Site-Selective Catalytic Deaminative Alkylation of Unactivated Olefins

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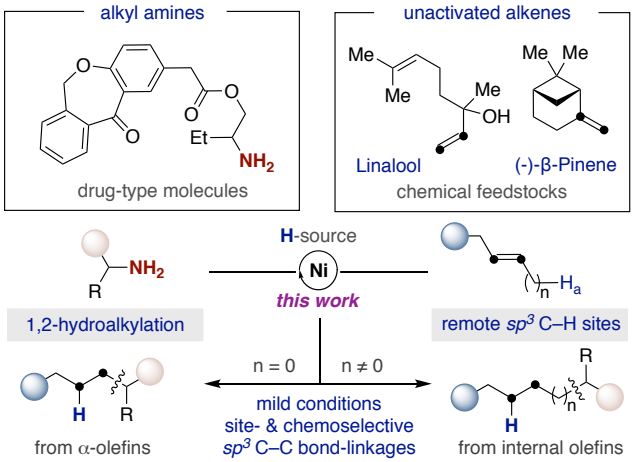
Supporting Information Placeholder

ABSTRACT: A catalytic deaminative alkylation of unactivated olefins is described. The protocol is characterized by its mild conditions, wide scope – including the use of ethylene as substrate –, and exquisite site-selectivity pattern for both α-olefins and internal olefins, thus unlocking a new catalytic platform to forge sp^3–sp^3 linkages, even in the context of late-stage functionalization.

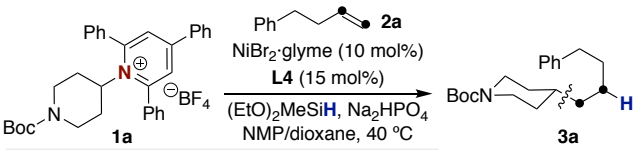
The recent years have witnessed an emerging demand for forging C–C bonds via functionalization of unactivated olefin feedstocks.[1] Among various scenarios, the catalytic addition of metal hydride species across an unactivated olefin constitutes an active frontier of contemporary catalysis research, as it formally generates a latent carbogenic nucleophile that can further be elaborated in the presence of an appropriate electrophilic partner.[2]

Scheme 1. Catalytic Deaminative sp^3–Alkylation of Olefins.

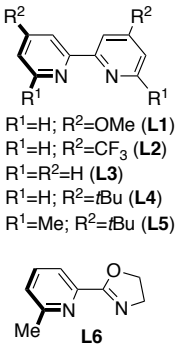


Driven by the prevalence of alkyl amines in pharmaceuticals and preclinical candidates,[3] chemists have recently been challenged to design catalytic sp^3 C–N cleavage techniques as a new tactic for lead generation in drug discovery.[4] Despite the elegant advances realized, C–C bond-forming scenarios remain currently confined to the use of well-defined organometallic reagents,[5] organic halide counterparts[6] or biased electron-deficient olefins.[7] Therefore, at the outset of our investigations it was unclear whether a site-selective catalytic deaminative alkylation could ever be implemented with unactivated α-olefins or even internal olefins, chemical feedstocks derived from the petroleum processing. If successful, such uncharted territory might not only provide an unrecognized opportunity to explore currently inaccessible chemical spaces in both olefin functionalization and deamination events, but also offer a new strategic approach for rapidly and reliably generate structural diversity via unconventional sp^3–sp^3 bond-disconnections.[8] In our continuing interest in Ni-catalyzed reactions,[9] we report herein the successful realization of this goal (Scheme 1). The salient features of this process are the mild conditions, high chemoselectivity profile, and exquisite site-selectivity for both α-olefins and internal olefins, even at late-stages. While *anti*-Markovnikov selectivity was found in the former,[10] the use of the latter results in bond-formation at remote sp^3 C–H sites enabled by chain-walking scenarios.[11]

Table 1. Optimization of the Reaction Conditions.[a]



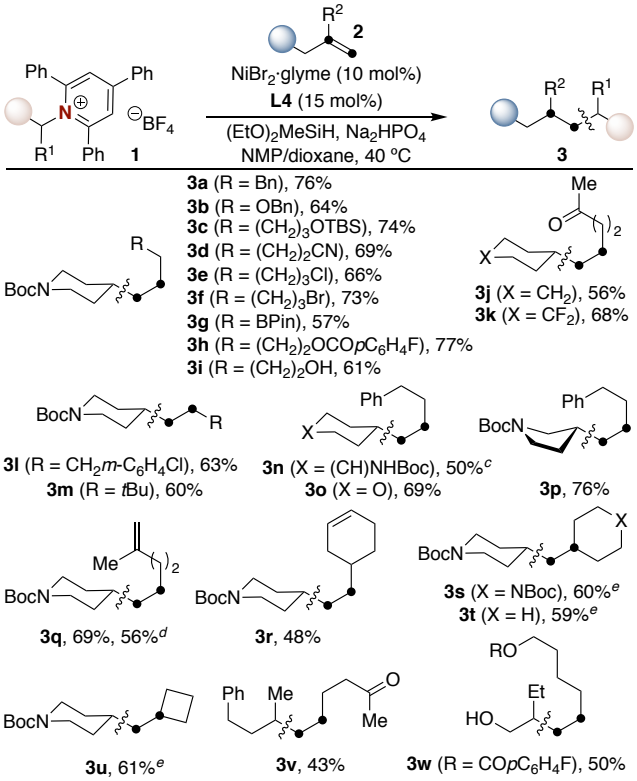
entry	deviation standard conditions	**3a** (%)[b]
1	***none***	*81 (80)*[c]
2	**L1** instead of **L4**	66
3	**L2** instead of **L4**	52
4	**L3** instead of **L4**	58
5	**L5** instead of **L4**	3
6	**L6** instead of **L4**	11
7	using $Ni(cod)_2$	33
8	using $(EtO)_3SiH$	32
9	using K_2CO_3 as the base	41
10	NMP as solvent	51
11	dioxane as solvent	6
12	no Ni, **L4**, Na_2HPO_4 or silane	0



[a] **1a** (0.20 mmol), **2a** (0.60 mmol), $NiBr_2$·glyme (10 mol%), **L4** (15 mol%), $(EtO)_2MeSiH$ (0.60 mmol), Na_2HPO_4 (0.40 mmol), NMP/dioxane (4:1) at 40 ºC for 14 h. [b] GC yields using 1-decane as internal standard. [c] Isolated yield.

We began our work by evaluating the deaminative alkylation of pyridinium salt **1a** – readily prepared from the corresponding alkyl amine congener on a large scale – with unactivated olefin **2a** (Table 1).[12] After careful evaluation of all reaction parameters,[13] we found that a combination of $NiBr_2$·glyme (10 mol%), **L4** (15 mol%), $(EtO)_2MeSiH$, Na_2HPO_4 in NMP/dioxane at 40 ºC provided the best results, affording **3a** in 80% isolated yield with an exquisite *anti*-Markovnikov selectivity. Among all of the ligands analyzed, 2,2'-bipyridine motifs turned out to be particularly suited for the targeted transformation (entries 2-6); unlike related reductive coupling reactions, an intimate interplay of electronic effects on the ligand backbone and the presence of substituents adjacent to the nitrogen atom were not critical for the reaction to occur.[14] Subtle changes on the nickel precatalyst, hydride source, inorganic base or solvent, however, had a deleterious effect on reactivity, invariably obtaining lower yields of **3a**, if any (entries 7-11). As anticipated, control experiments revealed that all of the parameters were essential for forging the sp^3–sp^3 linkage (entry 12).[15]

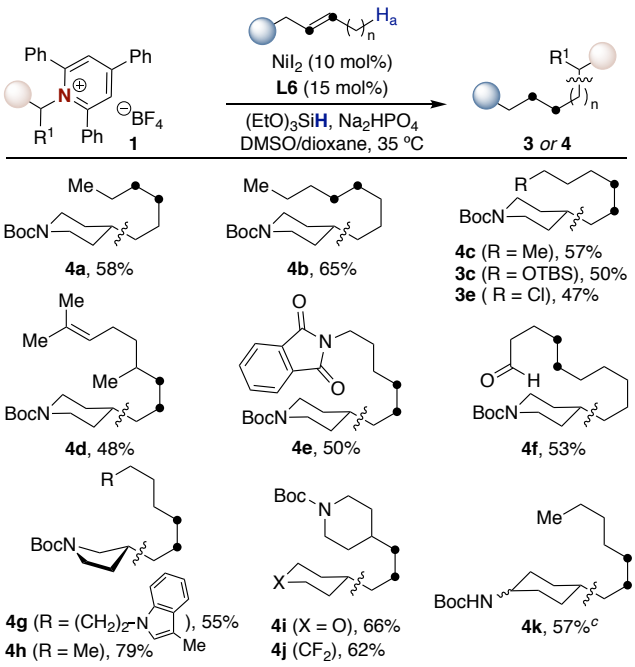
Table 2. Deaminative Alkylation with α-Olefins.[a,b]



[a] As Table 1 (entry 1). [b] Isolated yields, average of two independent runs. [c] dr = 1.5:1. [d] 2.0 mmol scale. [e] NiI_2 (10 mol%), **L6** (20 mol%) in DMSO/dioxane (3:1) at 35 ºC.

As evident from the results compiled in Table 2, our catalytic deaminative alkylation of α-olefins showed an excellent chemoselectivity profile, and nitriles (**3d**), esters (**3h, 3w**), carbamates (**3n, 3s**), silyl ethers (**3c**) or ketones (**3j, 3k, 3v**) were perfectly tolerated. Notably, organoborons (**3g**), alkyl halides (**3e**, **3f**, **3k**) or aryl halides (**3h, 3l, 3w**) could all be well-accommodated, thus providing ample opportunities for further derivatization via conventional cross-coupling reactions.[16] Even free alcohols do not interfere with productive sp^3–sp^3 bond-formation (**3i, 3w**). As expected, the deaminative alkylation of substrates possessing multiple unsaturation motifs occurred exclusively at the less-substituted olefin (**3q, 3r**). As shown for **3q**, the reaction could be executed on a 2 mmol scale without significant erosion in yield. Importantly, 1,1-disubstituted alkenes as substrates posed no problems (**3s-3u**). Likewise, the targeted sp^3–sp^3 bond-formation could be extended to cyclic analogues other than **1a** (**3j-k**, **3n-o** and **3p**) and to aliphatic congeners (**3v, 3w**).

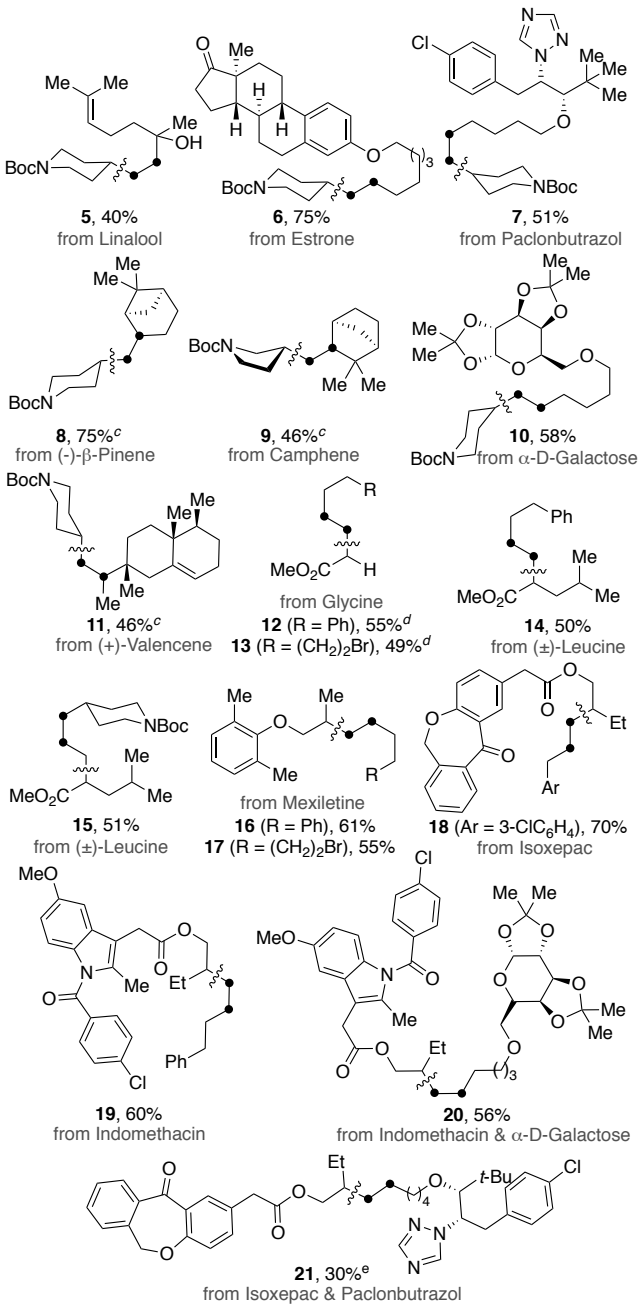
Table 3. Deaminative Alkylation with Internal Olefins.[a,b]



[a] As Table 1 (entry 1). [b] Isolated yields, average of two independent runs. [c] dr = 1.5:1.

The lower binding affinity of unactivated internal olefins to metal centers[17] and the inherent difficulty in discriminating both ends of the double bond left a reasonable doubt to whether our deaminative alkylation could be extended to internal olefins. Indeed, no sp^3–sp^3 formation was observed upon exposure of 2-heptene to **1a** under the Ni/**L4** regime shown in Table 2. Interestingly, however, the inclusion of substituents adjacent to the nitrogen atom on the ligand backbone enabled a deaminative sp^3–alkylation at remote sp^3 C–H sites.[11,18] After judicious evaluation of the reaction parameters, a combination of NiI_2 (10 mol%), **L6** (20 mol%), $(EtO)_3SiH$ (0.40 mmol), Na_2HPO_4 (0.80 mmol) in DMSO/1,4-dioxane afforded **4c** in 57% yield with > 36:1 selectivity (Table 3).[19,20] As shown, the reaction could also accommodate silyl ethers (**3c**), phthalimides (**4e**), aldehydes (**4f**), alkyl halides (**3e**), carbamates (**4i, 4j**) or nitrogen-containing heterocycles (**4g**).[15] Importantly, excellent site-selectivity for sp^3–sp^3 bond-formation at distal primary sp^3 C–H sites was found regardless of the position of the double bond, even at long-range (**4f**). Even branched substituents or trisubstituted olefins (**4d**) do not compete with the efficacy of the reaction,[21] with deaminative alkylation invariably occurring at the less-sterically hindered primary sp^3 C–H site.

Scheme 2. Advanced Synthetic Intermediates.[a,b]

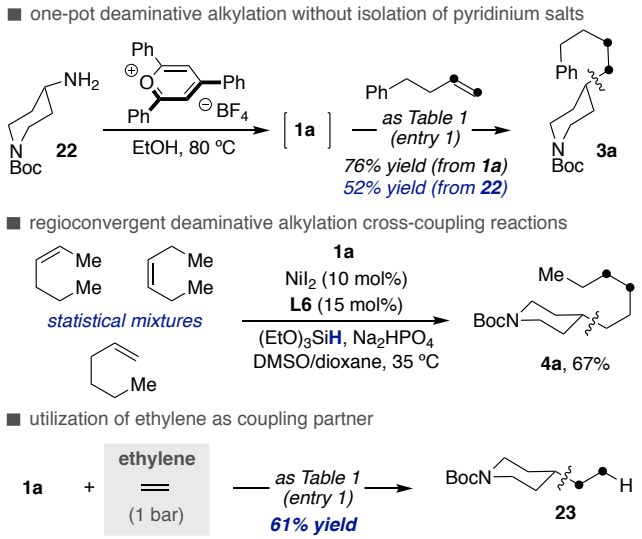


[a] α-Olefin: as Table 1 (entry 1); internal olefins: as Table 3. [b] Isolated yields, average of two runs. [c] **8** (dr = 97:3); **9** (dr = 46:40:7:7); **11** (dr = 9:1). [d] 80 °C. [e] $NiBr_2$·glyme (15 mol%).

With a reliable set of conditions in hand for both α-olefins and internal olefins, we wondered whether our protocol could be applied within the context of late-stage functionalization.[22] As shown in Scheme 2, this turned out to be the case. Although modest yields were obtained in certain cases, these results should be interpreted against the challenge that is addressed, particularly with substrates possessing multiple functional groups derived from linalool (**5**), paclonbutrazol (**7**), galactose (**10**) or valencene (**11**), with C–C bond-formation taking place exclusively at the least substituted olefin site. Similarly, β-pinene (**8**), camphene (**9**) or estrone derivatives (**6**) posed no problems.

The reaction could also be extended to amino acid derivatives (**12-15**), either using primary alkyl amines (**12-13**) or their secondary congeners (**14, 15**).[23] The ability to obtain **15** as a single regioisomer is particularly noteworthy, thus indicating that late-stage deaminative alkylation is not limited to α-olefins. As shown for **14-19**, our technique could be used to derivatize mexiletine, isoxepac or indomethacin via sp^3 C–N bond-cleavage with simple olefin counterparts. Even drug-type molecules such as **20-21** could be employed for forging sp^3–sp^3 linkages.

Scheme 3. Synthetic Application.[a]



The results shown in Scheme 3 further illustrates the synthetic value of our deaminative alkylation. Interestingly, **3a** was within reach from *N*-Boc 4-aminopiperidine (**22**) without the need for isolating pyridinium **1a** (*top*).[13] Although in an unoptimized 52% yield, this result shows that telescoping the formation of the latter might be a viable alternative for forging sp^3–sp^3 linkages. In addition, regioconvergent scenarios could be implemented from statistical mixtures of olefins, invariably leading to **4a** as single regioisomer (*middle*). Even ethylene – the largest-volume chemical produced in industry–[24] could be employed as substrate under atmospheric pressure en route to **23** (*bottom*). Taken together, the data shown in Tables 2-3 and Schemes 2-3 serve as a testament to the prospective impact of our deaminative alkylation of unactivated olefins, offering a counterintuitive new approach to forge sp^3–sp^3 bonds while expanding our ever-growing arsenal of olefin functionalization and deaminative events.

In summary, we have developed a catalytic deaminative alkylation of unactivated olefins that operates under mild conditions and is characterized by its wide substrate scope and exquisite site-selectivity profile, even in the context of ethylene valorization or late-stage functionalization. This new platform offers new vistas in both olefin functionalization and deamination events and a complementary activation mode to existing sp^3–sp^3 bond-forming reactions. Further studies into the mechanism and the extension to related transformations are currently ongoing.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, crystallographic data and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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No competing financial interests have been declared.

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(18) The utilization of **L5** resulted in 8% yield of **4c**, thus showing the superior performance of pyrox-type ligands such as **L6** in the targeted deaminative alkylation at remote *sp*^{3} centers.

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(20) The reaction temperature did not have a profound influence on the deaminative alkylation of internal olefins, obtaining similar results at T = 40 ºC. It is worth noting, however, that the utilization of α-olefins at T = 35 ºC (Table 2) led to ~10% erosion in yield of the targeted products.

(21) **4d** was obtained from *E/Z* mixtures of **2w**, thus indicating that the geometry of the starting olefin does not have a negative influence on product formation.

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(23) Although **14** and **15** were obtained from racemic Leucine, we found that the deaminative alkylation of L-Alanine (99% ee) with **2c** resulted in a racemate. This observation is consistent with a C–N scission occurring via single-electron transfer (SET). For preliminary mechanistic discussions and control experiments performed with either cyclopropyl derivatives as radical clocks or 3,4-dihydropyrrole derivatives as substrates, see Supporting information.

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