arylamidoallyl, methallyl, dimethylallyl, and geranyl esters 9. We speculate that the olefin functionality of substrates might be reacting with NIS (conditions B) faster than iodine (conditions A). Although our iodine-mediated IDC is successful in most of the cases, however, in few cases we have seen moderate yields of products. Thus, we decided to carry out IDC in the presence of organic bases as well.

Thus, for an alternative approach to 2-oxindoles bearing allyl, methallyl, dimethylallyl, and geranyl esters, we were interested for IDC using simple organic bases such as triethylamine, pyridine, and DABCO (Table 2) [64]. It was found that IDC can operate in the presence of organic bases to afford products only in 25–34% yields of 2-oxindoles (Table 2, entries 1, 2 and 4). These reactions were always associated with unreacted starting material (28–51%) and decomposition of the rest of the mass balance. Interestingly, when the base was changed to DBU (using 1.5 equiv DBU and 1.2 equiv of iodine) the desired 2-oxindole was isolated in 82% (conditions C).

With this result in hand, we thought of exploring IDC using C-alkylated substrates 10. For this purpose, a variety of C-alkylated β-N-arylamidoallyl, methallyl, dimethylallyl, and geranyl esters 10 were synthesized in good yields as per Figure 4. These substrates were then utilized in IDC-promoted by DBU/I2 and the results are summarized in Figure 5. Interestingly, under this conditions, we can synthesize a variety of 2-oxindoles 8 in moderate to good yields.

There are a large number of indole alkaloids bearing a 3-arylated-2-oxindole moiety that are known for their various biological activities [65-67]. In a quest for such structural scaffolds, C-arylated substrates (±)-11a–d were subjected to standard reaction conditions to afford compound 12a–d (Scheme 2). To our pleasure, C-arylated β-N-arylamidoesters (±)-11a–d afforded products (±)-12a–d in 59–89% yield after 1 h under conditions A and B.

Our synthetic methodology was further explored in the construction of spiro-fused oxindole ring systems (Scheme 3). The spiro-fused oxindoles such as coerulescine (15a) [68-72], horsfiline (15b) [73], and elacomine (16), are prevalently found in a huge number of indole-based alkaloids having analgesic properties. Our oxidative methodology offered us a direct access to the core structures of these alkaloids under the optimized IDC conditions in high yields (Scheme 3).

Next, we thought of carrying out the IDC without alkylations of compounds 3a and b and 17a and b (Scheme 4). Unfortunately, we could not isolate products due to decomposition under optimized IDC conditions. It was noticed that changing the solvent to THF effected very fast (within 5 minutes) dimerization of 3a and b at room temperature to afford 18a and b as sole products in 91–93% yield and in up to >20:1 dr (Scheme 4). This shows that formation of a stabilized tertiary radical probably facilitates the IDC process for the syntheses of 2-oxindoles.

However, if a tertiary radical is responsible for the oxidative process, then one would realize the formation of dimeric

---

**Table 2: IDC in the presence of organic bases. Reproduced from [46].**

| Entry | Base  | Time  | % of 8j | % of 10j |
|-------|-------|-------|---------|---------|
| 1.    | pyridine | 12 h  | 29      | 30      |
| 2.    | Et3N   | 12 h  | 25      | 28      |
| 3.    | DBU    | 40 min| 82      | –       |
| 4.    | DABCO  | 12 h  | 34      | 51      |

*Reactions were carried out on a 0.25 mmol of 10j using 0.50 mmol of base and 0.275 mmol of iodine in 1 mL of solvent for specified time.*
Figure 4: C-Alkylation of anilides using KOt-Bu.

2-oxindoles sharing vicinal all-carbon quaternary centers from dimeric β-N-arylamidoesters 18a and b (Scheme 4). The reason behind our interest towards this direction was due to the prevalence of various dimeric cyclotryptamine alkaloids containing 3a,3a'-bis-pyrrolo[2,3-b]indole subunits (core structure of alkaloids 22a and b, see, Scheme 5) [74-77], sharing a vicinal all-carbon quaternary stereogenic centers with extreme steric congestion at the C3a-C3a'-σ-bond as well as the attendant lability of this linkage. Under the optimized conditions, one-pot dimerization of β-N-arylamido ester 3a and b and 9a took place
in the presence of 1.2 equivalents of KOt-Bu and I$_2$ followed by a double IDC on treatment with 1.2 equivalents of KOt-Bu and I$_2$ affording the dimeric 2-oxindoles (+)-19a–c in poor to moderate yields (26–45% yield and 2:1 dr) along with 15–18% isolation of dimeric β-N-arylamidoesters (+)-18a–c (Scheme 5). This transformation is an efficient one-pot formation of three consecutive carbon–carbon bonds. X-ray crystal structure determination of (+)-19b proved the outcome of the reaction unambiguously. It was noteworthy to observe Pd-catalyzed highly enantio-, chemo-, and diastereoselective double decarboxylative allylations on dimeric β-N-arylamido allyl ester 19c to yield the enantiopure compounds of type 20a and b in good yields.
Scheme 2: Oxidative coupling of C-arylated anilides (±)-11a–d. The synthesis of 12b as per method A has been reproduced from reference [46].

Scheme 3: Synthesis of spirocyclic product through IDC The synthesis of 14 as per method A has been reproduced from reference [46]. Conditions A: KOt-Bu, iodine; conditions B: KOt-Bu, NIS.

Scheme 4: Dimerization of β-N-aryl-amidoesters 3a and b. Reproduced from [46].
Scheme 5: Synthesis of dimeric 2-oxindoles utilizing IDC. The syntheses of 19a and b have been reproduced from [46].

In all the cases, IDC was feasible with substrates having substituents at the carbon atom α- to the amides. This gave a clue for a radical-mediated process where a single electron transfer (SET) mechanism might be operating. A tentative mechanism has been proposed in Scheme 6, the reaction can adopt a SET mechanism leading to the intermediate 23a, after C-alkylation. Compound 23a in turn gets converted into intermediate aryl radical 23b. From this intermediate another intermediate aryl carbocation 23c is formed by transferring a single electron to the oxidant. Carbocation 23c is stabilized by the amide nitrogen as shown in 23d. Eventually, in the presence of base, rearomatization of 23d takes place to afford the final product of the oxidative coupling reaction.

Kündig et al. in their oxidative coupling process using 2.2 equivalent of CuCl₂ showed that it is important to have a tertiary carbon α- to the amide for the process to be radical mediated [38,39]. Also, it is well evident from literature that the oxidation processes using Mn(OAc)₃ as oxidant follow a radical pathway [82-86]. In fact, the reaction of 3a also afforded 2-oxindole 4a in 69% yield when the oxidative coupling was carried out in presence of 1.2 equiv of Mn(OAc)₃ (Scheme 7). A similar result was also observed when reaction was carried out using C-methyl β-N-arylamido ester 5a (Scheme 7) [82-86]. However, one can’t rule out the possibility of a substitution reaction on C-iodo product 24 from the adjacent aryl group.
Thus, the possibility of the addition at the 2-position of electron-rich N-acylated aniline 3a to the tertiary iodide intermediate was also investigated. Towards this, we thought of synthesizing the C-iodo intermediate using N-iodosuccinimide (NIS) or ICl in the presence of a base. Surprisingly, our all effort to prepare C-iodo compound 24 in the presence of KOt-Bu as a base only led to formation of 2-oxindole 4a in 72% and 69% yields, respectively (Scheme 8). Along the same line, C-methyl β-N-arylamido ester 5a also afforded product 4a in 80–85% yield when the reaction was carried out at elevated temperature (Scheme 8). We thought there could be the possibility of a substitution reaction of iodide compound 24 prepared in-situ to form directly 2-oxindole 4a under elevated temperature. Thus, it was decided to carry out the C-iodination at room temperature, where substitution reactions would be unlikely, considering the fact that the substitution has to occur at the sterically congested tertiary iodide 24. However, to our surprise, when C-iodination of 5a was carried out at rt, we found that it also afforded 2-oxindole 4a in 30–39% yield along with 43–52% of recovered starting material (Scheme 8) and no trace of C-iodide 24 was observed. These results suggest that, NIS and ICl also acts as oxidants and helping in a single electron transfer (SET) in the oxidative coupling reaction [87,88]. It is also well evident in the literature that, these can also be used as oxidants in variety of oxidative coupling reactions [87,88]. Further, oxidative coupling of 5a was carried out in presence of well-known t-BuOCl, which generally goes through a radical-mediated pathway [89,90]. Towards this, when the oxidative coupling was carried out in presence of in situ generated t-BuOCl [91], the reaction afforded oxidative coupling product (+)-4a in 68% yield, which is also probably indicating a radical pathway of the reaction (Scheme 8).
Shifting our attention towards the synthetic application of our IDC methodology, we put forward our effort towards the synthesis of 3-alkylated or arylated 2-oxindoles. Towards this, we subjected to react, the oxidative coupling products (±)-6, (±)-12c and d having benzyl (Bn) or p-methoxybenzyl (PMB) esters with a catalytic amount of Pd on activated charcoal (10% Pd on charcoal) under atmospheric pressure of hydrogen gas in MeOH/EtOH (Scheme 9).

Interestingly, we observed that the oxidative coupling products undergo deprotection of benzyl or p-methoxybenzyl group and provided the intermediate carboxylic acid, followed by decarboxylative protonation in the same pot gave us the desired products (±)-25a–h in excellent yields (Scheme 9 and Scheme 10).

Later, we envisioned that the oxidative coupling products having allyl, methallyl, dimethylallyl esters after Trost–Tsuji decarboxylative allylations could serve as an interesting platform for complex natural product synthesis after further synthetic elaboration and functionalization. A few substrates were treated under decarboxylative allylation (DcA) conditions in the presence of 10 mol % of Pd(PPh₃)₄ in refluxing tetrahydrofuran (7–8 h), which afforded products 26a–d in up to 99% yield (Scheme 11). Interestingly, oxidative coupling products with dimethylallyl esters 8j underwent smooth decarboxylative
Scheme 9: Synthesis of 3-substituted-2-oxindoles from benzyl esters.

Scheme 10: 3-Substituted-2-oxindoles from p-methoxybenzyl esters.

Conclusion
In summary, we have successfully demonstrated the synthesis of 2-oxindoles bearing an all-carbon quaternary center applying a ‘transition-metal-free’ intramolecular dehydrogenative coupling (IDC) strategy. The methodology has been broadly applied to a wide range of substrates affording 2-oxindoles in good yields in a facile one-pot C-alkylation concomitant with oxidative coupling strategy. These products serve as a great synthetic platform for several indole-based natural products. The methodology demonstrated here has several advantages: (i) C-alkylations can be carried in same pot; (ii) simple oxidants like iodine and N-iodosuccinimide (NIS) could be used in the absence of any transition metal which may be toxic and (iii)
substrates with a scope of further functionalization work equally well. The easy handling and the low cost of the reagents involved in this synthetic methodology offers profound opportunities to expand and explore the use of IDC in organic synthesis. Further applications of this strategy are under active investigation in our laboratory.

Supporting Information

Supporting Information File 1
Copies of $^1$H, and $^{13}$C NMR spectra for all new compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-12-111-S1.pdf]

Acknowledgements

Financial support from the Department of Science and Technology (DST) through FAST-TRACK scheme (SB/FT/CS-54/2011) and the Council of Scientific and Industrial Research (CSIR) [02(0013)/11/EMR-II], Govt. of India is gratefully acknowledged. N.K., S.G., and S.B. thank the CSIR, New Delhi, for predoctoral fellowships. We sincerely thank Dr. Subahdip De, Dr. Badrinath N. Kakde, and Dr. Amit Adhikary for preliminary studies. Facilities from the Department of Chemistry, IISER Bhopal is gratefully acknowledged.

References

1. Dyker, G., Ed. Handbook of C-H Transformations: Applications in Organic Synthesis; 2005; Vol. 2.
2. Stuart, D. R.; Fagnou, K. Science 2007, 316, 1172. doi:10.1126/science.1141956
3. Ashenhurst, J. A. Chem. Soc. Rev. 2010, 39, 540. doi:10.1039/B907809F
4. Le Bras, J.; Muzart, J. Chem. Rev. 2011, 111, 1170. doi:10.1021/cr100209d
5. Rossi, R.; Bellina, F.; Lessi, M. Synthesis 2010, 4131. doi:10.1055/s-0030-1258262
6. Scheuermann, C. J. Chem. - Asian J. 2010, 5, 436. doi:10.1002/asia.200900487
7. You, S.-I.; Xia, J.-B. Top. Curr. Chem. 2010, 292, 165. doi:10.1007/128_2009_18
8. Newhouse, T.; Baran, P. S.; Hoffmann, R. W. Chem. Soc. Rev. 2009, 38, 3010. doi:10.1039/b821200g
62. Okada, M.; Sato, I.; Cho, S. J.; Dubnau, D.; Sakagami, Y. Tetrahedron 2006, 62, 8907. doi:10.1016/j.tet.2006.06.074
See for the isolation of geranylated hexahydropyrrolo[2,3-b]indole alkaloids.

63. Rochfort, S. J.; Moore, S.; Craft, C.; Martin, N. H.; Van Wagoner, R. M.; Wright, J. L. C. J. Nat. Prod. 2009, 72, 1773. doi:10.1021/np900282j

64. One-pot alkylations followed by dehydrogenative-coupling was unsuccessful, thus, IDC was carried out C-alkylated substrates such as

10.

65. Burgett, A. W. G.; Li, Q.; Wei, Q.; Harran, P. G. Angew. Chem., Int. Ed. 2003, 42, 4961. doi:10.1002/anie.200352577

66. Nicolaou, K. C.; Hao, J.; Reddy, M. V.; BheemaRao, P.; Rassias, G.; Snyder, S. A.; Huang, X.; Chen, D. Y.-K.; Brenzovich, W. E.; Guiseppe, N.; Giannakakou, P.; O’Brate, A. J. Am. Chem. Soc. 2004, 126, 12897. doi:10.1021/ja040933a

67. Wu, Q.-X.; Crow, M. S.; Draskovic, M.; Sohn, J.; Johnson, T. A.; Tenney, K.; Valerio, F. A.; Yao, X.-J.; Bjeldanes, L. F.; Crews, P. Org. Lett. 2010, 12, 4458. doi:10.1021/ol101396n

68. Francke, W.; Kitching, W. Curr. Org. Chem. 2001, 5, 233. doi:10.2174/1385272013375652

69. Rosenberg, S.; Leino, R. Synthesis 2009, 2651. doi:10.1055/s-0029-1216892

70. Edmondson, S.; Danishfeky, S. J.; Sepp-Lorenzino, L.; Rosen, N. J. Am. Chem. Soc. 1999, 121, 2147. doi:10.1021/ja983778i

71. Deppermann, N.; Thomanek, H.; Prenzel, A. H. G. P.; Maison, W. J. Org. Chem. 2010, 75, 5994. doi:10.1021/jo101401z

72. Trost, B. M.; Brennan, M. K. Org. Lett. 2006, 8, 2027. doi:10.1021/ol060298j

73. De, S.; Das, M. K.; Bhunia, S.; Bisai, A. Org. Lett. 2015, 17, 5922. doi:10.1021/acs.orglett.5b03082
See for our approach using a thiourea catalyzed alid reaction with paraformdehylde.

74. May, J. A.; Stoltz, B. M. Tetrahedron 2006, 62, 5262. doi:10.1016/j.tet.2006.01.105

75. Steven, A.; Overman, L. E. Angew. Chem., Int. Ed. 2007, 46, 5488. doi:10.1002/anie.200700612

76. Schmidt, M. A.; Movassaghi, M. Synlett 2008, 313. doi:10.1055/s-2008-1032060

77. Ghosh, S.; Chaudhuri, S.; Bisai, A. Org. Lett. 2015, 17, 1373. doi:10.1021/acs.orglett.5b00032

78. Ghosh, S.; Chaudhuri, S.; Bisai, A. Chem. – Eur. J. 2015, 21, 17479. doi:10.1002/chem.201502878
See for an enantioselective approach using a key Pd-catalyzed decarboxylative alkylation from our group.

79. Overman, L. E.; Paone, D. V.; Stearns, B. A. J. Am. Chem. Soc. 1999, 121, 7702. doi:10.1021/ja981714g
See for an asymmetric sequential processes to set a vicinal all-carbon quaternary stereocenter.

80. Trost, B. M.; Osipov, M. Angew. Chem., Int. Ed. 2013, 52, 9176. doi:10.1002/anie.201302805

81. Ghosh, S.; Bhunia, S.; Kakde, B. N.; De, S.; Bisai, A. Chem. Commun. 2014, 50, 2434. doi:10.1039/c3cc49064e

82. Heba, E. I.; Dessau, R. M.; Koehl, W. J., Jr. J. Am. Chem. Soc. 1968, 90, 2706. doi:10.1021/ja01012a051
See for a Mn(III)-mediated radical process.

83. Bush, J. B., Jr.; Finkbeiner, H. J. Am. Chem. Soc. 1968, 90, 5903. doi:10.1021/ja01023a048

84. Nikishin, G. I.; Vinogradov, M. G.; Fedorova, T. M. J. Chem. Soc., Chem. Commun. 1973, 693. doi:10.1039/C39730000693

85. Corey, E. J.; Kang, M. J. Am. Chem. Soc. 1984, 106, 5384. doi:10.1021/ja00330a076

86. Iqbal, J.; Bhatia, B.; Nayar, N. K. Chem. Rev. 1994, 94, 519. doi:10.1002/anie.201009458

87. Newhouse, T.; Lewsi, C. A.; Eastman, K. J.; Baran, P. S. J. Am. Chem. Soc. 2010, 132, 7119. doi:10.1021/ja909402j

88. Foo, K.; Newhouse, T.; Mori, I.; Takayama, H.; Baran, P. S. Angew. Chem., Int. Ed. 2011, 50, 2716. doi:10.1002/anie.201008048

89. Akihar, M.; Barton, D. H. R. J. Am. Chem. Soc. 1964, 86, 1528. doi:10.1021/ja01062a016

90. Montoro, R.; Wirth, T. Org. Lett. 2003, 5, 4729. doi:10.1021/ol0359012

91. Preparation of i-BuOCl: A flame-dried round-bottom flask was charged with 0.6 mmol of i-BuONa in 0.5 mL of benzene. To this solution was added 0.6 mmol of I2 at room temperature. This solution was directly used for the oxidative coupling (see, reference [90]).

92. Ruchti, J.; Carreira, E. M. J. Am. Chem. Soc. 2014, 136, 16756. doi:10.1021/ja505893s

93. Thandavamurthy, K.; Sharma, D.; Ponwal, S. K.; Ray, D.; Viswanathan, R. J. Org. Chem. 2014, 79, 10049. doi:10.1021/jo501651z

License and Terms
This is an Open Access article under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The license is subject to the Beilstein Journal of Organic Chemistry terms and conditions: (http://www.beilstein-journals.org/bjoc)

The definitive version of this article is the electronic one which can be found at: doi:10.3762/bjoc.12.111