Organocatalytic Enantioselective Formal C(sp²)–H Alkylation

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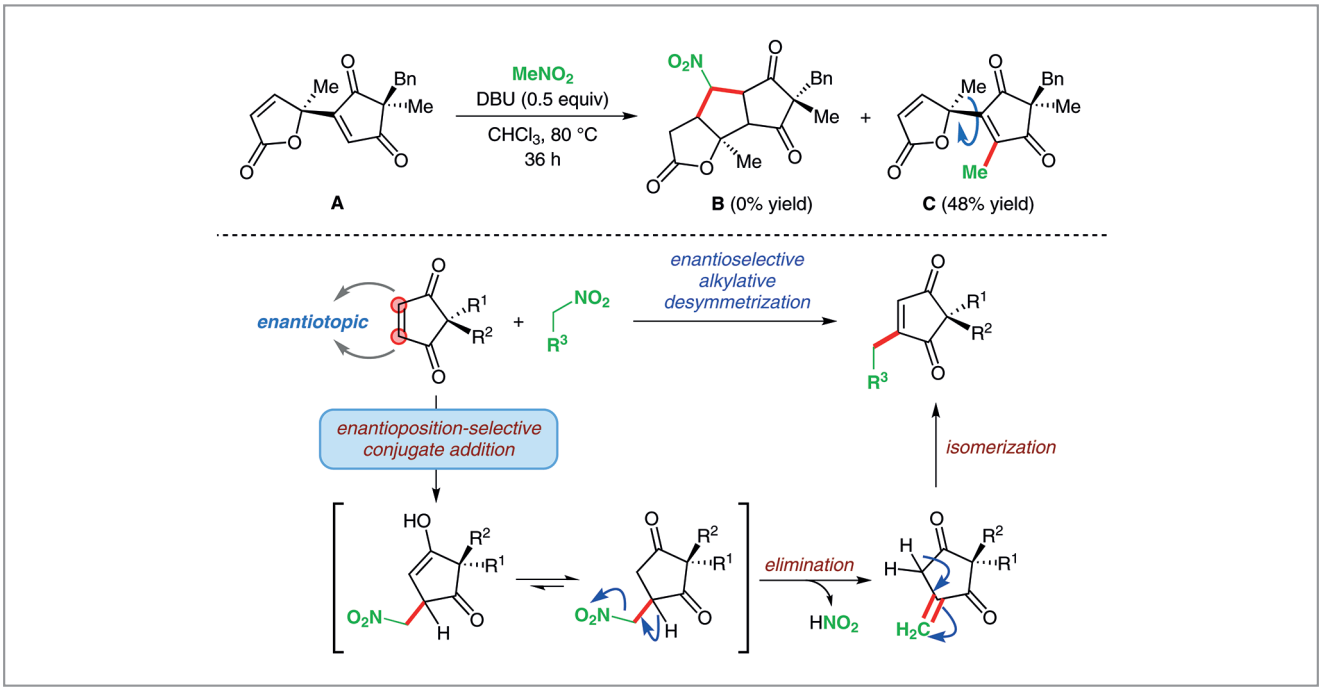
Organic compounds are characterized by the presence of various C–H bonds. Functionalization of a specific C–H bond in a molecule with a selected atom or group is among the most straightforward and desirable synthetic transformations in organic chemistry. This seemingly simple transformation is in fact a daunting challenge and often involves fancy or expensive reagents/catalysts and requires multiple synthetic steps. The present decade is witnessing a boom in direct C–H functionalization reactions. This field is dominated by transition-metal catalysts and the regioselectivity is almost always dictated by a directing group present within the same molecular framework. While the direct functionalization of C–H bonds with a functionalized alkyl group became possible through this approach, replacement of 'H' with a simple, non-functionalized alkyl group remained elusive.

The group of Professor Santanu Mukherjee at the Indian Institute of Science (Bangalore, India) has now developed a simple protocol for the direct alkylation of olefinic C(sp²)–H bonds, not only enantioselectively using an organocatalyst but more importantly without having to use any directing group.

"The C(sp²)–H alkylation itself does not generate any stereocenter at the reaction site, so an enantioselective alkylation must rely on a desymmetrization approach," said Professor Mukherjee. "Prochiral 2,2-disubstituted cyclopentene-1,3-diones were chosen as the substrate, considering the wide abundance of chiral cyclopentane derivatives in many natural and non-natural bioactive molecules."

Professor Mukherjee explained: "Desymmetrization has this unique advantage of setting up stereocenters away from the reaction site." While choosing this class of substrates, Professor Mukherjee and graduate student Madhu Sudan Manna realized that an enantioselective C–H alkylation would represent an ideal desymmetrization – one where no additional stereocenter would be generated and the existing functionalities would remain intact.

Such reactions are conventionally carried out following a two-step sequence consisting of an asymmetric conjugate addition and oxidation, and require expensive and air-sensitive metalloalkyl reagents. The group's aim was to achieve this transformation in a single step using an easily accessible,



Scheme 1 Discovery of nitroalkane as the alkyl source and the mechanistic hypothesis of the alkylative desymmetrization

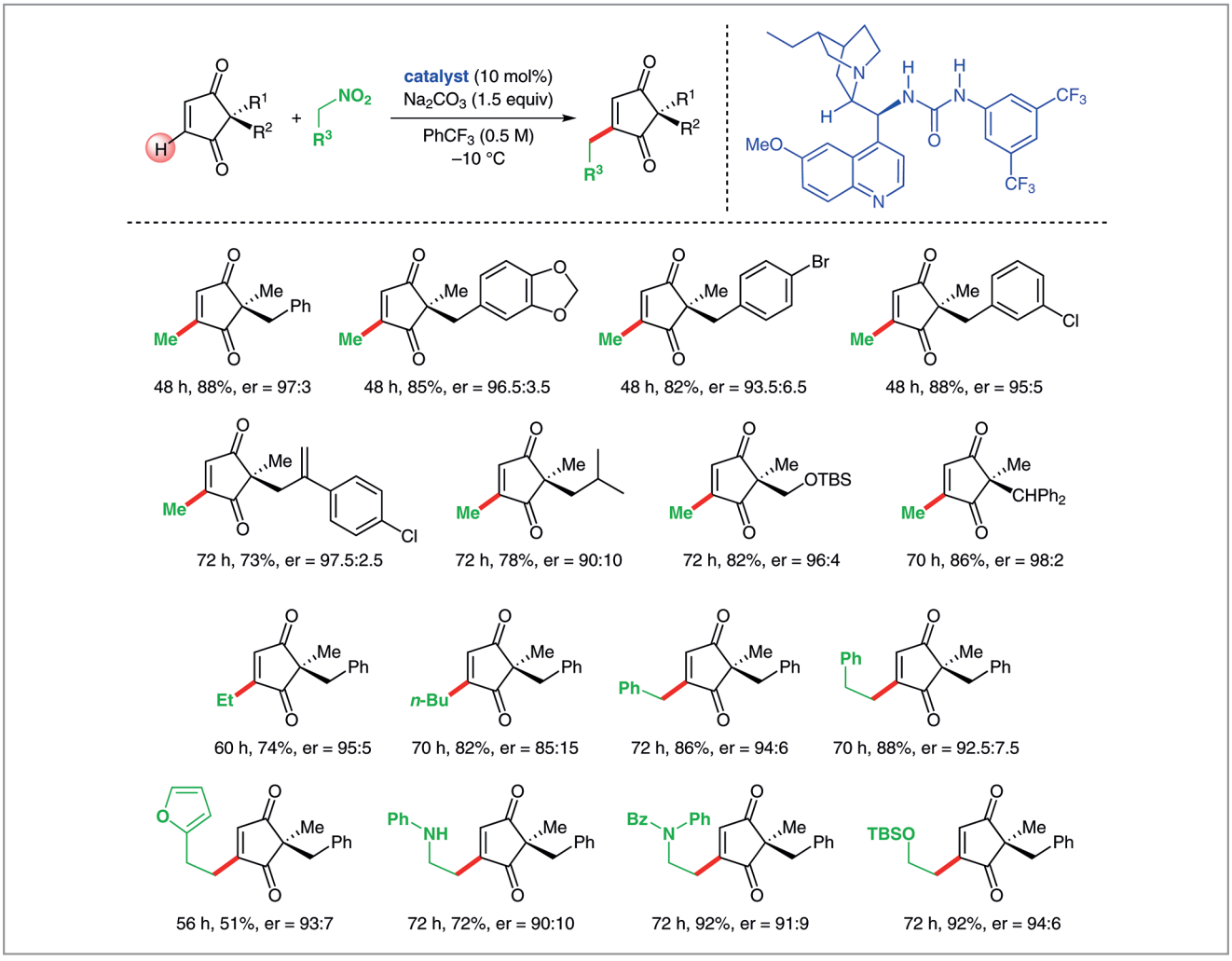
inexpensive and air-stable alkyl source. This was obviously not a trivial task.

Professor Mukherjee explained: "In a somewhat different context, our attempt to synthesize the tricyclic compound **B** from **A** through the double Michael addition of nitromethane under DBU failed and led to the formation of 'something else' as '1:1 mixture' according to NMR (Scheme 1). Luckily, my PhD student Mr. Madhu Sudan Manna took some time to figure out the structure of this 'undesired' product and found it to be the C(sp^2)–H-methylated product **C** as a mixture of two atropisomers." Clearly, nitromethane was acting as the source of the methyl group in this reaction. Even though this was surprising at first glance, the leaving group ability of nitro functions is well documented in the literature. This 'failed' experiment laid the foundation for the present work.

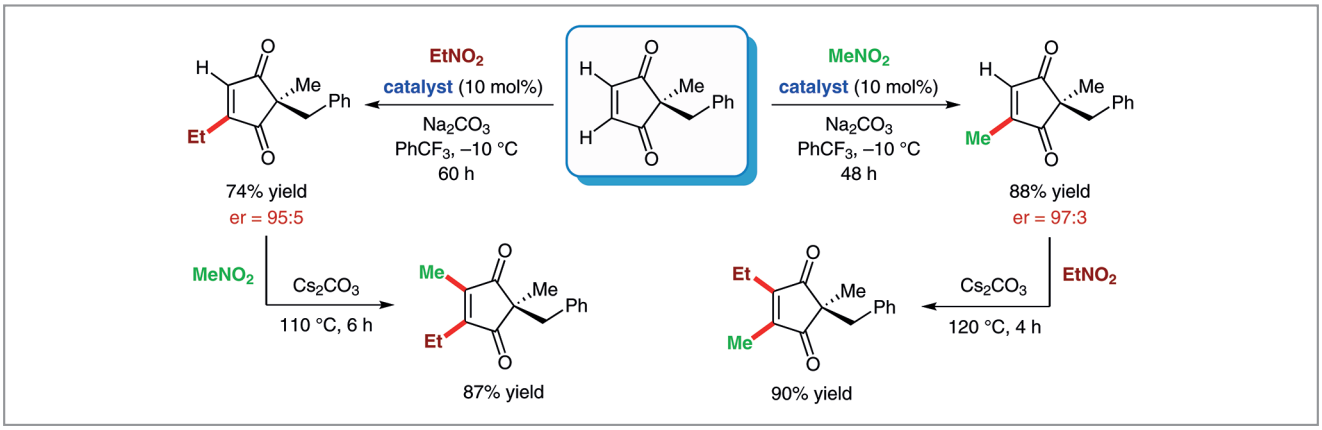
"Once we deciphered the mechanism of this reaction," said Professor Mukherjee, "its potential became clear to us."

"We immediately realized that an enantioselective conjugate addition to prochiral 2,2-disubstituted cyclopentene-1,3-diones is all that is required to achieve an alkylative desymmetrization," he continued. "We were convinced, based on our previous experience, that bifunctional tertiary amino(thio) urea derivatives could do this job." The choice of this catalyst candidate, however, gave rise to another issue. Since nitrous acid is a byproduct of this reaction, effective catalyst turnover would require the presence of a terminal base – one which would not catalyze the (non-selective) conjugate addition.

A rigorous yet systematic optimization study then established dihydroquinine-derived urea as the optimum catalyst and Na_2CO_3 as the terminal base. Finally, the organocatalytic



Scheme 2 Organocatalytic enantioselective C(sp^2)–H alkylation: representative examples



Scheme 3 Synthesis of unsymmetrical tetrasubstituted olefins by double C(sp²)–H alkylation

enantioselective C(sp²)–H alkylation was achieved, showing broad substrate scope in terms of both the prochiral electrophiles and the nitroalkanes (Scheme). Functionalized nitroalkanes could also be used for introducing functionalized alkyl groups. In almost all cases, the products were obtained in high yield.

"An advantage of our C(sp²)–H alkylation protocol is that the desymmetrized products can be further alkylated," said Professor Mukherjee. Using a different nitroalkane under elevated temperature, unsymmetrical tetrasubstituted olefins were obtained. "An even more remarkable feature is that, simply by changing the sequence of nitroalkanes, both the product enantiomers can be obtained under the influence of a single catalyst antipode (Scheme 3)," said Professor Mukherjee. "These compounds would be very difficult to synthesize by other means. To demonstrate the usefulness of this double alkylation protocol, the core structure of an antibiotic natural product (+)-madindoline B was synthesized."

"To summarize, a highly enantioselective organocatalytic olefinic C(sp²)–H alkylation has been developed in our labs," said Professor Mukherjee. "This alkylative desymmetrization of prochiral 2,2-disubstituted cyclopentene-1,3-diones makes use of inexpensive, easily accessible and air-stable nitroalkanes as the alkyl source, and generates synthetically useful five-membered carbocycles containing an all-carbon quaternary stereogenic center remote from the reaction site. This, to the best of our knowledge, is the first example of the use of nitroalkane as the alkyl source in an enantioselective transformation. We believe this work will inspire the development of other alkylative and related transformations including desymmetrizations," concluded Professor Mukherjee.

Professor Erick M. Carreira (ETH Zurich, Switzerland), a SYNTHESIS and SYNFACTS Editorial Board member, commented: "Mukherjee has managed to brilliantly amalgamate various concepts to generate a valuable synthetic transformation, and one that promises to impact the synthesis of complex structures at the level of both tactics and strategy. An optically active urea organocatalyst is employed to effect an enantioselective desymmetrization reaction of an achiral Michael acceptor bearing a quaternary prostereogenic center with nitroalkanes. But that is just the beginning: Mukherjee relies on the unique aspects of the nitro group as a 'chemical chameleon', in which it serves to enable the generation of a nucleophile and subsequently, having done its job marvelously, itself serves as a leaving group, or electrofuge. The end result of the reaction is the generation of optically active products that are not otherwise easily prepared. It is truly spectacular… I wish I had thought of it myself!"

About the authors

M. S. Manna

Madhu Sudan Manna received his B.Sc. (Chemistry Hons.) from Bajkul Milani Mahavidyalaya, West Bengal (India) in 2008, and his M.Sc. (Chemistry) from the Indian Institute of Technology, Guwahati (India) in 2010. He is currently pursuing his Ph.D. at the Indian Institute of Science, Bangalore (India) under the supervision of Professor Mukherjee. His research interests include the application of asymmetric organo-

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catalysis for studying vinylogous nucleophilic reactivity including asymmetric desymmetrization reactions.

Prof. S. Mukherjee

After receiving his M.Sc. from Indian Institute of Technology, Kanpur (India) in 2000, **Santanu Mukherjee** earned his Ph.D. (*summa cum laude*) in 2006 working with Professor Albrecht Berkessel at the Universität zu Köln (Germany). He worked as a Postdoctoral Fellow with Professor Benjamin List at the Max-Planck Institut für Kohlenforschung in Mülheim an der Ruhr (Germany) during 2006–2008 and with Professor E. J. Corey at Harvard University (USA) during 2008–2010. In 2010, he joined the Department of Organic Chemistry at Indian Institute of Science, Bangalore (India) as an Assistant Professor. His research interests revolve around various aspects of asymmetric catalysis. He is a recipient of the Thieme Chemistry Journals Award (2011) and the Indian National Science Academy (INSA) Medal for Young Scientists (2014).

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