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Brønsted Acid Catalyzed C–H Functionalization of *N*-Protected Tetrahydroisoquinolines via Intermediate Peroxides

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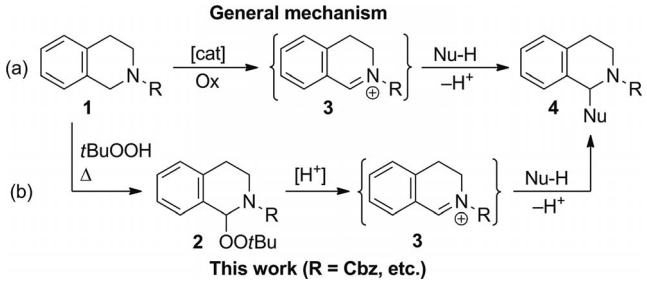
An organocatalytic oxidative synthesis of *N*-protected tetrahydroisoquinolines is described by C–H functionalization via intermediate peroxides. The peroxides were synthesized from *tert*-butylhydroperoxide under metal-free thermal conditions and were converted into the final products by Brønsted acid catalyzed substitution. The nucleophile scope was investigated in detail and proved to be broad; *N*-deprotection of the coupling products could also be achieved.

Introduction

Over the past years, oxidative coupling reactions[1] have received a lot of attention as a result of their attractiveness in terms of atom economy, directness, and potential to follow green chemistry principles.[2] Among these reactions, the C–H functionalization of amines and tetrahydroisoquinoline (THIQ) derivatives in particular has been the focus of many studies.[3] Following the pioneering work of Murahashi[4] and Li,[5] much progress has been made to extend the scope and to develop new methods for this type of reaction.[6] The generally accepted mechanism involves oxidation of amine **1** to corresponding iminium ion **3**,[7] which then reacts with a nucleophile to final coupling product **4** (Scheme 1, a). Although the nucleophile scope has been shown to be quite broad, most reported methods are limited to *N*-aryl-substituted amines. Although C1-substituted THIQs occur frequently in natural products and pharmaceuticals,[8] the synthetic utility of *N*-aryl THIQs is low, and successful attempts to remove the aryl group have not been reported so far.[6d,9]

Oxidative coupling reactions with amines bearing removable protecting groups are less well developed. Several methods have been reported, but the substrate scope is often limited and expensive reagents or catalysts are required.[9,10] Therefore, we thought that developing a cheap catalytic method and thoroughly exploring the nucleophile scope of *N*-protected THIQs would be an important step in the expansion of the synthetic utility of such reactions.

On the basis of mechanistic studies conducted in our laboratory on Cu-catalyzed oxidative coupling reactions with *N*-phenyl THIQ, we postulated that amino *tert*-butyl peroxide **2**, formed by a radical mechanism, is a precursor to iminium ion intermediate **3**.[11] Such peroxides derived from *N*-protected amines have previously been synthesized by Ru catalysis and used as precursors to substituted products in the presence of stoichiometric amounts of $TiCl_4$ at low temperature.[10j,10k,12] On the basis of this mechanistic understanding and our previous results using methanesulfonic acid as a catalyst for the substitution of a hydroperoxide group,[13] we envisioned that a strong Brønsted acid could be a general catalyst for such transformations. We decided to study the formation and substitution of such peroxides separately to reduce the risk of side reactions that might impair the yield of the final product (Scheme 1, b).



Scheme 1. (a) General mechanism for the oxidative coupling of THIQ derivatives; (b) this work: metal-free C–H functionalization via intermediate peroxides.

Results and Discussion

As a starting point, we selected *N*-Cbz-tetrahydroisoquinoline (**1a**) as a standard substrate for the optimization of the reaction conditions to synthesize *tert*-butyl peroxides (Table 1). We hypothesized that by heating *t*BuOOH we would be able to initiate a radical reaction, which would make the whole process metal free.

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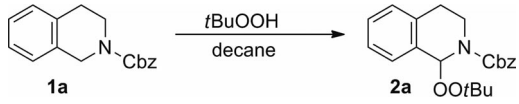
Table 1. Optimization of the thermal formation of peroxide **2a**.[a]



Entry[b]	*T* [°C]	Time [h]	*t*BuOOH [equiv.]	Yield [%]
1	80	48	3	66
2	90	28	3	65
3	100	8	3	72
4	105	4	3	73
5	110	4	3	70
6	120	2:15	3	67
7	105	4	2	37
8	105	4	4	73
9[b]	105	2	3	74[c], 73[d]

[a] Standard conditions: **1a** (1 mmol), *t*BuOOH (5.5 M in decane), decane (0.92 M concentration). [b] No additional decane. [c] Average of five experiments. [d] Performed on a 1.068-g scale.

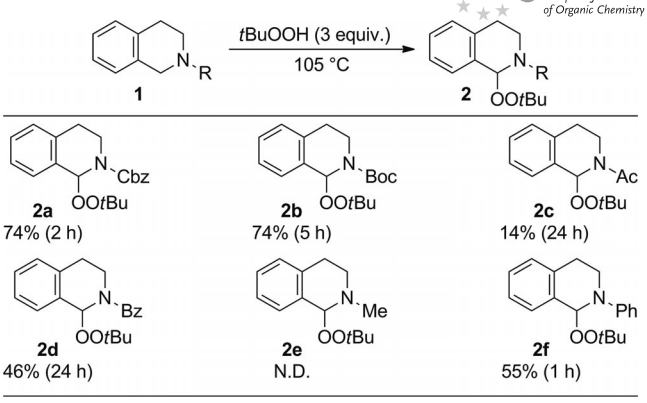
To our delight, heating compound **1a** at 80 °C in a *t*BuOOH/decane mixture gave the corresponding peroxide in reasonable yield (Table 1, entry 1). Careful optimization of the reaction temperature improved the yield to 73% at 105 °C (Table 1, entry 4), but both lower and higher temperatures gave lower yields (Table 1, entries 1 to 6). A decrease in the amount of *t*BuOOH used reduced the yield, whereas an increase in the amount used did not have any effect (Table 1, entries 7 and 8); therefore, 3 equiv. appeared to be optimal. Finally, performing the reaction under concentrated conditions further improved the yield to 74% while reducing the reaction time to 2 h (Table 1, entry 9). The reaction could also be performed on the gram scale without any loss in the yield.

Having these optimized conditions in hand, we could obtain a range of *N*-substituted tetrahydroisoquinoline peroxides (Scheme 2). Cbz-substituted peroxide **2a** was formed in only 2 h, whereas Boc analogue **2b** needed 5 h to give full conversion, yet an identical yield of 74% was obtained. Amide substrates gave poor (14% for **2c**) to moderate yields (46% for **2d**). *N*-Methyl-substituted product **2e** was not observed, and only products of overoxidation were detected. Finally, peroxide **2f** was the fastest to be formed with full conversion after 1 h, but it was isolated only in a moderate yield of 55%. If compounds **2a** and **2b** proved to be surprisingly stable on silica and to storage, it was not the case for others, particularly **2f**, which decomposed over time. Furthermore, if **2a** and **2b** were formed quickly and cleanly, the other substrates led to several byproducts and generally messier reactions and longer reaction times.

After having synthesized the starting materials, we studied the substitution of the peroxide group by a suitable nucleophile using methanesulfonic acid (MsOH) as a catalyst. For this purpose, we selected 1,3,5-trimethoxybenzene (**5**) and **2a** as test substrates (Table 2).

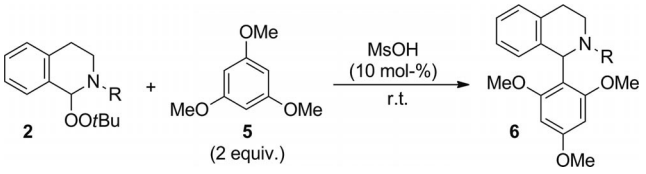
Pleasingly, corresponding coupling product **6a** was obtained in both toluene and dichloromethane (Table 2, entries 1 and 2), albeit in moderate yields. Surprisingly, even after a prolonged reaction time, we never saw the full consumption of the starting peroxide under these conditions, and this suggests deactivation of the acid catalyst. Increasing the amount of MsOH improved the yield, but stoichiometric amounts were needed to achieve full conversion (Table 2, entry 3; see the Supporting Information for more details). Adding acetic acid as a co-catalyst improved the yield (Table 2, entry 4), but only when the solvent was changed to acetic acid itself was a dramatic change in reactivity observed (Table 2, entry 5). Full conversion was achieved upon addition of methane sulfonic acid, and the coupling product was isolated in 83% yield. In the absence of MsOH, acetic acid could still mediate the reaction, but with a substantially reduced rate, to give only 46% yield after 18 h (Table 2, entry 6). Finally, only one equivalent of the nucleophile could be used without impairing the outcome of the reaction (Table 2, entry 7).

The generality of the reaction was then tested with other peroxides. *N*-Boc- and *N*-Bz-peroxides **2b** and **2d** gave satisfactory yields of 64 and 73% of the corresponding coupling products **6b** and **6d**, respectively, in a similarly short reaction time (Table 2, entries 8 and 9). In contrast, *N*-phenyl peroxide **2f** could not be coupled with **5**, which we attribute



Scheme 2. Formation of peroxide starting materials.

Table 2. Optimization of the coupling reaction and exploration of the electrophile scope.



Entry	R	Solvent	MsOH [mol-%]	Time [min]	Yield [%]
1	Cbz (**6a**)	CH_2Cl_2	10	60	37
2	Cbz (**6a**)	toluene	10	180	43
3	Cbz (**6a**)	toluene	100	60	57
4	Cbz (**6a**)	toluene	10	90	57[a]
5	Cbz (**6a**)	AcOH	10	1	83
6	Cbz (**6a**)	AcOH	–	18 h	46
7	Cbz (**6a**)	AcOH	10	1	83[b]
8	Boc (**6b**)	AcOH	10	1	64[b]
9	Bz (**6d**)	AcOH	10	1	73[b]

[a] 5 equiv. of AcOH were added. [b] 1 equiv. of **5** was used.

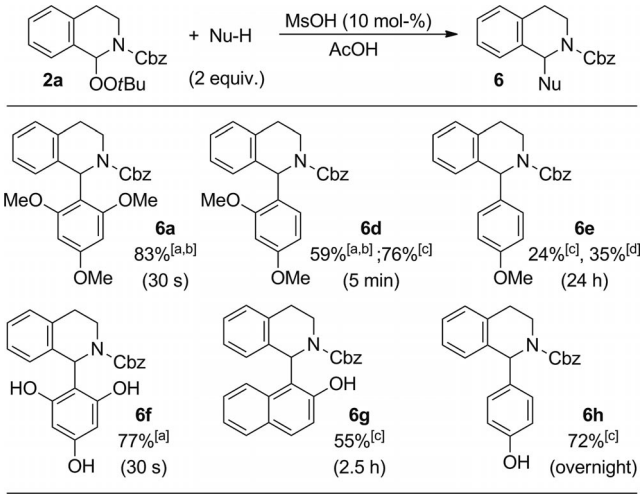
to the lower electrophilicity of corresponding iminium ion **3f** relative to that of the *N*-acyliminium ions derived from **2a**, **2b**, and **2d**. Using *N*-methylindole instead of **5**, the coupling product with **2f** could be formed (see the Supporting Information for details), which is in accordance with our previous estimation of the electrophilicity of **3f**.[11] This supports the generality of the substitution reaction and indicates that the failure of **2f** to react with **5** is most likely due to a lack of electrophilicity only.

Finally, we tried to combine these conditions to start from unoxidized THIQs. Unfortunately, the reaction of **1a** with **5** in the presence of *t*BuOOH in AcOH at 105 °C only led to a messy reaction, for which only trace amounts of the coupling product were detected. Performing the reaction in a one-pot, two-step fashion resulted in decreased yields and generally more difficult isolation of the coupling product (see the Supporting Information).

Carbamates are of particular interest for this process, as their corresponding peroxides **2a** and **2b** are easily formed and coupled in good yields. *N*-Acyl THIQs give satisfactory coupling yields but are less easily oxidized. *N*-Methyl peroxide **2e** could not be isolated and is therefore not a suitable substrate. Finally, *N*-Ph-THIQ was shown to react in a similar fashion, but this substrate has already been investigated in great detail.[4–6] Therefore, the Cbz group was selected for further experiments by using the two-step procedure.

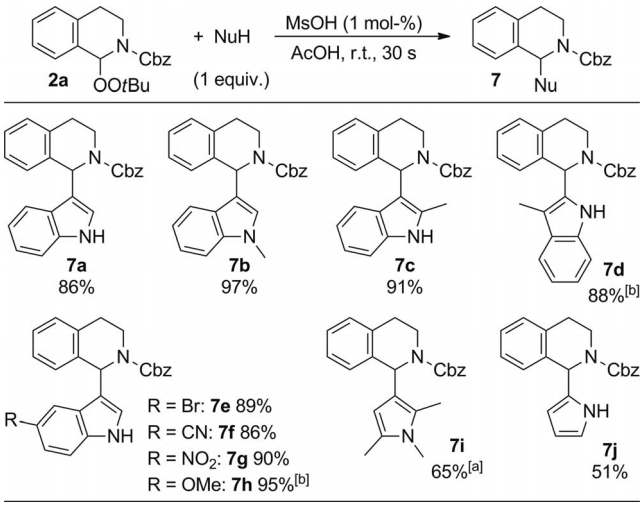
The nucleophile scope was then studied with **2a** and arene nucleophiles (Scheme 3). If **5** reacted smoothly under the previously optimized conditions, weaker nucleophiles needed heating and two equivalents to give moderate to good yields. Coupling product **6d** was obtained in 59% yield when using the previously optimized conditions but going up to 50 °C and using 2 equiv. of 1,3-dimethoxybenzene, a satisfactory yield of 76% was obtained. Even anisole reacted under these conditions to give product **6e** in 24% yield. This result is still remarkable, as comparable coupling reactions with anisole have not been reported at such a low temperature.[10e,14] It is also to be noted that the starting peroxide was re-isolated from the reaction mixture to give a yield of 35% for **6e** based on the recovered starting material. This result can be rationalized by the weaker nucleophilicity of anisole compared to that of the equivalent of *t*BuOOH released, which can continuously regenerate peroxide **2a** under the reaction conditions, thus preventing full conversion. Phenol derivatives were more reactive under these conditions. Phloroglucinol gave product **6f** in 77% yield at room temperature, whereas 2-naphthol and simple phenol needed heating at 50 °C to give products **6g** and **6h** in 55 and 72%, respectively. In the case of phenol, *ortho* addition was also observed in small amounts (8% yield).

Pleasingly, with indoles and pyrroles as nucleophiles, the catalyst loading could be reduced to 1 mol-% (Scheme 4). In almost all cases, the reaction was complete upon addition of the catalyst and gave excellent yields. Simple indole as well as methyl-substituted indoles in the 1-, 2-, or 3-position gave the corresponding products **7a**–**d** in excellent yields ranging from 86% to essentially quantitative yield. Substitution at the 5-position of the indole core showed



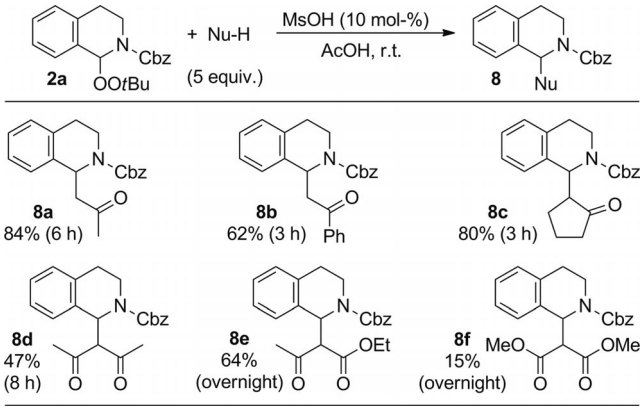
Scheme 3. Arenes as nucleophiles ([a] room temperature, [b] 1 equiv. of nucleophile, [c] 50 °C, [d] yield based on recovered starting material).

that electronic density had little to no effect on the yield: electron-withdrawing (i.e., **7e**–**g**) as well as electron-donating (i.e., **7h**) groups were tolerated and gave high yields in all cases. Products **7d** and **7h** both needed 30 min to achieve full conversion but still gave excellent yields. 1,2,5-Trimethylpyrrole gave product **7i** in 65% yield, whereas pyrrole gave **7j** in 51% yield as a single regioisomer.



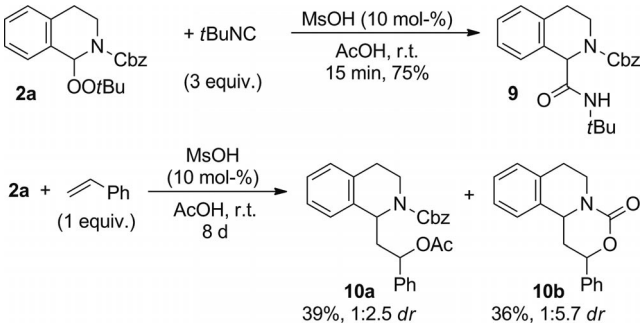
Scheme 4. Heteroarenes as nucleophiles ([a] 15 min reaction time, [b] 30 min reaction time).

Carbonyl nucleophiles were then tested under these conditions (Scheme 5). In general, 5 equiv. of nucleophiles had to be used to prevent multiple substitutions. Peroxide **2a** could be coupled with acetone, acetophenone, and cyclopentanone (products **8a**–**c**) with yields from 62 to 84%. Dicarbonyl nucleophiles were also competent in this transformation: acetylacetone gave product **8d** in 47% yield and ethyl acetoacetate gave 64% yield of inseparable diastereoisomers in a 1:0.8 ratio (product **8e**). Disappointingly, dimethylmalonate proved to be a rather poor nucleophile under these conditions, as it gave product **8f** in only 15% yield.



Scheme 5. Carbonyl compounds as nucleophiles.

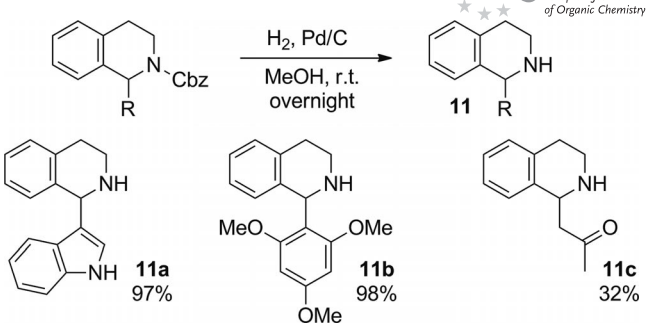
We also tested the reactivity of **2a** towards other C nucleophiles (Scheme 6). The reaction with an isocyanide gave amino acid derivative **9** in good yield after a short reaction time. The reaction with styrene[10d] proved to be more sluggish, as a mixture of acetate **10a** and cyclized product **10b** was obtained.



Scheme 6. Coupling of **2a** with alternative C nucleophiles.

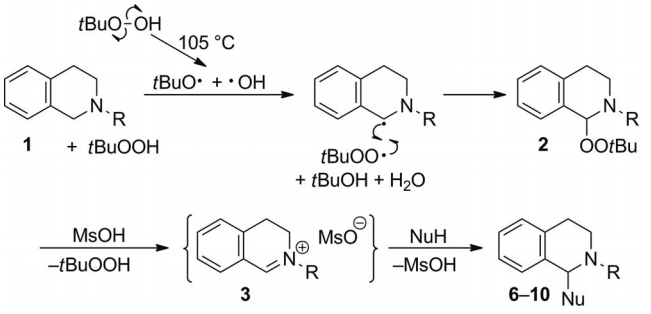
The reactivity of **2a** under these conditions is comparable to previous reports utilizing substrates such as **1a**,[9,10b–10d] which suggests that all these reactions indeed proceed via a common intermediate, most likely postulated iminium ion **3**. Compared with our mechanistic studies of *N*-phenyl-THIQ (**1f**),[11] the Cbz group increases the electrophilicity of the iminium ion by approximately five orders of magnitude: in terms of Mayr's nucleophilicity values,[15] the lowest possible nucleophilicity *N* in this study is approximately –1.2 (anisole),[16] whereas it was 3.8 for **1f**.[11]

To demonstrate the utility of our method and the use of an easily removed protecting group, we conducted the hydrogenation of some selected coupling products (Scheme 7). As expected from Cbz deprotection, free amines **11a** and **11b** were obtained in nearly quantitative yields. Although free amine **11a** could be isolated, it was more stable as the HCl salt. Not surprisingly, **11c** was not very stable to hydrogenation conditions and was isolated in only 32% yield.



Scheme 7. Deprotection of selected coupling products.

The proposed reaction mechanism is depicted in Scheme 8. Under thermal conditions, homolytic cleavage of *t*BuOOH generates two radicals, which abstract an H atom from amide **1** and from a second equivalent of *t*BuOOH. The corresponding radicals recombine to form peroxide **2**. The reason for the highly selective formation of **2** is not entirely clear, but similar results have been observed for related radical reactions.[17] In the second step, methanesulfonic acid activates the peroxide, which releases a molecule of *t*BuOOH and generates iminium ion **3**. This species is then trapped by a nucleophile to give the corresponding coupling products.



Scheme 8. Proposed reaction mechanism.

Conclusions

In this communication, we have described a novel metal-free method for the C–H functionalization of carbamates. A selective metal-free synthesis of intermediate *tert*-butyl peroxides **2** was achieved under thermal conditions. The peroxide unit can be substituted by a nucleophile often under rapid Brønsted acid catalysis. The nucleophile scope proved to be quite broad, including electron-rich arenes and heteroarenes such as indoles, pyrroles, and phenol derivatives, as well as carbonyl compounds, isonitriles, and styrene. Finally, the use of Cbz as an easily removable protecting group allows further functionalization of the coupling products. Further work to increase the scope of this reaction to include other protected amines is currently underway in our laboratory.

Experimental Section

Warning: Although we never experienced any problem in working with or handling the compounds described in this work, precautions should be taken when working with peroxides. In particular, exposure of the neat peroxides to heat or mixing them with metals or metal salts should be avoided as much as possible. Performing the thermal synthesis of the peroxides and concentrating their solutions behind a blast shield is recommended.

General Procedure for the Synthesis of *tert*-Butyl Peroxides from Tetrahydroisoquinolines: A 4-mL screw cap vial was charged with the corresponding tetrahydroisoquinoline (1 mmol) and a solution of *t*BuOOH (5.5 M in decane, 540 μL, 3 mmol) was added. The mixture was stirred at 105 °C by using an aluminum hotplate for the indicated time (see Table 2). After cooling, the resulting mixture was directly subjected to flash chromatography on silica gel to afford corresponding peroxide **2**.

Benzyl 1-(*tert*-Butylperoxy)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (2a): ^{1}H NMR (400 MHz, [D$_6$]DMSO, 80 °C): δ = 7.43–7.17 (m, 9 H), 6.59 (s, 1 H), 5.25–5.10 (m, 2 H), 4.12–3.98 (m, 1 H), 3.54–3.36 (m, 1 H), 2.88–2.77 (m, 2 H), 1.16 (s, 9 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO, 80 °C): δ = 154.26 (q), 136.31 (Ar q), 135.54 (Ar q), 129.81 (Ar q), 128.59 (ArH), 128.52 (ArH), 128.12 (ArH), 127.82 (ArH), 127.33 (ArH), 127.11 (ArH), 125.72 (ArH), 83.97 (CH), 79.54 (q), 66.17 (CH$_2$), 27.08 (CH$_2$), 25.80 (CH$_3$) ppm. MS (EI): *m*/*z* (%) = 355 (0.03), 266 (30), 222 (41), 91 (100). HRMS (ESI): calcd. for [C$_{21}$H$_{25}$NO$_4$Na]$^+$ [M + Na$^+$] 378.167791; found 378.167577

Synthesis of 6a as a Representative Coupling Procedure: In a 4-mL screw cap vial, peroxide **2a** (88.7 mg, 0.25 mmol) was dissolved in AcOH (1 mL). 1,3,5-Trimethoxybenzene (42 mg, 0.25 mmol) was then added followed by MsOH (1.77 μL, 0.025 mmol). The mixture was stirred at room temperature for 30 s, and the whole reaction mixture was then subjected to flash chromatography (elution with pentane/AcOEt, 85:15) on silica gel to afford coupling product **6a** (89 mg, 83%) as a clear oil, which gave a white solid upon standing at room temperature or cooling.

Benzyl 1-(2,4,6-Trimethoxyphenyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (6a): ^{1}H NMR (400 MHz, [D$_6$]DMSO, 80 °C): δ = 7.31–7.22 (m, 3 H), 7.17–7.10 (m, 3 H), 7.06 (tt, *J* = 2, 7.2 Hz, 1 H), 7.00 (td, *J* = 2, 7.7 Hz, 1 H), 6.69 (d, *J* = 7.7 Hz, 1 H), 6.46 (s, 1 H), 6.19 (s, 2 H), 5.05–4.95 (m, 2 H), 4.24 (ddd, *J* = 3, 5, 12.6 Hz, 1 H), 3.77 (s, 3 H), 3.58–3.49 (m, 7 H), 2.90–2.75 (m, 2 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO, 80 °C): δ = 159.89 (Ar q), 158.41 (Ar q), 154.46 (q), 136.79 (Ar q), 136.53 (Ar q), 134.08 (Ar q), 127.67 (ArH), 127.52 (ArH), 126.97 (ArH), 126.80 (ArH), 125.42 (ArH), 125.32 (ArH), 125.05 (ArH), 113.06 (Ar q), 91.62 (ArH), 65.59 (CH$_2$), 55.33 (CH$_3$), 54.81 (CH$_3$), 48.75 (CH), 39.28 (CH$_2$), 29.19 (CH$_2$) ppm. MS (EI): *m*/*z* (%) = 433 (5), 342 (4), 298 (100), 91 (27). HRMS (ESI): calcd. for [C$_{26}$H$_{27}$NO$_5$Na]$^+$ [M + Na$^+$] 456.178527; found 456.178146.

Supporting Information (see footnote on the first page of this article): Experimental procedures, product characterization, further details of the optimization studies, and copies of the ^{1}H NMR and ^{13}C NMR spectra.

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[1] a) C.-J. Li, *Acc. Chem. Res.* **2009**, *42*, 335–344; b) C. J. Scheuermann, *Chem. Asian J.* **2010**, *5*, 436–451; c) M. Klussmann, D. Sureshkumar, *Synthesis* **2011**, 353–369; d) C. S. Yeung, V. M. Dong, *Chem. Rev.* **2011**, *111*, 1215–1292; e) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem.* **2012**, *124*, 9092; *Angew. Chem. Int. Ed.* **2012**, *51*, 8960–9009.

[2] P. Anastas, N. Eghbali, *Chem. Soc. Rev.* **2010**, *39*, 301–312.

[3] a) K. M. Jones, M. Klussmann, *Synlett* **2012**, *23*, 159–162; b) E. A. Mitchell, A. Peschiulli, N. Lefevre, L. Meerpoel, B. U. W. Maes, *Chem. Eur. J.* **2012**, *18*, 10092–10142; c) K. R. Campos, *Chem. Soc. Rev.* **2007**, *36*, 1069–1084.

[4] a) S.-I. Murahashi, N. Komiya, H. Terai, T. Nakae, *J. Am. Chem. Soc.* **2003**, *125*, 15312–15313; b) S.-I. Murahashi, N. Komiya, H. Terai, *Angew. Chem.* **2005**, *117*, 7091; *Angew. Chem. Int. Ed.* **2005**, *44*, 6931–6933.

[5] a) Z. Li, C.-J. Li, *J. Am. Chem. Soc.* **2004**, *126*, 11810–11811; b) Z. Li, D. S. Bohle, C.-J. Li, *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 8928–8933.

[6] For representative examples, see: a) Z. Li, C.-J. Li, *Org. Lett.* **2004**, *6*, 4997–4999; b) A. J. Catino, J. M. Nichols, B. J. Nettles, M. P. Doyle, *J. Am. Chem. Soc.* **2006**, *128*, 5648–5649; c) O. Baslé, C.-J. Li, *Green Chem.* **2007**, *9*, 1047–1050; d) A. S.-K. Tsang, M. H. Todd, *Tetrahedron Lett.* **2009**, *50*, 1199–1202; e) S. Singhal, S. L. Jain, B. Sain, *Chem. Commun.* **2009**, 2371–2372; f) W. Han, A. R. Ofial, *Chem. Commun.* **2009**, 5024–5026; g) A. Sud, D. Sureshkumar, M. Klussmann, *Chem. Commun.* **2009**, 3169–3171; h) D. Sureshkumar, A. Sud, M. Klussmann, *Synlett* **2009**, 1558–1561; i) L. Chu, F.-L. Qing, *Chem. Commun.* **2010**, *46*, 6285–6287; j) A. G. Condie, J. C. González-Gómez, C. R. J. Stephenson, *J. Am. Chem. Soc.* **2010**, *132*, 1464–1465; k) J. H. Schrittwieser, V. Resch, J. H. Sattler, W.-D. Lienhart, K. Durchschein, A. Winkler, K. Gruber, P. Macheroux, W. Kroutil, *Angew. Chem.* **2011**, *123*, 1100; *Angew. Chem. Int. Ed.* **2011**, *50*, 1068–1071; l) D. P. Hari, B. König, *Org. Lett.* **2011**, *13*, 3852–3855; m) M. Rueping, C. Vila, R. M. Koenigs, K. Poscharny, D. C. Fabry, *Chem. Commun.* **2011**, *47*, 2360–2362; n) R. A. Kumar, G. Saidulu, K. R. Prasad, G. S. Kumar, B. Sridhar, K. R. Reddy, *Adv. Synth. Catal.* **2012**, *354*, 2985–2991.

[7] a) A. S.-K. Tsang, P. Jensen, J. M. Hook, A. S. K. Hashmi, M. H. Todd, *Pure Appl. Chem.* **2011**, *83*, 655–665; b) E. Boess, D. Sureshkumar, A. Sud, C. Wirtz, C. Farès, M. Klussmann, *J. Am. Chem. Soc.* **2011**, *133*, 8106–8109.

[8] M. Shamma, *The Isoquinoline Alkaloids: Chemistry and Pharmacology*, Academic Press, New York, **1972**, vol. 25.

[9] M. Ghobrial, K. Harhammer, M. D. Mihovilovic, M. Schnürch, *Chem. Commun.* **2010**, *46*, 8836–8838.

[10] For representative examples, see: a) L. Zhao, C.-J. Li, *Angew. Chem.* **2008**, *120*, 7183; *Angew. Chem. Int. Ed.* **2008**, *47*, 7075–7078; b) C. Dubs, Y. Hamashima, N. Sasamoto, T. M. Seidel, S. Suzuki, D. Hashizume, M. Sodeoka, *J. Org. Chem.* **2008**, *73*, 5859–5871; c) H. Richter, O. García Mancheño, *Eur. J. Org. Chem.* **2010**, 4460–4467; d) H. Richter, R. Fröhlich, C.-G. Daniliuc, O. García Mancheño, *Angew. Chem.* **2012**, *124*, 8784; *Angew. Chem. Int. Ed.* **2012**, *51*, 8656–8660; e) M. Ghobrial, M. Schnürch, M. D. Mihovilovic, *J. Org. Chem.* **2011**, *76*, 8781–8793; f) E. Shirakawa, N. Uchiyama, T. Hayashi, *J. Org. Chem.* **2010**, *76*, 25–34; g) C. Dai, F. Meschini, J. M. R. Narayanam, C. R. J. Stephenson, *J. Org. Chem.* **2012**, *77*, 4425–4431; h) K. M. Jones, P. Karier, M. Klussmann, *ChemCatChem* **2012**, *4*, 51–54; i) T. Shono, Y. Matsumura, K. Tsubata, *J. Am. Chem. Soc.* **1981**, *103*, 1172–1176; j) T. Naota, T. Nakato, S.-I. Murahashi, *Tetrahedron Lett.* **1990**, *31*, 7475–7478; k) S.-I. Murahashi, T. Naota, T. Kuwabara, T. Saito, H. Kumobayashi, S. Akutagawa, *J. Am. Chem. Soc.* **1990**, *112*, 7820–7822; l) K. T.

Wanner, I. Praschak, U. Nagel, *Arch. Pharm.* **1990**, *323*, 335–350.
[11] E. Boess, C. Schmitz, M. Klussmann, *J. Am. Chem. Soc.* **2012**, *134*, 5317–5325.
[12] S.-I. Murahashi, T. Naota, K. Yonemura, *J. Am. Chem. Soc.* **1988**, *110*, 8256–8258.
[13] a) Á. Pintér, A. Sud, D. Sureshkumar, M. Klussmann, *Angew. Chem.* **2010**, *122*, 5124; *Angew. Chem. Int. Ed.* **2010**, *49*, 5004–5007; b) Á. Pintér, M. Klussmann, *Adv. Synth. Catal.* **2012**, *354*, 701–711.
[14] S. J. Park, J. R. Price, M. H. Todd, *J. Org. Chem.* **2012**, *77*, 949–955.
[15] H. Mayr, A. R. Ofial, *J. Phys. Org. Chem.* **2008**, *21*, 584–595.
[16] H. Mayr, B. Kempf, A. R. Ofial, *Acc. Chem. Res.* **2003**, *36*, 66–77.
[17] a) A. Bravo, H.-R. Bjørsvik, F. Fontana, L. Liguori, F. Minisci, *J. Org. Chem.* **1997**, *62*, 3849–3857; b) A. Studer, *Chem. Eur. J.* **2001**, *7*, 1159; c) H. Fischer, *Chem. Rev.* **2001**, *101*, 3581–3610.
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