

# Metal-Free Oxidative C(sp<sup>3</sup>)-H Bond Couplings as Valuable Synthetic Tools for C-C Bond Formations

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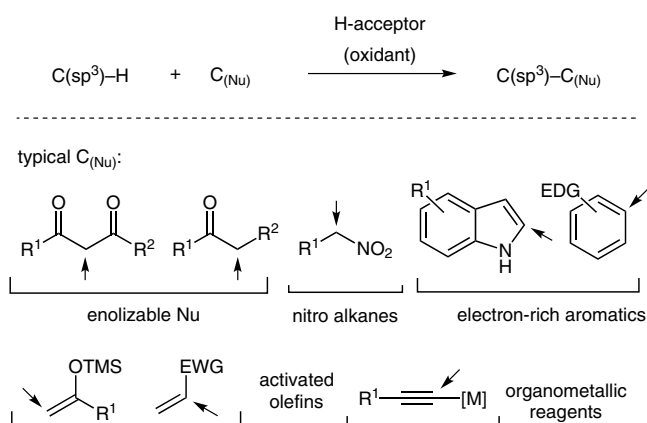
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Received: 05.10.2012; Accepted after revision: 24.10.2012

**Abstract:** Metal-free oxidative methods for the direct functionalization of C(sp<sup>3</sup>)-H bonds to form new C-C bonds remain challenging. In this article, previous and recent results, the latter devoted to expanding the scope and synthetic applicability, on these metal-free oxidative C-C coupling reactions are highlighted.

**Key words:** oxidation, C-H functionalization, metal-free, cross-coupling, alkenes

The effective and selective direct formation of C-C bonds from C-H bonds is still a challenge in organic synthesis.<sup>1,2</sup> In particular, the selective functionalization of C(sp<sup>3</sup>)-H bonds constitutes one of the most demanding task due to their ubiquitous presence in organic molecules and their relatively inert nature. In this regard, the oxidative coupling of C(sp<sup>3</sup>)-H bonds has recently been recognized as a powerful tool for the formation of new C(sp<sup>3</sup>)-C bonds,<sup>2</sup> providing novel synthetic disconnections for the constructions of organic molecules (Scheme 1). However, there are still some important limitations on the substrate scope. For example, the carbon nucleophiles typically employed are mostly restricted to enolizable carbonyl compounds, nitroalkanes, electron-rich aromatics and (in situ generated) organometallic reagents (Scheme 1, bottom).



**Scheme 1** General approach for C(sp<sup>3</sup>)-H oxidative coupling reactions and typical carbon-based coupling partners employed



**Renate Rohlmann** (left) received her Diploma in chemistry in 2010 at the University of Münster (Germany) under the mentorship of Dr. O. García Mancheño. Currently she is conducting her doctoral studies in the same group at the same university. Her research interests include asymmetric organocatalysis, oxidative C-H functionalizations and the synthesis of bioactive heterocycles.

**Olga García Mancheño** (right) studied chemistry at the Universidad Autónoma de Madrid (Spain). She received her MSc and PhD in organic chemistry from the same university under the guidance of Prof. J. C. Carretero. During her PhD, she also had the opportunity to carry out three-month research projects with Prof. M. T. Reetz (Max-Planck-Institut für Kohlenforschung, Germany) and Prof. K. A. Jørgensen (University of Aarhus, Denmark). After a postdoctoral stay with Prof. C. Bolm at RWTH-Aachen (Germany), she joined the faculty of Organic Chemistry at the University of Münster as a Habilitand (assistant professor) in October 2008.

On the other hand, whereas numerous examples of such metal-catalyzed oxidative coupling reactions, in which the metal catalyst often participates actively in the oxidation step,<sup>3</sup> have been reported, the related metal-free C(sp<sup>3</sup>)-H functionalizations are still rare.

This highlight focuses on the metal-free oxidative coupling reactions of C(sp<sup>3</sup>)-H bonds, in which electrochemical methods are not included. Moreover, some of the latest contributions devoted to broadening the scope of the nucleophilic coupling partner in oxidative C-C couplings, and therefore their synthetic applicability, are also presented.

In the metal-catalyzed methods for oxidative C-C forming coupling reactions of C(sp<sup>3</sup>)-H the predominant oxidants are organic peroxides. Conversely, the metal-free approaches generally rely on the use of quinones or oxygen as terminal oxidants. Thus, in 2006 C.-J. Li and co-workers presented the first metal-free direct dehydrogenative coupling reaction between α-C(sp<sup>3</sup>)-H bonds of benzylic ethers **1** and aliphatic ketones **2** at 100 °C employing

2,3-dichloro-5,6-dicyanoquinone (DDQ). They proposed two single electron transfer (SET) processes for the formation of an oxonium ion intermediate **4**, which undergo the nucleophilic attack of the in situ formed ketone-enolate to generate the coupling product **3** [Scheme 2, (a)].<sup>4</sup> Later on, the group of H. M. Todd described a milder version of a DDQ-mediated C-C bond-formation reaction. By changing the electrophile from benzyl ethers to tetrahydroisoquinolines **5** and using nitromethane as (pro)nucleophile, the reaction could be performed at room temperature [Scheme 2, (b)].<sup>5</sup> The oxidative coupling of allylic (**7**) and benzylic (**8**) C(sp<sup>3</sup>)-H bonds with various 1,3-dicarbonyl compounds under metal-free conditions using DDQ at 80 °C was also described by Y. Venkateswarlu et al. [Scheme 2, (c)].<sup>6</sup> Embracing this oxidative C-H bond coupling strategy, the group of Z. Li further investigated the reaction of benzyl thioethers **11**. In this case, the use of other quinone (*o*-chloranil) and the amount of this oxidant were crucial to achieve either a Pummerer-type **13** (1.5 equiv, 80 °C) or a Knoevenagel-type product **14** (3.0 equiv, 100 °C), the latter one by a subsequent elimination of the thiol group [Scheme 2, (d)].<sup>7</sup>

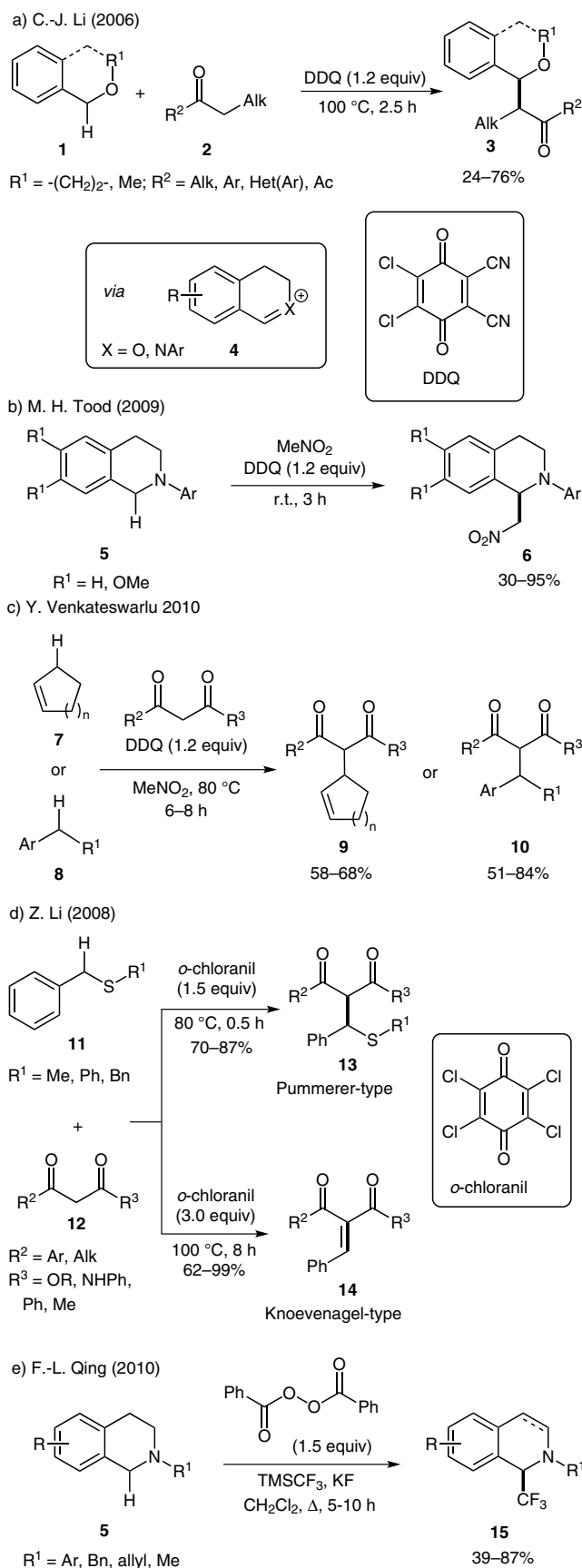
An example of metal-free oxidative C(sp<sup>3</sup>)-C(sp<sup>3</sup>) coupling reaction using organic peroxides has been reported by L. Chu and F.-L. Qing [Scheme 2, (e)].<sup>8</sup> They described an interesting trifluoromethylation reaction of tetrahydroisoquinolines **5** using the TMSCF<sub>3</sub>-KF system as source of CF<sub>3</sub><sup>-</sup> and benzoyl peroxide as oxidant.

As mentioned before, few examples using oxygen as terminal oxidant have also been reported under metal-free conditions. M. Klussmann and co-workers developed an oxidative method for the coupling of dibenzylic C-H bonds with 1,3-dicarbonyls or ketones **17**. An auto-oxidative mechanism in which O<sub>2</sub> forms the corresponding xanthane or acridane hydroperoxide **19** was proposed. These hydroperoxides **19** permit then an acid-catalyzed S<sub>N</sub>1-type reaction to generate the new C-C bond [Scheme 3, (a)].<sup>9</sup>

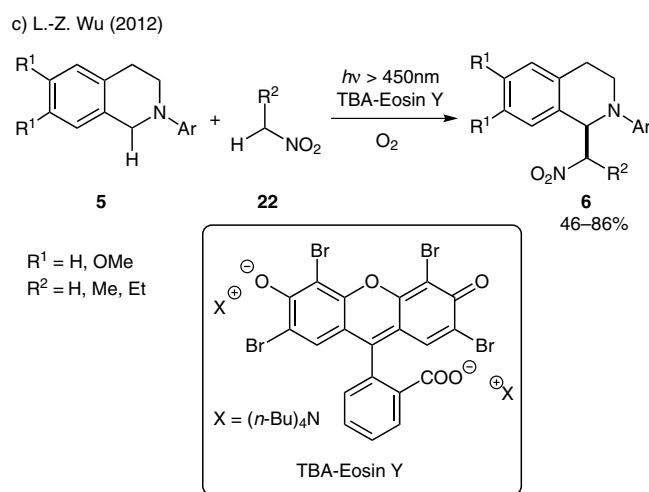
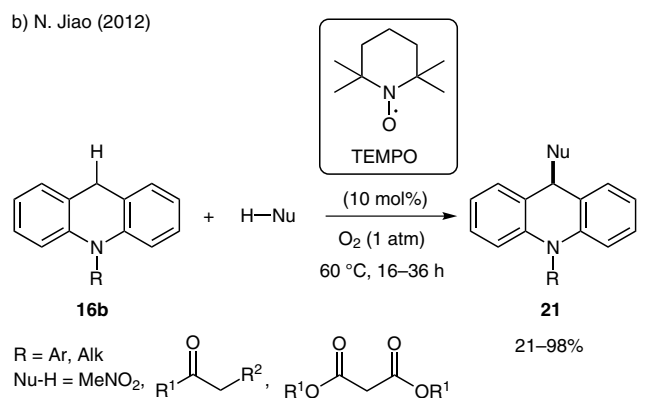
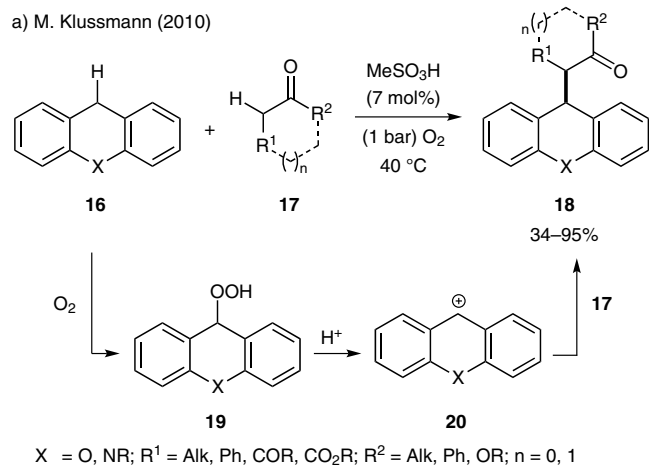
More recently, the use of catalytic amounts of 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) in the presence of oxygen for the coupling of 9,10-dihydroaridine **16b** and activated nucleophiles was described by N. Jiao [Scheme 3, (b)].<sup>10</sup> L. Z. Wu also reported on an efficient metal-free photocatalytic system for the coupling between the benzylic C-H bonds of tetrahydroisoquinolines and nitroalkanes. Mechanistic studies suggested a photo-induced radical pathway for the formation of the active iminium cation intermediate.<sup>11</sup>

Efficient metal-free, organocatalyzed asymmetric oxidative coupling reactions of benzylic C(sp<sup>3</sup>)-H bonds with aldehydes have recently also been achieved by the combination of known amine catalysis (MacMillan catalysts **25**) and the appropriate oxidant (DDQ or O<sub>2</sub>) (Scheme 4).<sup>12</sup>

In contrast to the classical activated nucleophiles depicted in Scheme 1, the use of simple olefins as soft nucleophiles is relatively unexplored. However, they offer tremendous opportunities for the scope expansion of this chemistry

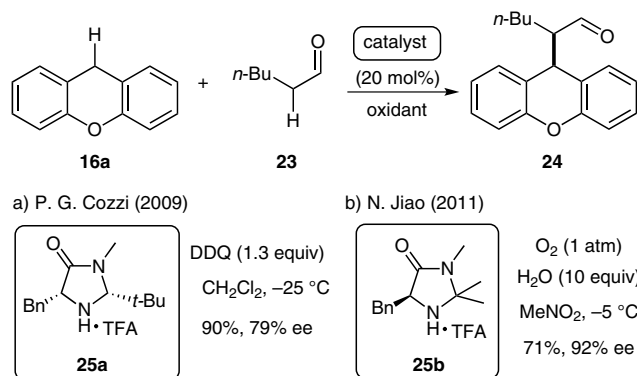


**Scheme 2** Representatives examples of metal-free oxidative couplings with quinone oxidants and peroxides



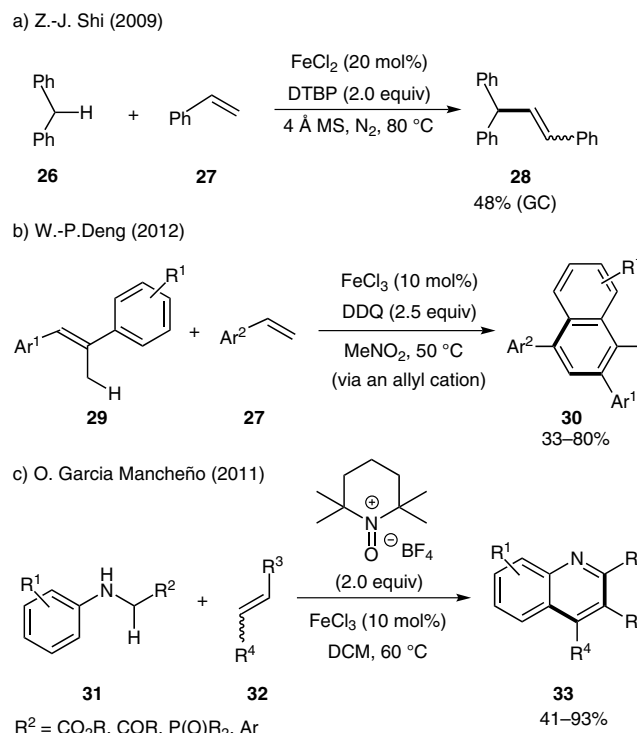
**Scheme 3** Metal-free C–C couplings using O<sub>2</sub> and an additive or co-oxidant

since a large number of olefins are readily available and cheap. To the best of our knowledge, only three reports on using simple olefins<sup>13</sup> as nucleophiles in oxidative couplings of C(sp<sup>3</sup>)–H bonds under metal-catalyzed conditions have been described. The first example was reported by the group of Z.-J. Shi in 2009.<sup>14</sup> A direct Fe-catalyzed olefination of diphenylmethane (**26**) with styrene (**27a**) to form the corresponding Heck-type product was achieved. However, only styrene could be employed, leading to **28** in a moderate 48% GC yield and accompanied by other inseparable by-products [Scheme 5, (a)]. Afterwards, W.-P.



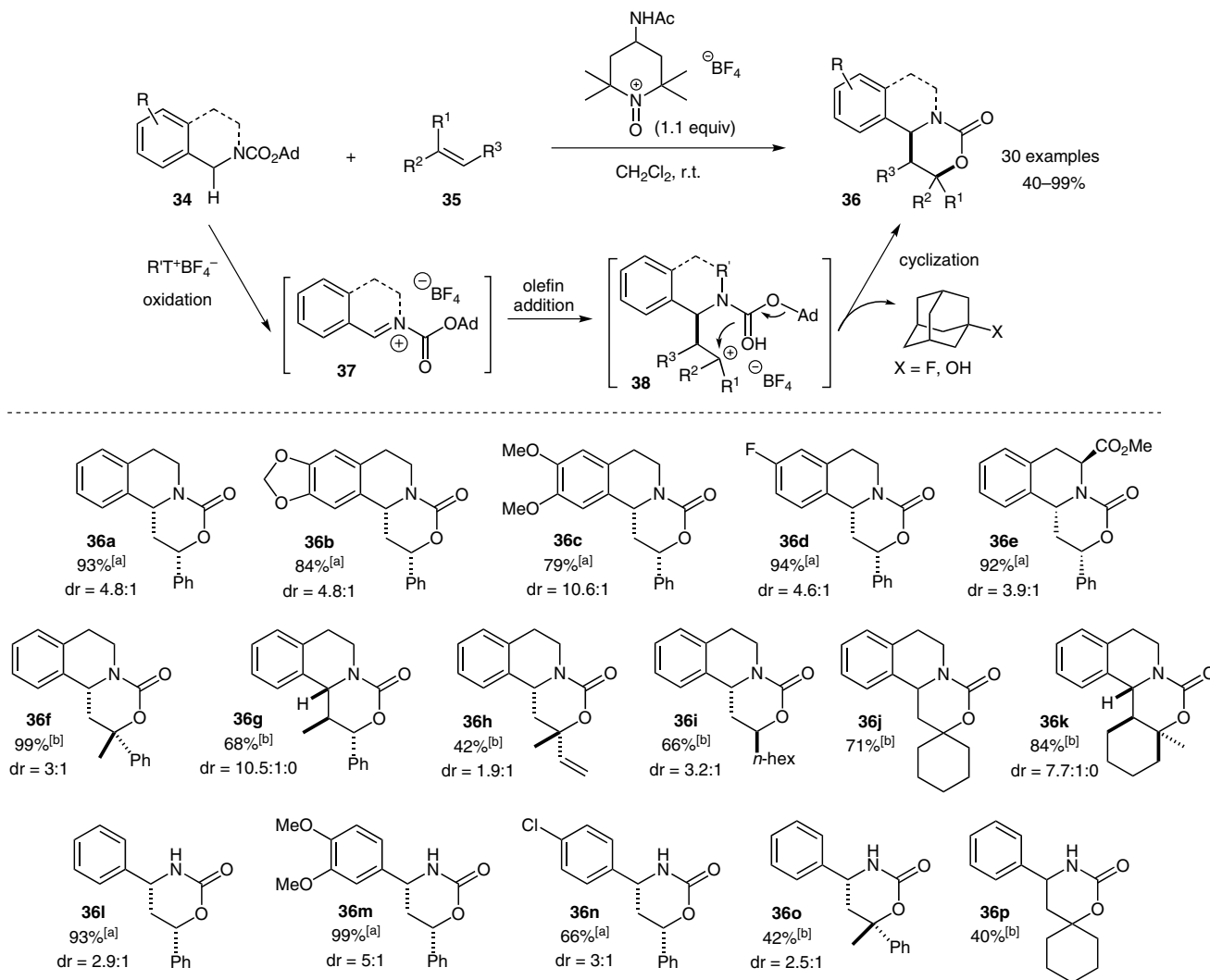
**Scheme 4** Representative examples of efficient metal-free, organo-catalyzed asymmetric oxidative C–C coupling reactions

Deng and co-workers presented a tandem cross-dehydrogenative coupling–benzoannulation of terminal allylic compounds **29** with styrenes **27** by a Fe(III)-catalyzed process [Scheme 5, (b)].<sup>15</sup> Our group also contributed to the development of a TEMPO oxoammonium salt mediated dehydrogenative Povarov–oxidation tandem reaction of *N*-alkyl anilines **31** with a variety of olefins **32**.<sup>16,17</sup> This approach permitted the straightforward synthesis of substituted quinolines **33** [Scheme 5, (c)].



**Scheme 5** Metal-catalyzed oxidative C–C couplings with simple olefins

With the aim of expanding the scope and applicability of oxidative couplings of C(sp<sup>3</sup>)–H bonds with olefins, we have recently found a very mild, metal-free cascade  $\alpha$ -alkylation–cyclization of *N*-benzyl carbamates with simple nonactivated olefins (Scheme 6).<sup>18</sup> Thus, after the direct oxidative  $\alpha$ -alkylation of carbamates **34** with olefins **35**, a



**Scheme 6** Representative scope of the present metal-free coupling study. [a] 1.2 equiv of olefin **35** used. [b] 5.0 equiv of olefin **35** used.

further nucleophilic attack of the carbamate-oxygen to the formed carbocationic intermediate **38** leads to the interesting N,O-heterocycles oxazines **36**. This methodology is very versatile and general, permitting the use of a variety of mono-, di- and trisubstituted olefins, in which not only the typically used styrenes but also alkyl-substituted alkenes can be employed. Moreover, beside the standard substrates tetrahydroisoquinolines, even the more challenging acyclic benzylic carbamates were also efficiently reacted to form the corresponding oxazines **36l–p**. The trick for success in this chemistry was the use of adamantyl carbamates, in which the 1-adamantly rest (Ad) serves as a good leaving group that cannot generate an olefin in situ (e.g., Boc leads to 2-methylpropene) that might compete in the first alkylation step.

In summary, though oxidative C(sp<sup>3</sup>)-H coupling reactions constitute a powerful tool for the formation of new C(sp<sup>3</sup>)-C bonds, one of the major drawbacks is still the lack of substrate/reagent generality of the methods published to date. With our studies on a metal-free tandem oxidative  $\alpha$ -alkylation-cyclization method, we have

established that new class of valuable nucleophiles (olefins) and substrates (simple benzylamides) can be efficiently used in this chemistry for the synthesis of interesting, highly decorated organic compounds. Due to the increasing importance of the development of C-H functionalizations under mild and environmentally friendly conditions, further innovative metal-free processes using a broader palette of reagents and starting materials are expected to be invented in the near future.

### Acknowledgment

The Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie and Prof. Frank Glorius are acknowledged for generous support. R.R. thanks the University of Münster within the Bonus-program for a predoctoral contract.

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